Tryptamines as Ligands and Modulators of the Serotonin 5-HT_{2A} Receptor

and the

Isolation of Aeruginascin from the Hallucinogenic Mushroom *Inocybe aeruginascens*

Dissertation

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultäten

der Georg-August-Universität zu Göttingen

vorgelegt von

Niels Jensen

aus Hamburg

Göttingen 2004

D 7

Referent: Prof. Dr. H. Laatsch

Korreferent: Prof. D. E. Nichols

Tag der mündlichen Prüfung: 4. November 2004

Table of Contents

Table of Contents III

List of Figures V

List of Tables IX

List of Abbreviations XI

Theoretical Part 1

Introduction 1

Psychoactive mushrooms 1

Inocybe aeruginascens 3

Aeruginascin 3

Aims of the aeruginascin project 4

Tryptamines as 5-HT receptor ligands 4

G-protein coupled receptors 7

Mechanism of hallucinogenic action 16

Pharmacology of 5-HT_{2A} ligands 23

Aims of the tryptamine project 26

Results and Discussion 29

Isolation of aeruginascin 29

New route to 4-hydroxytryptamines 29

Isolation of aeruginascin 37

Synthesis of aeruginascin 42

Serotonin receptor ligand synthesis 49

Pharmacological testing 63

IP accumulation assay results 73

Non-competitive modulation 99

Alleged "high affinity" 5-HT_{2A} receptor ligand 104

Summary of the aeruginascin project 107

Summary of the tryptamine project 110

Experimental Part 117

Materials and Methods 117

Pharmacological methods 117

Receptor binding experiments 118

Chemical syntheses 119

Chemical Experiments 121

4-Hydroxytryptamines: Ene synthesis route 121

Synthesis of baeocystin and norbaeocystin 125

Aeruginascin: Isolation, synthesis, and spectroscopic data 131
Synthesis of alcohols 135
Synthesis of alkyl halides 148
Synthesis of *N*-alkyl-*N*-methyltryptamines 164
Synthesis of *N*-(4-bromobenzyl)-5-methoxytryptamine 243

Appendix 247
Aeruginascin spectra 247
Tested compounds (Table 6) 251
Receptor binding data (Table 7) 255
Comparison of binding affinities (Table 8) 263
Functional 5-HT_{2A} data (Table 9) 271
Functional data compared to binding data (Table 10) 279

References 287

List of Figures

Figure 1: Chemical structures of the *Psilocybe* alkaloids and of aeruginascin. 2

Figure 2: Chemical structures of tryptamine, serotonin (5-HT), and psilocin. 7

Figure 3: Typical binding curve from a competitive binding experiment. 14

Figure 4: Typical dose-response curve from an IP accumulation assay. 15

Figure 5: Dose-response curves of agonists, partial agonists, and antagonists. 16

Figure 6: 5-HT_{2A} receptor ligands (I): Phenethylamines. 23

Figure 7: 5-HT_{2A} receptor ligands (II): Lysergamides. 24

Figure 8: 5-HT_{2A} receptor ligands (III): Tryptamines. 25

Figure 9: Alleged 5-HT_{2A} receptor ligand. 26

Figure 10: New 4-hydroxytryptamine synthesis. 30

Figure 11: Isomerization of diethyl-prop-2-ynyl-sulfonium bromide. 30

Figure 12: Mechanism of the annulation reaction. 31

Figure 13: Mechanism of the ene reaction. 31

Figure 14: Reaction of the *exo*-methylene compound with Eschenmoser's salts. 32

Figure 15: Isomerization of *exo*-methylene-tetrahydrofuranone. 33

Figure 16: Reaction mechanism of the ammonolysis. 33

Figure 17: Putative aromatization product. 35

Figure 18: Synthesis of baeocystin and norbaeocystin. 36

Figure 19: UV spectra of isolated and synthetic aeruginascin. 40

Figure 20: ^{1}H NMR spectra of isolated aeruginascin. 41

Figure 21: Decomposition products of aeruginascin detected by ESI MS. 43

Figure 22: Biosynthesis of *Psilocybe* alkaloids. 45

Figure 23: Aeruginascin, muscarine, and phosphorylcholine. 47

Figure 24: Superposition of aeruginascin and muscarine. 47

Figure 25: Aeruginascin and 5-HTQ. 48

Figure 26: ^{1}H-NMR spectra of the precursors and the final tryptamine. 52

Figure 27: Transition from a first order into a second order signal. 54

Figure 28: Synthesis of *N*-methyl-*N*-alkyltryptamine. 54

Figure 29: Synthesis of *N*-monomethyltryptamine. 56

Figure 30: ^{1}H NMR spectra of the unsubstituted *N*-methyltryptamine. 59

Figure 31: ^{13}C NMR spectra of the unsubstituted *N*-methyltryptamine.....60
Figure 32: Chemical structure of the ethylene-bis-tryptamine.....61
Figure 33: Structure of a quaternary byproduct of the bis-tryptamine.....61
Figure 34: Formation of the tetrahydro-β-carboline.....62
Figure 35: The synthesis of *N*-(4-bromobenzyl)-5-methoxytryptamine.....63
Figure 36: Abbreviating naming convention for the tryptamine derived ligands.....65
Figure 37: Chemical structures of tryptamine derived 5-HT receptor ligands.....66
Figure 38: Chemical structures of DOB derived 5-HT_{2A} agonists.....67
Figure 39: Chemical structures of 5-HT_{2A} antagonists.....67
Figure 40: First experiments showing a biphasic dose-response curve.....77
Figure 41: Biphasic dose-response curves.....79
Figure 42: Biphasic dose-response curves in the presence of 1 µM ketanserin.....81
Figure 43: The effect of 32 µM ketanserin and MDL 100,907 (I).....82
Figure 44: The effect of 32 µM ketanserin and MDL 100,907 (II).....83
Figure 45: Co-application of 2,5-Me-PE-NMT and 5-HT.....85
Figure 46: Structure of the β-adrenergic receptor antagonist propranolol.....86
Figure 47: The effect of monoamine neurotransmitters on the IP response.....86
Figure 48: The effect of monoamine receptor ligands on the IP response.....88
Figure 49: The effect of $sigma_1$ receptor ligands on the IP response.....89
Figure 50: The effect of monoamine receptor antagonists on the IP response.....90
Figure 51: Chemical structure of phenoxybenzamine (PBZ).....91
Figure 52: The effect of phenoxybenzamine (PBZ) on the IP response.....92
Figure 53: Human 5-HT_{2A} receptor, rat 5-HT_{2A} receptor, and wild type cells.....93
Figure 54: Over-maximal stimulation: human versus rat 5-HT_{2A} receptor cells.....94
Figure 55: Human 5-HT_{2A} receptor versus wild type cells.....95
Figure 56: Trace impurities or analysis artifacts detected by ESI MS.....99
Figure 57: Selected chemical structures of receptor modulators.....102
Figure 58: Chemical structures of putative 5-HT_{2A} receptor modulators.....103
Figure 59: Chemical structures of the *Psilocybe* alkaloids and of aeruginascin.....107
Figure 60: Chemical structures of aeruginascin and muscarine.....109
Figure 61: Superposition of aeruginascin and muscarine.....109

Figure 62: New 4-hydroxytryptamine synthesis. 110
Figure 63: Chemical structures of the tested tryptamines. 112
Figure 64: Biphasic dose-response curves. 114
Figure 65: Alleged 5-HT_{2A} receptor ligand....115
Figure 66: Ene synthesis: compound numbering scheme. 121
Figure 67: Structures and numbering scheme of norbaeocystin and baeocystin.....125
Figure 68: Structure and numbering scheme of aeruginascin.....131
Figure 69: General numbering scheme for intermediate alcohols.....135
Figure 70: General numbering scheme for intermediate alkyl halides. 149
Figure 71: General numbering scheme for *N*-substituted *N*-methyltryptamine. 168
Figure 72: MS spectra abbreviations for trace impurities and analysis artifacts. 169
Figure 73: General numbering schemes for 5-methoxytryptamine derivatives. 243
Figure 74: UV spectra of isolated and synthetic aeruginascin. 247
Figure 75: UV spectra of synthetic aeruginascin, baeocystin, and norbaeocystin. 248
Figure 76: Enlarged UV spectra of the synthetic *Psilocybe* alkaloids. 249

List of Tables

Table 1: Published binding data and functional activities of psilocin. 8

Table 2: R_f values of mushroom alkaloids and reference compounds. 38

Table 3: The effect of receptor ligands on the high-dose response....87

Table 4: Calculated parameters for the dose response curves of Figure 54. 93

Table 5: Selected modulators of G-protein coupled receptors. 100

Table 6: Compounds subjected to the pharmacological assays....251

Table 7: Receptor binding data....255

Table 8: Radioreceptor binding data - comparison of affinities....263

Table 9: Functional data at cells transfected with the 5-HT_{2A} receptor. 271

Table 10: Functional data in comparison to receptor binding data. 279

List of Abbreviations

5-HT:	serotonin (5-hydroxytryptamine)
8-OH-DPAT:	8-hydroxy-2-(*N,N*-dipropylamino)-tetraline, 5-HT_{1A} receptor ligand
AA:	arachidonic acid
Ac_2O:	acetic acid anhydride
AcOH:	acetic acid
AMPA-R:	glutamate receptor, ligand gated Na^+ / K^+ channel
APT NMR:	attached proton test NMR
AUC_{267}:	area under the curve (integral) at 267 nm
Bn:	benzyl
Bu:	butyl
Bz:	benzoyl
c:	concentration
CaM:	calmodulin
CaMKII:	calmodulin-dependent kinase II
cGMP:	cyclic guanosine monophosphate
cHex:	*cyclo*-hexyl
CI MS:	chemical ionization mass spectroscopy
COX-2:	inducible cyclooxygenase
cpm:	counts per minute
d:	density in g/ml
D:	deuterium
DAG:	*sn*-1,2-diacyglycerol
dH_2O:	distilled water
DMBA:	*para*-dimethylaminobenzaldehyde
DMT:	*N,N*-dimethyltryptamine
DOB:	2,5-dimethoxy-4-bromoamphetamine, 5-HT_2 receptor ligand
DOI:	2,5-dimethoxy-4-iodoamphetamine, 5-HT_2 receptor ligand
DR:	dorsal raphe nucleus
$EC_{50:}$	half-maximal effective concentration
ESI MS:	electro-spray ionization mass spectroscopy
Et:	ethyl
FT-ICR MS:	Fourier transform - ion cyclotron resonance mass spectroscopy
GDP:	guanosine diphosphate
GPCR:	G protein coupled receptor
GTP:	guanosine triphosphate
H/D:	hydrogen / deuterium

HCOOH: formic acid
HPLC: high performance / high pressure liquid chromatography
$IC_{50:}$ half-maximal inhibitory concentration
IP: inositol phosphates
IP_3: D-*myo*-inositol-1,4,5-trisphosphate
i.v.: intravenous
i-PrOH: isopropanol
KA: kainate
K_d: equilibrium dissociation constant
K_i: equilibrium inhibitor dissociation constant
k_{assoc}: rate of association
k_{dissoc}: rate of dissociation
LDA: lithium diisopropylamine
LSD: lysergic acid diethylamide
MAOI: monoamine oxidase inhibitor
MBT: *N*-methyl-*N*-benzyltryptamine
Me: methyl
MeCN: acetonitrile
MeO: methoxy substituent
MnR: median raphe nucleus
mPFC: medial prefrontal cortex
MS: mass spectroscopy
n: number of independent experiments
n-BuOH: butan-1-ol
NEt_3: triethylamine
NMDA: *N*-methyl-D-aspartate
NMDA-R: glutamate receptor, ligand gated Ca^{2+} channel
NMR: nuclear magnetic resonance spectroscopy
NMT: *N*-methyltryptamine
ON: over night
Pd/C: palladium on charcoal
PBS: phosphate buffered saline
PE: 2-phenethyl
PE-NMT: *N*-(2-phenethyl)-*N*-methyltryptamine
PEI: poly-(ethylene-imine)
PET: positron emission tomography
PI: phosphatidyl inositol
PIP_2: phosphatidylinositol bisphosphate

PKC: protein kinase C
PLA_2: phospholipase A_2
PLC: phospholipase C
PLD: phospholipase D
PPh_3: triphenylphosphine
PPh_3O: triphenylphosphine oxide
Pr: propyl
R_f: retention factor
RGS: regulator of G-Protein signaling protein
RT: room temperature
RT-PCR: reverse transcription polymerase chain reaction
SAR: structure-activity / structure-affinity relationships
SEM: standard error of mean
SERT: serotonin reuptake transporter
SPECT: single photon-emission tomography
SSRI: selective serotonin reuptake inhibitor
TBPP: tetrabenzylpyrophosphate
t-BuOK: potassium *tert.*-butoxide
THF: tetrahydrofuran
TLC: thin layer chromatography
TM: transmembrane domain
TMT: *N*,*N*,*N*-trimethyltryptamine

Theoretical Part

Introduction

Psychoactive mushrooms

The first recorded description of the use of "inebriating mushrooms" in Mexican ceremonies came from Spanish chroniclers of the 16th and 17th century. However, the modern scientific investigation of sacred mushroom use began not until 1936 - 1939 by the ethnobotanist Blas Pablo Reko, the anthropologists Robert J. Weitlaner, Jean Bassett Johnson, and Irmgard Weitlaner, and the botanist Richard E. Schultes. Their studies proved and documented the still continuing use of mushrooms in religious practices in remote regions of Mexico. The ethnomycologists Valentina Pavlovna Wasson and R. Gordon Wasson continued this work in 1953. In 1955 they were the first scientists allowed to actively participate in such ceremonies together with the photographer Alan Richardson. They confirmed the strong psychoactive effects of the mushrooms [289]. During an expedition in 1956 the mycologist Roger Heim identified the mushrooms as basidiomycetes of the genera *Psilocybe*, *Stropharia*, and *Conocybe,* and he was able to establish laboratory cultures of many of them together with the French mycologist Roger Cailleux. The Swiss chemist Albert Hofmann and the laboratory assistant Hans Tscherter from Sandoz were able to isolate the active principles psilocin (**7**) and its phosphate ester psilocybin (**3**) from these cultures in 1959, guided by self-administration (Figure 1) [128, 134, 133, 218]. Since then, psilocin (**7**) and psilocybin (**3**) have been detected in many other mushroom species of the genera *Agrocybe* [157], *Conocybe* [32], *Copelandia* [290], *Galerina* [34], *Gerronema*, *Gymnopilus* [125, 157, 161], *Hygrocybe*, *Inocybe* [103, 94, 255], *Mycena*, *Psilocybe*, *Stropharia* [93], Paneolus [227], *Paneolina*, *Pluteus* [96], and *Psathyrella* [157]. For a review see: [218], for an extensive collection of references see: [101].

Psychoactive effects

The *Psilocybe* alkaloids share psychoactive effects with a broad range of structurally divergent natural compounds and synthetic agents. Their subjective effects are nearly identical to those of the alkaloid mescaline (**8**), the active principle of several sacred Mexican cacti, to those of *N,N*-dimethyltryptamine (DMT, **45**) from South American psychoactive snuffs and potions, and to those of lysergic acid diethylamide (LSD, **12**), synthesized by Albert Hofmann in 1938 and 1943 [133, 218].

The mental effects caused by these compounds have been somehow inadequately described as "psychotomimetic", "psychodysleptic", or "hallucinogenic" throughout the scientific literature. More appropriate terms like "psychedelic" or the relatively new term "entheogenic" are widely used outside the scientific community but could not replace the established scientific standard term "hallucinogenic" [218].

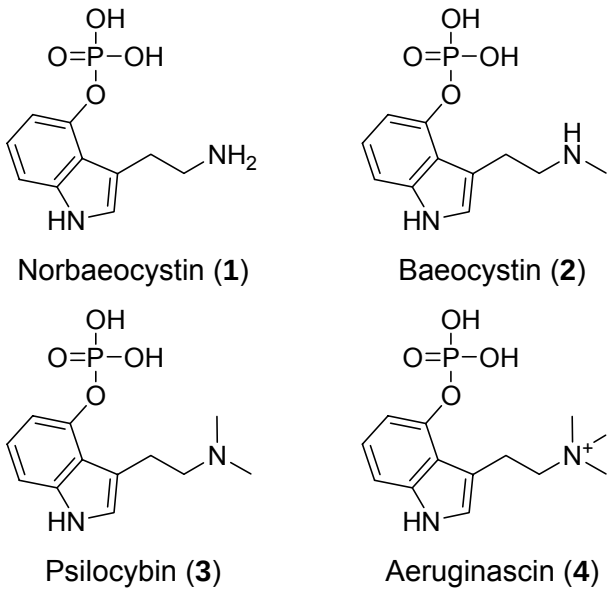


Figure 1: Chemical structures of the *Psilocybe* alkaloids and of aeruginascin.

Chemical structures of the *Psilocybe* alkaloids norbaeocystin (**1**), baeocystin (**2**), and psilocybin (**3**). The structure of the non-basic alkaloid-like compound aeruginascin (**4**) has been elucidated in this study. The compounds are ordered by increasing number of methyl substituents at the amino-group.

Hallucinogens do effect a powerful intensification of senses, feelings, memories, and self-awareness. In addition, they typically produce visual effects such as moving geometric patterns and brilliant colors, but not true hallucinations. The experience is usually remembered clearly. These characteristics separate this class of compounds from the, mostly anticholinergic, so-called "true hallucinogens" or "deliriants". Hallucinogens usually do not cause physical side effects, hangovers, or associated diseases, and they do not have addiction potential. This is in remarkable contrast to the widely abused drugs alcohol and nicotine as well as to opiates and cocaine. However, they can exhibit profound mental effects, and therefore certain rules have to be adhered to in order to prevent adverse reactions [120, 124, 133, 258, 259]. Despite rigorous prohibition, the use of hallucinogenic mushrooms and of *Psilocybe* alkaloids has a long history for recreation, self-experience, religious practice, and psychotherapy [120, 207] throughout the world and they are still widely used for these purposes. Currently, clinical studies in the USA, Switzerland, and Germany are underway to re-examine their use in psychotherapy and psychiatry [52, 124].

Biosynthesis of *Psilocybe* alkaloids

4-Hydroxylated or 4-methoxylated indoles are very rare in nature. Known examples beside the psilocybin-type alkaloids are the 4-hydroxylation of indol-3-yl-acetic acid by *Aspergillus*

niger strains [159], methoxylated β-carbolines from *Banisteriopsis argentea* [109, 110] and *Picrasma javanica* [18], the reserpine analog venenatine from *Alstonia venenata* [261], the yohimbine analogous mitragynines from *Mitragyna speciosa* [275], and the aminopyrimidyl-indolic meridianins from the tunicate *Aplidium meridianum* [113].

In contrast to the former alkaloids, psilocybin (**3**) has a relatively simple chemical structure. It is biosynthetically derived from the amino acid tryptophan (**34**) by enzymatic decarboxylation, indole-hydroxylation, *N*-methylations, and O-phosphorylation (Figure 22). Feeding experiments with putative intermediates, analogs of them, and radioactive precursors supported the view that the biosynthetic pathway starts with a decarboxylation and that *O*-phosphorylation is the final step. However, there is still uncertainty about the sequence of 4-hydroxylation and the *N*-methylation steps. Some authors even suppose a biosynthetic grid with multiple routes to psilocybin (**3**) [10, 54, 241].

Inocybe aeruginascens

The mushroom species *Inocybe aeruginascens* was first collected in Hungary in 1965 and was named by the Hungarian mycologist Babos in 1968 [25]. Since then it has been found widely distributed across central Europe, mainly in Germany and Hungary [39, 94, 102, 89, 88]. Its fruiting season is from May until October, with a peak between May and June. It always grows in sandy soils under deciduous trees, mostly at anthropogenic locations like parks and gardens, directly on sand or in short grass.

At least 23 unintentional intoxications due to its vague similarity with the common edible mushroom species *Marasmius oreades* (fairy ring mushroom) with characteristic hallucinogenic symptoms early from 1972 were reported first in1983 by Drewitz [70] and Babos [24]. Gartz and Drewitz could then demonstrate the occurrence of psilocybin (**3**) in *Inocybe aeruginascens* [103, 94]. This was the first report of this class of alkaloids in the genus *Inocybe* and several other groups could verify the occurence of psilocybin (**3**) in this and two related *Inocybe* species [34, 122, 271, 272].

Aeruginascin

In addition to the common alkaloids psilocybin (**3**) and psilocin (**7**), two additional compounds in *Inocybe aeruginascens* with color reactions similar to psilocybin (**3**) were described by Gartz. One of them could later be identified as baeocystin (**2**) [87, 271]. In subsequent publications the presence of the unknown compound was verified [103, 87, 90, 91, 88, 255] and it was named "aeruginascin" by Gartz [87, 90]. While screening dozens of hallucinogenic mushroom species of the genera *Psilocybe*, *Gymnopilus*, *Paneolus*, *Conocybe*, and *Inocybe* (including the psilocybin-positive species *Inocybe haemacta* (Berk. & Cooke) Sacc.) for the presence of aeruginascin (**4**) over the last 20 years, Jochen Gartz could detect this compound exclusively in *Inocybe aeruginascens* [86].

Aeruginascin (**4**) was shown by TLC to be more hydrophilic than psilocybin (**3**) and baeocystin (**2**) and to give a color reaction with Ehrlich's reagent similar to these alkaloids, with the exception that its pink or mauve spot did not change in color to bluish violet on storage. A small sample isolated from TLC plates has been reported to give an UV spectrum similar to that of psilocybin (**3**) [90, 85]. Unfortunately, several attempts to isolate higher amounts of sufficiently pure compound were hampered by its hydrophilicity [90, 117] and possibly by its chemical sensitivity.

Aims of the aeruginascin project

Extracts of *Inocybe aeruginascens* have been previously analyzed by Jochen Gartz and later by Luydmila Gurevich in the group of H. Laatsch in Göttingen. Purified preparations could be obtained by these researchers and UV spectra have been recorded. Unfortunately, the isolated amounts were too small for ^{1}H NMR or ^{13}C NMR measurements, and CI MS analysis did not give conclusive results. So the main aim of the current study was to elucidate the structure of the natural product aeruginascin.

Due to the limited amount of dried *Inocybe aeruginascens* material we planned to first synthesize norbaeocystin (**1**) and baeocystin (**2**) as analytical reference compounds. We were also in need of larger amounts of 4-hydroxylated tryptamines for the synthesis of potential 5-HT_{2A} receptor ligands. We therefore planned to develop a new efficient synthetic strategy leading to 4-hydroxylated tryptamines. In the case that aeruginascin could not be identified by comparison with known compounds we planned to isolate an analytical sample from *Inocybe aeruginascens* fruit bodies for spectroscopic structure determinations.

Tryptamines as 5-HT receptor ligands

Hallucinogenic compounds, including *Psilocybe* alkaloids, act by their interaction with the serotonergic system of the brain. More specifically, they mimic the action of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT, **6**) at a certain subset of serotonin receptors, the 5-HT_{2A} receptor. Serotonin (**6**) is one of the major neurotransmitters in the brain as well as a potent peripheral hormone and signal mediator. The serotonergic system is an important target for therapeutic agents and drugs, from a medicinal as well as from an economical standpoint (for a review see: [146]). Thirteen different serotonin receptors have been identified and characterized in vertebrates (for reviews see: [27, 137]). With the exception of the 5-HT_3 receptor they all belong to the class of "G-protein coupled", "heptahelical", or "seven transmembrane domain" receptors. Serotonin receptors are divided into seven distinct families, based on their primary structure and their signal transduction properties. The 5-HT_2 family comprises the three subtypes 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} which exhibit a high amino acid sequence identity and a similar pharmacology (for a review see: [248]). There exist subtype

selective antagonists for each of the 5-HT_2 receptors, as well as 5-HT_{2B} and 5-HT_{2C} receptor selective agonists. However, no 5-HT_{2A} receptor selective agonist has been described yet.

The serotonergic system as a pharmacological target

The new compounds from this study have been tested at three different 5-HT receptor subtypes, the 5-HT_{1A}, the 5-HT_{2A}, and the 5-HT_{2C} receptor. All these receptors are important pharmacological targets and have been associated with the mechanism of hallucinogenic compounds.

The 5-HT_{2A} receptor has a key role in current drugs to treat schizophrenia (for a review see: [192]). Compared to classical neuroleptics like haloperidol, the newer atypical neuroleptics like clozapine, olanzapine, or risperidone lack the acute extrapyramidal and irrerversible long-term side effects like tardive dyskinesia. All these atypical antipsychotic compounds have in common a potent antagonism of 5-HT_{2A} receptors in combination with a weaker antagonism of dopamine D_2 receptors. Moreover, there are indications that 5-HT_{2A} receptor antagonists increase the effectiveness of antidepressive therapies with selective serotonin reuptake inhibitors (SSRI) [181]. The 5-HT_{2A} receptor has also long been implicated in the function of memory. Indeed, patients treated with preferential 5-HT_{2A} receptor antagonistic neuroleptics developed deficits in memory related test while these measures improved in patient treated with classical neuroleptics [278]. In human there exists a frequent allele of the 5-HT_{2A} receptor with a histidine to tyrosine substitution at the C-terminal position 452. This variation results in receptors with an altered second messenger response [219]. Recently it has been shown that human heterozygote carriers of this allele have measurable memory deficits [64].

On the other hand there is compelling evidence that the hallucinogenic effects of compounds like psilocin (**7**), LSD (**12**), or mescaline (**8**) are mediated by activation of 5-HT_{2A} receptors (for an excellent review on the action of hallucinogens see: [207]). The mechanism and the pharmacology of these compounds will be discussed in detail below. Interestingly, 5-HT_{2A} receptor agonists are also effective in lowering the intraocular pressure after topical application and are currently under development as a glaucoma treatment [188] [189]. Even the still unknown mechanism of action of the widely used analgesic drug paracetamol (acetaminophen) has been associated with an indirect downregulation of central 5-HT_{2A} receptors [250, 267]. 5-HT_{2A} receptors are also located outside the central nervous system in many tissues like blood platelets or vascular smooth muscle cells including the umbilical vein. Indeed, the latter has been used in early assays for measuring hallucinogenic activity [247].

A single nucleotide polymorphism in the promoter region of the 5-HT_{1A} receptor is highly associated with major depression and suicide. The substitution has been shown to abolish binding of the NUDR repressor, thereby resulting in enhanced expression levels of the 5-HT_{1A} receptor [168]. Not surprisingly, partial agonists of the 5-HT_{1A} receptor like buspirone or gepirone are in use as anxiolytics in medicine. Similarly, the association of suicidal behavior

with mutations of the serotonin reuptake transporter (SERT) gene locus has recently been confirmed in a meta-study [15]. Inhibitors of the axonal serotonin reuptake process, the selective serotonin reuptake inhibitors (SSRI) like fluoxetine, citalopram, paroxetine, or sertraline are the currently most widely prescribed antidepressives in the treatment of obsessive compulsive disorders, depression, and panic anxiety.

The 5-HT_{2B} receptor is predominantly located peripherally and has a high abundance in the gastrointestinal, the pulmonary, and the cardiovascular system. Another early *in vitro* system to test hallucinogenic compounds, the rat fundus strip preparation, was actually targeting the 5-HT_{2B} receptor in this tissue [29]. A typical valvular heart disease caused by extended use of the anorectic drug fenfluramine as well as by certain 5-HT (**6**) secreting tumors, is probably mediated by activation of 5-HT_{2B} receptors located in the heart valve [76]. Despite its mostly peripheral location the 5-HT_{2B} receptor is also located in several brain areas [149] and has been shown to mediate anxiolytic-like action [153], hyperphagia [152], and increased wakefulness [149] in rats.

5-HT_{2C} receptor agonists were recently under development as potential therapeutics for depression and obsessive compulsive disorder because they lacked the serious side effects typical for 5-HT reuptake inhibitors [42, 185]. However, in more specific animal models a 5-HT_{2C} receptor agonists demonstrated marked sedative-, but not anxiolytic-like effects [151] while a selective 5-HT_{2C} receptor antagonist / inverse agonist had an anxiolytic-like profile [294]. More recently it has been found that 5-HT_{2C} receptor agonists are effective as anti-obesity drugs due to their appetite suppressing action [126]. Indeed, a 5-HT_{2C} receptor gene promoter polymorphism has been suggested as a risk factor for obesity [228].

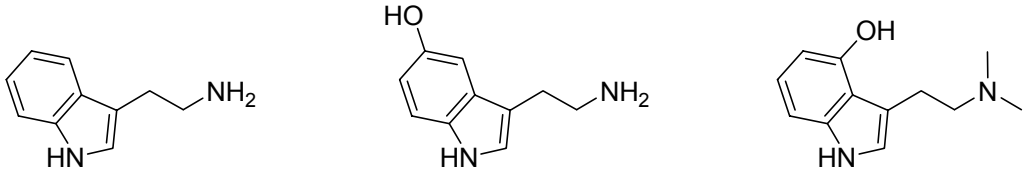
5-HT_{2A} receptor species variants

The existence of intra-species [111] as well as inter-species variants of the 5-HT_{2A} receptor has been described. While the amino acid sequence of the transmembrane regions of the receptor is identical between human, pig, and rhesus monkey, the rat receptor has three substitutions [144]. One of them is a serine to alanine substitution at position 242 (S_{242}-A) in helix 5, located in the agonist binding pocket. This substitution alters the structure-activity relationships of ergolines and tryptamines so that indole-N(1)-alkylated ligands bind preferentially to the rat variant while indole-N(1) unsubstituted compounds bind preferentially to the human variant. This has been attributed to direct interactions of the amino acid side-chain with the ligand [12, 145, 144]. Additionally, 15-fold higher affinities of psilocin (**7**) for the human sequence variants of the 5-HT_{2A} receptor have been demonstrated [12] (Table 1).

5-HT receptor selectivity of psilocin

Uncertainty exists about the binding profile of the hallucinogenic compound psilocin (**7**) at serotonin receptor subtypes in humans. In some publications it is therefore referred to as a

mixed 5-HT_2 / 5-HT_1 receptor agonist [124, 286]. Unfortunately, comparable binding data at human receptors does not exist so far (Table 1). A low, two-fold selectivity of psilocin (**7**) for the rat 5-HT_{2A} over the rat 5-HT_{1A} receptor has been measured in transfected cells [37]. Taking into account the 15-fold higher affinity of psilocin (**7**) for the human over the rat 5-HT_{2A} receptor [81], psilocin (**7**) might be a reasonably 5-HT_{2A}-selective ligand in humans.



Tryptamine (**5**) Serotonin (5-HT, **6**) Psilocin (**7**)

Figure 2: Chemical structures of tryptamine, serotonin (5-HT), and psilocin.

G-protein coupled receptors

The 5-HT_{2A} receptor is a member of a huge class of structurally homologous transmembrane receptors, the G-protein coupled receptors (GPCR). They all consist of seven helical transmembrane domains (TM1 - TM7) and are therefore synonymously called "heptahelical receptors" or "seven-transmembrane receptors". Another cytosolic helix 8 has recently been discovered in the rhodopsin crystal structure [194]. Most G-protein coupled receptors, including all monoamine neurotransmitter receptors, have their agonist binding pocket in the upper transmembrane region. A common mode of binding has been found for the monoaminergic receptors. The protonated amine of these agonists binds to a negatively charged aspartate side-chain of helix 3, while their aromatic hydroxy groups are able to form hydrogen bonds with threonine or serine side-chains of helix 5. The aromatic nucleus interacts with aromatic side-chains of helix 6. The rest of the binding pocket is lined with lipophilic and, especially around the salt bridge, aromatic residues [51, 116].

Receptor modeling

For cytosolic proteins the generation of crystal structures by x-ray diffraction is a standard laboratory procedure today. Unfortunately, this is not true for membrane spanning proteins. The only G-protein coupled receptor for which partial crystal structures down to a resolution of 2.6 Å exist, is the light sensing rhodopsin [160, 215, 220]. Currently the only method to generate molecular models of G-protein coupled receptors is by homology modeling using this rhodopsin structure as a template. This is based on the assumption of a similar structure and signaling mechanism for all G-protein coupled receptors.

Table 1: Published binding data and functional activities of psilocin.

Binding data and functional activities of psilocin (**7**) at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors from different species and at receptors with amino acid substitutions. Binding data are given as the K_i values followed by the applied radioligand. Functional activity is given as the EC_{50} value, followed by the relative efficacy as the percentage of maximal stimulation by 5-HT, and the test system (PLA_2-AA: phospholipase mediated arachidonic acid release; PLC-IP: phospholipase C mediated IP accumulation).

5-HT_{1A} Receptor	**K_d or EC_{50}**	**Assay**	**Reference**
5-HT_{1A} rat	49 nM	[^{3}H]8-OH-DPAT	[37]
	190 nM	[^{3}H]8-OH-DPAT	[190]

5-HT_{2A} Receptor	**K_d or EC_{50}**	**Assay**	**Reference**
5-HT_{2A} human	81 nM	[^{3}H]Ketanserin	[12]
	95 nM	[^{3}H]Ketanserin	[71]
	340 nM	[^{3}H]Ketanserin	[81]
	366 nM, 7% (*sic*!)	PLC-IP	[71]
5-HT_{2A} human S_{159}-A	360 nM	[^{3}H]Ketanserin	[71]
	495 nM, 59%	PLC-IP	[71]
5-HT_{2A} rat	6 nM	[^{125}I]DOI	[190]
	25 nM	[^{125}I]DOI	[37, 164]
	390 nM	[^{3}H]Ketanserin	[106]
	5100 nM	[^{3}H]Ketanserin	[81]
	86 nM, 42%	PLA_2-AA	[164]
	2300 nM, 46%	PLC-IP	[164]
5-HT_{2A} bovine	410 nM	[^{3}H]Ketanserin	[190]
5-HT_{2A} human S_{242}-A	259 nM	[^{3}H]Ketanserin	[12]

5-HT_{2C} Receptor	**K_d or EC_{50}**	**Assay**	**Reference**
5-HT_{2C} human	140 nM	[^{3}H]Mesulergine	[12]
5-HT_{2C} human A_{242}-S	73 nM	[^{3}H]Mesulergine	[12]
5-HT_{2C} rat	10 nM	[^{125}I]DOI	[37]

Several uncertainties and problems have been observed by using homology modeling procedures. First, in many works extracellular and cytosolic loop regions have been omitted despite their important function in receptor structure. Such regions include the recently discovered cytosolic helix 8 [194] and the extracellular loop between helix 4 and 5 with its disulfide bridge to helix 3, close to the agonist binding site. Also problematic is the omission of the lipidic and aqueous environment ("*in vacuo*" simulation) which often results in erroneous hydrogen bonding. Moreover, a functional role of water molecules has been suggested for the structure and function of rhodopsin [215]. Other problems arises from omitting the broad number of associated proteins, most importantly the G-protein [191]. However, the currently greatest drawback of homology modeling is that rhodopsin crystal structures only exist for the inactive state of the receptor. This structure is probably not adequate for modeling the agonist binding site. In a recent work the inactive state of rhodopsin has therefore been isomerized *in silico* into an assumed active state [51]. Other recent studies have generated an active state receptor model by applying a broad range of diverse published experimental results as distance constraints during molecular dynamics simulations [116].

Most studies agree that activation of the receptors includes the rotation and relative movement of several transmembrane domains, probably accompanied by disruption of a strong ionic interaction of the transmembrane helices 3 and 6 [256, 283] and reordering of a "switch-region" in helix 7 [229]. In the 5-HT_{2A} and related receptors binding of an agonist might also induce the reordering of a network of aromatic residues on helix 6 at and below the binding site [291].

G-protein coupled receptor signaling cascade

The binding of agonists to the binding pocket of G-protein coupled receptors results in the activation of complex intracellular second messenger cascades, ultimately resulting in cellular responses such as a fast modulation of protein function as well as delayed changes in gene expression. The second messenger pathways play an important role in the amplification of the receptor generated signal, for its integration over time and over different receptors ("receptor crosstalk"), and for transmitting the signal from the cell membrane to other cell compartments, including the nucleus.

G-proteins, the first mediators of activation of G-protein coupled receptors, are hetero-trimeric proteins composed of the Gα subunit and the tightly associated complex of the Gβ and the Gγ subunit. Both the Gα and the G$\beta\gamma$ subunits are membrane bound through lipid anchors. G-proteins serve as the first amplification step of the signal cascade because the receptor-ligand complex is able to activate multiple G-proteins. G-proteins are also adaptors, mediating the signal transduction between an enormous number of G-protein coupled receptors and a relatively small number of effector pathways. G-proteins are classified by their Gα subunits, based mainly on the different effector pathways they are coupled to.

G-proteins are activated by the receptor in a cyclic process, starting with the association of the $G\alpha\beta\gamma$-GDP complex with the receptor. Upon binding of an agonist, the receptor changes its conformation and thereby induces the release of GDP from $G\alpha$ and the subsequent binding of GTP. This results in the release of $G\alpha$ and $G\beta\gamma$ from each other and from the receptor. Both subunits then activate different effectors. The cycle is terminated by the hydrolysis of GTP to GDP by the inherent enzymatic activity of $G\alpha$ and the subsequent reassociation of $G\alpha$-GDP with $G\beta\gamma$.

It has been shown that the 5-HT_{2A} receptor is able to activate several different pathways. The phospholipase C (PLC) pathway is the historically most investigated one [63, 164, 235]. It is mediated by $G\alpha_q$ and $G\alpha_{11}$, which upon stimulation activate the membrane associated phospholipase Cβ (PLCβ). This enzyme then hydrolyzes the common membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 is a diffusible cytosolic messenger and activates the IP_3 receptor, a Ca^{2+} channel located in the membrane of the endoplasmic reticulum (ER). The resulting increase in cytoplasmic Ca^{2+} is able to activate many different cellular targets by mediation of the Ca^{2+} binding protein calmodulin (CaM). One example of such a protein is the serine / threonine protein phosphatase calcineurin. The still cell membrane bound diacylglycerol (DAG) recruits the protein kinase C (PKC) to the membrane and, together with Ca^{2+}, activates this enzyme. The activated PKC in turn phosphorylates serine and threonine residues on a variety of intracellular proteins, including receptors and proteins of the signaling cascade itself, but also ion channels like the AMPA glutamate receptor [47, 60].

More recently, it has been shown that the 5-HT_{2A} receptor couples also to other signaling pathways, mediated by small monomeric G-proteins like RhoA, Ras, and ARF1. The RhoA and Ras pathways activate phospholipase A_2 (PLA_2) in a complex convergent pathway, one probably through sequential activation of $G\alpha_{12}$ / $G\alpha_{13,}$ RhoA, PKN / MEKK, MKK, p38, PLA_2, and the other one through $G\alpha_{i/o}\beta\gamma$, $G\beta\gamma$, Ras, Raf, MEK, ERK, PLA_2 [163]. Activated PLA_2 in turn hydrolyzes membrane phospholipids, generating arachidonic acid (AA), an important signaling molecule and neuromodulator on its own as well as a precursor for a variety of eicosanoid hormones, including prostaglandins, thromboxanes, and leukotrienes. The ARF1 signaling pathways is mediated by the direct stimulation of the small G-protein ARF1 by the receptor, stimulation of phospholipase D (PLD), and subsequent hydrolysis of the membrane lipid phosphatidylcholine into the second messenger phosphatidic acid [197, 245].

Gene activation

Ultimately, stimulation of G-protein coupled receptors also leads to changes in gene expression. A number of immediate early genes regulated by 5-HT_{2A} receptor activation has been identified. 5-HT_{2A} receptor agonists induced the genes of the transcription factors *C/EBPβ*,

krox20, *egr-1*, *egr-2*, *period1*, and *nur77/N10*, the transcription factor inhibitor *Iκβ*, the nuclear hormone receptor *nor1*, the signaling protein *cyr61/CCN1*, the arrestin homolog *ilad-1*, the MAP kinase phosphatase *mkp-1*, the MAP kinase activated kinase *sgk*, the metabotropic glutamate receptor signaling related genes *ania3a* and *homer1a*, and inducible cyclooxygenase *cox-2*, while the gene for the protein kinase *sty* was repressed [114, 173, 205, 204, 206]. 5-HT_{2A} receptor stimulation also induced the A_1 adenosine receptor gene *AR1* while 5-HT_{1A} receptor stimulation had the opposite effect [114]. The expression of the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors genes remained unchanged upon 5-HT_{2A} receptor stimulation [205].

A general problem with these studies is to decide if gene expression is altered as a direct result of a receptor mediated signaling cascade or indirectly, possibly even in other cells. The best studied immediate early gene is the *c-fos* gene product, a transcription factor [114, 172, 205, 204, 222, 252, 299] However, induction of *c-fos* was found to correlate more with general neuronal activity as a response to glutamate release [114]. Indeed, the *c-fos* gene was induced in cells not expressing 5-HT_{2A} receptors [172, 252, 299], possibly GABAergic interneurons. The *c-fos* induction by 5-HT_{2A} receptor agonists in these cells was dependent on arachidonic acid, inducible cyclooxygenase (COX-2) [174, 173], glutamate release [299], and stimulation of AMPA / KA glutamate receptors. Moreover, thalamic lesions attenuated cortical *c-fos* induction [252]. The 5-HT_{2A} receptor mediated gene activation of *arc* was found to resemble that of *c-fos* in many respects [222].

Receptor associated proteins

Receptors, including G-protein coupled receptors, are not isolated entities but part of extended protein complexes. A common motif on many of these signaling cluster proteins is a PDZ-binding domain which mediates the association with synaptic scaffold proteins [31, 30, 297]. A recent study has indeed demonstrated the direct interaction of the C-terminus of the 5-HT_{2C} receptor with a synaptic scaffold protein (post synaptic density protein PSD95) [30] and several other proteins like calmodulin, protein kinase theta, cytoskeletal and cytoskeletal binding proteins (β-actin, spectrin), signaling proteins (neuronal nitric oxide synthase nNOS), and an internalization related protein (dynamin).

Other direct or functional interactions and co-localizations of 5-HT_2 receptors include further internalization related proteins (caveolin-1 [35], the G-protein coupled receptor kinase GRK [288], spinophilin, [288], arrestins [36, 105, 119, 230], dynamin [30, 36]), further cytoskeletal and trafficking related proteins (MAP1A [59]), small G-proteins (ARF1, RhoA [197, 245]), and G-protein binding related proteins (RGS proteins [108, 129]).

Many enzymes of the G-protein coupled receptor signaling cascade are either membrane bound or membrane embedded proteins and are most probably aggregated in synaptic multiprotein complexes. This includes the G-proteins, phospholipase C, calmodulin, activated

protein kinase C, phospholipase A_2, and phospholipase D. Many second messengers are small diffusible molecules, and clustering of the signaling enzymes has obvious advantages for the speed and efficiency of signaling.

Several receptor associated proteins exhibited profound effects on the signaling properties of G-protein coupled receptors. Disrupting the association of caveolin-1 with several receptors, including the 5-HT_{2A} receptor, led to profound decreases in signaling, probably by interfering with receptor-$G\alpha_q$ coupling [35]. Disrupting the interaction with the synaptic scaffold proteins PSD95 increased the signaling properties of the 5-HT_{2A} receptor by interfering with agonist-induced receptor internalization [296]. Overexpression of the "regulator of G-protein signaling" (RGS) proteins RGS2 and RGS7 decreased 5-HT_{2A} / $G\alpha_q$ mediated cellular activation [129].

Receptor dimerization

There is now broad evidence for the oligomerization of G-protein coupled receptors under physiological conditions (e.g. [78], for reviews see: [8, 43]). Homo- as well as hetero-dimerization has been demonstrated in living tissue as well as in cell culture systems. These receptor-receptor interactions have been shown to influence ligand binding affinity, structure-affinity relationships, G-protein coupling efficacy as well as selectivity, and internalization kinetics. In addition, an allosteric interaction between the two binding sites has been demonstrated for several (hetero-) dimeric receptor pairs. One prominent example is the $GABA_B$ receptor where only heterodimerization between the $GABA_{B1}$ and the $GABA_{B2}$ subtype forms a functional receptor which is able to activate G-proteins.

Agonist directed trafficking

The 5-HT_{2A} receptor is able to activate second messenger cascades by direct interaction with several different G-proteins ($G\alpha_{i/o}$, $G\alpha_q$ / $G\alpha_{11}$, $G\alpha_{12}$ / $G\alpha_{13}$) as well as the small G-protein ARF1. It is therefore not surprising that ligands and ligand classes are able to activate different signaling pathways with varying potencies through the same receptor, a concept called "agonist directed trafficking" [164, 163]. Also other binding-related events like desensitization and internalization are expected to show comparable ligand-dependent effects. Indeed, 5-HT_{2A} and 5-HT_{2C} receptors have atypical regulation properties in that not only agonists, but also most synthetic antagonists induce the internalization process [280].

Cellular effects of 5-HT_{2A} activation

Several cellular responses to activation of neuronal 5-HT_{2A} receptors have been observed. Activation of 5-HT_{2A} receptors modulated dendritic voltage gated Na^+ channels by a $G\alpha_q$ / phospholipase Cβ (PLCβ) / protein kinase C (PKC) dependent pathway, thereby reducing the amplitude and increasing the duration of dendritic action potentials [46]. Activation of 5-HT_{2A} receptors also led to stimulation of $Ca_v1.2$ L-type voltage gated Ca^{2+} channels by activation

of the $G\alpha_q$ / PLCβ / IP_3 / calcineurin second messenger cascade [63]. In addition, 5-HT_{2A} receptor agonists decreased NMDA glutamate receptor mediated currents by a Ca^{2+} / calmodulin-dependent kinase II (CaMKII), but protein kinase C (PKC) independent pathway [19, 20]. Similarly, arachidonic acid, a second messenger of 5-HT_{2A} receptor activation, has been shown to potentiate AMPA glutamate receptor currents through the same pathway [210]. 5-HT_{2A} as well as 5-HT_{1A} receptor activation resulted in an increase in cGMP content of cortical brain slices by potentiation of a NMDA receptor mediated response. The responsible pathway has not been fully elucidated yet but probably involves glutamate release, NMDA receptor activation, stimulation of neuronal nitric oxide synthase (nNOS), and increased nitric oxide (NO) release [238, 237]. The enzyme inducible cyclooxygenase (COX-2) is also transiently up- as well as downregulated by the 5-HT_{2A} agonist DOI (**10**), the expression of this enzyme slightly decreases in the cortical layers I to IV, but strongly increases in layers V and VI [173].

Receptor binding experiments

One of the most important parameters for characterizing receptor ligands is their potency, i.e. the concentration at which a compound has an effect on the receptor. This value is directly related to the strength or "affinity" with that a receptor binds a ligand. More accurately, the affinity of a ligand has been defined as the equilibrium dissociation constant K_d. This value is identical to the equilibrium constant K when applying the law of mass action to the bimolecular receptor / ligand system. K_d is therefore also identical to the relation of the rate constants of ligand release (dissociation) k_{dissoc} and ligand binding (association) k_{assoc}:

$$K_d = \frac{[\text{receptor}] \cdot [\text{ligand}]}{[\text{receptor - ligand complex}]} = \frac{k_{assoc}}{k_{dissoc}}$$

Lower values of K_d indicate higher affinities. Common neurotransmitters and drugs usually have affinities for G-protein coupled receptors in the nanomolar range. The K_d value of a compound can be determined experimentally in saturation binding experiments ("Scatchard experiments") by incubating variable amounts of the radiolabeled ligand with the receptor and measuring the receptor-bound radioactivity. Because this method requires large amounts of expensive radioactively labeled ligands, an indirect method has been developed to determine affinity, the competitive binding experiment. A receptor preparation is incubated with a constant small amount of radioactive ligand ("radioligand", "radiolabel", or "tracer") and varying concentrations of the test ligand. Both compounds then compete for binding to the receptor, depending on the affinities and their concentration. At the end of the incubation, the receptor membranes are separated from the solution, e.g. by filtration and the receptor bound radioactivity is measured. The measured radioactivity (as cpm, counts per minute) is then plotted against the logarithmic concentration of the test ligand, resulting in a typical sigmoidal binding curve (Figure 3). From this curve the half-maximal inhibiting concentration

(IC_{50}) is determined and the binding affinity K_i of the test compound is calculated using the Cheng-Prusoff equation. Under ideal conditions the K_i determined in competitive binding experiment equals the K_d determined in saturation binding experiments and both values can be used as a measure of affinity.

$$K_i = \frac{IC_{50}}{1 + \frac{[\text{radioligand}]}{K_{d\,(\text{radioligand})}}} \quad \text{(Cheng-Prusoff equation)}$$

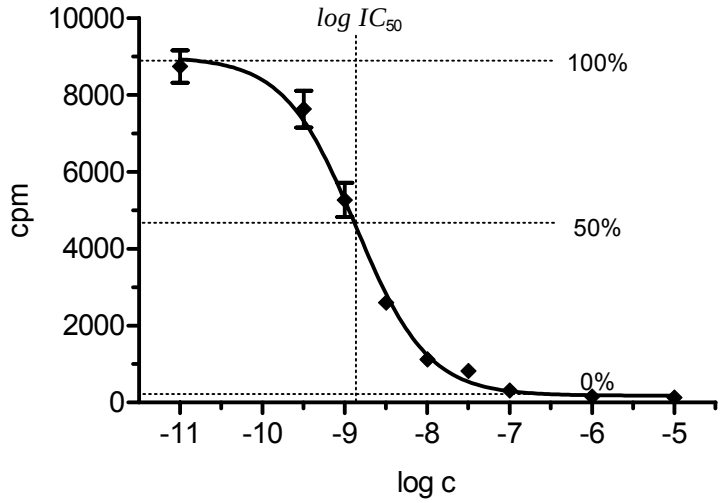


Figure 3: Typical binding curve from a competitive binding experiment.

The concentration is plotted on a logarithmic scale, resulting in a typical sigmoidal binding curve. The IC_{50} value is the half-maximal inhibiting concentration from which the affinity K_i can be calculated. For this curve compound **11** was tested at the rat 5-HT_{2A} receptor with [^{3}H]ketanserin as radioligand.

Functional assays

While receptor binding experiments give a measure of ligand affinity, it is not possible to decide from binding data if a ligand is able to activate the receptor. To determine if a ligand acts as an agonist, a partial agonist, or an antagonist, the response of living cells to the binding event must be measured ("functional assay"). As described above, 5-HT_{2A} receptors are able to activate the enzyme phospholipase C (PLC), mediated by the G-protein $G\alpha_q$. PLC in turn catalyzes the hydrolysis of the membrane lipid phosphatidyl-D-*myo*-inositol-4,5-bisphosphate

(phosphatidylinositol bisphosphate, PIP_2) into D-*myo*-inositol-1,4,5-trisphosphate (inositol trisphosphate, IP_3) and *sn*-1,2-diacyglycerol (DAG). This early step in the signaling cascade can be utilized for an assay of receptor mediated cellular response.

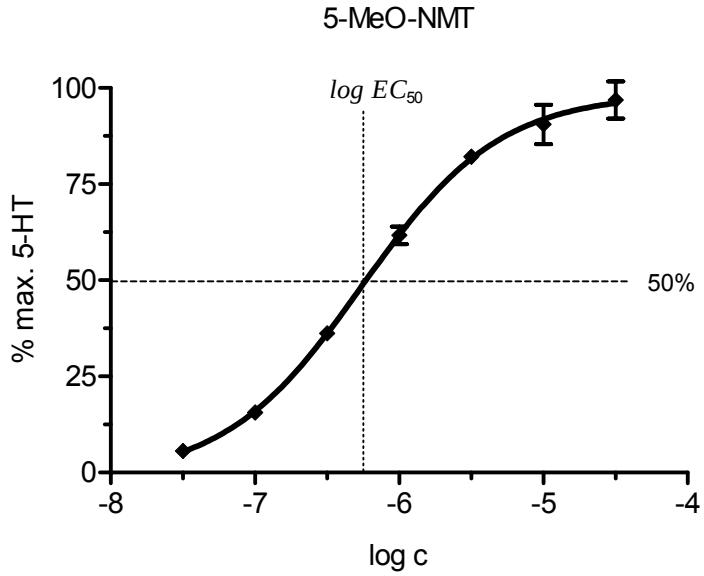


Figure 4: Typical dose-response curve from an IP accumulation assay.

The EC_{50} value is used as a measure of potency in functional assays. This value is the concentration at which a test compound elicits a half-maximal response. The concentration is plotted on a logarithmic scale, resulting in a sigmoidal dose-response curve. In this experiment 5-MeO-NMT (**208**) was tested at cells transfected with the human $5\text{-}HT_{2A}$ receptor.

Cells are preincubated with [^{3}H]PIP_2 and then treated with the test compound. After cell permeabilization the amount of liberated, tritium labeled inositol phosphates (IP) can then be measured. This type of assay is known as "phosphatidyl inositol (PI) turnover assay" or "IP accumulation assay". Similar to the receptor binding experiments, a dose-response curve is obtained (Figure 4). If the activation is caused by a single mechanism, this dose-response curve has a typical sigmoidal shape if plotted on a logarithmic concentration axis. The EC_{50} value is used as a measure of potency, and is defined as the concentration at which the compound elicits a half-maximal response. The maximal height of the curve in relation to the maximal height elicited by the natural ligand is called the "intrinsic activity" or, more accurately, "relative efficacy". Full agonists usually have a relative efficacy of 100%, while partial agonists have a lower value. Antagonists do not elicit a response at all and therefore have a

relative efficacy of 0%. There are two common ways to experimentally identify antagonists: Either as compounds hat exhibit a high binding affinity for the receptor in radioligand binding assays but that do not elicit a response in functional assays, or, alternatively, by measuring their inhibiting properties on agonist-induced stimulation in co-application experiments.

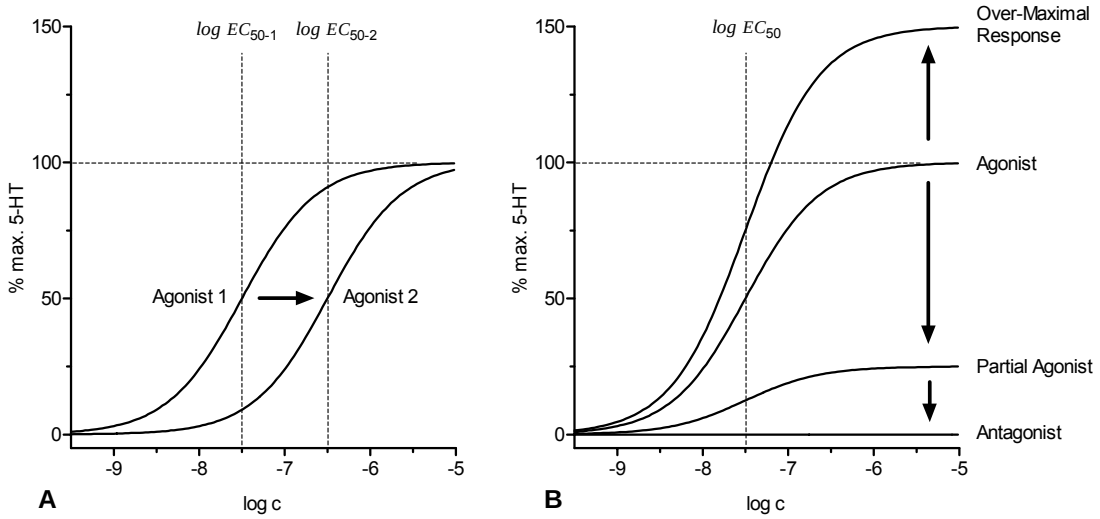


Figure 5: Dose-response curves of agonists, partial agonists, and antagonists.

Agonists of different potencies have different EC_{50} values and horizontally shifted dose-response curves (**A**). In contrast, agonists, partial agonists, and antagonists differ by their maximal stimulation, resulting in a vertical shift of the dose-response curves (**B**). An over-maximal response above 100%, higher than the response caused by the natural agonist, is a very uncommon phenomenon. The maximal stimulation is independent of the potency or the EC_{50} value, i.e. further increases in concentration have no effect once the maximal response has been reached.

Mechanism of hallucinogenic action

It is now widely accepted that hallucinogens primarily act through their agonistic action at 5-HT_{2A} receptors. This has been shown by correlation of behavioral activity in man and animals to receptor affinities as well as by rat drug discrimination tests involving specific and subtype-selective 5-HT_{2A} receptor antagonists. Moreover, the hallucinogenic action of psilocybin (**3**) in humans could be completely blocked by administration of the antagonists ketanserin (**48**) and risperidone [287]. (For an excellent review see: [207]).

Serotonergic system

5-HT_{2A} receptors are activated by the neurotransmitter serotonin (**6**). This neurotransmitter is released from axons and axon terminals of serotonergic neurons. All these projections emerge from the raphe nuclei, a complex of neuron clusters located near the midline of the whole brainstem. The upper raphe complex with the caudal linear nucleus, dorsal raphe nucleus (DR), and the median raphe nuclei (MnR) project primarily to the forebrain, including the cerebral cortex. Reciprocally, prefrontal cortex pyramidal cells project back to the raphe nuclei (for a review see: [136]). In addition to serotonergic neurons the raphe nuclei also contain non-serotonergic inhibitory GABAergic and excitatory glutamatergic neurons. 5-HT_{1A} as well as 5-HT_{2A} and 5-HT_{2C} receptors are expressed on both types of cells [40, 49, 184, 251]. Stimulation of the raphe nuclei with 5-HT receptor subtype-selective ligands therefore results in a complex modulation, further complicated by the mixed, excitatory as well inhibitory, control on other brain areas, and the reciprocal modulation from these projection areas [3, 4].

Hallucinogens and cortical activation

The hallucinogen psilocybin (**3**) caused an increased activation of most brain areas when examined in humans in a [^{18}F]deoxyglucose PET scan study [286]. The highest activations where seen in the prefrontal and the temporal cortex as well as the thalamus ("hyperfrontality"). A similar activation pattern was also seen in a human SPECT imaging study using the hallucinogen mescaline [130]. Likewise, the hallucinogens DOI (**10**) and LSD (**12**) caused increased extracellular levels of the main excitatory neurotransmitter glutamate in the cortex [201, 253]. Indeed, enhancing glutamate release by $mGluR_{II/III}$ autoreceptor antagonists resulted in potentiation of the effects of different hallucinogenic compounds in animal models while $mGluR_{II/III}$ agonists blocked them [107, 293]. Common mechanisms have been suggested for the effects of hallucinogenic compounds, dissociative drugs, and natural psychoses, involving a disruption of thalamo-cortical information processing [284].

Cortical localization of 5-HT receptors

The study of hallucinogens on cortical activation has focused on the prefrontal cortex, mainly because this area has the highest density of 5-HT_{2A} receptors [5, 58, 142, 298] and is preferentially activated by hallucinogens. The neocortex consists of six layers which are defined by their different staining characteristics and cellular architecture. These layers are numbered from I to VI, starting from the outside. The 5-HT_{2A} receptor in the cortex is predominantly located on dendrites of pyramidal cells located in layer III and V [298] [58, 59, 141, 142, 195]. While earlier studies reported an exclusive localization at dendritic shafts in intracellular compartments, a recent study was able to demonstrate the 5-HT_{2A} also at dendritic spines and synapses. This discrepancy was attributed to the use of different primary antibodies [195]. Cortical 5-HT_{2A} receptors

were also found on presynaptic, putatively dopaminergic, monoaminergic axons and synapses, on astrocytes [57, 142, 195, 298], and on GABAergic interneurones [61, 141, 251].

Pyramidal cells

Pyramidal cells have a large, characteristically shaped cell body located in layers III and V. They are integrating signals vertically throughout the upper layers with a single long apical dendritic tree which extensively arborizes in the superficial layers. Additionally, basal dendrite trees emerge from the soma and spread out horizontally in the same cortical layer. Their axons are the only efferences of the cortex and project either to subcortical brain regions or to other cortical regions.

In the case of cortico-cortical interconnections, pyramidal cells in layer V project to lower cortical areas (descending feedback connections) while layer III pyramidal cells project to higher cortical areas (ascending feedforward connections). Projections from higher cortical areas terminate mainly in layers I and VI while projections from lower areas target excitatory spiny-stellate cells in layer IV, which in turn activate basal dendrites of pyramidal cells in layers II and III. Thalamic projections usually terminate in layer IV, contacting the apical dendrites of layer V pyramidal cells. [266]

Pyramidal cells are excitatory glutamatergic cells. In the prefrontal cortex a high proportion of cortical layer V pyramidal cells expresses the 5-HT_{2A} receptor, nearly always in co-expression with the 5-HT_{1A} receptor [14, 186, 251]. However, both receptor subtypes are targeted to different cellular locations. The 5-HT_{2A} receptors are predominantly located on the apical dendrites in layer V to III [298] [58, 141, 142] including synaptic spines [195] while the 5-HT_{1A} receptors seem to be predominantly located in the region of the axon hillock and in the proximal portion of the pyramidal axon [65].

Both receptor types are activated by different serotonergic afferents. Two main dense plexuses of horizontal serotonergic axons innervate the cortex in layer Va and I, respectively. The fibers in layer V probably activate pyramidal 5-HT_{1A} receptors. Between the cortical layers V and I serotonergic fibers run vertically in parallel to the pyramidal dendrites [142]. These fibers probably interact with the dendritic pyramidal 5-HT_{2A} receptors. Prefrontal cortex pyramidal cells also express 5-HT_{2C} receptors, albeit in a lower density compared to 5-HT_{2A} receptors [46, 56, 63]. Not much information on cellular localization and function of these 5-HT_{2C} receptors is currently available. In single-cell RT-PCR experiments 5-HT_{2C} receptors were found in partial cellular co-expression with the 5-HT_{2A} receptor in one study [46], but not in another study [63].

There are hardly any defined synapses detectable between serotonergic axons and pyramidal cells. This has also been observed in other brain areas [4, 67] and it is widely assumed that slow signaling through the G-protein coupled 5-HT_{1A} and 5-HT_{2A} receptors proceeds extra-

synaptically by short distance diffusion in the extra-cellular space ("paracrine" or "volume transmission") [58, 65, 142].

There are also indirect serotonergic effects on pyramidal cells. They are all inhibitory and are mediated by the following three mechanisms. The raphe nuclei activate cortical inhibitory GABAergic neurons (dendrite-targeting interneurons) through 5-HT_3 receptors, especially in layer I [141, 233]. Recent experiments suggest also a direct contact of GABAergic axons from the raphe nuclei with pyramidal cells [231]. Large GABAergic interneurones in layer V targeting the pyramidal soma and proximal dendrite (perisomatic chandelier and basket cells) express the 5-HT_{2A} [141, 251] and, to about the same extent, 5-HT_{1A} receptors [23, 251]. This cell type is involved in pyramidal feed-forward inhibition.

The action of hallucinogens *in vitro*

Groundbreaking work on the effects of serotonin (**6**) and hallucinogenic drugs on nerve cells has been done in the group of George K. Aghajanian at Yale University, USA, using neurophysiological methods on brain slice preparations. They showed profound effects of serotonin (**6**), LSD (**12**), and DOI (**10**) on the firing rate of pyramidal cells in layer V of the medial prefrontal cortex (mPFC). Serotonin (**6**) applied to cortical brain slices resulted in a strong increase in spontaneous pyramidal cell firing. This effect was stronger in the medial prefrontal cortex compared to other cortical regions while in subcortical regions 5-HT (**6**) even had inhibitory effects. Serotonin (**6**) applied in close proximity to the dendrites of the pyramidal cells dramatically increased their firing rate after several seconds. This effect was most pronounced in layer IV/Va in a dendritic region close to the cell body, but still observable in layer I/II, a more distant dendritic region. Application 100 - 200 µm away from the vertical dendrites did not result in activation. Also application onto the pyramidal cell body in layer Vb or into the basilar dendritic field in layer Vb/VI below the cell body did not result in increased firing [7].

The pyramidal firing in the experiments above was mediated by 5-HT_{2A} receptors as shown by antagonist experiments. However, 5-HT_{2A} receptor activation did not cause a pronounced membrane depolarization and therefore could not directly induce firing of pyramidal cells [7, 17, 19, 46]. This suggested a presynaptic modulation of excitatory inputs, i.e. an increase in glutamate release from glutamatergic terminals. Indeed, blocking the postsynaptic pyramidal AMPA glutamate receptor decreased the basal firing activity and eliminated the firing response to 5-HT. Furthermore, activation of regulatory presynaptic glutamate autoreceptors with a variety of a group II/III metabotropic glutamate receptor ($mGluR_{II/III}$) agonists had the same effects as blocking the postsynaptic receptor [183]. A similar presynaptic negative modulation could be obtained by activation of µ-opioid [180, 178, 177] and adenosine A_1 receptors [273], while activation of presynaptic muscarinic acetylcholine and α_1-adrenergic receptors had the opposite effect and induced pyramidal firing [17, 179]. A decrease in 5-HT_{2A} agonist mediated

pyramidal cell firing was also observed after elimination of thalamo-cortical terminals by lesioning the medial thalamus [182].

All these findings supported the hypothesis that cortical pyramidal cells are indirectly activated by a presynaptic 5-HT_{2A} receptor modulation of glutamate release. However, the observed effects were independent of incoming axonal impulse flow, i.e. no firing neurons in the 5-HT (**6**) sensitive regions could be detected in the brain slices preparations and hardly any 5-HT_{2A} receptor containing glutamatergic terminals could be detected by immuno-labeling and electron microscopy [140, 195]. On the contrary, it was shown that the pyramidal cells itself express 5-HT_{2A} receptors at a high density in their proximal dendrites [298] [58, 141, 142, 195], accounting for the vast majority of 5-HT_{2A} receptors in this region.

The existence of a retrograde messenger was postulated to overcome this discrepancy. In this extended hypothesis the stimulation of 5-HT_{2A} receptors on pyramidal cells results in the secretion of a retrograde messenger which causes a presynaptic release of the excitatory neurotransmitter glutamate [6, 178]. Indeed, in further studies it could be shown that the 5-HT_{2A} receptor mediated, delayed, and impulse-independent "asynchronous" glutamate release [7] was caused by inhibition of presynaptic K_v 1.2 voltage gated potassium channels [165]. Intriguingly, these channels are blocked by extracellular arachidonic acid which is known to be secreted upon 5-HT_{2A} receptor stimulation in cell cultures [164, 163] and *in vivo* where immediately-early genes like *c-fos* in non-pyramidal non-5-HT_{2A} containing cortical neurons are induced by activation of the arachidonic acid signaling pathway [174, 173, 252].

The action of hallucinogens *in vivo*

A major drawback of electrophysiological studies of cortical slice preparation is the missing connectivity to other brain areas. Indeed, the importance of other brain areas on the effect of 5-HT_{2A} receptor ligands on cortical pyramidal cells has been demonstrated more recently in *in vivo* studies, especially in the group of Francesc Artigas in Barcelona, Spain. In many of these experiments brain microdialysis probes were used as a tool for local drug application and for sampling local neurotransmitter concentrations.

The results of the *in vitro* slice experiments described above could essentially be replicated by these *in vivo* methods. A cortical glutamate release by stimulation of the thalamus resulted in pyramidal cell activation (measured as a local 5-HT release by a mechanism discussed below). This activation was blocked by μ-opioid receptor activation. Surprisingly, μ-opioid receptor agonists in fact blocked the pyramidal cell activation induced by thalamic stimulation, but not that upon local DOI (**10**) application. Furthermore, thalamic lesions did not affect the activating effect of local DOI (**10**). The effect of local DOI (**10**) was, however, mediated by 5-HT_{2A} and AMPA glutamate receptors, but not by NMDA glutamate receptors

[13, 21, 22, 41, 186, 232], and the local application of DOI (**10**) and LSD (**12**) was able to increase local glutamate levels [201, 253].

Currently the following hypotheses can explain the local action of hallucinogenic substances in the cortex *in vivo*. For both possibilities 5-HT_{2A} receptors are located postsynaptically on pyramidal neurons and glutamate is released primarily from non-thalamic sources.

- Positive modulation of pyramidal AMPA glutamate receptors (AMPA potentiation hypothesis).
- Positive modulation of presynaptic glutamate release, possibly through the action of a retrograde messenger (retrograde messenger hypothesis).

Much evidence has been collected for the retrograde messenger hypothesis in *in vitro* brain slice experiments, but in *in vivo* experiments this mechanism seems to be of less importance, as described above. The AMPA potentiation hypothesis is supported by findings that arachidonic acid, a second messenger of 5-HT_{2A} receptor activation [164, 163], potentiates AMPA glutamate receptor currents by a Ca^{2+} / calmodulin-dependent kinase II (CaMKII) pathway [210, 269]. AMPA receptors are also positively regulated by protein kinase C (PKC) phosphorylation [47, 60]. However, in *in vivo* medial prefrontal cortex brain slice experiments the 5-HT_{2A} receptor agonist DOB (**9**) increased AMPA receptor mediated currents only in a minority of the tested cells. In contrast, NMDA receptor mediated currents were strongly increased in all tested neurons [19].

The action of hallucinogens on the raphe nuclei

Another focus of recent *in vivo* experiments was the interaction of the cortex with the upper raphe nuclei. It could be shown that local application of the 5-HT_{2A} receptor agonist DOI (**10**) to the medial prefrontal cortex increased the firing rate of pyramidal neurons projecting to the raphe nuclei as well as the reciprocal cortical 5-HT release from back-projecting raphe neuron afferents [186, 232].

Electrical stimulation of the dorsal and the median raphe nuclei results in a complex modulation of pyramidal cell firing. As described above, projections from the raphe nuclei control pyramidal cell activation by excitatory dendritic 5-HT_{2A} receptors as well as by inhibitory axonal 5-HT_{1A} receptors, pyramidal $GABA_A$ receptors, and 5-HT_{1A}, 5-HT_{2A}, and 5-HT_3 receptors on GABAergic interneurones. The net effect of raphe stimulation on pyramidal cells seems to be dependent on the location of stimulation in the raphe nuclei, suggesting an independent activation of excitatory dendritic 5-HT_{2A} receptors and inhibitory somato-axonal 5-HT_{1A} receptors and interneurones [14, 176, 233, 231]. In general, the inhibitory effects of raphe stimulation on pyramidal activation were outweighing excitatory effects.

The raphe nuclei consist of serotonergic, GABAergic, and glutamatergic cells. Individual serotonergic as well as non-serotonergic cells are excited as well as inhibited by stimulation of

5-HT_{1A} and 5-HT_{2A} receptors in *in vitro* slice experiments, suggesting a complex internal raphe connectivity [184]. In several studies it could be demonstrated that the net effect of systemic 5-HT_{2A} receptor stimulation on raphe nuclei activity and cortical 5-HT release *in vivo* was inhibitory [40, 84, 123, 186, 295].

These findings suggested the following hypothesis. Pyramidal cells are activated by systemic administration of hallucinogenic 5-HT_{2A} receptor agonist through the following synergistic effects:

- The inhibitory input from the raphe nuclei onto pyramidal cells is decreased (raphe mechanism).
- Stimulation of dendritic 5-HT_{2A} receptors increases pyramidal excitation (cortical mechanism).

Both mechanisms might contribute to the action of hallucinogenic 5-HT_{2A} receptor agonists. The raphe mechanism is supported by the following results. In the somatosensory cortex a fast desensitization of glutamate release after intracortical administration of the 5-HT_{2A} receptor agonist DOI (**10**) was found. In contrast, no desensitization was seen over several hours after systemic administration of DOI (**10**) [253]. Similar fast desensitizations of 5-HT_{2A} receptor mediated NMDA receptor induced currents [19] and 5-HT (**6**) induced membrane depolarizations [17] were observed in the prefrontal cortex. A similar mechanism in the action of hallucinogenic 5-HT_{2A} agonists and the dissociative NMDA antagonists with respect to their increase in cortical activation has been suggested [285]. Indeed, similar to 5-HT_{2A} agonists, systemically applied NMDA as well as AMPA glutamate receptor antagonists decrease cortical 5-HT release through their action on raphe neurons [49].

On the other hand a cortical mechanism might be suggested by the following experiments: Electrical stimulation of the dorsal raphe nucleus resulted in generalization to LSD (**12**) [131] and to DOI (**10**) [198] in rat drug discrimination tests and led to increased cortical activity [62]. These results appear somewhat conflicting with the above hypotheses. However, the raphe nuclei project to most other brain areas and raphe stimulation might indirectly increase excitatory input onto pyramidal cells. Indeed, electrical stimulation of the dorsal raphe nucleus has been shown to increase activation of the mediodorsal thalamus nucleus. This nucleus is reciprocally connected to the prefrontal cortex [62] and is also innervated by serotonergic raphe projections [115, 162].

Bell shaped dose-response

5-HT_{2A} agonists locally administered to the prefrontal cortex had a biphasic, bell shaped dose-response effect on pyramidal cell firing in *in vivo* studies [21, 22] as well as in *in vitro* studies measuring their effect on membrane depolarization [17] and NMDA receptor mediated currents [20]. While the compounds had an activating effect at lower concentrations they became

inhibitors at higher concentrations. Both effects were mediated by 5-HT_{2A} receptors as shown by 5-HT_{2A} antagonist experiments. This effect might be related to a 5-HT_{2A} receptor mediated activation of inhibitory GABAergic interneurones. Remarkably, the increase in *c-fos* gene expression in non-glutamatergic, 5-HT_{2A} receptor negative neurons was observed after administration of 5 - 8 mg/kg DOI (**10**) [174, 252], a very high concentration compared to their human hallucinogenic potency of about 0.04 mg/kg [258].

Pharmacology of 5-HT_{2A} ligands

The structure-activity relationships (SAR) of hallucinogenic compounds have been under continuous investigation for about 50 years. Especially noteworthy is the chemist Alexander T. Shulgin, who has synthesized and tested the human hallucinogenic activity of a broad range of substituted phenethylamines and amphetamines since 1963 [260], using the natural compound mescaline (**8**) as a lead structure [258]. He first synthesized and characterized compounds like DOB (**9**) and DOI (**10**) which are now widely used as potent 5-HT_2 receptor probes and agonist radioligands. Further optimization of these structures in the laboratory of David E. Nichols at Purdue University, USA, resulted in the development of the currently most potent 5-HT_{2A} agonist, the benzodifuranyl-isopropylamine **11** [50, 221] (Figure 6).

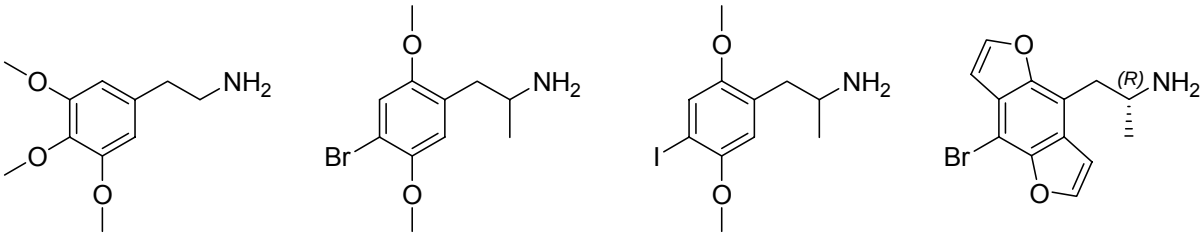
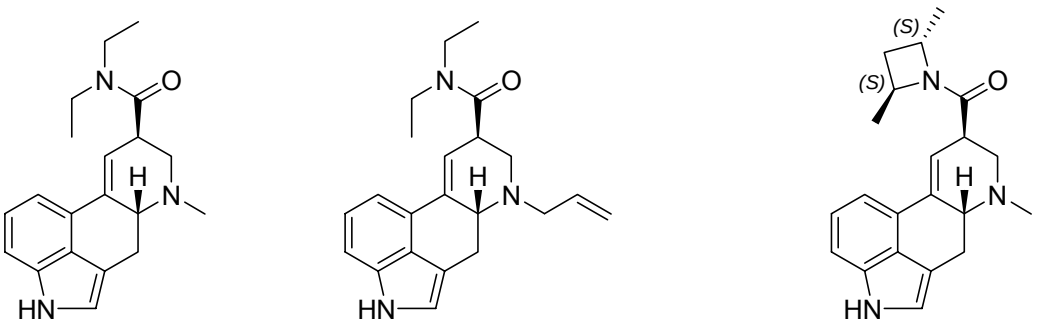


Figure 6: 5-HT_{2A} receptor ligands (I): Phenethylamines.

The natural compound mescaline (**8**), the widely used receptor probes DOB (**9**) and DOI (**10**), and the currently most potent 5-HT_{2A} agonist, the benzodifuranyl-isopropylamine **11** [50, 221].

Also in the Nichols group a structure optimization of LSD (**12**) led to *N*(6)-alkyl derivatives with enhanced potency in rat drug discrimination studies [132] and to the sterically constrained amide-sidechain analog *(S,S)*-2,4-dimethylazetidine **14** with retained affinity and enhanced efficacy and animal potency [209] (Figure 7).



LSD (**12**) *N*-allyl Analog **13** *(S,S)*-2,4-dimethylazetidine Analog **14**

Figure 7: 5-HT_{2A} receptor ligands (II): Lysergamides.

LSD (**12**), the *N*-allyl analog **13** [132], and the sterically constrained amide-sidechain *(S,S)*-2,4-dimethylazetidine analog **14** [209].

The third main class of 5-HT_{2A} ligands are the tryptamines. The natural agonist, the neurotransmitter serotonin (5-HT, **6**) and the natural alkaloid 5-MeO-DMT (**15**) belong to this group. Their structure has been optimized for 5-HT_{2A} receptor affinity and subtype-selectivity, yielding sterically constrained analogs with dihydropyrano structure like **16** [106], with a pyrrolidin-2-yl-methyl side-chain like **17** [188] [175], or with a cyclopropylamino side-chain like in **18** [281] (Figure 8).

5-HT_{2A} receptor modeling

Recent advances in homology modeling of G-protein coupled receptors, especially the availability of the rhodopsin crystal structures and the increase in computing power, allowed the construction of more reliable models of the 5-HT_{2A} receptor in its agonist binding conformation as discussed above [51]. 5-HT_{2A} receptor agonists were docked into these models, thereby for the first time merging the relatively well known pharmacophores of the three main classes of compounds into a molecular model of the ligand binding site. Such work significantly benefits from the previous development of sterically constrained high-affinity ligands. In a reciprocal process these receptor models serve as tools for the design of new ligands with improved affinity and subtype-selectivity, and the receptor models are continuously improved by adjusting them to experimental data obtained from those compounds.

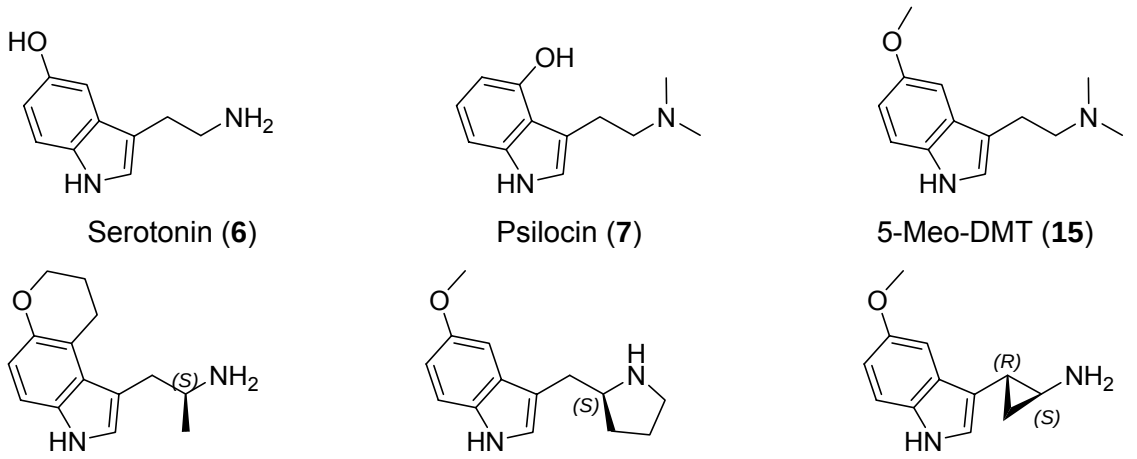
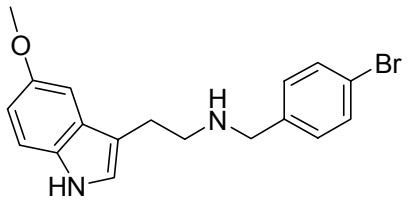


Figure 8: 5-HT_{2A} receptor ligands (III): Tryptamines.

Serotonin (5-HT, **6**), psilocin (**7**), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT, **15**), and the sterically constrained dihydropyrano tryptamine **16** [106], the pyrrolidin-2-yl-methyl tryptamine analog **17** [175, 188], and the cyclopropanated tryptamine analog **18** [281].

N-alkylated tryptamines

In a previous study from the group of Richard A. Glennon from the Virginia Commonwealth University, USA, exceptional high binding affinities and possible agonistic activity at 5–HT_{2A} receptors have been reported for several analogs of DOB (**9**) and 5-MeO-tryptamine (**358**) with an additional extended amine substituent. One example from that series is *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) (compound number 33 in [112]) (Figure 9). The substance is also commercially available (Tocris, USA), marketed as a "very potent and selective ligand at 5-HT_{2A} receptors" with a claimed affinity for the 5-HT_{2A} receptor of 5 nM using [^{3}H]ketanserin as a radioligand and 0.1 nM using [^{125}I]DOI as a radioligand [1]. This study is of particular interest because it is the only published study in which longer alkyl substituents at the amine group have been systematically investigated until now. No other such data are available on mono-alkyl or unsymmetrical methyl-alkyl substituted tryptamines. This is somewhat surprising because for other serotonin receptors, especially of the 5-HT_1 family, the *N*-terminal extension strategy has yielded ligands with improved affinities in the past, e.g. the partial 5-HT_{1A} agonists buspirone and gepirone, the full 5-HT_{1A} agonists alniditan, flesinoxan, repinotan (BAY × 3702), xaliproden (SR 57746A), and certain *N*-linked bivalent compounds [167], and the 5-HT_{1B} / 5-HT_{1D} receptor agonist avitriptan.



19

Figure 9: Alleged 5-HT_{2A} receptor ligand.

This commercially available *N*-alkylated tryptamine has been reported as a very potent 5-HT_{2A} receptors ligand with putative agonist activity [112]. However, in the current study this compounds turned out to be a weak antagonist.

Natural *N*-alkylated tryptamines

Simple substituted tryptamines like *N,N*-dimethyltryptamine (DMT, **45**), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT, **15**), 5-hydroxy-*N,N*-dimethyltryptamine (bufotenine), or 5-hydroxytryptamine (serotonin, 5-HT, **6**) are common alkaloids in a broad range of plants, mushrooms, and animals [218, 217]. But also a number of more complex *N*-substituted tryptamines of yet unknown pharmacology at serotonergic receptors have been described, e.g. the sterically constrained tryptamine alkaloid peduncularine from the plant *Aristotelia peduncularis* [154], the 4-hydroxytryptamine side-chain analogs meridianin A from the tunicate *Aplidium meridianum* [113], or *N*-methyl-*N*-(indol-3-yl-methyl)-5-MeO-tryptamine from the plant *Antirhea lucida* [292].

Aims of the tryptamine project

With the exception of the single mentioned study [112], no data on the structure-affinity relationships of *N*-terminally substituted tryptamines at the 5-HT_{2A} receptor so far exists. For the current project we therefore planned to test the effect of a broad range of structurally diverse *N*-terminal substituents on 5-HT_{2A} receptor affinity. Tertiary *N*-alkyl-*N*-methyltryptamine have less flexibility in their binding to the receptor compared to secondary *N*-alkyltryptamine, but usually show similar binding affinities at 5-HT_{2A} receptors. So we decided to test *N*-alkyl substituted *N*-methyltryptamine as well as their 5-methoxy ring-substituted analogs. In the above mentioned series of *N*-terminally extended analogs a very narrow structure dependency of 5-HT_{2A} and 5-HT_{2C} receptor affinities was observed [112]. Relatively small changes, like a chlorine to bromine substitution, resulted in large differences in binding affinity, sometimes up to three orders of magnitude. We therefore decided to explore one series of ring-substituted phenethyl-tryptamines in depth.

We were especially interested in finding ligands with improved 5-HT_{2A} receptor affinity and increased selectivity over other 5-HT_2 receptor subtypes. As discussed above, no 5-HT_{2A} over 5-HT_{2C} receptor subtype selective agonist has been described yet. We therefore decided to test the compounds in a functional assay of receptor mediated cellular activation for agonist activity. Additionally, we planned to test the ligands at two more receptors, the 5-HT_{2C} and the 5-HT_{1A} receptor. While the 5-HT_{2C} receptor was chosen in order to identify subtype-selective ligands, the 5-HT_{1A} receptor was selected as a prototypical member of the 5-HT_1 family of receptors with their distinct structure-affinity relationships. Moreover, all three tested receptor subtypes are also important pharmacological targets and have been associated with the mechanism of hallucinogenic compounds.

Results and Discussion

Isolation of aeruginascin

From previous UV spectra and TLC data we expected aeruginascin (**4**) to be a relatively simple alkaloid related to psilocybin (**3**), e.g. its bis-desmethyl analog norbaeocystin (**1**) or a pyrophosphate analog. Due to the limited amount of *Inocybe aeruginascens* material we decided to start with the synthesis of norbaeocystin (**1**) as an analytical reference compound for the TLC analysis.

New route to 4-hydroxytryptamines

The established routes to 4-hydroxytryptamines are usually lengthy and require expensive precursors like 4-hydroxyindole. We have applied a new synthetic strategy for the preparation of 4-hydroxylated tryptamines to the synthesis of norbaeocystin (**1**). This new reaction sequence is based on an ene reaction of *exo*-methylene-tetrahydrofuranone **59** with a Schiff base as the key step. Using this route, the dialkylaminoethyl side chain could be introduced in a single reaction. The resulting tetrahydrofuranones **61** could then be converted into the tetrahydroindolones **65** by ammonolysis. Aromatization of this compound, e.g. by catalytic dehydrogenation, would give the final 4-hydroxytryptamines **21** (Figure 10).

Exo-methylene benzofuranone

The synthesis of the key intermediate 3-methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (**60**) with its *exo*-methylene group was achieved by annulation of 1,3-cyclohexanedione with diethyl-prop-2-ynyl-sulfonium bromide following a published procedure [214] (Figure 10): 3-Bromopropyne (propargyl bromide) was reacted with diethylsulfide (MeCN, 75%) and the resulting diethyl-prop-2-ynyl-sulfonium bromide (**59**) was annulated with 1,3-cyclohexanedione to yield 3-methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (*t*-BuOK, THF, 7 h, 0 °C, 65%).

The mechanism of this reaction type has been explored earlier [72]. The first step is assumed to be the isomerization of diethyl-prop-2-ynyl-sulfonium bromide (**59**) to the mesomerically stabilized allenic diethyl-propa-1,2-dienyl-sulfonium bromide (**22**) in the presence of a strong base like potassium *tert.*-butanolate (Figure 11). The enolate of 1,3-cyclohexanediol (**23**) then adds to the positively polarized carbon C(2) of the allene. In a second reaction step the substituted cyclohexadienone is deprotonated again, thereby forming an enolate. The negatively charged oxygen then attacks the activated carbon and diethylsulfide is split off (Figure 12).

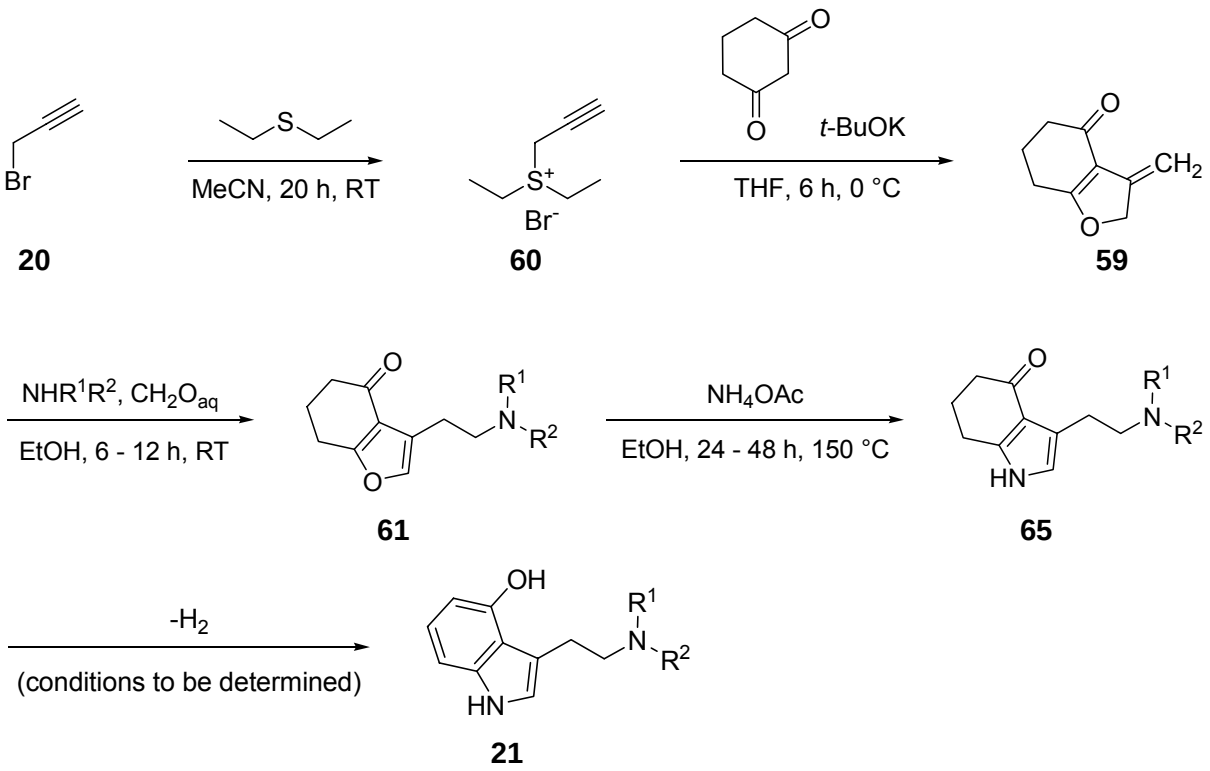
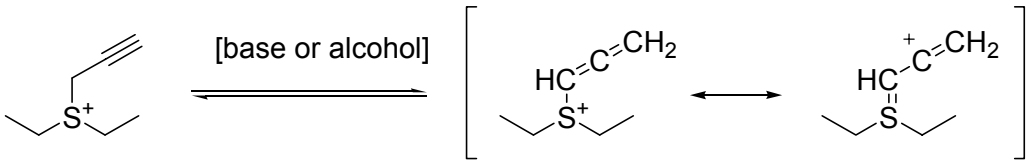


Figure 10: New 4-hydroxytryptamine synthesis.

3-Bromopropyne (propargyl bromide, **20**) was reacted with diethylsulfide (MeCN, 75%) and the resulting diethyl-prop-2-ynyl-sulfonium bromide **59** was annulated with 1,3-cyclohexanedione to the 3-methylene-tetrahydrobenzofuranone **60** (*t*-BuOK, THF, 7 h, 0 °C, 65%). Ene-reactions with the Mannich-bases of dialkylamines and formaldehyde yielded **61** ($R^{1,2}$ = Me, Bn) (EtOH, NHR^1R^2, AcOH, CH_2O_{aq}, RT). Ammonolysis gave the tetrahydroindolone **65** ($R^{1,2}$ = Me, Bn) (EtOH, NH_4OAc, 24 h, 150 °C, 87%). Conditions for the final aromatization step have not yet been identified.



59 22

Figure 11: Isomerization of diethyl-prop-2-ynyl-sulfonium bromide.

Diethyl-prop-2-ynyl-sulfonium bromide (**59**) isomerizes to allenic resonance stabilized diethyl-propa-1,2-dien-yl-sulfonium bromide (**22**) in the presence of bases or alcohols [16].

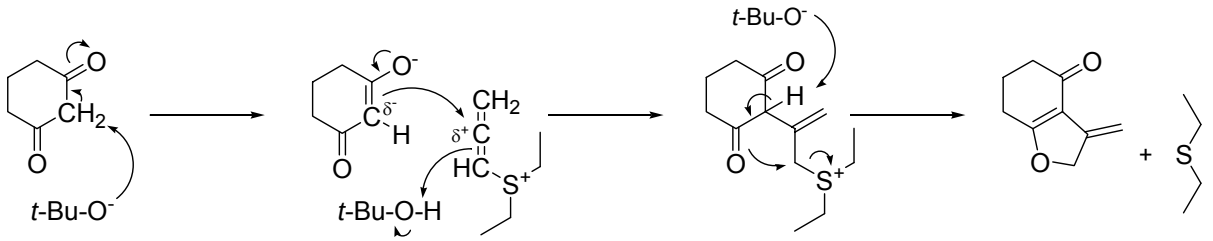


Figure 12: Mechanism of the annulation reaction.

The allenic diethyl-propa-1,2-diene-yl-sulfonium bromide (Figure 11) reacts with 1,3-cyclohexanedione (**23**) in the presence of potassium *tert.*-butoxide to the *exo*-methylene-tetrahydrofuranone **60** [72].

Ene reaction

The ene reaction mechanism is a [2+4] cycloaddition related to the Diels-Alder reaction. It allows the formation of a new carbon-carbon single bond between two unsaturated termini. The prerequisites are an electron-rich ene-compound with an allylic hydrogen atom and an electron-deficient enophile. In the present reaction the *exo*-methylene group of **60** with its C(2) hydrogens reacts as the ene component and the ternary iminium cation **25** reacts as the enophile (Figure 13) in a fast and quantitative conversion [214].

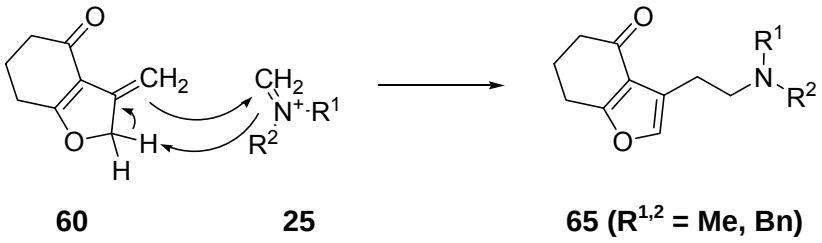


Figure 13: Mechanism of the ene reaction.

In this ene reaction the *exo*-methylene group of **60** with its allylic hydrogens reacts as the ene component and the ternary iminium cation **25** reacts as the enophile [214].

The preformed and isolated ternary iminium hydrochloride **58**, an Eschenmoser's salt, was synthesized from the aminoacetal of a secondary amine (**57**) [234] and reaction of the resulting liquid with trichloromethylsilane (Figure 14) [246]. It could be shown in this work that the same ene reaction proceeds also with *in situ* generated iminium species, albeit with drastically reduced reaction rates (Figure 10). While with the preformed iminium hydrochloride the reaction proceeds instantly, the reaction with aqueous formaldehyde solution and dialkylammonium acetates in ethanol took up to 48 h for completion. Heating the reaction above room temperature had to be avoided in order to prevent the isomerization of the labile 3-*exo*-methylene compound **60** into the energetically favored 3-methylfuranone (**29**) (Figure 15).

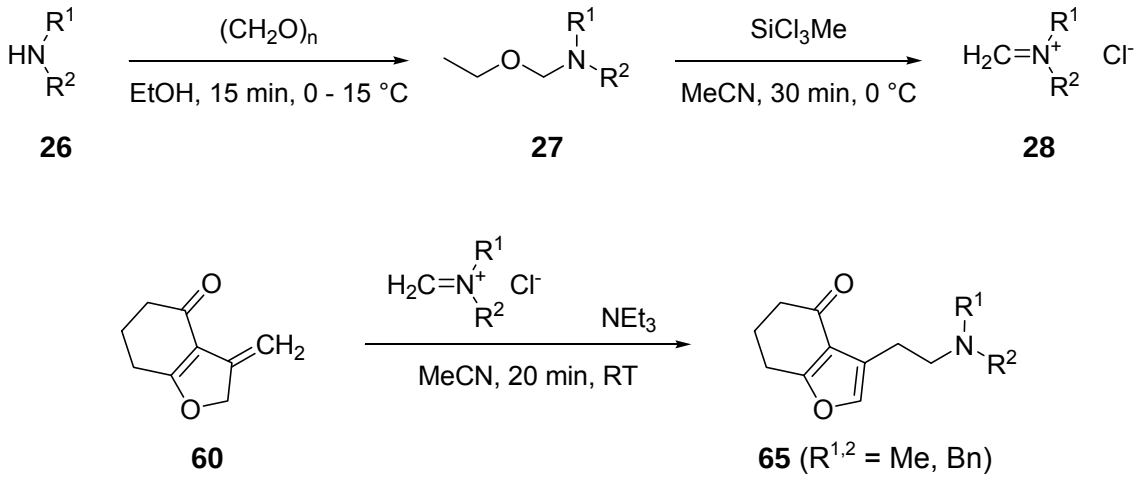


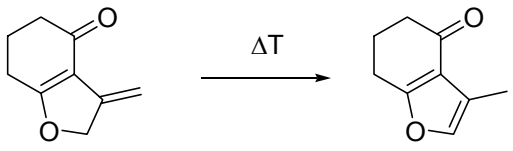
Figure 14: Reaction of the *exo*-methylene compound with Eschenmoser's salts.

Eschenmoser's salts (preformed salts of Schiff bases) were synthesized in a two-step procedure from the respective amine **26** and paraformaldehyde (EtOH, K_2CO_3, 20 min, RT (cooling), 67%) [234] and reaction of the resulting aminoacetal **27** with trichloromethylsilane (MeCN, 0 °C, 30 min, 98%) [246]. The *exo*-methylene-tetrahydrofuranone **60** reacts cleanly with Eschenmoser's salts [214] to the tetrahydrofuranone **65**. This reaction proceeds faster than with *in situ* generated Schiff bases (Figure 10).

Ammonolysis

Tetrahydrofuranones of structure to **61** can be converted to their tetrahydroindolone enaminone congeners simply by incubation with ammonia or primary amines at elevated temperatures (Figure 16). For lower amines like ammonia this reaction has to be carried out in a sealed glass ampul in order to prevent rapid evaporation of the reagent. The use of pure

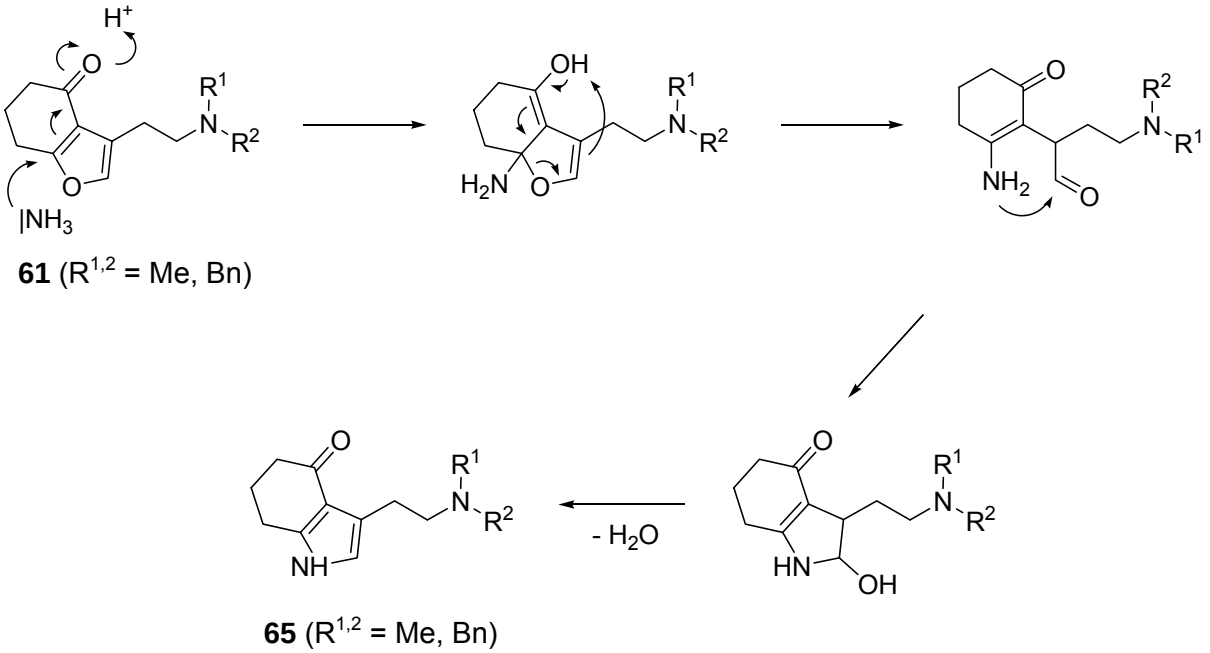
ethanol and ammonium acetate was preferable over 95% ethanol or aqueous ammonia and the tetrahydroindolone **65** ($R^{1,2}$ = Me, Bn) was obtained in a yield of 87% on a 10 g scale.



60 **29**

Figure 15: Isomerization of *exo*-methylene-tetrahydrofuranone.

At elevated temperatures or upon prolonged storage at room temperature *exo*-methylene-tetrahydrofuranone (**60**) isomerizes into the energetically more stable aromatic 3-methyltetrahydrofuranone (**29**).



61 ($R^{1,2}$ = Me, Bn)

65 ($R^{1,2}$ = Me, Bn)

Figure 16: Reaction mechanism of the ammonolysis.

Tetrahydrofuranones can be converted to their tetrahydroindolone congeners by reaction with amines at elevated temperatures.

Aromatization

It was planned to obtain the final 4-hydroxytryptamines **21** by aromatization of the tetrahydroindolones **65**. Unfortunately, reagents like DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) cannot be used due to the instability of the resulting 4-hydroxyindoles in the presence of this reagent. An alternative way to accomplish the aromatization is the use of noble metal catalysts under elevated temperatures. This reaction is similar to catalytic hydrogenations, with the equilibrium shifted to the dehydrogenated product by removal of H_2 and, thermodynamically, by working at high temperatures. Similar compounds like the unsubstituted tetrahydroindolone and 3-alkyl- tetrahydroindolones have been successfully aromatized in other studies with palladium on charcoal in high-boiling solvents like *p*-cymene, tetraline, diisobutylketone, mesitylene, or ethyleneglycol-monobutylether under reflux. [79, 80, 147, 155, 187, 202, 226, 239, 243, 279].

Unfortunately, the aromatization of the tetrahydroindolone **65** ($R^{1,2}$ = Me, Bn) could not be accomplished in our hands using platinum and palladium catalysts in a broad range of different solvents and with different hydrogen acceptors and organic acids. From test reactions of **65** ($R^{1,2}$ = Me, Bn) and palladium on charcoal in refluxing tetraline with and without benzoic acid, a small amount of a reaction product could be obtained by isolation from TLC plates. The EI MS spectra of this fraction showed a main peak of *m/z* = 172.2. The R_f values on silica gel with basic and acidic eluents suggested this product to be a lipophilic weak base. The staining with Ehrlich's reagent resulted in a blue spot. This compound was most probably 1,2,3,5-tetrahydro-1-methylpyrrolo[4,3,2-*de*]quinoline (**66**), generated by a H_2 transfer cycling mechanism with elimination of H_2O and toluene as judged from its mass spectrum and TLC data (Figure 17).

Similar problems to effect aromatization of tetrahydroindolones have been reported earlier and were attributed to highly varying activities of the palladium catalysts [239]. Other factors which might have contributed to the failure of the last reaction step might have been catalyst poisoning by sulfur containing trace impurities or side reactions as described above. Finally, this route had to be abandoned in favor of an established route to baeocystin (**2**) and norbaeocystin (**1**). A promising and so far untested method would be the use of elemental sulfur in boiling xylene. This reagent system has been used previously to aromatize certain tetrahydro-β-carbolines in good yields [263]. The advantage of this method would be its compatibility with benzyl groups as well as catalyst poisons.

Baeocystin and norbaeocystin

Due to the problems related to the aromatization of tetrahydroindolone **65** ($R^{1,2}$ = Me, Bn), a classical route for the synthesis of baeocystin (**2**) and norbaeocystin (**1**) as reference compounds in the isolation of aeruginascin (**4**) had to be followed (Figure 18). The 4-hydroxytryptamines were synthesized by the Speeter-Anthony procedure with indolylglyoxyl-amides

as intermediates and subsequent lithium aluminum hydride reduction [45, 265]. The phosphorylation of the free phenolic 4-hydroxy group was accomplished by a recently published method using tetrabenzylpyrophosphate as reagent followed by catalytic debenzylation [121, 208, 257].

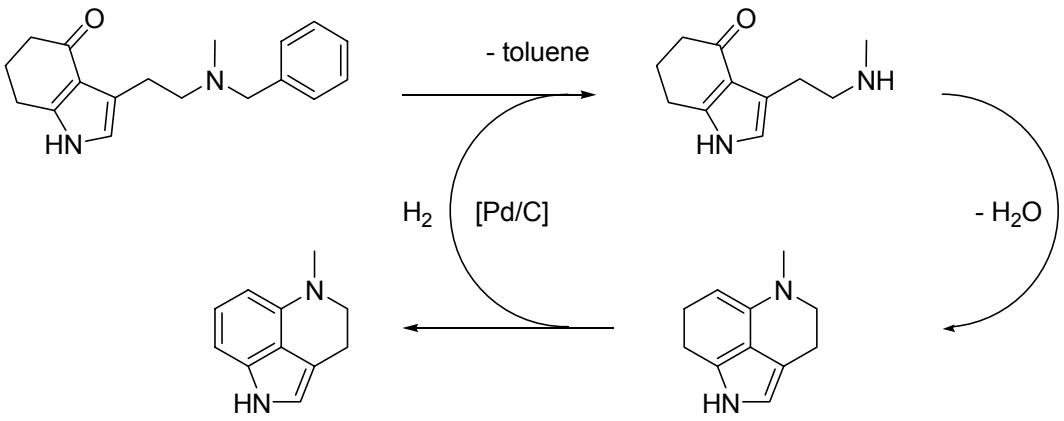


Figure 17: Putative aromatization product.

The tetrahydroindolone **65** probably reacts by elimination of toluene and H_2O in a H_2 transfer cycling mechanism, yielding putative 1,2,3,5-tetrahydro-1-methyl-pyrrolo[4,3,2-*de*]quinoline (**66**).

In short, 4-acetoxyindole (**67**) was synthesized from an available sample of 4-benzyloxy-indole (**30**) by catalytic debenzylation over palladium on carbon in acetone in the presence of acetic acid anhydride. 4-Acetoxyindol-3-yl-glyoxylic acid chloride (**68**) was obtained by reaction of 4-acetoxyindole (**67**) with oxalylchloride in ether. Reaction with methyl-benzylamine and dibenzylamine resulted in 4-acetoxy-*N*-methyl-*N*-benzyl-indol-3-yl-glyoxylamide (**69**) and 4-acetoxy-*N,N*-dibenzyl-indol-3-yl-glyoxylamide (**72**), respectively. Reduction with lithium aluminum hydride in refluxing dioxane gave 4-hydroxy-*N*-methyl-*N*-benzyltryptamine (**70**) and 4-hydroxy-*N,N*-dibenzyltryptamine (**73**). The final products baeocystin (**2**) and norbaeocystin (**1**) were obtained by phosphorylation of the indolic hydroxy groups by reaction with tetrabenzylpyrophosphate after deprotonation with LDA and subsequent catalytic debenzylation.

For the *N*-methyl-*N*-benzyl-indolylglyoxylamide **69** with its unsymmetrical amide substituents the existence of two different isomers was detected by TLC analysis using several different solvent systems. In contrast, the symmetrically substituted *N,N*-dibenzyl-indolylglyoxylamide **72** was homogenous by TLC. A similar effect has been seen for the *N*-methyl-*N*-ethyl analog of these compounds in a previous study. Two conformers of this compound were detected in NMR experiments with a *syn*-periplanar (68%) and an *anti*-periplanar conformation (32%) of

the ethyl substituent and the amide-carbonyl. A rotational barriere between both conformers of 88 kJ/mol has been measured, explaining their relative stability at room temperature [264].

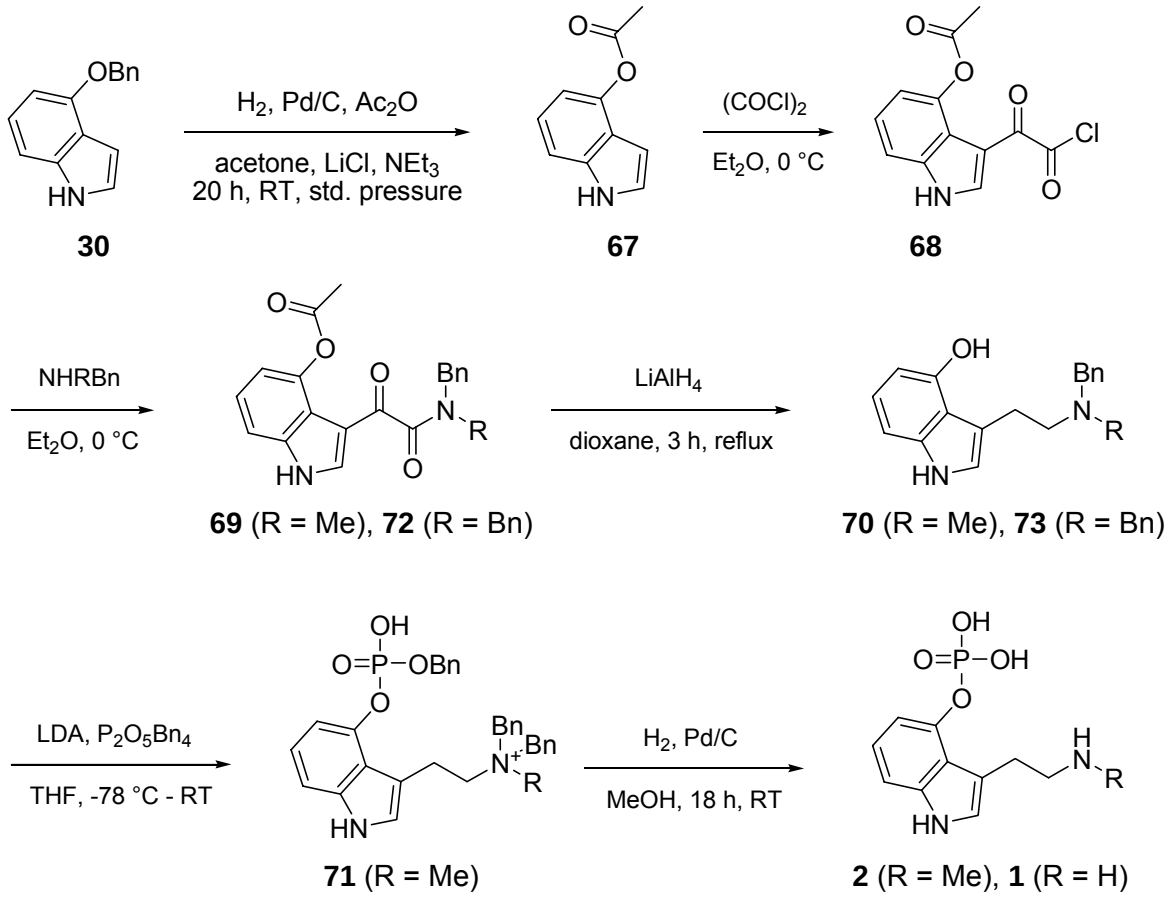


Figure 18: Synthesis of baeocystin and norbaeocystin.

4-Benzyloxyindole (**30**) was debenzylated to 4-acetoxyindole (**67**) (H_2, Pd/C, Ac_2O, acetone, LiCl, NEt_3, 20 h, RT, std. pressure). By reaction with oxalyl chloride the indolylglyoxylchloride (**68**) was obtained (Et_2O, $(COCl)_2$, 0 °C). By reaction with benzyl-methylamine or dibenzylamine the corresponding indolylglyoxylamides **69** (R = Me) and **72** (R = Bn) were synthesized (NHRBn, Et_2O, 0 °C) and subsequently reduced to the 4-hydroxytryptamines **70** (R = Me) and **73** (R = Bn) with lithium aluminum hydride ($LiAlH_4$, dioxane, 3 h, reflux). The phenolic OH group was phosphorylated by reaction with tetrabenzylpyrophosphate (TBPP), yielding monobenzylphosphates like **71** (R = Me) (LDA, TBPP, THF, -78 °C - RT), which on catalytic debenzylation gave the final products baeocystin (**2**, R = Me) and norbaeocystin (**1**, R = H) (H_2, Pd/C, MeOH, 18 h, RT).

Isolation of aeruginascin

Because of the published similarity of the UV spectrum of aeruginascin (**4**) with psilocybin (**3**) and its TLC staining characteristics we expected aeruginascin (**4**) to be a relatively simple hydroxylated indolic compound. Possible candidates included the desmethyl analog norbaeocystin (**1**), the pyrophosphate analogs of psilocin (**7**), 4-hydroxy-*N*-methyltryptamine, or 4-hydroxytryptamine, or the positional isomers with a 5-, 6-, or 7-phosphoryloxy substitution. Therefore, in initial experiments we tested a crude aqueous methanolic mushroom extract [86] by TLC against known *Psilocybe* alkaloids and analogs thereof. Using the published eluent systems, the occurence of aeruginascin (**4**) could be verified. The R_f of it was lower than that of any of the known alkaloids psilocybin (**3**), baeocystin (**2**), norbaeocystin (**1**), and psilocin (**7**), as well as the reference compounds 5-hydroxytryptophan and 5-hydroxytryptamine (**6**) (Table 2). Several R_f values including that for psilocybin (**3**) and aeruginascin (**4**) differ from previously published values [103, 94]. This is often observed for TLC data. An unambiguous assignment of the spots is nevertheless easy due to their relative positions and their specific color reactions.

TLC color reactions

Psilocin (**7**) with its free phenolic hydroxy groups shows a bluish gray color reaction with Keller's reagent ($FeCl_3$ / MeOH / HCl) while the phosphorylated alkaloids like baeocystin (**2**) and psilocybin (**3**), as well as aeruginascin (**4**) are Keller-negative.

With Ehrlich's reagent (*p*-dimethylaminobenzaldehyde / MeOH, HCl) the 4-hydroxytryptamines like psilocin (**7**) show a violet color reaction which changes to bluish violet on storage. The 4-phosphoryloxytryptamines show a distinct purple color which changes to violet on storage. Aeruginascin (**4**) is unique in that the immediate color reaction is identical to that of psilocybin (**3**) but that the color does not change on short-term storage (Table 2).

Alkaline phosphatase

Next we tested the possibility that aeruginascin (**4**) is either the phosphorylated derivative of serotonin (**6**) or 5-hydroxytryptophan or the dephosphorylated derivative of one of the minor alkaloids baeocystin (**2**) or norbaeocystin (**1**). Therefore, aeruginascin (**4**) as well as psilocybin (**3**), baeocystin (**2**), and norbaeocystin (**1**) were dephosphorylated by incubation with alkaline phosphatase and the products were immediately analyzed by TLC. After incubation, the spot of aeruginascin (**4**) became invisible and a new, very weakly stained spot appeared. This spot was not identical to psilocybin (**3**), baeocystin (**2**), and norbaeocystin (**1**), to their dephosphorylation products 4-hydroxy-*N,N*-dimethyltryptamine (**7**), 4-hydroxy-*N*-methyltryptamine, and 4-hydroxytryptamine, as well as to the reference compounds 5-hydroxytryptophan and 5-hydroxytryptamine (**6**) (Table 2).

Aeruginascin purification

Because in initial TLC experiments none of the tested reference compounds did match the aeruginascin (**4**) spot, we decided to isolate a pure analytical sample of this alkaloid. A new batch of dried fruiting bodies of *Inocybe aeruginascens* was extracted and aeruginascin was purified by column chromatography on silica gel using different eluents and by size-exclusion chromatography on Sephadex. The fractionation steps were monitored by TLC and UV_{267} absorption. Aeruginascin (**4**) is relatively stable in dried mushrooms, even at room temperature [103, 87, 90, 88], however, we could not exclude an enhanced sensitivity under the conditions of the isolation. Therefore, we kept the temperature at or below 45 °C and avoided extreme pH values throughout the whole procedure.

UV, NMR, and mass spectra of isolated aeruginascin

The resulting pure compound was first analyzed by UV spectroscopy. As reported previously [90, 85], the UV spectrum closely matched those of the reference compounds baeocystin (**2**) and norbaeocystin (**1**) as well as the published data of psilocybin (**3**) [134, 225, 244, 277]. The spectra showed the typical global maximum at 219 nm as well as the local maximum at 267 nm and the two shoulders at around 282 nm and at 288 nm (Figure 19, Figure 74). This made the presence of the 4-hydroxyindole chromophore in this molecule very likely.

Table 2: R_f values of mushroom alkaloids and reference compounds.

TLC system: silica gel TLC sheets, run length around 60 mm. Compounds: aeruginascin (**4**) in an enriched *Inocybe aeruginascens* extract; synthetic aeruginascin (**4**) from baeocystin; psilocin (**7**) in a crude extract of *Psilocybe azurescens*; psilocybin (**3**) in an enriched *Inocybe aeruginascens* extract; synthetic baeocystin (**2**); synthetic norbaeocystin (**1**); commercial samples of tryptophan (**34**), tryptamine (**5**), 5-hydroxytryptophan, and serotonin (**6**) creatinine sulfate; putative 4-hydroxy-*N,N,N*-trimethyltryptamine (4-OH-TMT), 4-hydroxy-*N*-methyltryptamine (4-OH-NMT), and 4-hydroxytryptamine from crude aeruginascin (**4**), synthetic baeocystin (**2**), and synthetic norbaeocystin (**1**), respectively, by incubation with alkaline phosphatase.

(*) Although isolated and synthetic aeruginascin (**4**) gave slightly differing R_f values with these eluents, co-application of both samples resulted in a single spot in all three systems tested.

Compound	**Ehrlich's reagent color** (immediately)	**Ehrlich's reagent color** (after 48 h)	***n*-BuOH / AcOH / H_2O** (2 + 1 + 1) (n = 3, ±SEM)	***n*-BuOH / AcOH / H_2O** (24 + 10 + 10) (n = 3, ±SEM)	***n*-PrOH / NH_3 6%** (5 + 2)	***n*-BuOH / AcOH / *i*-PrOH / H_2O** (8 + 2 + 3 + 5)	***n*-BuOH / AcOH / *i*-PrOH / H_2O** (8 + 2 + 1 + 5)	***n*-PrOH / NH_3 28%** (5 + 3)	***n*-PrOH / AcOH / H_2O** (10 + 3 + 3) (n = 3, ±SEM)	**MeOH / H_2O / NH_3 28%** (70 + 30 + 0.2)	**MeOH / H_2O / formic acid** (80 + 20 + 0.2)
Aeruginascin (enriched extract)	purple	purple	0.30* (±0.02)	0.25* (±0.02)	0.08	0.31	0.35	0.20	0.25* (±0.03)	0.23	0.40
Aeruginascin (synthetic)	purple	purple	0.29* (±0.02)	0.24* (±0.01)	0.09	0.30	0.34	0.21	0.21* (±0.01)	0.23	0.38
Psilocin (crude extract)	violet	bluish violet	0.66 (±0.03)	0.62 (±0.04)	0.72	0.70	0.66	0.92	0.63 (±0.03)	0.32	0.71
Psilocybin (enriched extract)	purple	violet	0.42 (±0.03)	0.37 (±0.03)	0.14	0.46	0.49	0.32	0.38 (±0.03)	0.51	0.56
Baeocystin (synthetic)	purple	violet	0.49 (±0.03)	0.46 (±0.03)	0.12	0.55	0.54	0.22	0.51 (±0.03)	0.83	0.69
Norbaeocystin (synthetic)	purple	violet	0.60 (±0.02)	0.56 (±0.02)	0.13	0.64	0.60	0.18	0.64 (±0.03)	0.93	0.74
Tryptophan	violet	bluish green	0.75 (±0.03)	0.71 (±0.05)	0.62	0.77	0.72	0.69	0.82 (±0.03)	0.88	0.82
Tryptamine	purple, then violet	bluish green	0.74 (±0.03)	0.68 (±0.04)	0.66	0.75	0.69	0.78	0.80 (±0.02)	0.21	0.83
5-OH-Tryptophan	blue	blue	0.70 (±0.03)	0.66 (±0.05)	0.58	0.73	0.69	0.64	0.79 (±0.02)	0.87	0.84
Serotonin	blue	blue	0.77 (±0.06)	0.68 (±0.03)	0.60	0.74	0.69	0.72	0.80 (±0.02)	0.22	0.84
4-OH-TMT (from Aeruginascin)	gray	-	-	-	-	-	-	0.62	-	-	-
4-OH-NMT (from Baeocystin)	blue	-	-	-	-	-	-	0.67	-	-	-
4-OH-Tryptamine (from Norbaeocystin)	blue	-	-	0.78	-	-	-	0.68	0.70	-	-

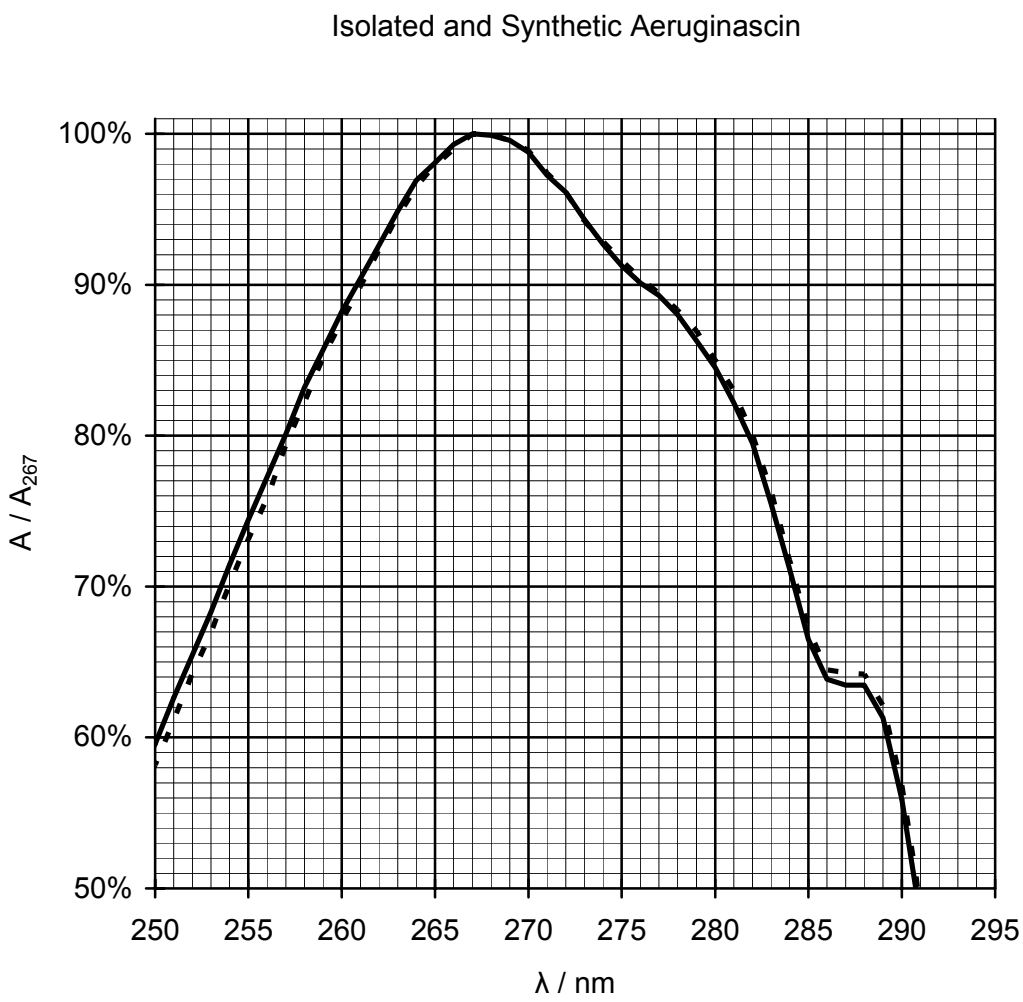


Figure 19: UV spectra of isolated and synthetic aeruginascin.

Detailed view of the UV spectra of isolated (continuous line) and synthetic (dotted line) aeruginascin (**4**). The absorption has been normalized to A_{267}.

In the ^{1}H NMR spectrum of aeruginascin (**4**) (Figure 20) the typical tryptamine (**5**) signals could be seen, i.e. four aromatic protons as well as two side chain methylene groups. The indole-NH signal was not visible due to H/D exchange in D_2O. A prominent sharp singlet at δ = 3.2 with the intensity of nine protons gave the first evidence for the presence of a quaternary trimethylammonium group in the molecule.

ESI MS of purified aeruginascin (**4**) gave an $[M]^+$ signal of *m/z* = 299.2 as well as the respective $[M - H + Na]^+$, $[2M + H]^+$, $[2M + Na]^+$, and $[M - H + K]^+$ adducts as minor peaks. This together with the ^{1}H NMR data was strongly suggesting 4-phosphoryloxy-*N,N,N*-trimethyltryptamine as the most probable structure of aeruginascin (**4**). But additional spectroscopic experiments were needed to confirm this assignment because of two reasons: On the one hand

the sulfate group ·OSO_3H has the same mass as the phosphate group ·OPO_3H_2, and on the other hand the ^{1}H NMR data did not allow deciding unambiguously between 4-hydroxy and 7-hydroxy substitution of the indole ring.

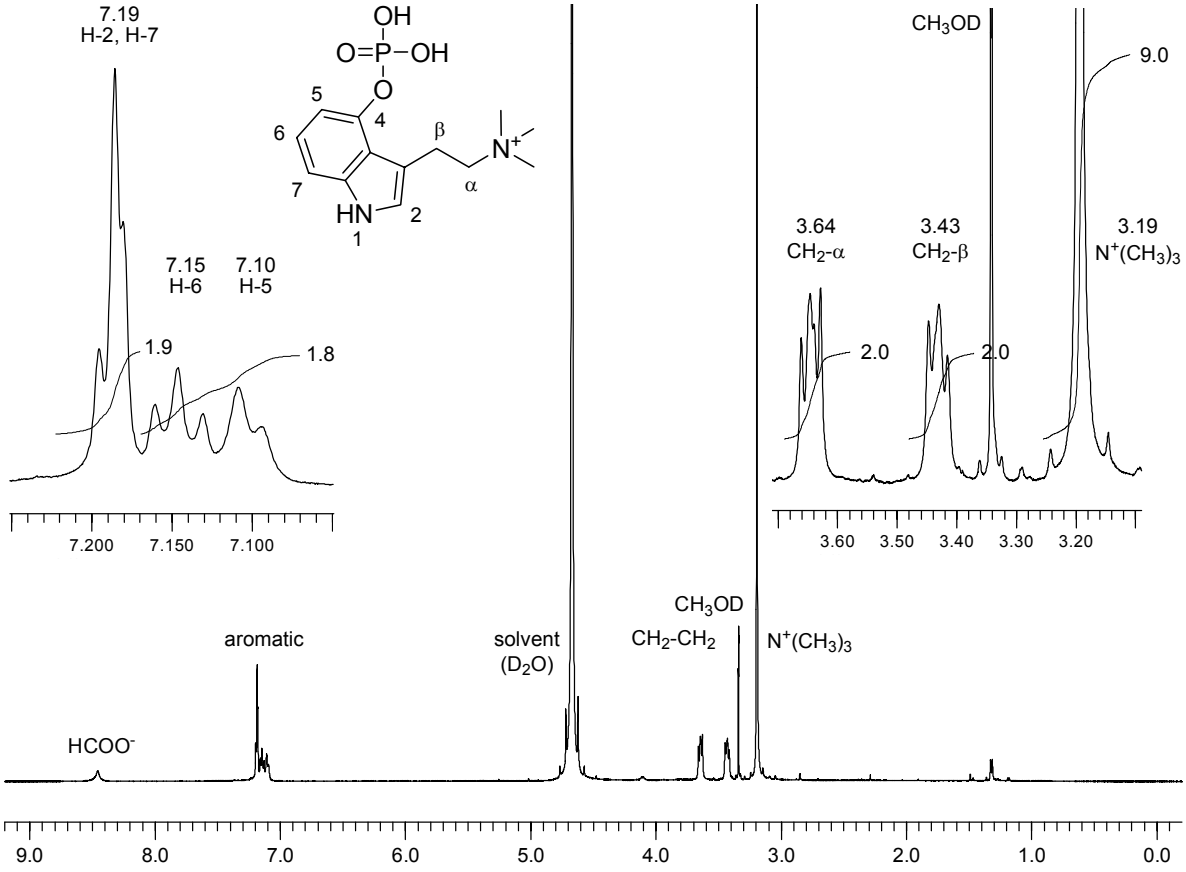


Figure 20: ^{1}H NMR spectra of isolated aeruginascin.

^{1}H NMR spectra of aeruginascin (**4**) under unbuffered conditions (500 MHz, D_2O). The chemical shifts of the aromatic protons were pH-sensitive and the signals could be separated under the acidic conditions used in the following experiments.

To make a decision between the phosphoric acid ester and the sulfuric acid ester, a ^{31}P NMR spectrum of the isolated aeruginascin (**4**) was recorded. This spectrum indeed showed a small signal at around δ = 0.7. Unfortunately, interpretation was exacerbated by the broadness of the signal and its low intensity compared to the background. To finally decide between both esters, a high-resolution value for the molecular peak $[M]^+$ of *m/z* = 299.1 was obtained by ESI FT-ICR mass spectrometry. The thus obtained high-resolution value of *m/z* = 299.115477 was best fitted by the phosphate structure (formula: $[C_{13}H_{20}N_2O_4P]^+$, calculated: m = 299.115520, difference: Δm = 0.14 ppm). The sulfate analog had a mass differ-

ence more than two orders of magnitude higher (formula: $[C_{13}H_{19}N_2O_4S]^+$, calculated: m = 299.115520, difference: Δm = 31.67 ppm, cut-off: Δm = 5 ppm). This provided strong evidence that aeruginascin (**4**) is most likely the phosphate and not the sulfate ester.

Synthesis of aeruginascin

To be sure about the phosphoryloxy position on the indole ring we decided to synthesize 4-phosphoryloxy-*N,N,N*-trimethyltryptamine (**4**) from a sample of baeocystin (**2**) obtained earlier in this work. A small amount of baeocystin (**2**) was reacted with methyl iodide in a water / methanol mixture in the presence of diisopropylethylamine and the product was purified by silica gel column chromatography and Sephadex size-exclusion chromatography similar to the purification procedure used for aeruginascin (**4**). The product was identical to aeruginascin (**4**) by R_f and Ehrlich's color reaction on TLC using eight different solvent systems (Table 2). Additionally, the UV spectrum of the synthetic aeruginascin (**4**) was superimposable with that of the isolated sample (Figure 19, Figure 74).

Surprisingly the ^{1}H NMR shifts of the aromatic protons H-7 and H-5 differed by as much as 0.06 ppm, thereby questioning the structure assignment. Suspecting a pH related effect due to different ionization states of the phosphate group, the spectra of the synthetic compound were re-recorded in the presence of either formic acid or triethylamine. Indeed, most aromatic signals showed a strong pH and solvent dependency. Under basic conditions the aromatic proton signals H-5, H-6, and H-7 could not be resolved due to their overlap. Because the same protons gave clearly separated signals under acidic conditions, the sample of isolated aeruginascin (**4**) was measured again in the presence of formic acid. Indeed, by using the same acidic solvent, the isolated and the synthetic compound gave identical ^{1}H NMR spectra ($\Delta\delta \leq 0.02$).

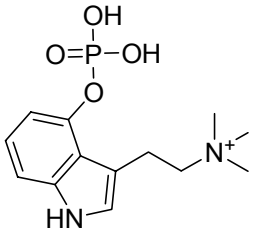
^{13}C NMR spectra of aeruginascin

The identity of the isolated aeruginascin (**4**) and the synthetic 4-phosphoryloxy-*N,N,N*-trimethyltryptamine was further verified by ^{13}C NMR experiments using the same acidic solvent as for the ^{1}H NMR experiments. Again both samples gave identical spectra ($\Delta\delta \leq 0.22$).

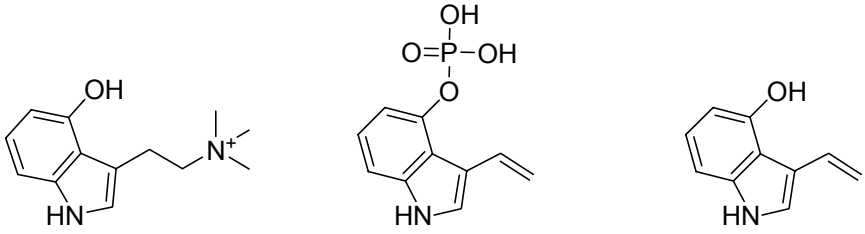
Degradation pathways

Quaternary trimethyl-alkylamines are subject to a Hofmann elimination of trimethylamine in the presence of strong bases or under elevated temperatures. Additionally, the phosphate group of aeruginascin (**4**) can hydrolyze under basic or strongly acidic conditions as well as by enzymatic activity, yielding its 4-hydroxyindole derivative **31**. Indeed, the signals of all possible products resulting from these two degradation reactions could be detected in the ESI MS spectra of the isolated sample of aeruginascin (**4**): *m/z* = 240.0 for the 4-phosphoryloxy-vinylindole (**32**) (deaminated aeruginascin), *m/z* = 219.1 for the dephosphorylation

product **31**, and *m/z* = 160.2 for the deaminated and dephosphorylated compound **33** (Figure 21). The presence of these degradation products probably attributes to the relative chemical instability of aeruginascin (**4**) in non-neutral solutions at elevated temperature.



Aeruginascin (**4**)



31 **32** **33**

Figure 21: Decomposition products of aeruginascin detected by ESI MS.

The quaternary trimethyl-alkylammonium group of aeruginascin (**4**) can eliminate as trimethylamine in a Hofmann elimination resulting in the 3-vinylindole **32**. Additionally, the phosphate group can hydrolyze under acidic or basic conditions as well as by enzymatic action, yielding the 4-hydroxyindoles **31** and **33**. All possible degradation products from both degradation pathways could be detected by ESI MS of aeruginascin (**4**).

MS H/D exchange

Additional experiments were run in order to confirm the number of acidic protons by ESI MS. Isolated aeruginascin (**4**) was dissolved in D_2O to effect an H/D exchange. Under these conditions a peak of *m/z* = 323.3 became the main peak representing the species $[M - 3H + 2D + Na]^+$. The second prominent peak of *m/z* = 623.3 was assigned the species $[2M - 6H + 5D + Na]^+$. Additionally, the peak of one of the degradation products with *m/z* = 221.2 of dephosphorylated aeruginascin $[M - PO_3H - 2H + 2D]^+$ could be detected. This experiment therefore indicated the presence of three exchangeable protons in the aeruginascin (**4**) molecule. This is in accordance with the proposed structure with two of these acidic protons belonging to the phosphate group and one to the indole-NH. Although the latter position has only a very low

acidity as indicated by its pK_a = 17 for 4-hydroxyindole [200] a signal from this proton was also absent in all ^{1}H NMR spectra recorded in D_2O, thus supporting its exchange in D_2O at room temperature.

Psilocybe alkaloid biosynthesis

Despite several studies on the psilocybin (**3**) biosynthesis, the pathway is still discussed controversially. 4-Hydroxytryptophan, fed as a radioactive precursor to *Psilocybe cubensis* mycelium culture, was not incorporated into alkaloids, in contrast to tryptophan (**34**), tryptamine (**5**), *N*-methyltryptamine (**212**), *N,N*-dimethyltryptamine (**45**), *N,N*-diethyltryptamine, 4-hydroxytryptamine, and psilocin (**7**) [9, 10, 44, 54]. Additionally, tryptamine (**5**) has been detected in small amounts in psilocybin (**3**) containing mushrooms [10, 54, 98, 270]. These results suggest that the first step in psilocybin (**3**) biosynthesis is the decarboxylation of tryptophan (**34**) to tryptamine (**5**). This is in contrast to the mammalian serotonin (5-hydroxytryptamine, **6**) synthesis from tryptophan (**34**), where 5-hydroxylation is the first reaction [54].

Feeding tryptamine (**5**) to *Psilocybe cubensis* resulted in the highest amounts of psilocybin (**3**) ever detected in mushrooms [97]. In contrast, feeding of tryptophan (**34**) had no effect on the psilocybin (**3**) content of *Psilocybe baeocystis* [171] or *Psilocybe cubensis* [48], suggesting that decarboxylation of tryptophan (**34**) is the rate limiting step in the biosynthetic pathway.

The incompletely methylated psilocin (**7**) and psilocybin (**3**) congeners 4-hydroxytryptamine [241], norbaeocystin (**1**) [92, 169, 193, 240, 242], and baeocystin (**2**) [92, 95, 98, 104, 99, 169, 170, 193, 240, 241] have been detected in several *Psilocybe* species as minor alkaloids. Feeding *N*-methyltryptamine (**212**) to *Psilocybe semilanceata* resulted in unusual high levels of baeocystin (**2**) and elevated levels of psilocybin (**3**) [100]. Feeding *N,N*-diethyltryptamine to *Psilocybe cubensis* resulted in the formation of the diethyl homologs of psilocin (**7**) and, to a lesser extent, of psilocybin (**3**) [100]. Feeding 4-hydroxytryptamine to *Psilocybe cubensis* resulted in the formation of norbaeocystin (**1**) and baeocystin (**2**) together with incorporation into psilocybin (**3**) [10]. It has also been shown that incorporation of *N*-methyltryptamine (**212**) and *N,N*-dimethyltryptamine (**45**) into psilocybin (**3**) occurred without prior demethylation in *Psilocybe cubensis* [54].

These findings prove that the 4-hydroxylating and 4-O-phosphorylating enzyme systems are capable of tolerating *N*-methyl and *N*-ethyl substitutions as well as that the *N*-methylating system is capable of tolerating 4-hydroxy groups. The major pathway *in vivo* has not been established yet due to the known instability of 4-hydroxylated indole derivatives in solution, the uncertainties of precursor uptake into living mycelium, and the possible interference with pathway regulating mechanisms. Some authors even suppose a biosynthetic grid with multiple routes to psilocybin (Figure 22) [10, 54, 241]. There might even be multiple enzymes with different substrate specificities for the nodes of the grid.

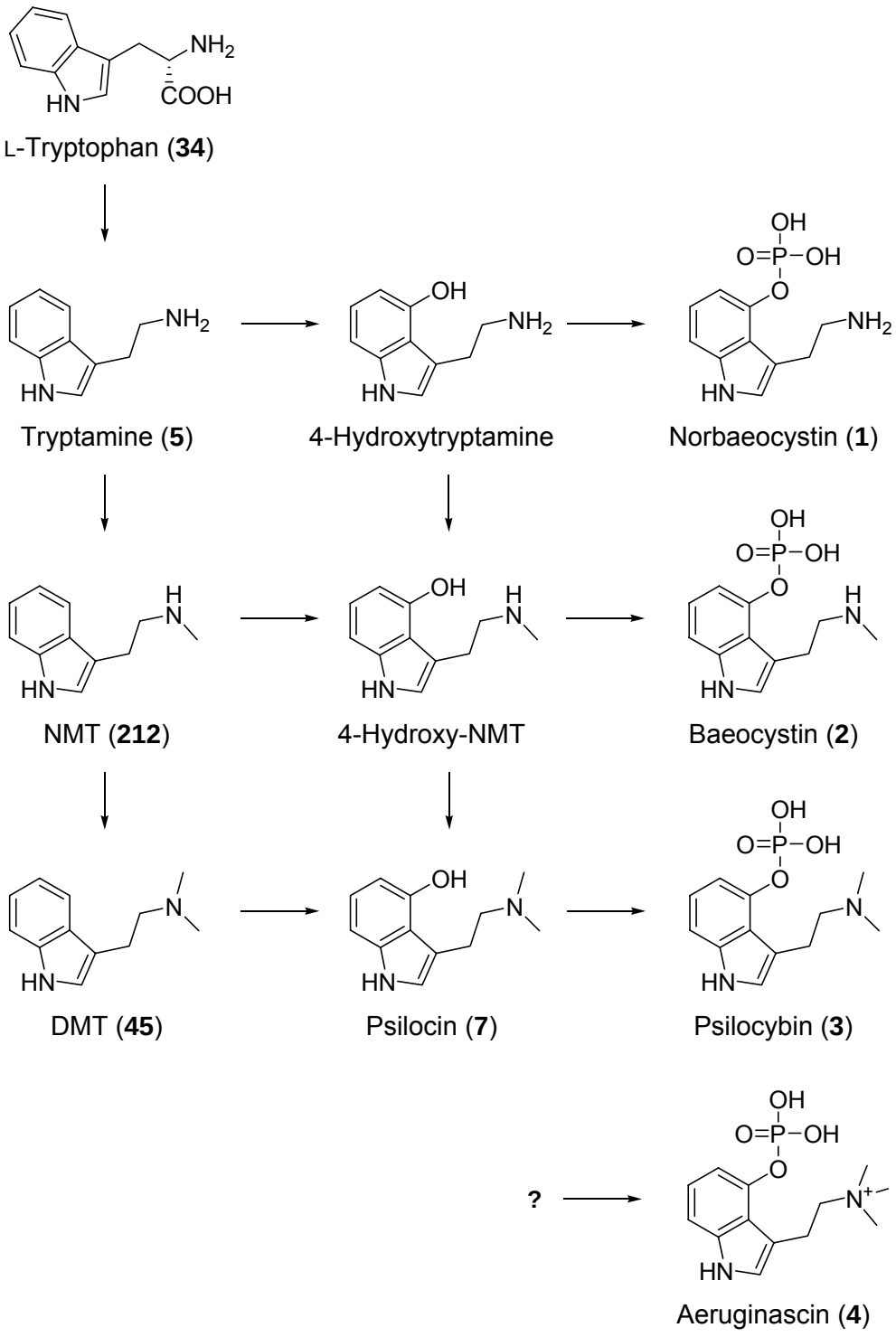


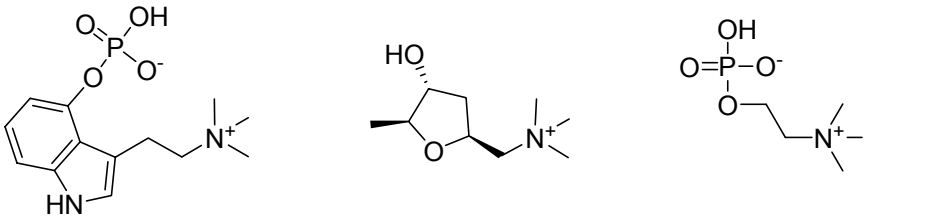
Figure 22: Biosynthesis of *Psilocybe* alkaloids.

The *Psilocybe* alkaloids psilocybin (**3**), baeocystin (**2**), and norbaeocystin (**1**) are biosynthetically derived from tryptophan (**34**) by the following reaction steps: decarboxylation, indole-4-hydroxylation, *N*-methylation, and O-phosphorylation. There is still uncertainty about the sequence of the indole hydroxylation and *N*-methylation steps. Some authors suppose a biosynthetic grid as shown in this scheme.

Biosynthesis of aeruginascin

Aeruginascin (**4**) shares striking molecular similarities with muscarine (**35**), a common mushroom toxin mainly found in the genera *Inocybe* and *Clitocybe* (Figure 23) [143]. Both compounds can be superimposed in their minimal energy conformations so that the hydroxy groups and the quaternary nitrogen atoms have the same distance of 5.4 Å and the 2-methyl group of muscarine (**35**) points to the indole-*C*(4) position of aeruginascin (**4**). The 2-methyltetrahydrofuran-3-ol fragment of muscarine (**35**) and the phosphate group of aeruginascin (**4**) are isosteric and have nearly identical molecular volumes (Figure 24). It is possible that the same methyltransferase enzyme that catalyzes the final methylation step in the biosynthesis of muscarine (**35**) in other *Inocybe* species is responsible for the synthesis of aeruginascin (**4**) from psilocybin (**3**) in *Inocybe aeruginascen*s [211]. Indeed, it has been shown that most enzymes of the secondary metabolism have a rather low substrate specificity [75].

Aeruginascin (**4**) and muscarine (**35**) also have a molecular similarity with the lipid precursor phosphorylcholine (**35**) (Figure 23). In flowering plants and mammalian nerve tissue this compound can be synthesized from phosphoethanolamine by sequential methylations that are catalyzed by the single enzyme phosphoethanolamine *N*-methyltransferase (*S*-adenosyl-L-methionine:ethanolamine-phosphate *N*-methyltransferase, EC 2.1.1.103) [212]. One might speculate that a closely related enzyme participates in the biosynthesis of aeruginascin (**4**) and muscarine (**35**).



Aeruginascin (**4**) Muscarine (**35**) Phosporylcholine (**36**)

Figure 23: Aeruginascin, muscarine, and phosphorylcholine.

Aeruginascin (**4**) shows remarkable molecular similarity to the mushroom toxin muscarine (**35**) and to the lipid precursor phosphorylcholine (**36**).

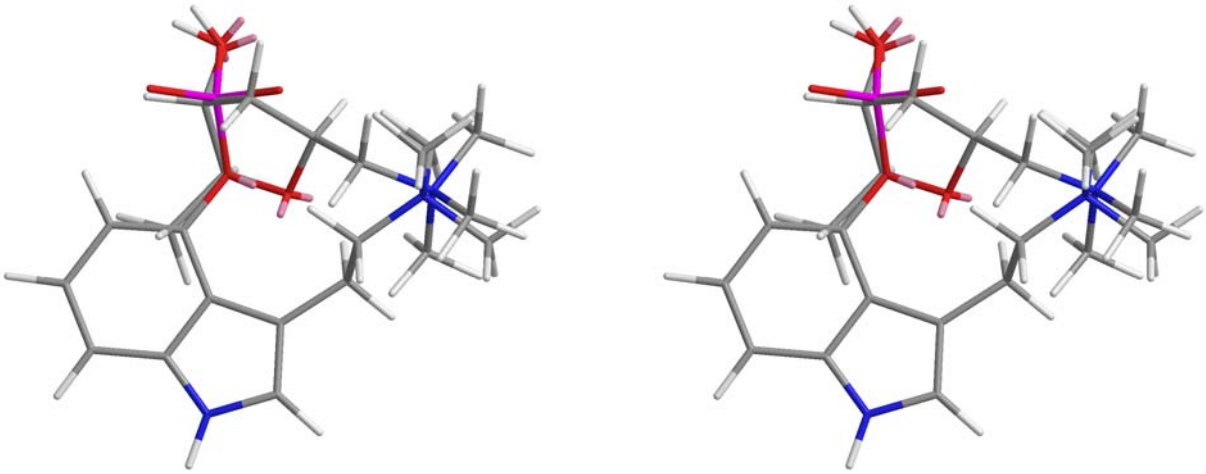
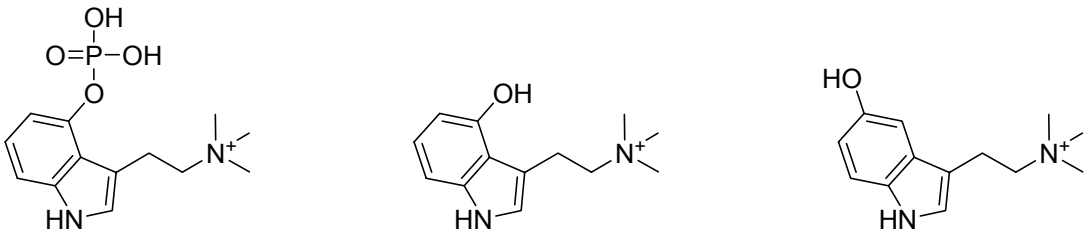


Figure 24: Superposition of aeruginascin and muscarine.

Aeruginascin (**4**) and muscarine (**35**) have been superimposed in their minimal energy conformations. The respective hydroxy groups and the quaternary nitrogen atoms have a distances of 5.4 Å in both compounds and the 2-methyl group of muscarine (**35**) points to the indole-*C*(4) position of aeruginascin (**4**). The 2-methyl-tetrahydrofuran-3-ol ring of muscarine (**35**) and the phosphate group aeruginascin (**4**) are isosteric and have nearly identical molecular volumes.

Toxicology of aeruginascin

The human pharmacology and toxicology of aeruginascin (**4**) has not been tested yet. However, several unintentional intoxications with *Inocybe aeruginascens* have been reported and this mushroom is consumed for its hallucinogenic effects. Due to the quaternary ammonium group it is unlikely that aeruginascin (**4**) is able to pass the blood-brain barrier, a requirement for hallucinogenic effects in human. However, aeruginascin (**4**) might have profound peripheral effects. Aeruginascin (**4**) is assumed to undergo a rapid metabolism into its dephosphorylation product **31** by analogy to the known *Psilocybe* alkaloids. This metabolite has a striking similarity with the peripherally acting 5-HT_3 receptor agonist *N,N,N*-trimethylserotonin (5-HTQ, **37**) (Figure 25).



Aeruginascin (**4**) Dephosphorylated Aeruginascin (**31**) 5-HTQ (**37**)

Figure 25: Aeruginascin and 5-HTQ.

The structure of aeruginascin (**4**) and its dephosphorylation product **31** in comparison with the peripherally acting 5-HT_3 receptor agonist *N,N,N*-trimethylserotonin (5-HTQ, **37**).

Serotonin receptor ligand synthesis

For the pharmacological characterization of *N*-terminally substituted tryptamines at 5-HT receptors it was necessary to synthesize a large number of similar *N*-methyltryptamine and *N*-methyl-5-methoxytryptamines, varying in their second amino substituent. At the beginning of this work a reaction scheme had to be found meeting the following requirements:

- All precursors had to be either commercially available or on stock in the chemical collections of the institute.
- The synthesis scheme had to be convergent in order to minimize reaction steps and the amount of expensive precursors.
- Small scale reactions on a sub-millimolar scale should be practicable.
- The purification processes had to be simple, without product distillations or complex chromatographic procedures.
- The reactions had to be parallelizable so that many reactions could be run in parallel, thereby excluding complex setups.
- The procedure had to be compatible with a variety of chemical groups present in the compounds.
- The procedure had to be general so that the same procedure could be used for all compounds.

Several methods for the preparation of the precursors as well as the final compounds have been tested. One of these schemes was the reaction of tryptamines with acyl chlorides and subsequent reduction of the resulting amides to the required amines. Because of the limitations of this approach with respect to the number of reaction steps and large reflux setups this route was abandoned.

As an alternative, the reaction of *N*-methyltryptamine with alkyl halides has been investigated and optimized. Carboxylic acids were reduced with borane in THF and the resulting primary alcohols were halogenated using a reagent system consisting of triphenylphosphine, iodine or bromine, and imidazole in methylene chloride. The resulting alkyl halides were reacted with *N*-methyl-*N*-alkyltryptamine in the presence of diisopropylethylamine as an acid scavenger in acetonitrile and the final tryptamines were isolated as their hydrogen oxalate salts (Figure 28).

Reduction of carboxylic acids and derivatives

Carboxylic acids proved to be adequate precursors due to their commercial availability and their modest cost. The carboxylic acids were reduced with borane to primary alcohols. This borane reduction proceeded under mild conditions (0 °C to room temperature) in 1 h in ex-

cellent yields and the reaction was compatible with a broad range of substituents. This made borane superior to lithium aluminum hydride as a reducing agent. Most phenethyl-*N*-methyl-tryptamine (PE-NMT and PE-5-MeO-NMT) were synthesized from substituted phenylacetic acids using the borane procedure [216]. Lithium aluminum hydride in THF was the reagent of choice for the reduction of carboxylic acid chlorides and esters but has also been used for several carboxylic acids. However, the required reflux setup and the workup were much more time and space consuming compared to the borane procedure. A typical proton NMR spectrum of ring-substituted 2-phenylethanols is shown in (Figure 26).

Halogenation of primary alcohols

For the synthesis of iodides from primary alcohols, a reagent system consisting of iodine, triphenylphosphine (PPh_3), and imidazole allowed the synthesis of the required alkyl iodides in excellent yields under very mild conditions (0 °C to room temperature) [158]. This system was developed originally for carbohydrate chemistry and is becoming increasingly popular [83, 82]. In accordance with a recent publication it could be shown independently during this work that the same procedure can also be used to synthesize alkyl bromides, simply by replacing iodine with bromine [166]. For both reaction variants most of the byproduct triphenylphosphine oxide (PPh_3O) could be filtered off as a white solid. Remaining minor amounts were inert in the following reaction and were removed during the work-up after the next step.

A typical ^1H NMR spectrum of ring-substituted 2-phenethyl iodides is shown in Figure 26. The ethylene protons of (3-methylphenyl)-ethyl iodide (**143**) have moved together compared the signals in the precursor (3-methylphenyl)-ethanol (**81**), resulting in a second order signal as indicated by the marked roof effect of the triplet-like signals. In a series of spectra for the related of 2-substituted phenethyl iodides recorded on a 200 MHz spectrometer, the influence of different ring-substituents on the shape of the CH_2-CH_2 group of signals can be studied (Figure 27). For R = 2-OH an almost first order signal for this A_2X_2 spin system is seen, consisting of two separated triplets, albeit with a noticeable roof effect. In the order R = H, 2-OMe, 2-F, 2-Cl, 2-Me, and 2-Br the chemical shifts of the two CH_2 proton pairs move together. At the same time the signal changes into a second order multiplet with a complex symmetrical structure, typical for an A_2B_2 spin system. Finally, a sharp pseudo-singlet is observed for R = 2-NO_2. Such transition of first order into second order signals is always seen when the chemical shift difference in a spin system approaches the coupling constant J.

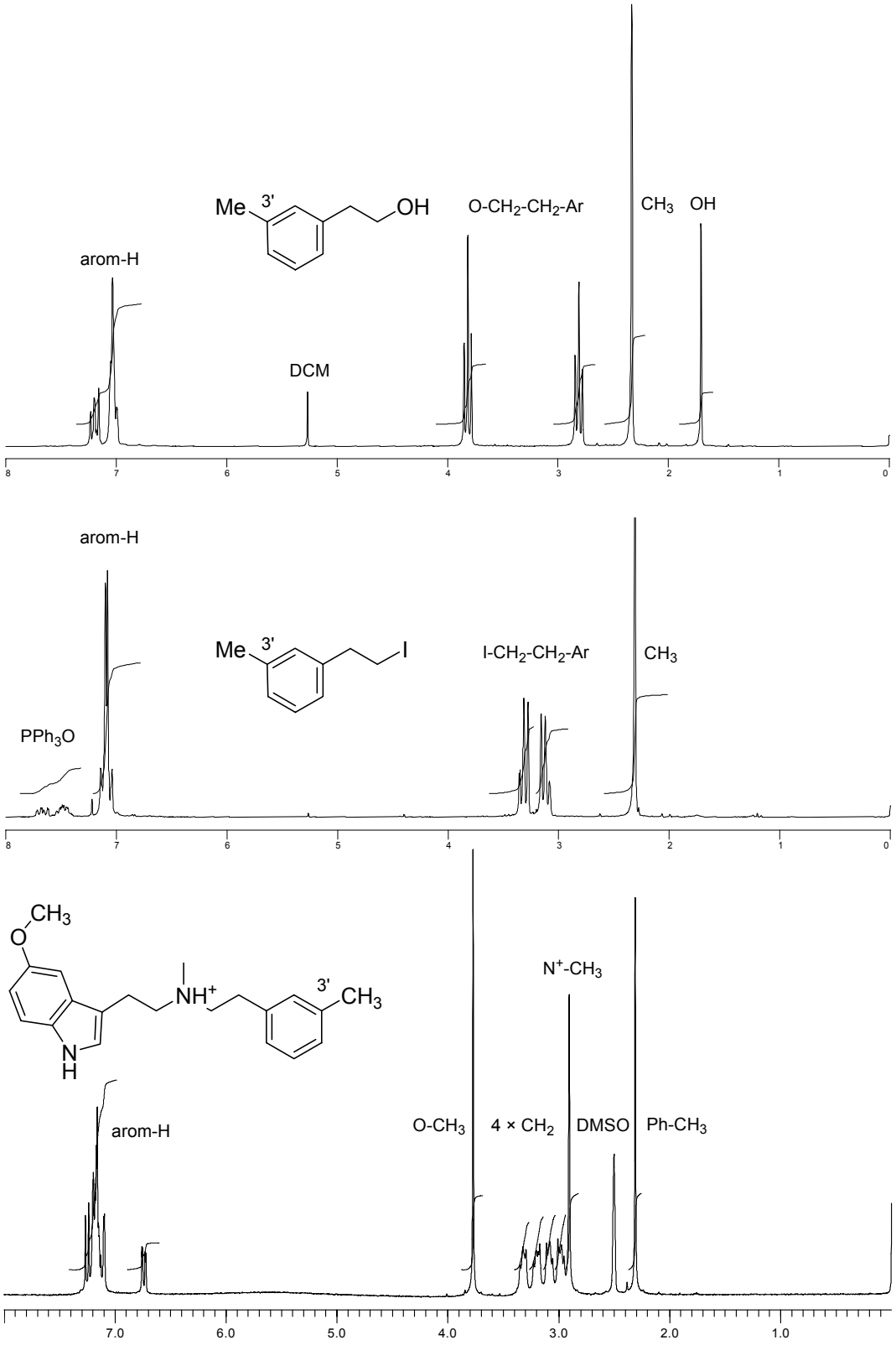

Me
3'
OH
O-CH2-CH2-Ar
CH3
OH
arom-H
DCM
8
7
6
5
4
3
2
1
0
arom-H
Me
3'
I
I-CH2-CH2-Ar
CH3
PPh3O
O
CH3
NH+
3'
CH3
N
H
N+-CH3
arom-H
O-CH3
4 × CH2
DMSO
Ph-CH3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Figure 26: ^{1}H-NMR spectra of the precursors and the final tryptamine.

^{1}H NMR spectra of the precursors (3-methylphenyl)-ethanol (**81**) (200 MHz, $CDCl_3$) and 2-(3-methylphenyl)-ethyl iodide (**143**) (200 MHz, $CDCl_3$), and of the final compound 3-Me-PE-5-MeO-NMT (**238**) (300 MHz, DMSO-d_6).

N-alkylation of tryptamines

The final compounds where synthesized from the alkyl halides, in most cases iodides, and *N*-methyltryptamine (**211**) or *N*-methyl-5-methoxytryptamine (**208**) in the presence of diisopropylethylamine as an acid scavenger in acetonitrile. As verified by TLC analyses, this reaction usually proceeds at room temperature overnight in a homogenous phase without stirring. In order to ensure that no unreacted *N*-methyltryptamine are carried over into the product, acetic acid anhydride was added and the reaction was let stand at room temperature for one hour. After an alkaline washing step to hydrolyze the reagent and to remove acetic acid the tertiary tryptamines were precipitated as their hydrogen oxalates in THF and the products were recrystallized from THF. Using this procedure crude alkyl iodides from the previous reaction step could be used, thereby skipping the chromatographic removal of the byproduct triphenylphosphine oxide (PPh_3O).

Two side reactions in this alkylation step were observed. On the one hand over-alkylation to quaternary amines was seen, especially for the less sterically hindered alkyl halides. On the other hand a base catalyzed dehydrohalogenation of the alkyl halides to alkenes occurred. The latter side reaction took place especially with phenethyl iodides resulting in resonance-stabilized styrenes as byproducts. These byproducts were especially favored when electron withdrawing substituents such as nitro groups were present on the aromatic ring. No attempts were made to optimize the reaction conditions for single compounds in favor of a general and widely applicable standard routine. It turned out to be difficult to remove the quaternary impurities from the products, probably due to the unexpectedly high lipophilicity of these permanently charged species. Indeed, traces of these byproducts could be demonstrated in many of the final compounds by the highly sensitive ESI MS analysis.

Another observed problem was the low tendency of several final products to crystallize as hydrogen oxalates. This was probably related to the high lipophilicity of the hydrogen oxalates in combination with the presence of quaternary byproducts. The use of other solvents, including diethyl ether, hexane, ethanol, and mixtures thereof, and the use of other acids, including hydrochloric acid, sulfuric acid, phosphoric acid, and citric acid, did not result in crystallization of any of the tested crude products. In those cases the compounds were excluded from pharmacological analysis in favor of synthesizing as many ligands as possible.

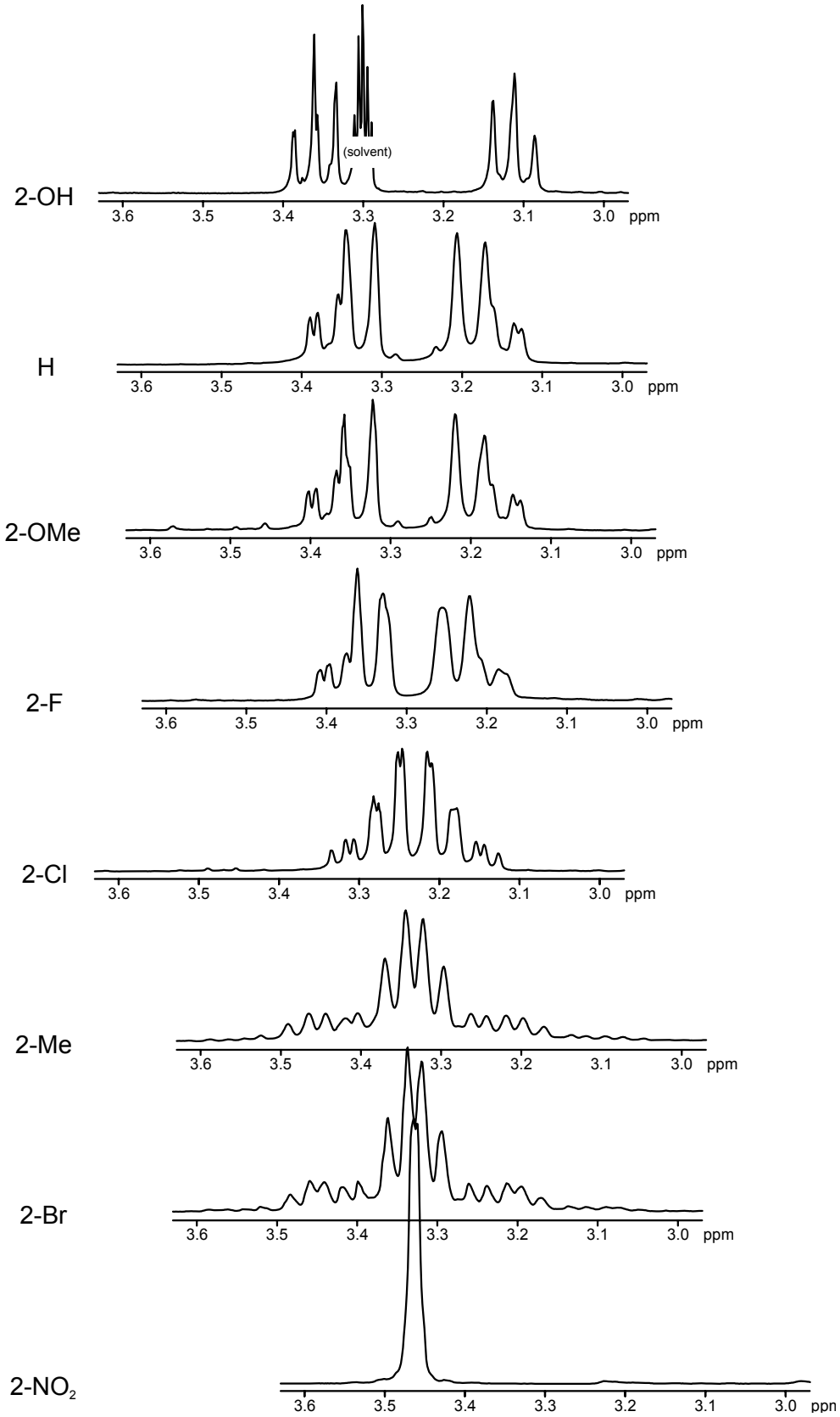

2-OH
(solvent)
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
H
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-OMe
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-F
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-Cl
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-Me
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-Br
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2-NO2
3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm

Figure 27: Transition from a first order into a second order signal.

The ^{1}H NMR (200 MHz) signals of the CH_2-CH_2 protons in 2-substitued phenethyl iodides change gradually from an almost first order A_2X_2 spin system (R = 2-OH) into a complex second order A_2B_2 spin system (R = H, 2-OMe, 2-F, 2-Cl, 2-Me, 2-Br), ultimately resulting in a pseudo-singlet for R = 2-NO_2.

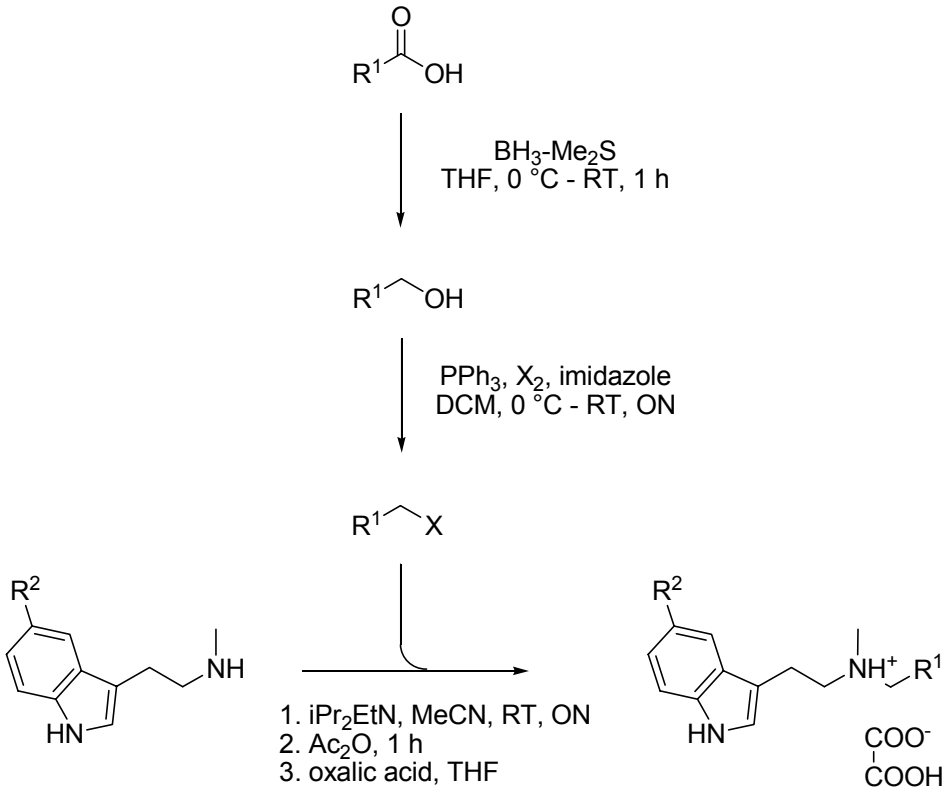


Figure 28: Synthesis of *N*-methyl-*N*-alkyltryptamine.

Substituted carboxylic acids were reduced (BH_3-Me_2S, THF, 0 °C - RT, 1 h) and the resulting alcohols were converted into alkyl halides (PPh_3, X_2, imidazole, DCM, 0 °C - RT, ON). Secondary *N*-methyltryptamine were reacted with these halides, yielding tertiary *N*-methyl-*N*-alkyltryptamine that were isolated as their hydrogen oxalates (1. *i*-Pr_2EtN, MeCN, RT, ON; 2. Ac_2O, 1 h; 3. oxalic acid, THF).

Synthesis of the *N*-monomethyltryptamine

Initially the preparation of the intermediate *N*-methyltryptamine was accomplished by a Speeter-Anthony reaction scheme [265]. Indole was reacted with oxalylchloride, and the resulting indol-3-yl-glyoxylchloride was reacted with methylamine to produce indol-3-yl-glyoxylamide. Unfortunately, the use of lithium aluminum hydride in the following reduction step gave unacceptably low yields under a variety of different reaction conditions, including the solvent systems diethyl ether, THF, or a mixture of both. Similar disappointing results were obtained for the lithium aluminum reduction of *N*-formyltryptamine, synthesized from tryptamine (**5**) and formic acid / acetic anhydride.

A literature search then revealed similar difficulties for the reduction of secondary indol-3-yl-glyoxylamides and secondary amides of tryptamine [28, 135, 148]. A similar effect has also been observed for the reduction of the secondary indol-3-yl-glyoxylic acid propylamide (**353**) and the tertiary indol-3-yl-glyoxylic acid dipropylamide (**354**) in this study. *N*-Propyltryptamine (**355**) and *N,N*-dipropyltryptamine (**356**) were obtained in the substantially different yields of 37% and 78%, respectively, under identical reaction conditions. Tertiary indol-3-yl-glyoxylamides adopt an orthogonal conformation of the two carbonyl groups, mainly due to steric hindrance. However, primary and secondary glyoxylamides are planar due to the formation of intramolecular hydrogen bonds between the amide proton and the keto group [264]. The difficulties to reduce indol-3-yl-glyoxylamides might be related to these differences in conformation. Another possibility might be the formation of metal complexes between reaction intermediates and the reducing agent. The use of high boiling solvents and extended reaction times might partially overcome the experienced limitations of this reaction.

Several alternative routes to *N*-monomethyltryptamine have been considered, such as the hydrogenolytic debenzylation of *N*-methyl-*N*-benzyl derivatives synthesized by Speeter-Anthony reaction or the lithium aluminum hydride reduction of carbamides of tryptamine [135, 242]. Finally, with the relatively high price of 5-methoxyindole in mind, the desired key intermediates *N*-methyltryptamine (**211**) and 5-methoxy-*N*-methyltryptamine (**208**) have been prepared by a Fischer-type indole synthesis [53]. The appropriately substituted phenylhydrazines were reacted with *N*-methyl-*N*-benzyl-aminobutyraldehyde diethyl acetal and the product was catalytically debenzylated with H_2 and Pd/C (Figure 35). During the condensation step in 4% aqueous H_2SO_4 it seemed to be essential to hold the reaction temperature meticulously at or below 60 °C during the addition of the acetal in order to obtain good yields of around 80%.

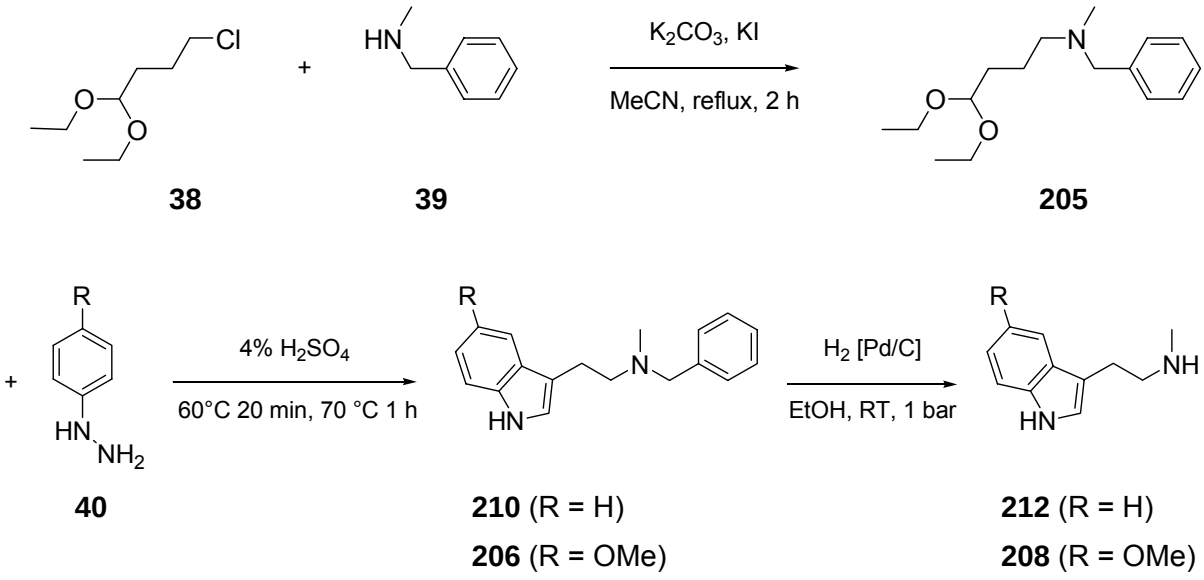


Figure 29: Synthesis of *N*-monomethyltryptamine.

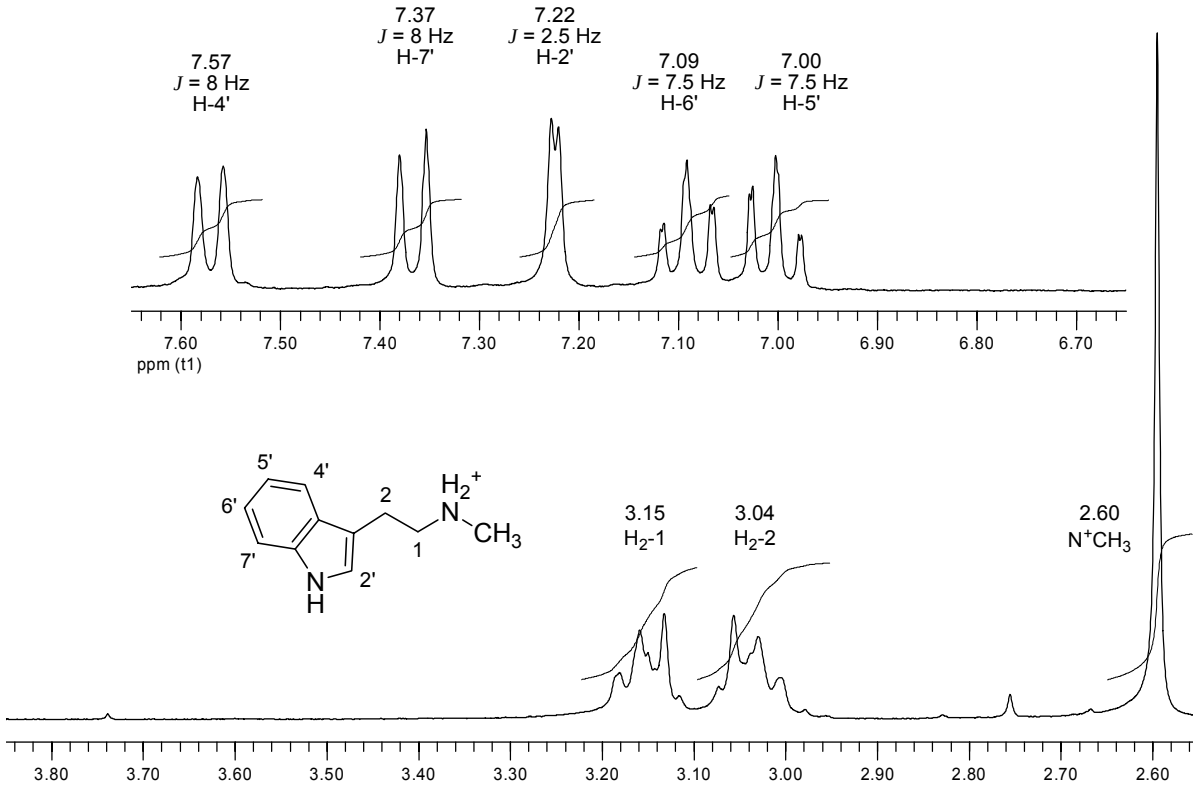
N-methyl-*N*-benzyl-aminobutyraldehyde diethyl acetal (**205**) was synthesized from *N*-methyl-*N*-benzylamine (**39**) and 4-chlorobutyraldehyde diethyl acetal (**38**) (MeCN, K_2CO_3, KI, reflux, 2 h). Subsequent reaction with phenylhydrazines of structure (**40**) gave the *N*-benzyl-*N*-methyltryptamine **210** (R = H) and **206** (R = OMe) (4% H_2SO_4, 60 °C 20 min, 70 °C 1 h). On catalytic debenzylation the *N*-monomethyltryptamine **212** (R = H) and **208** (R = OMe) were obtained (EtOH, Pd/C, H_2, 1 bar, RT).

Spectra of *N*-methyltryptamine

The ^{1}H NMR spectra of *N*-methyltryptamine hydrogen oxalate (**212**) and 5-methoxy-*N*-methyltryptamine hydrogen oxalate (**209**) are shown in Figure 30. They show a typical pattern of signals which is also seen in the final *N*-substituted tryptamines. In the aromatic region the signal of the indole-NH proton can be found between δ = 11.0 and δ = 10.7 as a broad singlet in aprotic solvents like DMSO-d_6. This signal was not visible in protic solvents like MeOH-d_4 and D_2O due to H/D exchange. The aromatic protons can be found in the range from δ = 7.57 - 7.00 (*N*-methyltryptamine, **212**) and δ = 7.25 - 6.74 (5-methoxy-*N*-methyltryptamine, **209**). The 5-methoxy group has a strong shielding effect on the adjacent protons H-4' and H-6', thereby shifting their signals upfield by 0.49 ppm and 0.35 ppm, respectively. The sharp singlet of the OCH_3 group appears at δ = 3.77. As discussed above for the ethylene groups of substituted phenethyl iodides, the sidechain CH_2-CH_2 protons form an A_2B_2 spin system, resulting in a second order signal of two symmetrical multiplets at δ = 3.2 (Ind-CH_2) and δ = 3.0 (CH_2-N^+), respectively. As expected, the protonation state of the amino nitrogen has a

strong influence on the chemical shifts of the attached groups. The *N*-methyl signal of 5-methoxy-*N*-benzyl-*N*-methyltryptamine base (**206**) at δ = 2.26 (N-CH_3) is shifted downfield to δ = 2.63 (N^+-CH_3) in the hydrogen oxalate salt **207**.

The ^{13}C NMR APT spectra of *N*-methyltryptamine hydrogen oxalate (**212**) and 5-methoxy-*N*-methyltryptamine hydrogen oxalate (**209**) are shown in Figure 31. The chemical shifts of the indole carbon atoms in these two compounds are practically identical to those found in the tertiary tryptamines. This has greatly simplified the signal allocation for the final compounds. The *N*-methyl signal at δ = 32.4 in the secondary tryptamines is found at δ = 39.3 in the tertiary tryptamines. Similarly the CH_2-1 signal is shifted downfield from δ = 48.7 to δ = 55.4. At δ = 164 the signal of the oxalate counterion can be seen in contrast to the proton NMR spectra.


7.57
J = 8 Hz
H-4'
7.37
J = 8 Hz
H-7'
7.22
J = 2.5 Hz
H-2'
7.09
J = 7.5 Hz
H-6'
7.00
J = 7.5 Hz
H-5'
7.60 7.50 7.40 7.30 7.20 7.10 7.00 6.90 6.80 6.70
ppm (t1)
5' 4' 6' 2 H_2^+ N CH_3 7' 1 2' N H
3.15
H_2-1
3.04
H_2-2
2.60
N^+CH_3
3.80 3.70 3.60 3.50 3.40 3.30 3.20 3.10 3.00 2.90 2.80 2.70 2.60

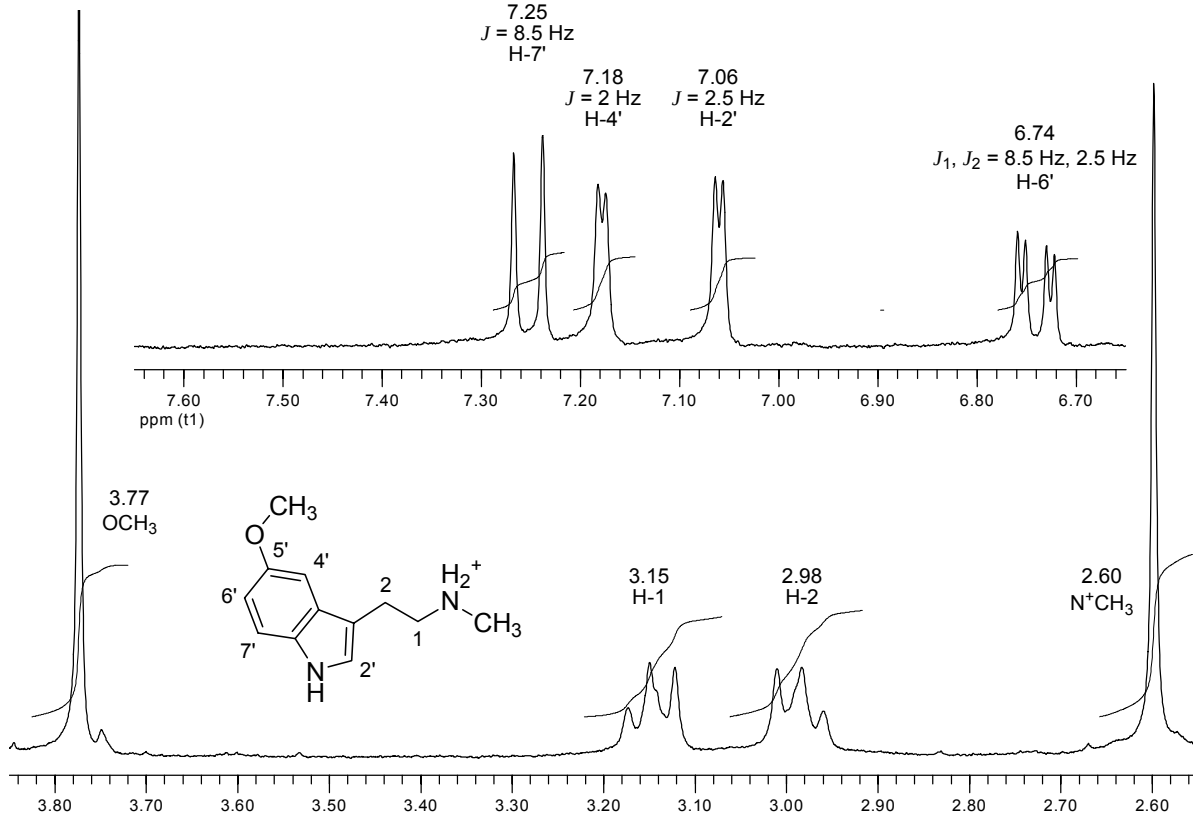

7.25
J = 8.5 Hz
H-7'
7.18
J = 2 Hz
H-4'
7.06
J = 2.5 Hz
H-2'
6.74
J_1, J_2 = 8.5 Hz, 2.5 Hz
H-6'
7.60 7.50 7.40 7.30 7.20 7.10 7.00 6.90 6.80 6.70
ppm (t1)
3.77
OCH_3
CH_3 O 5' 4' 6' 2 H_2^+ N CH_3 7' 1 2' N H
3.15
H-1
2.98
H-2
2.60
N^+CH_3
3.80 3.70 3.60 3.50 3.40 3.30 3.20 3.10 3.00 2.90 2.80 2.70 2.60

Figure 30: ^{1}H NMR spectra of the unsubstituted *N*-methyltryptamine.

^{1}H NMR spectra of key intermediates *N*-methyltryptamine (**212**) and 5-methoxy-*N*-methyltryptamine (**209**) as their hydrogen oxalate salts (300 MHz, DMSO-d_6). The broad signals of the indole-NH at δ = 10.99 (*N*-methyltryptamine) and δ = 10.81 (5-methoxy-*N*-methyltryptamine) are not shown.

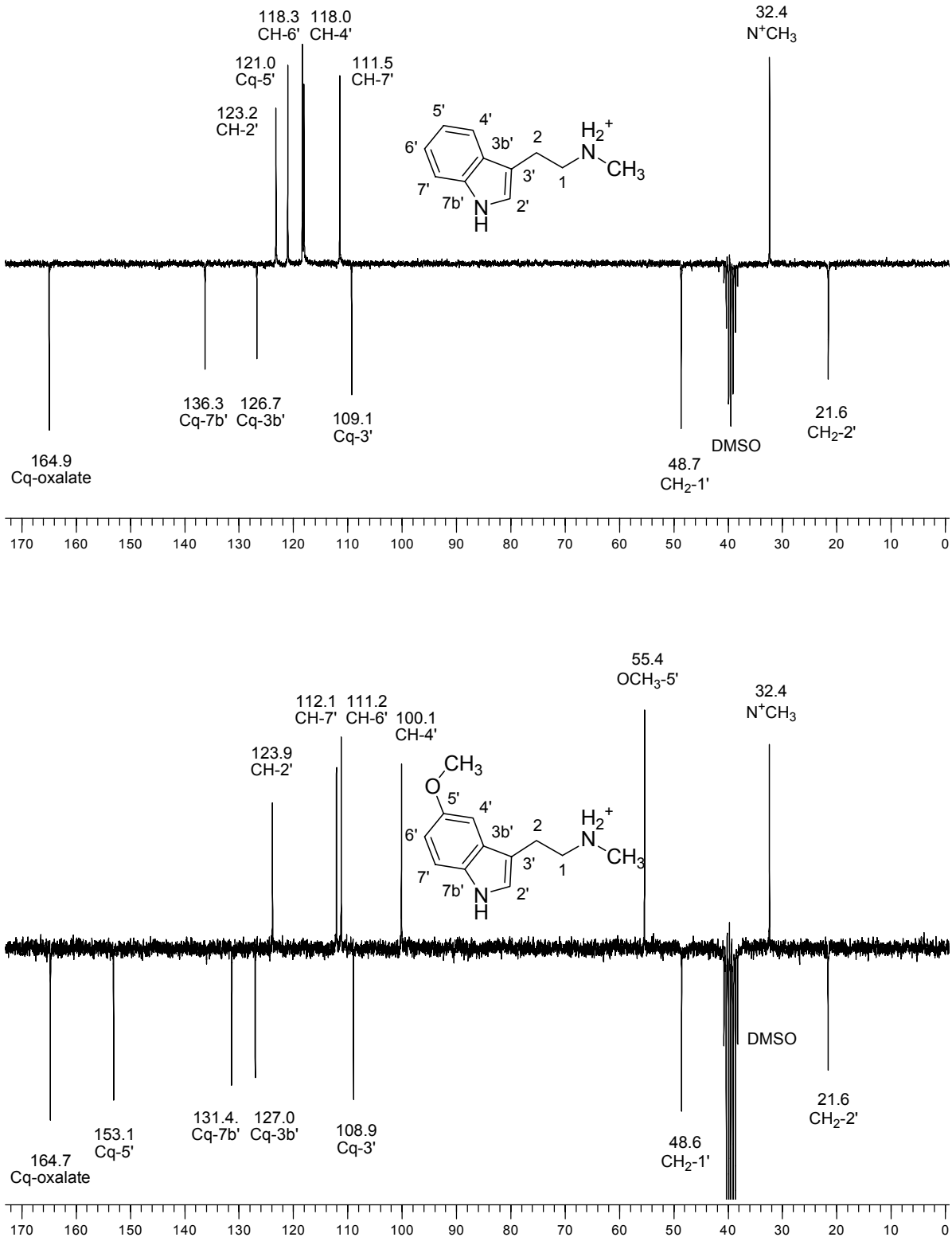
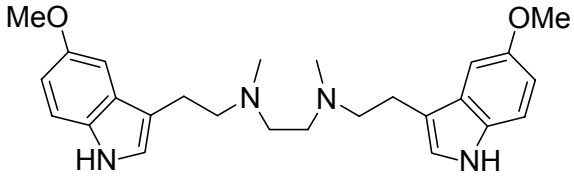


Figure 31: ^{13}C NMR spectra of the unsubstituted *N*-methyltryptamine.

^{13}C NMR APT spectra of key intermediates *N*-methyltryptamine (**212**) and 5-methoxy-*N*-methyltryptamine (**209**) as their hydrogen oxalate salts (50.3 MHz, DMSO-d_6).

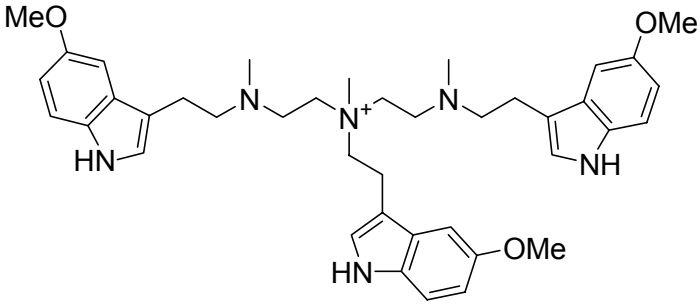
Ethylene-bis-tryptamine

From the reaction of *N*-methyl-5-methoxytryptamine with 1-chloro-2-iodoethane a non-crystalline amorphous brown powder was isolated. Crystallization could not be achieved using several solvents. The substance was identified as the symetrically disubstituted ethylene-bis(*N*-methyl-5-methoxytryptamine) (**303**) (Figure 32). In the ^{1}H NMR and ESI MS spectra the presence of impurities like **41** could be detected (Figure 33). Nevertheless, this interesting but impure compound was subjected to the pharmacological tests.



303

Figure 32: Chemical structure of the ethylene-bis-tryptamine.



41

Figure 33: Structure of a quaternary byproduct of the bis-tryptamine.

6-Methoxy-2-methyl-tetrahydro-β-carboline

Unexpectedly, the reaction of chloroacetonitrile with *N*-methyl-5-methoxytryptamine (**208**) gave 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (**226**). Both starting materials were reacted under the standard conditions with diisopropylethylamine in acetonitrile. This class of compounds is usually obtained by a Pictet-Spengler cyclization of tryptamines with alde-

hydes or ketones under acidic conditions. However, the reaction conditions were strongly basic and therefore a typical Pictet-Spengler pathway seems to be unlikely. A possible mechanism would be the base catalyzed elimination of CN^- from *N*-cyanomethyl-5-MeO-*N*-methyltryptamine (**42**) (Figure 34). This type of reaction has not been reported before und might be an interesting synthetic tool for Pictet-Spengler-like cyclizations of acid-labile compounds.

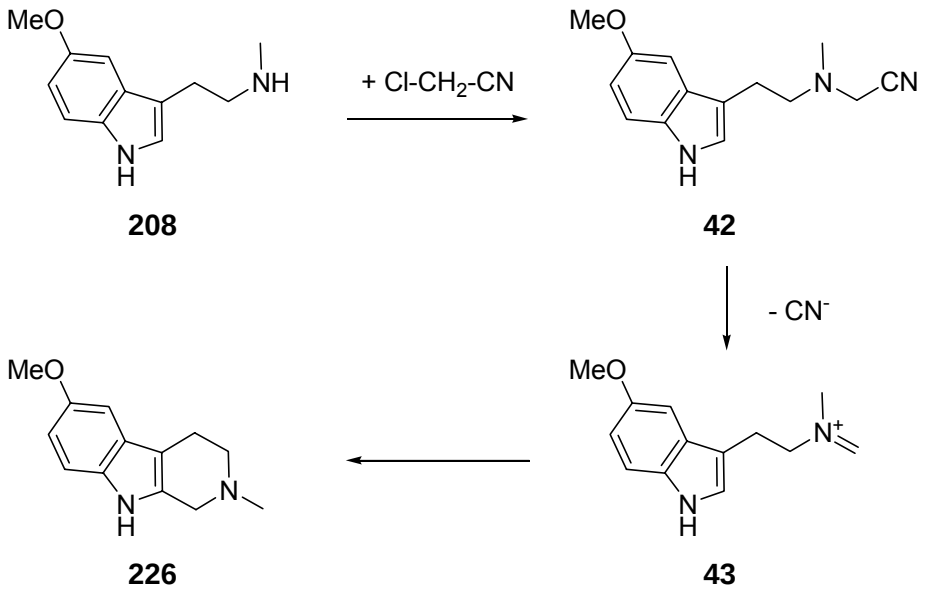


Figure 34: Formation of the tetrahydro-β-carboline.

Hypothetical reaction mechanism resulting in the unexpected formation of the tetrahydro-β-carboline **226** from the intermediate *N*-methyl-*N*-cyanomethyl-5-MeO-tryptamine (**42**) by elimination of CN^-.

Synthesis of *N*-(4-bromobenzyl)-5-methoxytryptamine

In order to verify the published pharmacological data for **19** (compound number 33 in [112]), the synthesis of this ligand has been reproduced, closely following the published procedure [112] (Figure 28). In short, 5-methoxytryptamine (**358**) was synthesized from the available intermediate 3-(2-iodoethyl)-5-methoxyindole (**176**) by reaction with 1-methyl-benzylamine (MeCN, 24 h, RT) and subsequent catalytic debenzylation (H_2, Pd/C, EtOH, 24 h, RT, 4 bar). The intermediate 5-methoxytryptamine (**358**) was then reacted with 4-bromobenzoylchloride (THF, NEt_3, RT, ON) and the resulting tryptamide **359** was reduced with aluminum hydride (AlH_3) to the final *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) ($LiAlH_4$, $AlCl_3$, Et_2O, 5 h, RT)

which was isolated and recrystallized as its hydrogen oxalate. The identity of this product has been confirmed by ^{1}H NMR, ^{13}C NMR, and ESI mass spectrometry.

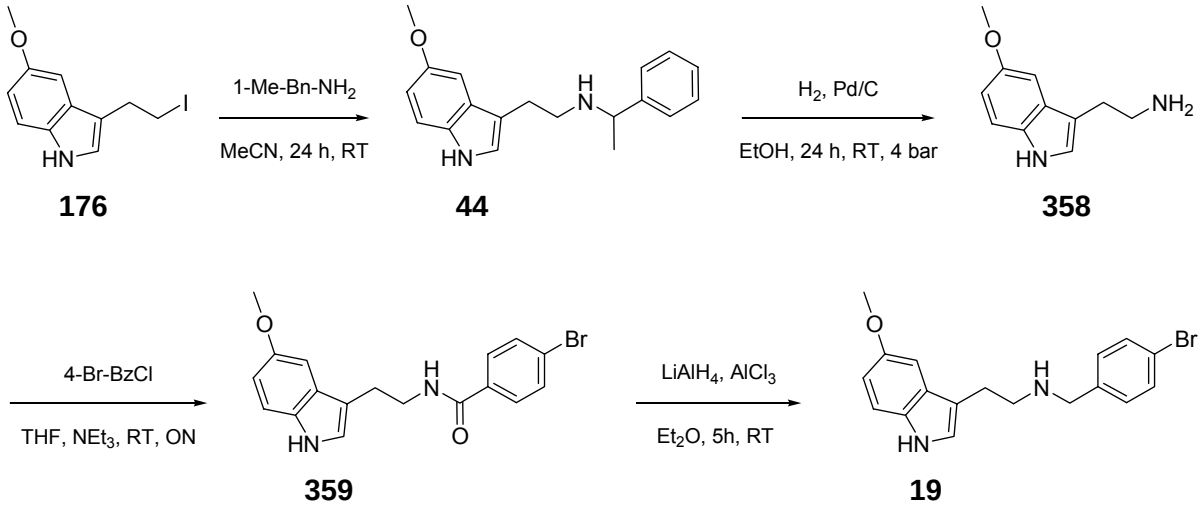


Figure 35: The synthesis of *N*-(4-bromobenzyl)-5-methoxytryptamine.

5-Methoxytryptamine (**358**) was synthesized from 3-(2-iodoethyl)-5-methoxy-indole (**176**) by reaction with 1-methyl-benzylamine (MeCN, 24 h, RT) and subsequent catalytic debenzylation of **44** (H_2, Pd/C, EtOH, 24 h, RT, 4 bar). The resulting 5-methoxytryptamine (**358** was then reacted with 4-bromobenzoylchloride (THF, NEt_3, RT, ON) and the resulting tryptamide **359** was reduced with aluminum hydride to *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) ($LiAlH_4$, $AlCl_3$, Et_2O, 5 h, RT), which was isolated as its hydrogen oxalate salt.

Pharmacological testing

Kinetic binding experiments

Binding assays give reliable results only under equilibrium conditions, i.e. when the association and the dissociation rates of the test ligand and the radiolabel at the receptor have reached constant values. Antagonists in particular often have low rates of association or dissociation, especially at the very low concentrations they are used. To find the optimal incubation time for [^{3}H]ketanserin binding experiments, the time curves of association and dissociation of [^{3}H]ketanserin from the 5-HT_{2A} receptor were measured. Membrane preparations were incubated for different times under the standard conditions of the assay with 2.35 nM [^{3}H]ketanserin. For the dissociation experiments 10 µM cinanserin was added after 60 min of incubation with [^{3}H]ketanserin and the incubation was terminated at different time points. From these time curves the following half-lives were calculated:

$$k = \frac{1}{t_{½}\sqrt{2}}$$

$t_{½\ \text{obs-assoc}}$ = 5.3 min (95% confidence interval: 4.8 - 5.8 min)

$k_{\text{obs-assoc}}$ = 0.13 min^{-1} (95% confidence interval: 0.12 - 0.14 min^{-1})

$t_{½\ \text{dissoc}}$ = 29 min (95% confidence interval: 24 - 26 min)

k_{dissoc} = 0.024 min^{-1} (95% confidence interval: 0.021 - 0.027 min^{-1})

$$k_{\text{assoc}} = \frac{k_{\text{obs-assoc}} - k_{\text{dissoc}}}{[\text{radioligand}]}$$

k_{assoc} = (0.13 min^{-1} - 0.024 min^{-1}) / 2.35 nM = $4.51 \cdot 10^{7}$ $\text{M}^{-1}\text{min}^{-1}$

$$K_{\text{d}} = \frac{k_{\text{assoc}}}{k_{\text{dissoc}}}$$

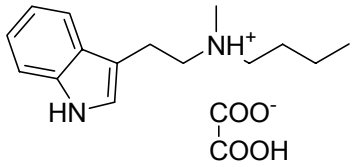
K_{d} = 0.024 min^{-1} / $4.51 \cdot 10^{7}$ $\text{M}^{-1}\text{min}^{-1}$ = 0.53 nM.

As a rule of thumb, the optimal incubation time is four to five times $t_{½\ \text{dissoc}}$ [199]. However, that would have resulted in extremely long incubation times of 2 to 2:30 h. Such extreme durations are usually avoided in order to minimize artifacts resulting from possible degradation of the membranes. As a compromise between short incubations times and true equilibrium binding, an incubation time of 60 min was chosen for all further experiments.

Structure and nomenclature of the ligands

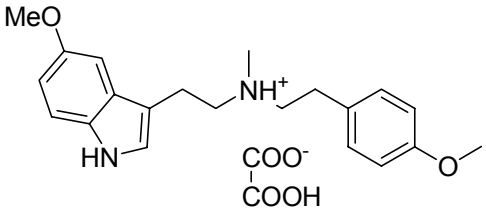
An abbreviating naming convention will be used in the following text. The short form for *N*-butyl-*N*-methyltryptamine hydrogen oxalate (**331**) would be "butyl-NMT", where NMT stands for *N*-methyltryptamine (**211**). Similarly, the short form of *N*-[2-(4-methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate (**250**) would be "4-MeO-PE-5-MeO-NMT", where 4-MeO-PE stands for the *para*-methoxylated 2-phenethyl substituent (Figure 36).

Several reference compounds were used in order to be able to compare results from this and other studies. Compounds included for this purpose were the natural ligand 5-HT (**6**) and the simple unsubstituted and *N*-methylated tryptamines, namely tryptamine (**5**) itself, NMT (**212**), and DMT (**45**), as well as their 5-methoxy analogs 5-MeO-tryptamine (**358**), 5-MeO-NMT (**208**), and 5-MeO-DMT (**15**) (Figure 37). As 5-HT_{2A} receptor selective ligands the DOB-derived 5-HT_{2A} agonist **11**, **46**, and **47** (Figure 38), and the 5-HT_{2A} antagonists ketanserin (**48**), MDL 100,907 (**49**), and AC-90179 (**50**) were included. Ketanserin (**48**) is a relatively specific and subtype-selective 5-HT_{2A} ligand, but has also low affinities for 5-HT_{2C}, α_1, and σ_1 sigma receptors. MDL 100,907 (**49**) is a specific and subtype-selective 5-HT_{2A} ligand with additional low affinities for 5-HT_{2C}, 5-HT_{2B}, 5-HT_{1D}, α, and D receptors [150]. AC-90179 (**50**) is a new specific and 5-HT_{2A} receptor selective antagonist [282] (Figure 39).



N-butyl-*N*-methyltryptamine hydrogen oxalate or:

n-butyl-NMT (**331**)



N-[2-(4-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate or:

4-MeO-PE-5-MeO-NMT (**250**)

Figure 36: Abbreviating naming convention for the tryptamine derived ligands.

The abbreviations NMT and 5-MeO-NMT stand for *N*-methyltryptamine (**211**) and 5-MeO-*N*-methyltryptamine (**208**), respectively, PE stands for the 2-phenethyl substituent.

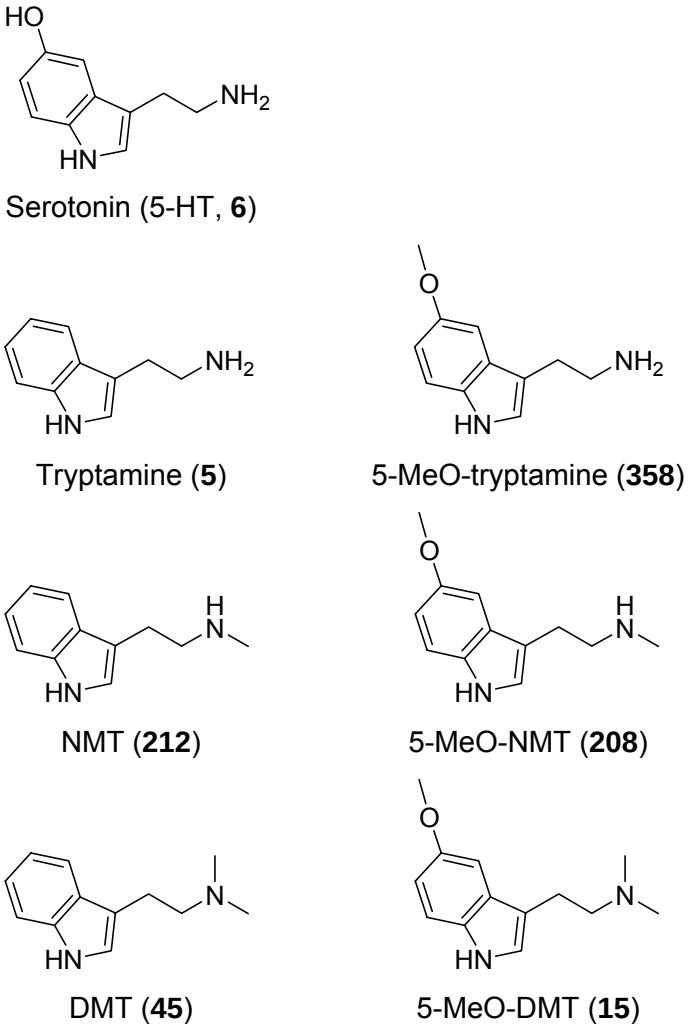
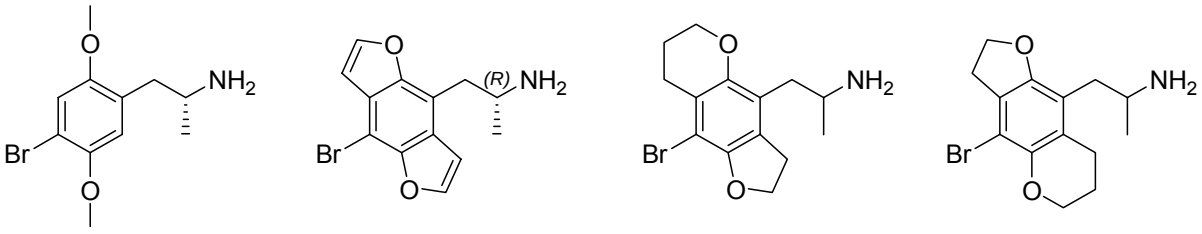


Figure 37: Chemical structures of tryptamine derived 5-HT receptor ligands.

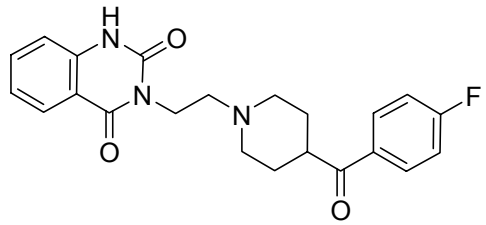
Substituted tryptamines used as reference compounds at serotonin receptors: The natural ligand serotonin (5-HT, **6**), tryptamine (**5**), NMT (**212**), and DMT (**45**), and their 5-methoxy analogs 5-MeO-tryptamine (**358**), 5-MeO-NMT (**208**), and 5-MeO-DMT (**15**).



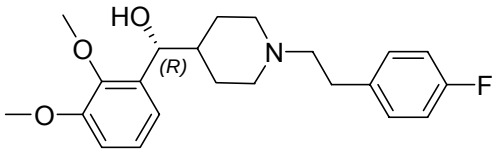
(R)-DOB (**9**) **11** **46** **47**

Figure 38: Chemical structures of DOB derived 5-HT_{2A} agonists.

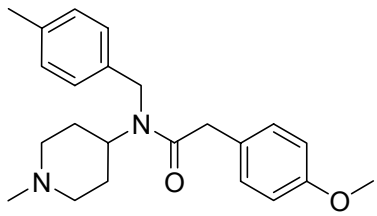
The 5-HT_{2A} agonist DOB (**9**) and its analogs **11**, **46**, and **47** were used as reference ligands at the 5-HT_{2A} receptor.



Ketanserin (**48**)



MDL 100,907 (**49**)



AC-90179 (**50**)

Figure 39: Chemical structures of 5-HT_{2A} antagonists.

Ketanserin (**48**), MDL 100,907 (**49**), and AC-90179 (**50**).

Binding Data for the 5-HT_{1A} receptor

The simple tryptamines NMT (**212**), and DMT (**45**) had very similar affinities for the 5-HT_{1A} receptor of around 40 nM, whereas their 5-methoxy analogs 5-MeO-NMT (**208**) and 5-MeO-DMT (**15**) had affinities of around 3 nM. 5-HT (**6**) itself had an affinity of 0.9 nM.

Introduction of a 5-methoxy group resulted in about a tenfold increase in affinity for most tested *N*-substitutions. The few exceptions to this general observation with less than a 5-fold increase in affinity were 4-Ph-PE (**241**, **242**) (4-fold), 4-Br-PE (**269**, **270**) (4-fold), 4-NO_2-PE (**253**, **254**) (3-fold), and 3,4,5-MeO-phenylpropyl (**321**, **322**) (4-fold). Compound pairs with a more than 20-fold gain in affinity by 5-methoxylation were the plain tryptamines (**5**, **358**) (23-fold), 2-Cl-PE (**259**, **260**) (46-fold), 3-Me-PE (**237**, **238**) (28-fold), 2-F-PE (**235**, **256**) (27-fold), PE (**233**, **234**) (22-fold), 2,5-Me-PE (**196**, **272**) (22-fold), and cyclohexylpropyl (**313**, **314**) (22-fold).

Benzylation of the amine group had detrimental effects on binding affinities. A plain benzyl group as in **210** and **207** decreased affinity 50 to 100-fold. Substitution with the larger 4-Br-benzyl group as in **221**, **222**, and **359** still decreased affinity 5 to 15-fold.

In general, the phenethyl substituted tryptamines had affinities comparable to the simple tryptamines, most of them in the range of 0.5 to 2-fold that of the simple tryptamines. The exceptions with high affinities up to 6-fold over those of the simple tryptamines were most 3-mono-substituted-PE and some 3-disubstituted-PE. On the other hand, 2 to 6-fold lower affinities were measured for 4-MeO-PE (**249**, **250**), 3,4-MeO-PE (**277**, **278**), and 4-Ph-PE (**241**, **242**). For the 5-unsubstituted compounds the following rank order of affinities was found: 3-substituted > 2-substituted > unsubstituted ~ 4-substituted. For 5-methoxy compounds the following slightly different rank order was observed: 3-substituted ~ unsubstituted ~ 2-substituted > 4-substituted. Subnanomolar affinities for the 5-HT_{1A} were seen for the following substituted *N*-phenethyl-5-MeO-NMTs: 2-Cl-PE (**264**), 3-Me-PE (**238**), 3-Br-PE (**268**), and 2,5-Me-PE (**272**).

By substituting the simple phenyl group of the phenethyl series with various aromatic systems, the affinity increased slightly up to 3-fold. A striking exception was (5-MeO-3-indolyl)-ethyl-NMT (**284**) with a 25-fold higher affinity of 1.6 nM compared to the unsubstituted PE-NMT. However, due to the molecule's symmetrical structure, this compound can also be considered as a (3-indolyl)-ethyl substituted 5-MeO-NMT and fits into the expected range of affinities for 5-methoxylated ligands. The also symmetrical bis-methoxy analog (5-MeO-3-indolyl)-ethyl-5-MeO-NMT (**286**) had one of the highest measured affinities from this study of 0.3 nM.

In the 5-unsubstituted series the homologation of the phenethyl substituent (**233**) to phenylpropyl (**315**) and phenylbutyl (**335**) resulted in a 2-fold increase in affinity, whereas (3,4,5-MeO-phenyl)-propyl (**321**) and phenylsulfanyl-propyl (**325**) had a 4-fold higher affinity

of around 10 nM. However, in the 5-methoxylated series the same homologations did not alter binding affinity significantly. As discussed above, shortening the chain to benzyl (**210**, **207**) resulted in a huge loss in affinity down to 1/40 - 1/60 that of the phenethyl or methyl substituents.

Several straight chain alkyl compounds were tested. Butyl substituted compounds (**331**, **332**) showed only 1/2 to 1/5-fold the affinity of simple methyl substituted ligands. However, on further stepwise elongation of the chain, the affinity increased and reached an optimum with the *n*-octyl substituent (**343**, **344**). For even longer chains the affinity decreased and for the *n*-octadecyl the affinity was as low as about 10 µM for the 5-unsubstituted (**349**), and about 1 µM for the 5-methoxylated compound (**350**).

Branching of the alkyl chain at C(2), yielding more sterically demanding substituents, reduced affinity to about 1/10 that of simple tryptamines and to about 1/2 that of plain alkyl substituents of comparable size. In these compounds the loss in affinity resembled that seen with the benzyl group.

In the group of three-carbon chain substituents the allyl compounds (**305**, **306**) had affinities about equal to the simple tryptamines, whereas the more constrained propargyl compounds (**307**, **308**) had only half the affinities of the methyl substituted tryptamines.

In the group of compounds with a ring attached to a three-carbon spacer, the 5-unsubstituted phenylallyl (**317**) and cyclohexylpropyl (**315**) analogs had a slightly lower affinity compared to phenylpropyl (**313**), while the cyclohexylpropyl-5-MeO-NMT (**314**) had a subnanomolar affinity, about twice that of propyl-phenyl-5-MeO-NMT (**316**).

Introduction of a carbonyl functionality into the substituent had a detrimental effect on affinity for all tested compounds if compared to the methyl substituent as well as compared to straight alkyl groups of comparable length.

In the 5-unsubstituted series the highest binding affinities were measured for *n*-heptyl (**341**) (12 nM), *n*-octyl (**343**) (9 nM), (3,4,5-MeO-phenyl)-propyl (**321**) (9 nM), phenylsulfanylpropyl (**325**) (11 nM), 3-MeO-PE (**247**) (12 nM), 3-Br-PE (**267**) (11 nM), 2,5-Me-PE (**196**) (13 nM), 2,5-MeO-PE (**275**) (10 nM), 3,4-Cl-PE (**281**) (13 nM), and (2-naphthyl)-ethyl (**289**) (13 nM). In the 5-methoxy series all substituted phenethyl substituted compounds had affinities below 10 nM with the exception of 4-NO_2-PE (**254**) and 4-Ph-PE (**242**). Compounds showing excellent subnanomolar affinities below that of 5-HT (**6**) itself were 2-Cl-PE (**260**) (0.5 nM), 2,5-Me-PE (**272**) (0.6 nM), 3-Me-PE (**238**) (0.8 nM), 3-Br-PE (**268**) (0.8 nM), (5-MeO-indolyl)-ethyl (**286**) (0.3 nM), *n*-octyl (**344**) (0.3 nM), and cyclohexylpropyl (**314**) (0.9 nM).

5-HT_{2A} receptor binding data

The simple parent compounds tryptamine (**5**), NMT (**212**), and DMT (**45**) displayed low affinities between 1 µM and 2 µM for the ketanserin (**48**) labeled 5-HT_{2A} receptor. By 5-methoxy-

lation affinity could be increased to 150 nM for 5-MeO-tryptamine (**358**) and to about 550 nM for 5-MeO-NMT (**208**) and 5-MeO-DMT (**15**). 5-HT (**6**) itself had an affinity of 140 nM, comparable to that of 5-MeO-tryptamine (**358**).

The tested *N*-benzylated NMT derivatives **210** and **207** exhibited affinities between 800 nM and 900 nM, independent of 5-methoxylation. 5-MeO-*N*-(4-Br-benzyl)-tryptamine (**19**) had an affinity of only 530 nM, not different to that of 5-MeO-NMT (**208**) and only 1/4 that of 5-HT (**6**) and the *N*-unsubstituted 5-MeO-tryptamine (**358**). This result will be discussed in detail below.

Attaching a phenethyl group to the parent compounds resulted in an increase in affinity between 15-fold and 26-fold. Attaching substituents to the phenyl group further enhanced affinity, usually between 2-fold and 5-fold. Only the 4-MeO-PE (**249**, **250**), the 4-Ph-PE (**241**, **242**), and especially the 4-NO_2-PE (**253**, **254**) compounds from both series showed a decreased affinity, compared to the respective plain PE substituted tryptamines (**233**, **234**). In general, substitution in position 2 of the phenyl ring (*ortho*) resulted in higher affinities compared to those in position 3 (*meta*) or 4 (*para*). The highest affinities with values below 10 nM were seen in the 5-unsubstituted series for 2-Cl-PE (**259**) (6 nM) and 3,5-Me-PE (**273**) (8 nM), and in the 5-methoxylated series for 2-F-PE (**256**) (4 nM), 2-Cl-PE (**260**) (6 nM), and 3-Br-PE (**268**) (4.5 nM).

For the ethylene spaced aromatic rings remarkably high affinities were seen for the (3-indolyl)-ethyl substituent (**283**, **284**) with affinities of around 10 nM in both series. Attaching a second 5-methoxy group onto this symmetrical core as in (5-MeO-indolyl)-ethyl-5-MeO-NMT (**286**) was less favorable, with a three-fold loss in affinity, comparable to that of phenethyl (**234**). In both series the (1-naphthyl)-ethyl compounds **287** and **288** had affinities of about 10 nM, while the (2-naphthyl)-ethyl compounds (**289**, **290**) had affinities two to three-fold lower, but still higher than that of plain phenethyl (**233**, **234**).

Homologation of the phenethyl substituent (**233**) to phenylpropyl (**315**) and phenylbutyl (**335**) increased affinity 4-fold in the 5-unsubstituted series. In the 5-methoxy series the affinities were similar to the phenethyl compound (**207**), the phenylpropyl compound **316** had a slightly lower, and the phenylbutyl compound **336** had a slightly higher affinity. Interestingly, with the exception of the phenethyl substitution, the ligands from the 5-unsubstituted series all had higher affinities compared to their 5-methoxy counterparts. The additional ring-substituents in (3,4,5-MeO-phenyl)-propyl lower the affinity two-fold (5-unsubstituted, **322**) and 5-fold (5-methoxy, **322**).

With an affinity of 1.8 nM the 5-unsubstituted phenylsulfanyl-propyl ligand **325** had the highest affinity of all tested compounds at the 5-HT_{2A} receptor, similar to that of ketanserin (**48**) (1 nM), 76-fold that of 5-HT (**6**), and 40-fold higher than that of plain phenethyl (**233**). Its 5-methoxy congener (**326**) still had an affinity of 9 nM, twice that of the PE-5-MeO-NMT

(**234**). As discussed above, the benzyl homologs **210** and **207** had greatly reduced affinities compared to all other arylalkyl compounds.

Binding affinities of straight chain alkyl compounds at the 5-HT_{2A} receptor

For the group of straight chain alkyl compounds increasing the chain length stepwise resulted in a parallel increase in affinity with an optimum at *n*-octyl (**343**) with 17 nM in the 5-unsubstituted series. With a further increase in chain length the affinity declined, and for *n*-octadecyl-NMT (**349**) an affinity of 5 µM even below that of NMT (**212**) was reached. Starting with chain lengths of *n*-pentyl (**338**) the 5-methoxy compounds had lower affinities compared to their unsubstituted counterparts, in sharp contrast to what has been seen at the 5-HT_{1A} receptor. Again, the highest affinity was measured for *n*-octyl-5-MeO-NMT (**344**) with 155 nM, 22-fold lower than that of *n*-octyl-NMT (**343**).

Branching the alkyl chain at C(2) or adding double or triple bonds resulted in compounds of roughly comparable affinity compared to *n*-alkyl compounds of the same length, but without an obvious relation to structural features.

Saturating the phenyl group of the phenylpropyl substituent as in **315** and **316**, yielding the cyclohexylpropyl substituted compounds **313** and **314**, resulted in a three-fold drop in affinity. Introduction of a double bond into the side chain, as in the phenylallyl compounds **317** and **318**, also resulted in distinctly lower affinities.

As seen for the 5-HT_{1A} receptor, adding carbonyl functionalities to the side chain had strongly detrimental effects on binding affinity. Especially the more hydrophilic CH_2-$CONH_2$ substituted compounds **231** and **232** showed negligible binding affinity. Only the longer and more lipophilic (CH_2-CH_2-$CONEt_2$)-5-MeO-DMT (**302**) had similar affinity to 5-MeO-NMT (**208**) and 5-MeO-DMT (**15**).

The highest affinities for 5-unsubstituted ligands at the 5-HT_{2A} receptor were seen for 2-Me-PE (**235**) (12 nM), 2-Cl-PE (**259**) (6.1 nM), 3-Me-PE (**237**) (12 nM), 3,5-Me-PE (**273**) (8.4 nM), 1-naphthyl (**287**) (10 nM), (3-indolyl)-ethyl (**283**) (12 nM), *n*-octyl (**343**) (17 nM), and phenylsulfanyl-propyl (**325**) (1.8 nM). In the 5-methoxy series the highest affinities were measured for 2-F-PE (**256**) (4.3 nM), 2-Cl-PE (**260**) (5.5 nM), 3-Cl-PE (**262**) (12 nM), 3-Br-PE (**268**) (4.5 nM), 3,5-Me-PE (**274**) (12 nM), (3-indolyl)-ethyl (**284**) (9.9 nM), and phenylsulfanyl-propyl (**326**) (9.1 nM).

At the 5-HT_{2A} receptor most 5-methoxy compounds had comparable affinities to their 5-unsubstituted analogs in the range of 0.5 to 2-fold. Exceptions were 5-MeO-tryptamine (**358**) (9-fold), 5-MeO-NMT (**208**) (4-fold), 2-F-PE (**256**) (4-fold), 3-Br-PE (**268**) (4-fold), 2,5-MeO-PE (**276**) (0.2-fold), 3-Me-PE (**238**) (0.4-fold), (3,4,5-MeO-phenyl)-propyl (**322**) (0.3-fold), phenylbutyl (**336**) (0.4-fold), phenylsulfanyl-propyl (**326**) (0.2-fold), *n*-octyl (**344**) (0.1-fold), isobutyl (**310**) (0.3-fold), and cyclohexylpropyl (**314**) (0.3-fold). (3-indolyl)-ethyl-

5-MeO-NMT (**284**) had 0.3-fold the affinity of (3-indolyl)-ethyl-NMT (**283**), but this is again explained by the symmetrical structure of the molecule.

Binding affinities at the 5-HT$_{2C}$ receptor

Affinities for the 5-HT$_{2C}$ receptor followed closely those for the 5-HT$_{2A}$ receptor. For most compounds the differences between both series were in the range from one-third to three-fold. However, a considerably higher affinity at the 5-HT$_{2C}$ site has been measured for the following simple tryptamines and bulky, lipophilic ligands: 5-HT (**6**) (9-fold), tryptamine (**5**) (23-fold), NMT (**212**) (12-fold), 2,6-Cl-PE-NMT (**259**) (6-fold), 4-Ph-PE-NMT (**241**) (6-fold), (3-indolyl)-ethyl-NMT (**283**) (4-fold), (1-naphthyl)-ethyl-NMT (**287**) (4-fold), (2-naphthyl)-ethyl-NMT (**289**) (4-fold), 5-MeO-NMT (**208**) (6-fold), and (3,4,5-MeO-phenyl)-propyl-NMT (**321**) (7-fold).

Similar to the 5-HT$_{2A}$ receptor, the effect of the 5-methoxy group on affinity was in the range from one-half to two-fold for most compounds. An even higher relation was seen for 5-MeO-T (**358**) (5-fold). Lower relations, indicative of some 5-HT$_{2C}$ receptor selectivity, were observed for 3,5-Me-PE-5-MeO-NMT (**274**) (0.4-fold), 2,5-MeO-PE-5-MeO-NMT (**276**) (0.1-fold), 3-Me-PE-5-MeO-NMT (**246**) (0.2-fold), (5-MeO-3-indolyl)-ethyl-5-MeO-NMT (**276**) (0.3-fold), phenylsulfanyl-propyl-5-MeO-NMT (**326**) (0.2-fold), and *n*-dodecyl-5-MeO-NMT (**346**) (0.1-fold).

The highest affinities below 10 nM at the 5-HT$_{2C}$ receptor in the 5-unsubtituted series have been detected for 2-MeO-PE (**245**) (7.4 nM), 2-Cl-PE (**259**) (4.5 nM), 2,5-Me-PE (**196**) (7.7 nM), 3,5-Me-PE (**273**) (2.5 nM), 2,5-MeO-PE (**275**) (5.2 nM), 3,4-MeO-PE (**277**) (8.7 nM), (3-indolyl)-ethyl (**283**) (3.1 nM), (1-naphthyl)-ethyl (**287**) (2.5 nM), (2-naphthyl)-ethyl (**289**) (7.7 nM), and phenylsulfanyl-propyl (**325**) (3.3 nM). The highest affinities for 5-methoxy ligands were found for 2-F-PE (**256**) (9.1 nM), 2-Cl-PE (**260**) (3.0 nM), 3,5-Me-PE (**274**) (6.4 nM), 3-Br-PE (**268**) (5.2 nM), (5-MeO-3-indolyl)-ethyl (**286**) (4.2 nM), and (1-naphthyl)-ethyl (**288**) (4.9 nM).

Binding affinities at the 5-HT$_{1A}$ compared to the 5-HT$_{2A}$ receptor

Not a single compound from this project showed more than a five-fold selectivity for the 5-HT$_{2A}$ over the 5-HT$_{1A}$ receptor, while a few compounds with greater than 50-fold selectivity for the 5-HT$_{1A}$ over the 5-HT$_{2A}$ receptor could be identified. The latter are the simple tryptamines 5-MeO-tryptamine (**358**) (95-fold), 5-MeO-NMT (**208**) (275-fold), and 5-MeO-DMT (**15**) (134-fold), the alkyl substituted ligands *n*-butyl-5-MeO-NMT (**332**) (72-fold), *n*-pentyl-5-MeO-NMT (**338**) (69-fold), *n*-octyl-5-MeO-NMT (**344**) (479-fold), cyclopentylmethyl-5-MeO-NMT (**216**) (62-fold), cyclohexylmethyl-5-MeO-NMT (**218**) (65-fold), isobutyl-5-MeO-NMT (**310**) (96-fold), allyl-5-MeO-NMT (**306**) (108-fold), cyclohexylpropyl-5-MeO-NMT (**314**) (177-fold), and cyanoethyl-5-MeO-NMT (**294**) (43-fold), as well as the aromatic ring-

substituted compounds (5-MeO-3-indolyl)-ethyl-5-MeO-NMT (**288**) (105-fold), (3,4,5-MeO-phenyl)-propyl-5-MeO-NMT (**322**) (65-fold). In a recent work structurally related *N,N*-di-(2-arylethyl)-*N*-propylamines, with the aryl group being phenyl and naphthyl, have been tested at 5-HT_{1A} receptors [274]. The compounds had affinities of around 100 nM. These results show the importance of an intact tryptamine (**5**) moiety and confirm that a 2-arylethyl amino-substituent contributes to high 5-HT_{1A} binding affinities. The gain in affinity caused by 5-methoxylation was usually higher at 5-HT_{1A} receptors compared to 5-HT_{2A} receptors. This might indicate a binding mode of the tested compounds different to that of the simple agonists at the 5-HT_{2A} receptor. Indeed, most compounds turned out to be antagonists in the functional experiments discussed below.

N-bridged ethylene-bis-tryptamine

Ethylene-bis(*N*-methyl-5-methoxytryptamine (**303**) (Figure 32) was obtained as an amorphous, impure compound, contaminated with traces of the quaternary reaction product (**304**). Nevertheless, this unpurified compound has been subjected to the receptor binding assays. Surprisingly, this ligand proved to be one of the most interesting compounds tested. The binding affinities were 1.9 nM at the 5-HT_{1A} receptor, 1696 nM at the 5-HT_{2A} receptor, and 612 nM at the 5-HT_{2C} receptor (Table 7). This nearly 900-fold selectivity for the 5-HT_{1A} receptor over the 5-HT_{2A} receptor is the highest one observed in this study. Bivalent analogs of 5-HT_{1A} receptor ligands have previously been shown to possess enhanced affinities at 5-HT_1 receptors. These ligands were bridged on their aromatic substituent [224, 223] as well as on their amine group [167]. In the latter study the highest affinities were indeed obtained for compounds with spacer chain lengths of two (ethylene) and seven carbon atoms.

IP accumulation assay results

IP accumulation was measured in living adherent and confluent cells in tissue culture plates after preincubation overnight with [^{3}H]PIP_2. The monoamine oxidase inhibitor (MAOI) pargyline was added to the incubation medium in order to inhibit deamination of the test compounds. Lithium chloride was added to prevent IP dephosphorylation by inhibiting D-*myo*-inositol-1-phosphatases. IP in the supernatant of permeabilized cells was separated using anion exchange resin columns and measured in a scintillation counter. The measured radioactivity was usually around 5,000 cpm after full activation with 10 µM 5-HT, with a span of 3,000 to 11,000 cpm between different experiments. The signal to background ratio under full stimulation conditions was usually around 30-fold, with a range of 9 to 51-fold.

Biphasic response

During the first IP accumulation experiments an unexpected biphasic response for several of the tested compounds was noticed. In addition to a normal sigmoidal response at lower concentrations ("low-dose response"), an unusual second rise was seen at concentrations of 3.2

and 10 µM, the highest concentrations used in these experiments ("high-dose response") (Figure 40).

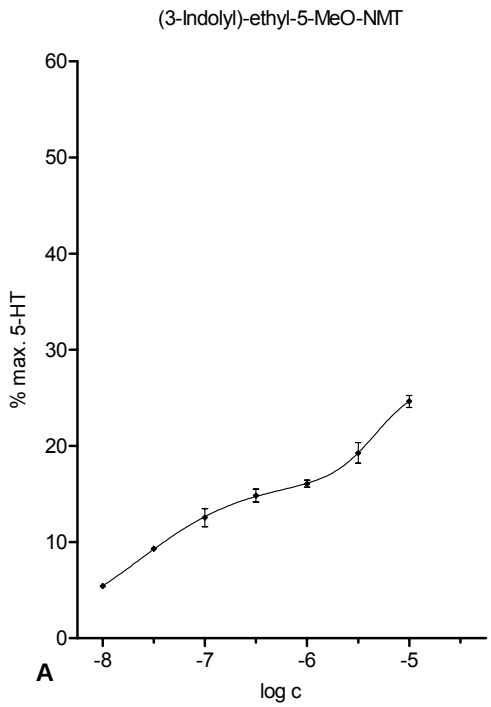
To further explore this effect, more experiments were carried out using additional compounds and evaluating a broader concentration range of up to 32 µM ($10^{-4.5}$ M) (Figure 41). In these experiments the existence of an unusual high-dose response could be verified for a subset of the tested compounds. These compounds were cyclohexylpropyl-5-MeO-NMT (**314**) and the arylethyl tryptamines (3-indolyl)-ethyl-NMT (**283**), 3-MeO-PE-NMT (**247**), (3-indolyl)-ethyl-5-MeO-NMT (**284**), 3,5-Me-PE-NMT (**273**), (1-naphthyl)-ethyl-NMT (**287**), and 2,5-Me-PE-NMT (**271**).

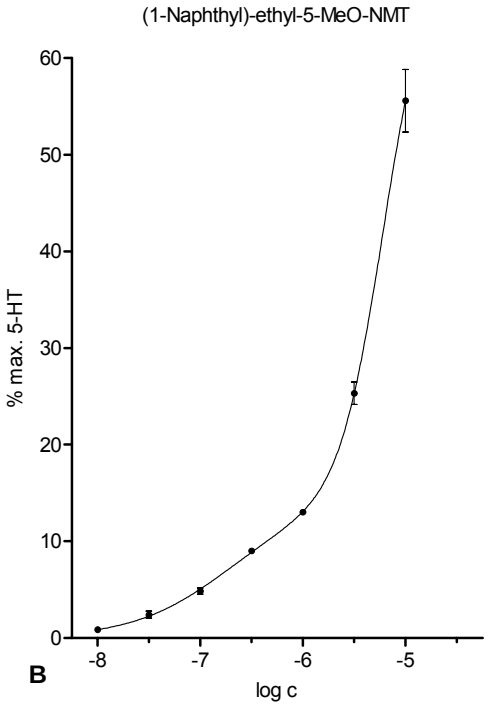
A high-dose response was not seen for the lower-alkyl or unsubstituted tryptamines 5-HT (**6**), NMT (**212**), 5-MeO-NMT (**208**), DMT (**45**), 5-MeO-NMT (**209**), 5-MeO-DMT (**15**), for 4-Br-benzyl-5-MeO-tryptamine (**359**), for the phenylisopropylamines **11**, **46**, and **47**, for thio-DOB, 2C-T-2, 2-MeO-naphthyl-isopropylamine, 2,6-Br-mescaline, and Aleph-2 (data not shown), and for (CH2-CH2-CONEt$_2$)-5-MeO-NMT (**324**) and (3,4,5-MeO-phenyl)-propyl-5-MeO-NMT (**321**).

With the exception of 4-Br-Bn-NMT (**221**) and cyclohexylpropyl-5-MeO-NMT (**314**), all high-dose activating compounds tested showed a partial-agonistic response at lower concentrations, resulting in the initially observed biphasic dose-response curves.

Fitting

In order to be able to analyze the dose-response-curves using a fitting procedure, especially to determine the low-dose $EC_{50\text{-}1}$, a formal method had to be found to mathematically separate both parts of the curves. Therefore, the biphasic curves were treated as an additive overlay of two independent sigmoidal responses. Because in most cases the plateau of the high-dose response was not reached, the Hill slope ($slope_2$) and the maximum (max_2) of the high-dose term could not be calculated conclusively from the datasets and had to be constrained to constant values. Although this procedure does not allow getting reliable parameters for the high-dose response, it is essential for fitting the low-dose response to a standard dose-response curve.


(3-Indolyl)-ethyl-5-MeO-NMT
% max. 5-HT
log c
A


(1-Naphthyl)-ethyl-5-MeO-NMT
% max. 5-HT
log c
B

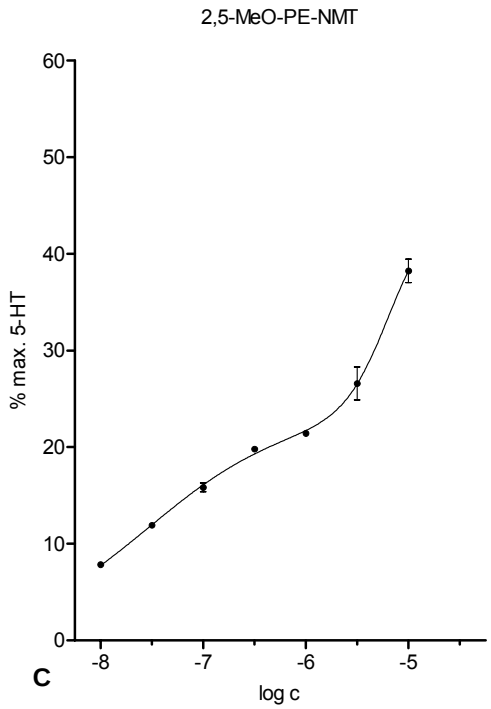

2,5-MeO-PE-NMT
% max. 5-HT
log c
C

Figure 40: First experiments showing a biphasic dose-response curve.

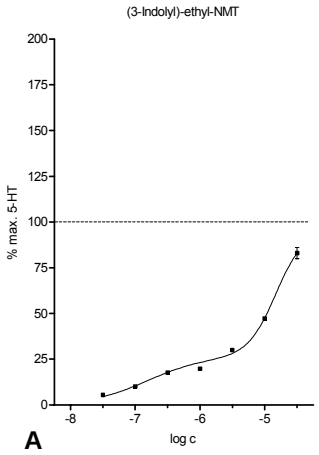
Biphasic IP accumulation dose-response curves of (**A**) (1-naphthyl)-ethyl-5-MeO-NMT (**288**), (**B**) 2,5-MeO-PE-NMT (**275**), and (**C**) (3-indolyl)-ethyl-5-MeO-NMT (**284**) in human 5-HT_{2A} cells. All curves have a high-dose response with a slope above unity.

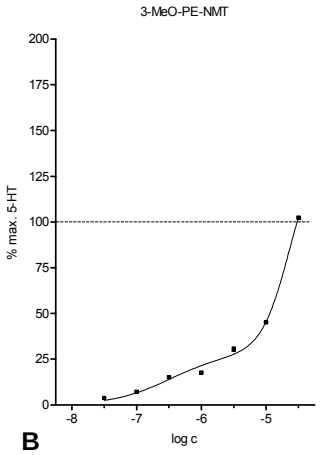
Steep slopes

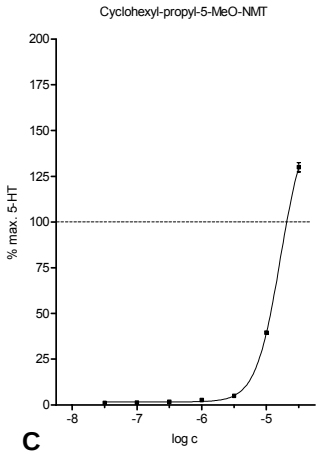
In those cases where the non-linear regression fitting procedure converged without a constraint on the slope of the high-dose response, values clearly above 1.0 were obtained. Where the Hill-$slope_2$ had to be constrained, the best fittings, as determined by inspection, were reached with values around 2.0. Therefore, constraints of either 1.5 or 2.0 were used in those cases. The Hill-$slope_1$ for the low-dose terms of curves with a distinct plateau between the two responses was always close to unity. In other cases with fitting ambiguities, a constraint of 1.0 had to be set for $slope_1$ in order to obtain reliable values for $EC_{50\text{-}1}$ of the low-dose response.

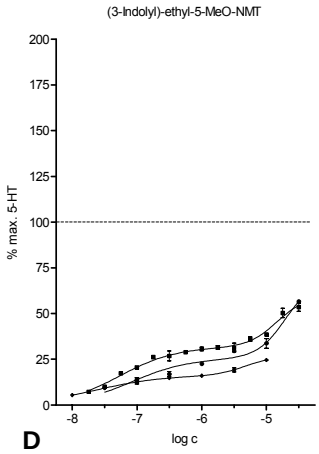
Over-maximal stimulation

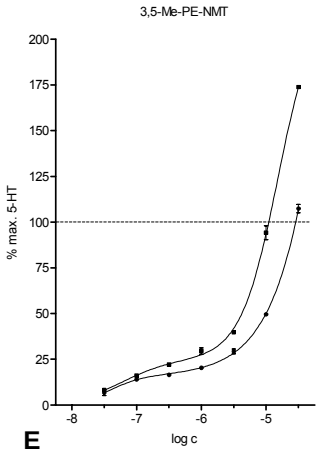
As can be seen in the curves (Figure 41), there was considerable inter-assay variability between the maximal stimulation of the test compounds for both the low-dose as well as the high-dose response. For example, the maximal response seen at 10 µM of 2,5-Me-PE-NMT (**196**) varied from 72% to 190% in six independent experiments. Additionally, the maximum stimulation of the low-dose and of the high-dose responses seem to be independent of each other as they were affected oppositely between different experiments, e.g. for 2,5-Me-PE-NMT (**196**) (Figure 41).

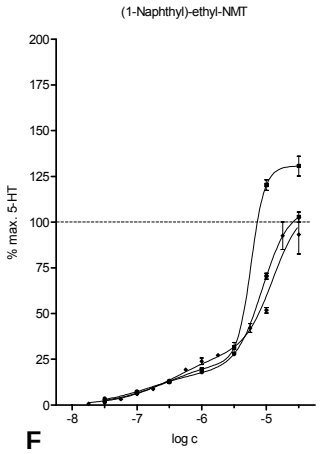

(3-Indolyl)-ethyl-NMT
% max. 5-HT
log c
A


3-MeO-PE-NMT
% max. 5-HT
log c
B


Cyclohexyl-propyl-5-MeO-NMT
% max. 5-HT
log c
C


(3-Indolyl)-ethyl-5-MeO-NMT
% max. 5-HT
log c
D


3,5-Me-PE-NMT
% max. 5-HT
log c
E


(1-Naphthyl)-ethyl-NMT
% max. 5-HT
log c
F

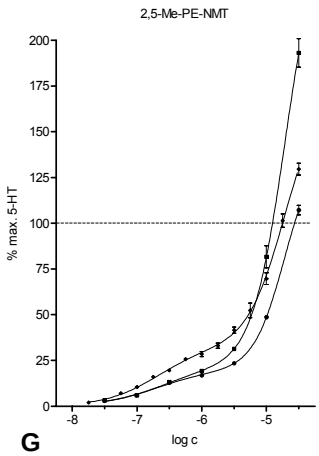

2,5-Me-PE-NMT
% max. 5-HT
log c
G

Figure 41: Biphasic dose-response curves.

Biphasic dose-response curves from several independent experiments for (3-indolyl)-ethyl-NMT (**283**) (**A**), 3-MeO-PE-NMT (**247**) (**B**), cyclohexylpropyl-5-MeO-NMT (**314**) (**C**), (3-indolyl)-ethyl-5-MeO-NMT (**284**) (**D**), 3,5-Me-PE-NMT (**273**) (**E**), (1-naphthyl)-ethyl-NMT (**287**) (**F**), and 2,5-Me-PE-NMT (**196**) (**G**) in human 5-HT_{2A} receptor cells. For most curves the high-dose response has a steep slope above unity.

Several lines of evidence suggest the authenticity of the over-maximal stimulation as it is seen in a subset of the high-dose activating compounds:

- The maximal stimulations observed for reference compounds like 5-HT, for a broad range of phenethylamine analogs, and for all tested simple tryptamines were in close agreement with literature values and never exceeded 100%.
- As seen from the activation curves the maximal high-dose activation never reached a plateau (with the single exception of (1-naphthyl)-ethyl-NMT (**287**) (Figure 41).
- Interpolation of the steep dose-response curves to higher concentrations strongly suggests the existence of over-maximal responses for even more of the tested compounds.

In some experiments data from the outer border of the cell-culture well-plates showed systematically decreased values and had to be excluded from data analysis. During some early assays the standard conditions were located at these positions and potentially erroneous, too-high stimulation values could have been drawn from these experiments. However, this effect cannot be responsible for the over-maximal stimulation phenomenon:

- Over-maximal stimulation was also seen in the following experiments where the positions of the standard condition had been moved.
- Over-maximal stimulations were also seen in plates not affected by a border-effect.
- The decrease in stimulation caused by the border-effect was maximally 25% in the relevant concentration range, usually less. An erroneous standardization based on these values could therefore not account for stimulations above 130% that were detected in those experiments.

Mechanism of the high-dose response

To further explore the nature of the unexpected high-dose stimulation, more experiments were performed. In particular, we examined whether this effect was mediated by the 5-HT_{2A} receptor or by other cellular targets, e.g. other receptors or second messenger systems. The following approaches were used:

- Antagonist inhibition experiments.
- Co-application of 5-HT.
- Testing ligands for common receptors.
- Inactivation of monoaminergic receptors.
- Utilization of other cell lines.

5-HT_{2A} antagonists

To test the ability of 5-HT_{2A} antagonists to block or shift the high-dose response, 5-HT_{2A} antagonists were co-applied with the test compounds. Although ketanserin (**48**), an antagonist with subnanomolar affinity, completely abolished the low-dose response at a concentration of 1 µM, it had no obvious effect on the isolated high-dose responses (Figure 42). The high-dose response is merely shifted downwards due to inhibition of the low-dose response. These results further supported the view that both responses are indeed independent phenomena and raised the question as to whether this effect was mediated by the 5-HT_{2A} receptor.

However, in later experiments unusually high concentrations of ketanserin (**48**), as well as of the potent, specific, and subtype-selective 5-HT_{2A} antagonist MDL 100,907 (**49**) did indeed substantially inhibit the response to (1-naphthylethyl)-NMT (**287**) and 2,5-Me-PE-NMT (**196**) in the human (Figure 43) as well as the rat (Figure 44) 5-HT_{2A} receptor cell line. Although these high doses of antagonists still did not completely block the high-dose response of the test compounds, the response to 32 µM 5-HT (**6**) was completely abolished.

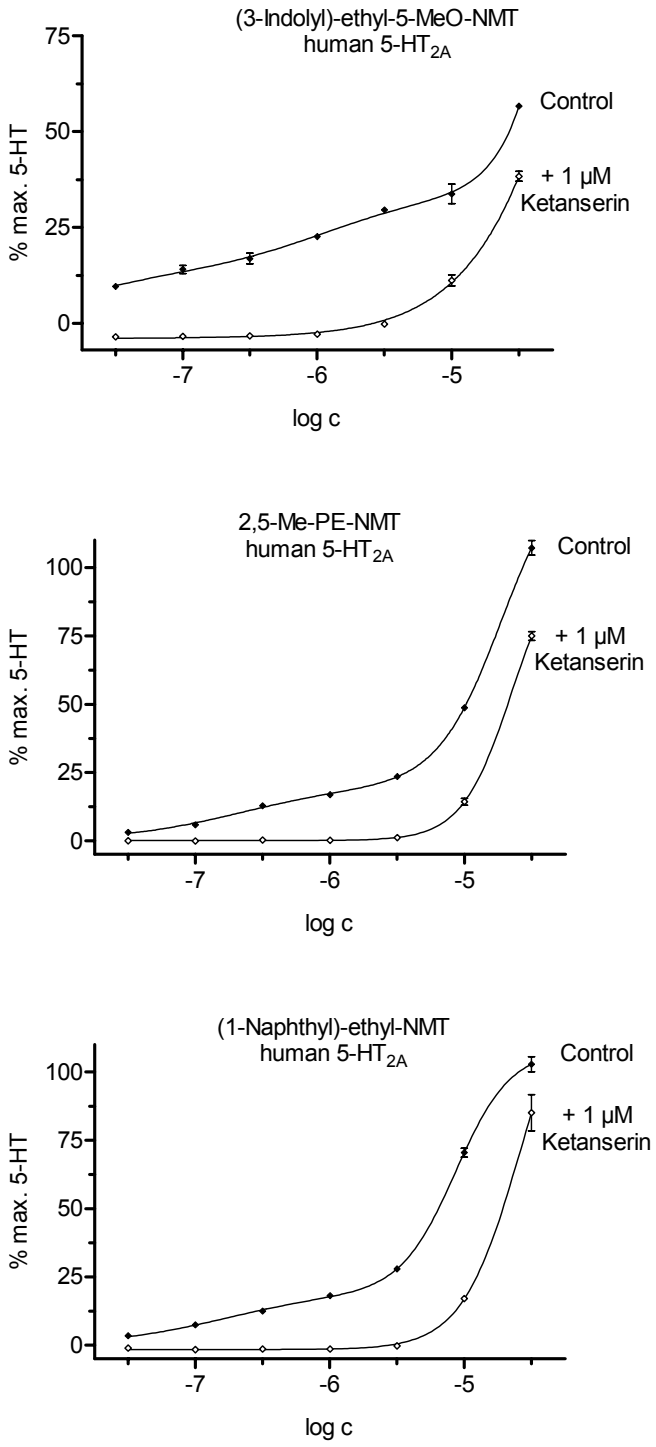


Figure 42: Biphasic dose-response curves in the presence of 1 µM ketanserin.

Dose-response curves for (3-indolyl)-ethyl-5-MeO-NMT (**284**) (**A**), 2,5-Me-PE-NMT (**196**) (**B**), and (1-naphthyl)-ethyl-NMT (**287**) (**C**) in the presence of 1 µM of the 5-HT_{2A} receptor antagonist ketanserin (**48**) in human 5-HT_{2A} cells. The antagonists completely blocks the low-dose response, but has no effect on the size of the high-dose response.

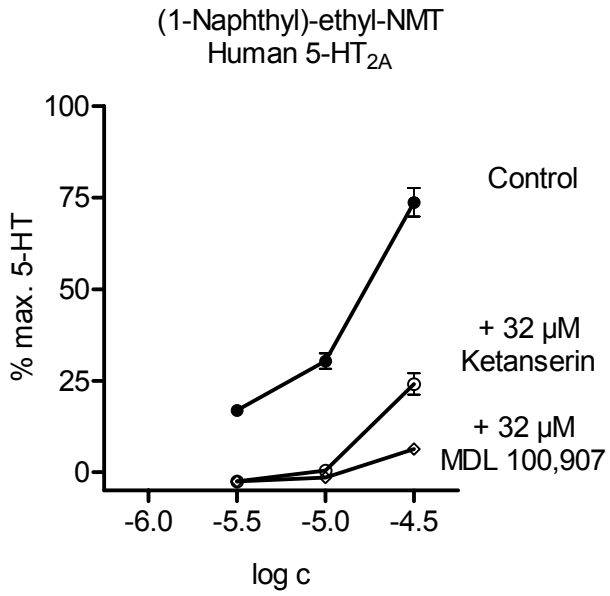


Figure 43: The effect of 32 µM ketanserin and MDL 100,907 (I).

Dose-response curves for (1-naphthyl)-ethyl-NMT (**287**) in the presence of 32 µM of the potent 5-HT_{2A} receptor antagonists ketanserin (**48**) or MDL 100,907 (**49**) in human 5-HT_{2A} cells.

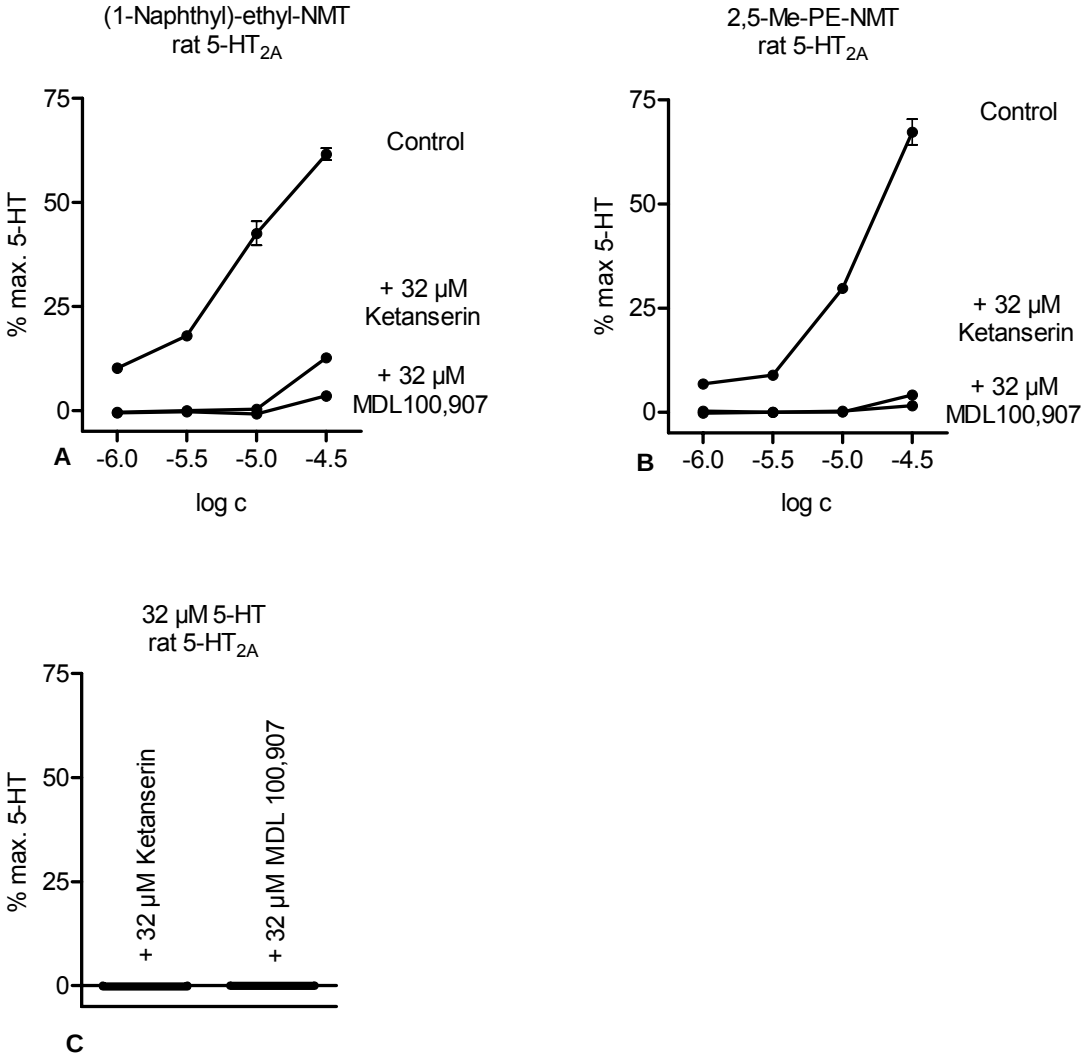


Figure 44: The effect of 32 µM ketanserin and MDL 100,907 (II).

Dose-response curves for 2,5-Me-PE-NMT (**196**) (**A**) and (1-naphthyl)-ethyl-NMT (**287**) (**B**) in the presence of 32 µM of the potent 5-HT_{2A} receptor antagonists ketanserin (**48**) or MDL 100,907 (**49**). In a control experiment the response to 32 µM 5-HT (**6**) could be completely blocked by both antagonists in rat 5-HT_{2A} receptor cells (**C**).

Co-application of 5-HT

In order to detect additive or even synergistic effects between 5-HT (**6**) and the test compounds, both compounds were co-applied in the next experiments. Such additive stimulations would be indicators for the involvement of other receptor types, other targets downstream of the receptor, or of regulatory receptor sites.

Therefore, different concentrations of 2,5-Me-PE-NMT (**196**) in the presence of 10 µM 5-HT (Figure 45 A), as well as different concentrations of 5-HT (**6**) in the presence 3.2 µM and 32 µM of 2,5-Me-PE-NMT (**196**) (Figure 45 B) were tested.

10 µM 5-HT (**6**) increased the response to 2,5-Me-PE-NMT (**196**) at lower concentrations (3.2 µM and 10 µM). However, the response did not reach the control level of 10 µM 5-HT (**6**) alone. At the higher concentration of 32 µM 2,5-Me-PE-NMT (**196**), the addition of 10 µM 5-HT (**6**) did not alter the response. In a similar experiment a broad range of test compounds was tested at a concentration of 32 µM in the presence of 0.1 µM 5-HT (**6**) on the rat 5-HT_{2A} cell line. The addition of 5-HT (**6**) did not alter the activation compared to the control condition by more than 10 percentage points. The obvious exceptions were compounds having 5-HT_{2A} receptor affinities clearly above 1 µM such as (cyclopentylmethyl)-NMT (**333**), (CH_2-COOMe)-NMT (**227**), dodecyl-NMT (**345**), octadecyl-NMT (**349**), (CH_2-$CONH_2$)-NMT (**293**), or cyanoethyl-NMT (**293**). For these compounds the activation at higher concentrations most probably reflects their low potency (partial) agonist nature instead of an unusual high-dose response.

In the 5-HT (**6**) dose-response experiment (Figure 45 B) 3.2 µM 2,5-Me-PE-NMT (**196**) caused a down- or rightwards shift of the 5-HT response curve. At higher concentrations of 32 µM 2,5-Me-PE-NMT (**196**) the 5-HT (**6**) concentration became less important in determining the activation, resulting in a nearly horizontal response.

These results show that at lower concentrations 2,5-Me-PE-NMT (**196**) behaves as would be expected for a classical partial agonist competing with 5-HT (**6**) for a common receptor site. However, at higher concentrations 2,5-Me-PE-NMT (**196**) acts as a 5-HT-independent full agonist. If the high-dose response had been caused by the simultaneous activation of other 5-HT receptors, then the addition of 5-HT (**6**) to a medium dose (3.2 µM or 10 µM) of 2,5-Me-PE-NMT (**196**) would be expected to result in an additive activation. That effect could not be demonstrated, however, thus making that mechanism unlikely.

Hypothetically, high concentrations of 2,5-Me-PE-NMT (**196**) could also activate different targets in the signaling cascade downstream of the receptor leading to IP accumulation. In that case the addition of a high dose of 2,5-Me-PE-NMT (**196**) to a medium or high concentration of 5-HT (**6**) would also be expected to result in an additive response. This mechanism is also unlikely because in the 5-HT (**6**) co-application experiments the observed response did not exceed the response caused by 2,5-Me-PE-NMT (**196**) alone. However, these experiments are consistent with the involvement of a second activation site in the 5-HT_{2A} receptor, an hypothesis that has been tested in detail and will be discussed below.

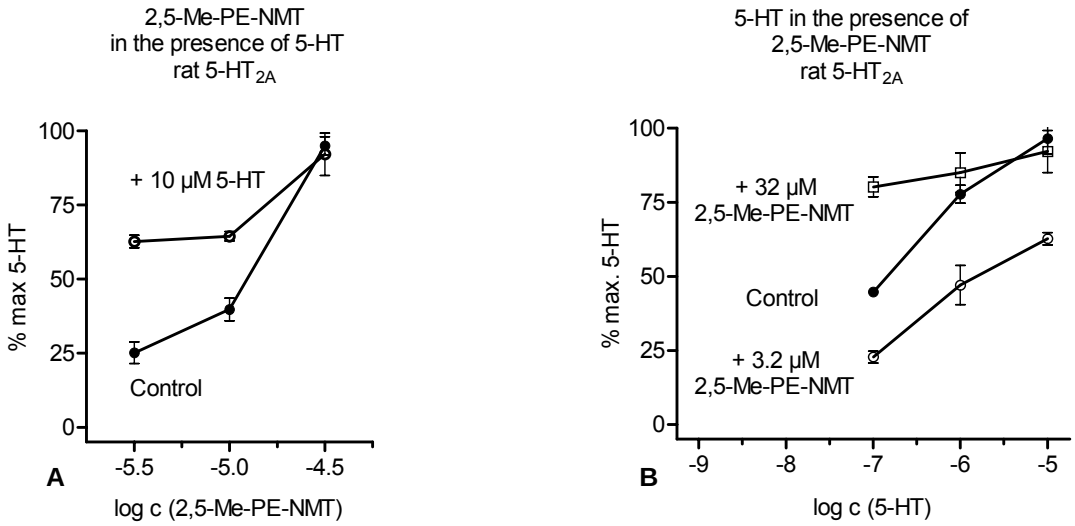


Figure 45: Co-application of 2,5-Me-PE-NMT and 5-HT.

(**A**) Different concentrations of 2,5-Me-PE-NMT (**196**) in the presence of 10 µM 5-HT.

(**B**) Different concentrations of 5-HT (**6**) in the presence of 3.2 µM and 32 µM of 2,5-Me-PE-NMT (**196**) in rat 5-HT_{2A} cells.

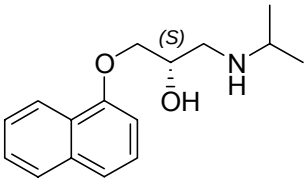
Various receptor ligands

Another possible mechanism of the high-dose response to exclude was the involvement of other receptor systems. Indeed, transfected mammalian cell lines often express a background of other neurotransmitter receptors. To check for the involvement of such receptors, a broad range of agonists and antagonists for monoamine neurotransmitters (Figure 47, Figure 48), sigma, and opioid sites (Figure 49) was tested for modifying the response to the test compounds (Table 3).

Neither did the agonists tested produce a response above background, nor did the antagonists tested block the response to the test compounds in the human 5-HT_{2A} receptor or in the rat 5-HT_{2A} receptor cell lines. As an exception, the co-administration of 1 µM propranolol (**51**) did indeed increase the response to 32 µM of 2,5-Me-PE-NMT (**196**) and (1-naphthyl)-ethyl-NMT (**287**) from about 75% to 90% (Figure 50). Propranolol (**51**) is an antagonist of β-adrenergic, 5-HT_{1A}, and 5-HT_{1B} receptors. The stimulation of PLC by one of these receptors would be surprising, especially when considering the preferential coupling of these receptors to adenylate cyclase instead of PLC. Instead, the potentiation by propranolol (**51**) might re-

flect a high-dose effect at the 5-HT_{2A} receptor caused by propranolol (**51**) itself, but that has not been tested in the absence of the other ligands.

The results of these experiments make the involvement of other serotonin (**6**), adrenergic, dopamine, histamine, acetylcholine, $GABA_A$, NMDA, opioid, or σ_1 sigma receptors in the high-dose response unlikely.



Propranolol (**51**)

Figure 46: Structure of the β-adrenergic receptor antagonist propranolol.

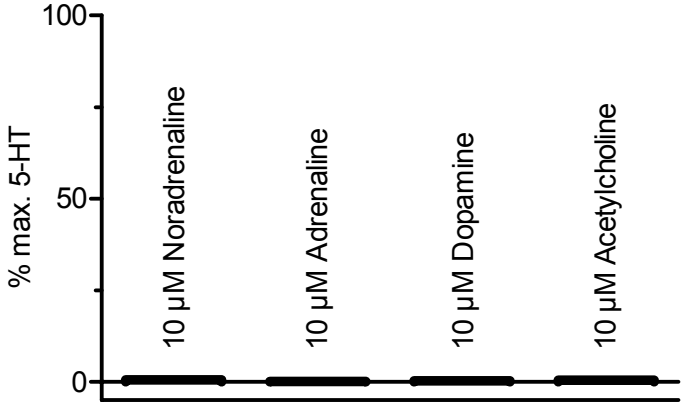


Figure 47: The effect of monoamine neurotransmitters on the IP response.

Noradrenaline, adrenaline, dopamine, and acetylcholine at a concentration of 10 µM did not elicit a response in human 5-HT_{2A} cells.

Table 3: The effect of receptor ligands on the high-dose response.

The influence of various neurotransmitter receptor ligands on IP accumulation, either alone or in combination with compounds from this study. The receptor sites at which these compounds are acting as well as their agonistic or antagonistic action are listed.

Ligand	Conc.	Receptor	Action	Effect	Figure
5-HT	10 µM	5-HT	agonist	no effect on high-dose response	Figure 45
Ketanserin	1 - 32 µM	5-HT_{2A} (5-HT_{2C}, 5-HT_{2B}, 5-HT_{1D}, α, D)	antagonist	no stimulation, inhibition of high-dose response at 10 µM	Figure 42 Figure 43 Figure 44 Figure 48
MDL 100,907	1 - 32 µM	5-HT_{2A} (5-HT_{2C}, α_1, σ_1)	antagonist	no stimulation, inhibition of high-dose response at $\geq$ 10 µM	Figure 43 Figure 44
Noradrenaline	10 µM	α, β	agonist	no stimulation	Figure 47
Adrenaline	10 µM	α, β	agonist	no stimulation	Figure 47
Prazosin	1 µM	α_1	antagonist	no effect on high-dose response	Figure 50
Propranolol	1 µM	β, 5-HT_{1A}, 5-HT_{1B}	antagonist	slight increase of high-dose response	Figure 50
Dopamine	10 µM	D	agonist	no stimulation	Figure 47
Haloperidol	1 µM	D, 5-HT_{2A}, α_1, σ_1	antagonist	no effect on high-dose response, no stimulation	Figure 49
Histamine	1 µM	H	agonist	no stimulation	Figure 48
Diphenhydramine	1 µM	H_1	antagonist	no effect on high-dose response	Figure 48
Acetylcholine	10 µM	mACh, nACh	agonist	no stimulation	Figure 47
Pilocarpine	1 µM	mACh	agonist	no stimulation	Figure 48
Atropine	1 µM	mACh	antagonist	no effect on high-dose response	Figure 48
Pregnenolone	1 µM	σ_1, $GABA_A$, NMDA	agonist / positive modulator	no effect on high-dose response, no stimulation	Figure 49
Naloxone	1 µM	σ_1, μ, δ, κ	antagonist	no effect on high-dose response, no stimulation	Figure 49

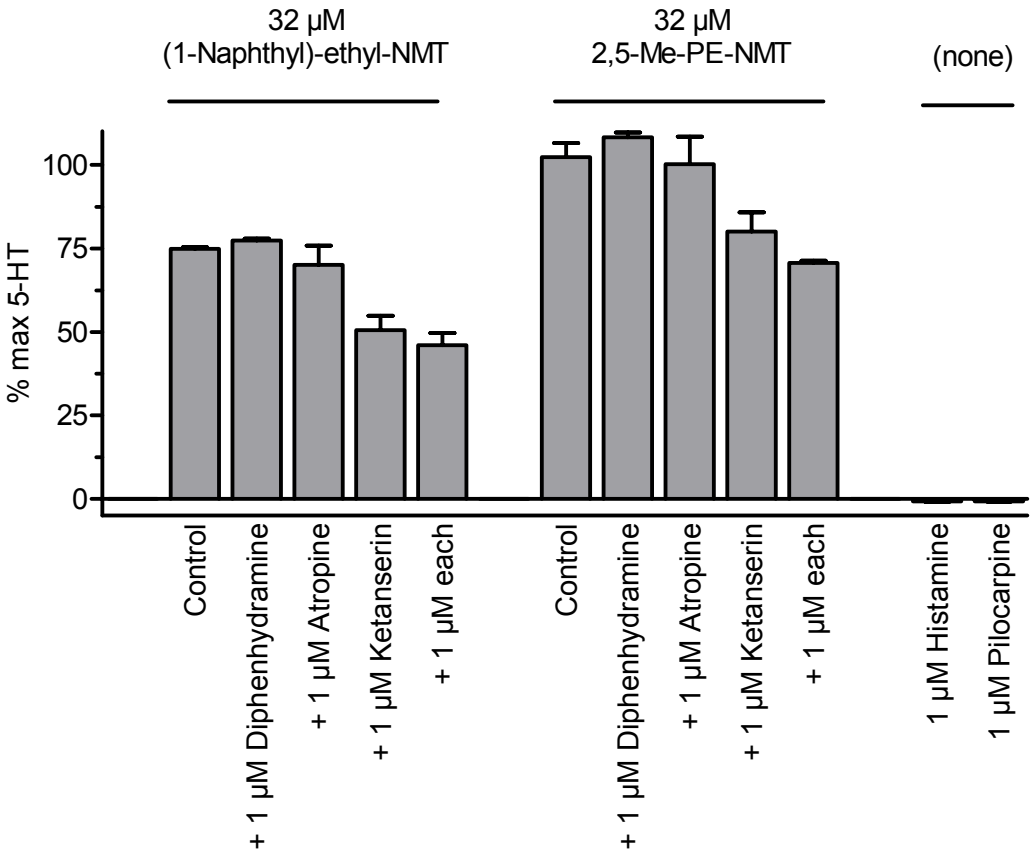


Figure 48: The effect of monoamine receptor ligands on the IP response.

The antagonists diphenhydramine (H_1) and atropine (mACh) at concentrations of 1 µM did not block the response to 32 µM (1-naphthyl)-ethyl-NMT (**287**) or 2,5-Me-PE-NMT (**196**). 1 µM Ketanserin (**48**) (5-HT_2, 5-HT_{1D}, α, D) caused a slight inhibition, probably due to elimination of the low-dose response. The agonists histamine and pilocarpine at concentrations of 10 µM did not elicit a response in human 5-HT_{2A} cells.

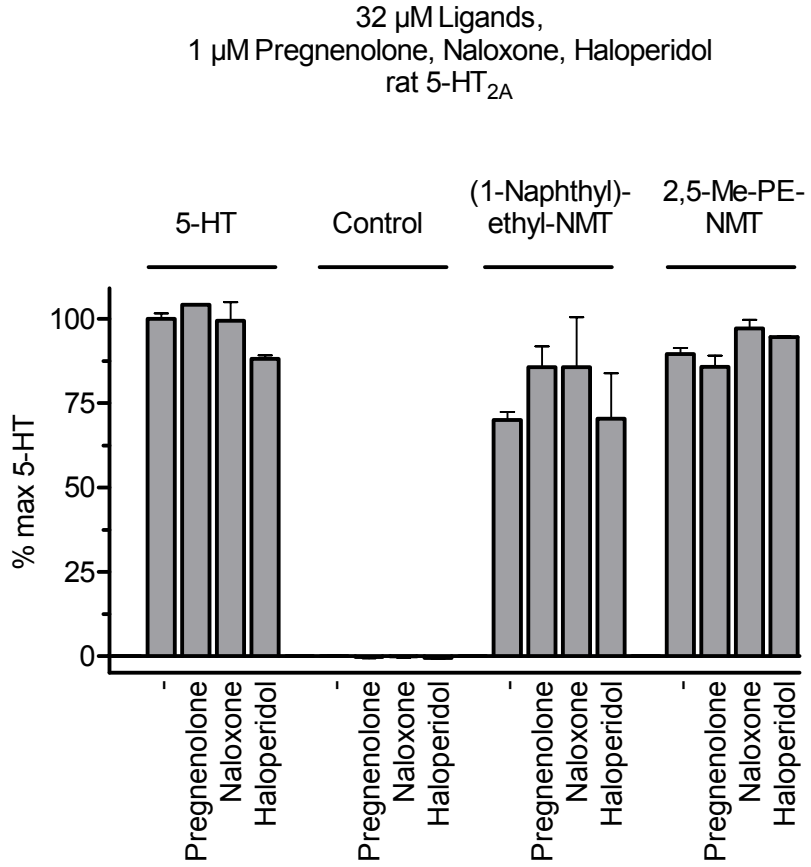


Figure 49: The effect of sigma$_1$ receptor ligands on the IP response.

The non-specific σ_1 receptor ligands pregnenolone (σ_1, $GABA_A$, NMDA), naloxone (σ_1, µ, δ, κ), and haloperidol (σ_1, D, 5-HT_{2A}, α_1) at concentrations of 1 µM did not substantially alter the response to 32 µM 5-HT, (1-naphthyl)-ethyl-NMT (**287**), or 2,5-Me-PE-NMT (**196**) nor did they elicit a response on their own in rat 5-HT_{2A} cells.

Monoamine receptor inactivation

In the following experiments phenoxybenzamine (PBZ, **52**), an irreversible receptor antagonist for many monoamine receptors, has been used as a tool for receptor inactivation (Figure 51). A concentration of 1 µM PBZ (**52**) has previously been shown to completely block the response to 10 µM 5-HT (**6**) in the same rat 5-HT_{2A} cell line used in this study [163].

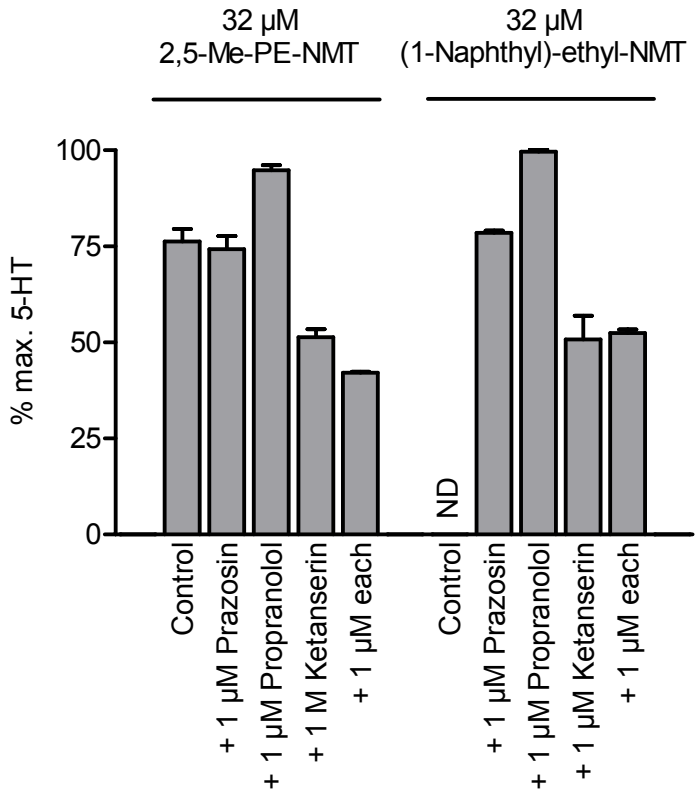


Figure 50: The effect of monoamine receptor antagonists on the IP response.

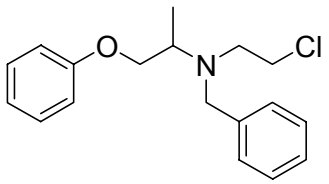
The effect of adrenergic antagonists and ketanserin (**48**) on the response to 32 µM 2,5-Me-PE-NMT (**196**) and (1-naphthyl)-ethyl-NMT (**287**) in rat 5-HT_{2A} cells. The α_1-adrenergic antagonist prazosin at a concentration of 1 µM of did not change the responses to the test compounds. The non-specific β, 5-HT_{1A}, and 5-HT_{1B} receptor antagonist propranolol (**51**) at a concentration of 1 µM caused an increase in activation. 1 µM ketanserin (**48**) (5-HT_2, 5-HT_{1D}, α, D) caused a slight inhibition, probably due to elimination of the low-dose response.

1 µM of PBZ (**52**) only moderately lowered the response to 32 µM (1-naphthyl)-ethyl-NMT (**287**) and 32 µM 2,5-Me-PE-NMT (**196**) from 151% and 133% to 110% and 118%, respectively. A substantial block of the response to 15% and 5%, respectively, was only seen for PBZ (**52**) at the very high concentrations of 100 µM (Figure 52). The action of 1 µM PBZ (**52**) was similar in magnitude to the decrease caused by 1 µM of the 5-HT_{2A} antagonist ketanserin (**48**). Most probably this inhibition similarly reflects the block of the low-dose response without a modification of the high-dose part of the response. PBZ (**52**) as an irreversible receptor antagonist is assumed to act by covalently binding to the antagonist binding site of monoamine receptors. Therefore, effects similar to the reversible 5-HT_{2A} antagonists tested are not surprising. Interestingly, both types of antagonist share the ability to block the high-

dose response at extremely high concentrations, 32 µM for the reversible antagonists ketanserin (**48**) and MDL 100,907 (**49**), and 100 µM for the irreversible antagonist PBZ (**52**). Because PBZ (**52**) is assumed to irreversibly block a broad range of receptors, especially monoaminergic neurotransmitter receptors, these results further supported the view that non-5-HT_{2A} monoaminergic receptors are not involved in the high-dose response. Instead, these results further supported the possibility of 5-HT_{2A} receptor activation by a non-standard mechanism, independent of the classical agonist and antagonist binding sites.

Other cell lines

Although the above experiments suggested a 5-HT_{2A} receptor mediated mechanism for the high-dose response, only testing other cell lines could give more conclusive answers. Therefore, in addition to the human 5-HT_{2A} receptor transfected human lung carcinoma cell line A549, the A549 wild type cell line and the rat 5-HT_{2A} receptor transfected NIH-3T3 mouse fibroblast cell line were tested. In both independent 5-HT_{2A} transfected cell lines, all compounds tested gave qualitatively similar results. In particular, in both cell lines comparable monophasic or biphasic curves, respectively, and maximal stimulations above 100% were observed (Figure 53, Figure 54, Table 9, and data not shown here). Although in both transfected cell-lines a robust activation 20 to 25-fold over basal was detected, the wild-type cell line A549 showed no activation above background after stimulation with 10 µM 5-HT, 32 µM 2,5-Me-PE-NMT (**196**), 32 µM (1-naphthyl)-ethyl-NMT (**287**), or 32 µM 3,5-Me-PE-NMT (**273**) (Figure 55). These results are again suggesting the direct involvement of the 5-HT_{2A} receptor in both types of response, the low-dose as well as the unusual high-dose response.



PBZ (**52**)

Figure 51: Chemical structure of phenoxybenzamine (PBZ).

PBZ (**52**) is an irreversible receptor antagonist and has been used as a tool to inactivate monoaminergic receptors.

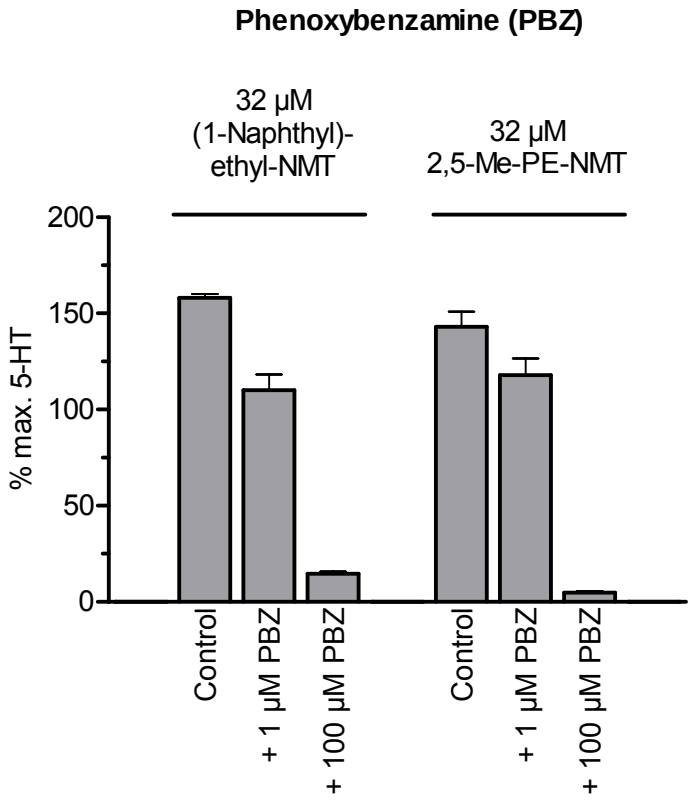


Figure 52: The effect of phenoxybenzamine (PBZ) on the IP response.

The effect of 10 µM and 100 µM of the irreversible inhibitor phenoxybenzamine (PBZ, **52**) on the IP response to 32 µM (1-naphthyl)-ethyl-NMT (**287**) and 2,5-Me-PE-NMT (**196**) in human 5-HT_{2A} cells.

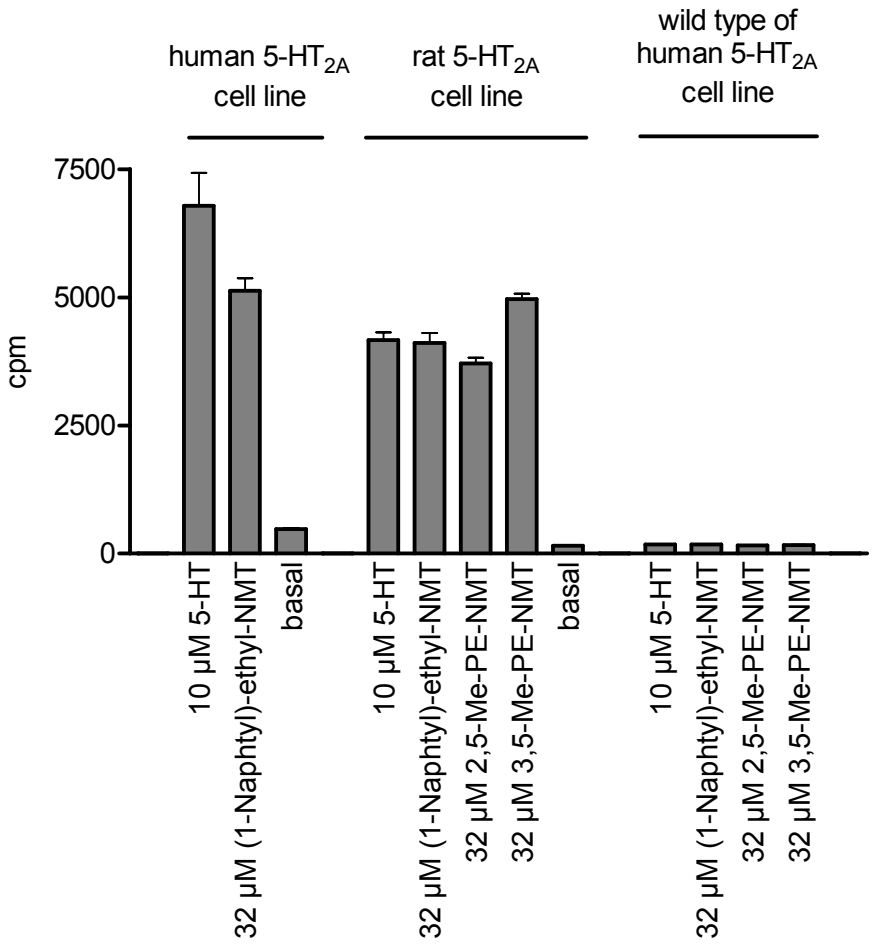


Figure 53: Human 5-HT_{2A} receptor, rat 5-HT_{2A} receptor, and wild type cells.

The effect of stimulation with 10 µM 5-HT, 32 µM (1-naphthyl)-ethyl-NMT (**287**), 32 µM 2,5-Me-PE-NMT (**196**), and 32 µM 3,5-Me-PE-NMT (**273**) on the IP response in the human 5-HT_{2A} receptor transfected A549 cell line, the rat 5-HT_{2A} receptor transfected NIH-3T3 cell line, and the untransfected A549 cell line.

Table 4: Calculated parameters for the dose response curves of Figure 54.

EC_{50}, Hill slope, and maximal activation data for the dose response curves from Figure 54. The wild type, the human 5-HT_{2A}, and the rat 5-HT_{2A} transfected receptor cell lines were stimulated with 3,5-Me-PE-NMT (**273**). Hill slopes had to be set constant for the curve fitting procedure as explained in the text.

		Low-Dose Response			High-Dose Response	
Receptor	**Cell Line**	**EC_{50}**	**Hill Slope**	**% max 5-HT**	**Hill Slope**	**% max 5-HT**
untransfected	A549 wild type	-	-	0%	-	0%
human 5-HT_{2A}	A549-h5-HT_{2A}	65 nM	1.0	25%	1.5	164%
rat 5-HT_{2A}	NIH-3T3-r5-HT_{2A}	68 nM	1.0	22%	1.5	107%

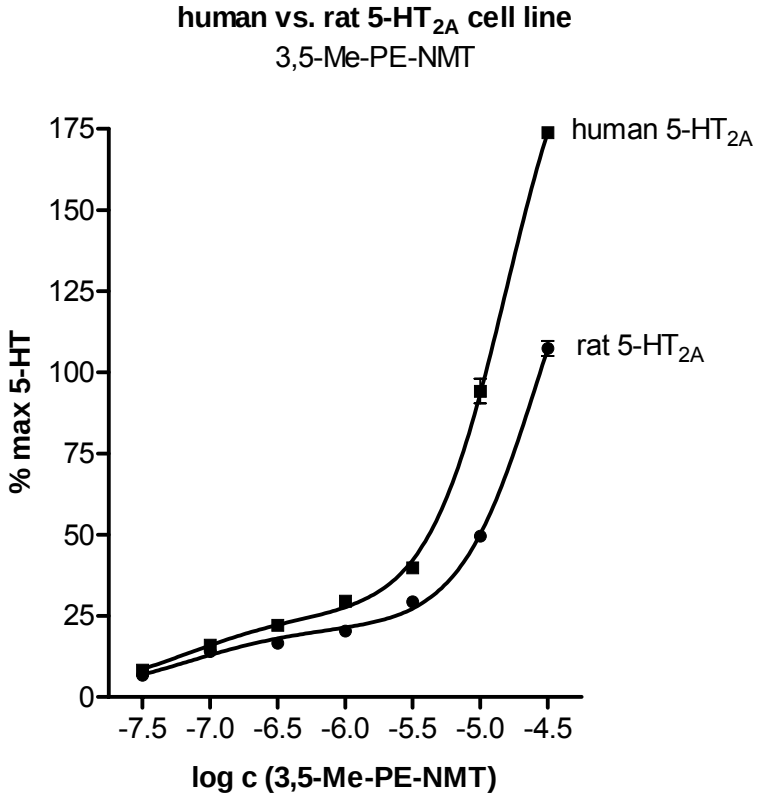


Figure 54: Over-maximal stimulation: human versus rat 5-HT_{2A} receptor cells.

Biphasic and over-maximal dose-response curves of 3,5-Me-PE-NMT (**273**) in the human 5-HT_{2A} receptor transfected A549 cell line and in the rat 5-HT_{2A} receptor transfected NIH-3T3 cell line.

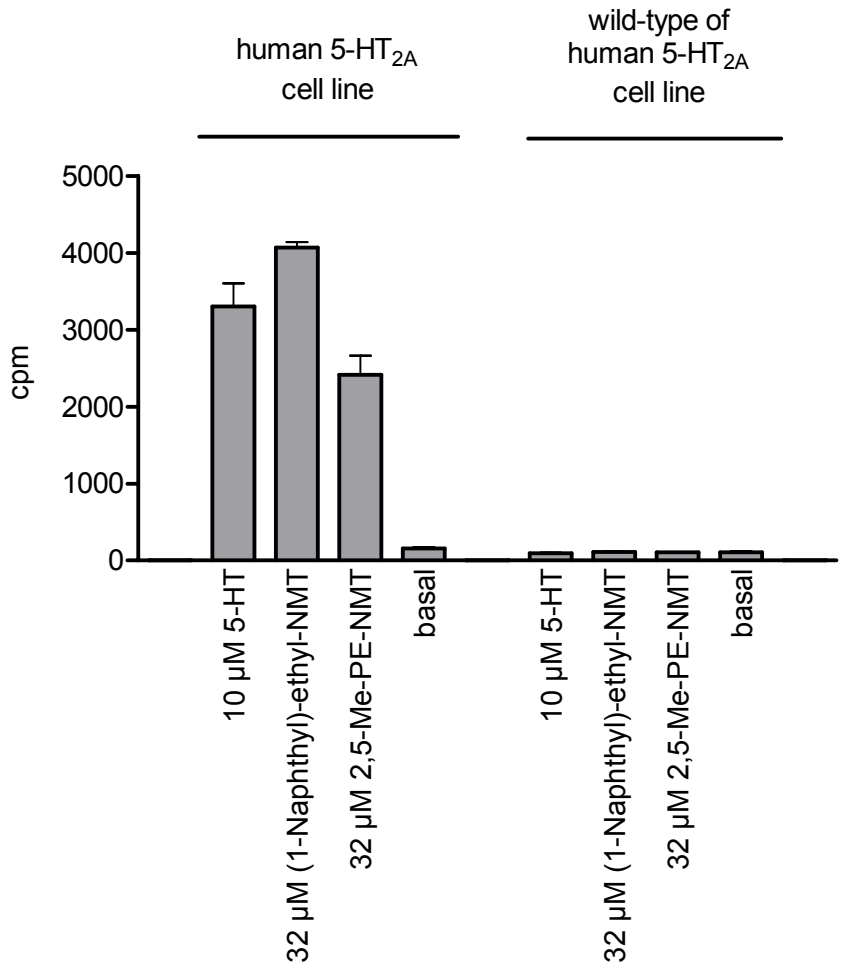


Figure 55: Human 5-HT_{2A} receptor versus wild type cells.

The effect of stimulation with 10 µM 5-HT, 32 µM (1-naphthyl)-ethyl-NMT (**287**) and 32 µM 2,5-Me-PE-NMT (**196**) on the IP response in human 5-HT_{2A} cells and in the untransfected wild type cell line A549.

Discussion of the high-dose mechanism

A hypothesis about the mechanism of the high-dose response must explain all of the following experimental results:

- The high dose response has not been seen for a broad range of structurally diverse reference compounds, but only for a subset of bulky methyl-alkyltryptamine from this study.

- The high dose response was independent of the standard low-dose (partial) agonistic response of the tested compounds.
- The high dose response had a steep dose response curve with a Hill-slope of around two.
- The high dose response sometimes resulted in over-maximal stimulation at the highest doses tested, in other curves there was a clear trend to over-maximal responses.
- The high dose response was blocked only by extremely high concentrations of reversible and irreversible 5-HT_{2A} antagonists.
- The high dose response was not affected by antagonists for other receptors (except propranolol (**51**) which increases the response).
- The high dose response was not affected by co-administration of 5-HT (**6**) and agonists for other receptors.
- The high dose response was not blocked by the non-specific irreversible antagonist PBZ (**52**) at a concentration of 1 µM.
- The high dose response was seen in two unrelated cell lines transfected with two different 5-HT_{2A} receptor homologs.
- There was no stimulation of the cell lines by a variety of neurotransmitter receptor agonists.
- There was no stimulation above background by 5-HT (**6**) and other neurotransmitter receptor agonists in 5-HT_{2A} receptor untransfected cell lines.

Exclusion of possible high-dose mechanisms

Based on the above observations several explanations can be ruled out. These will be discussed in detail in the following section.

One could argue that the applied concentrations of 10 µM to 32 µM are somehow "unphysiological" conditions and that the observed effects simply represent non-specific interactions with membranes or proteins. But this view is not supported by the following facts:

- The concentrations used are not exceptionally high compared to commonly used therapeutic drug concentrations. For example, the analgetically effective plasma-concentration of salicylic acid of 30 - 110 µg/ml corresponds to a molar concentration of 217 - 796 µM.
- The high-dose response is very specific for a subset of the tested compounds and is susceptible to minor changes of the molecular structures. Additionally, there is no obvious relationship between high-dose activity and overall lipophilicity.

The possibility that the high-dose response is caused by traces of synthetic precursors such as NMT (**212**) and 5-MeO-NMT (**208**) can be ruled out. In that case a biphasic response with a maximum of 69% and 98%, respectively, and two Hill-slopes of 1.0 would be expected. Additionally, such a biphasic response would be completely eliminated by relatively low concentrations of 5-HT_{2A} antagonists and by the non-specific irreversible antagonist PBZ (**52**).

It is also unlikely that the high-dose response is caused by direct activation of the PLC second messenger system independent of the receptor. In that case the wild-type cell line would also show activation. This argument is based on the reasonable assumption that the second messenger system is not down-regulated below the detection threshold in non-transfected cells. This postulate could be further verified in the future using cell lines that over-express unrelated receptors which activate PLC.

The tested compounds could activate an as yet unidentified receptor or other signaling pathways, leading to PLC stimulation. This hypothesis cannot explain the requirement for the 5-HT_{2A} receptor as shown in the wild-type cell line experiments.

Another conceivable mechanism could be a receptor independent activation of the second messenger system after selective intracellular uptake of the ligands by a 5-HT_{2A} mediated mechanism, e.g. through receptor internalization. In this case the co-application of 5-HT_{2A} ligands would be expected to compete for the uptake process. However, 5-HT (**6**) as well as antagonists at relatively high concentrations did not modify the high dose response.

Inhibition of receptor desensitization or of receptor internalization would be expected to cause an enhanced response in the IP accumulation assay [118]. Indeed, such an effect has been seen in cells with disrupted internalization of the 5-HT_{2A} receptor upon stimulation with 5-HT (**6**) [296]. This mechanism can only enhance existing responses, however, and is therefore dependent on receptor activation. However, there exist high-dose compounds that are pure antagonists at lower concentrations. Additionally, the high-dose response is insensitive to co-application of 5-HT (**6**) as well as antagonists at relatively high concentrations. This fact makes a simple potentiation of an existing response implausible.

It is also unlikely that the high-dose response is caused by some kind of serotonergic self-stimulation during the 30 min incubation period. Such a mechanism would be inhibited by 5-HT_{2A} antagonists.

Any mechanism relying on transcriptional regulation can most probably be excluded because the incubation time did not exceed 30 min, a time usually considered too short for effects caused by altering *de novo* protein synthesis.

The observed high-dose response most probably does not result from a direct interaction with the assay procedure. The IP accumulation assay used measures the concentration of accumulated IP by fractional elution from a strongly basic anion exchange resin. The test ligands are removed with the buffer after incubation, so that only negligible amounts of less

than the maximally added 50 - 200 ng could have been present during permeabilization and IP fractional elution. To explain erroneously increased values, these trace amounts would either have to hydrolyze [^{3}H]phosphoinositides during the acidic cell permeabilization overnight at 4 °C, enhance adsorption of undegraded [^{3}H]phosphoinositides to the resin, or improve an incomplete adsorption of IP to the resin. Such an effect had to be counteracted by high concentrations of 5-HT_{2A} antagonists and the effect had to be very specific with respect to minor structural changes of the test compounds. Such a scenario seems highly unlikely. Also, the absence of a signal in the wild-type cell line clearly speaks against an assay artifact.

The free Gα subunit has a very low GTPase activity and external GTPase activator proteins (GAP) are needed to terminate its activation by hydrolysis of the G_α bound GTP to GDP. Such GAP activity resides in PLCβ as well as in a large class of regulators of G protein signaling proteins (RGS). A compound blocking the GTPase activation would lead to an increase in duration of the response and thereby to an increase in IP accumulation. However, the initial activation still had to be receptor mediated and thereby sensitive to antagonists. This is not in accordance with the data from the wild-type cell-lines and the antagonist experiments.

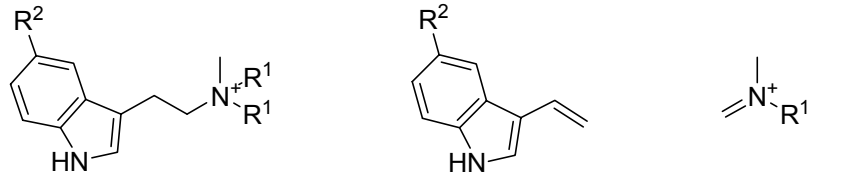
In summary, the following explanations for the high-dose response can be ruled out:

- "Extreme" concentrations
- Contamination of ligands with precursors
- Direct action on the second messenger system
- Stimulation of other receptors or pathways
- Receptor mediated intracellular uptake
- Desensitization or inhibition of internalization
- Cellular self stimulation
- Transcriptional regulation
- Assay artifacts
- Anti-GAP activity.

Trace impurities

Several trace impurities could be detected in the HPLC analysis and the ESI MS spectra of the tested ligands, most notably the quaternary ammonium salts resulting from over-alkylation of the *N*-methyltryptamine. Also 3-vinylindoles from Hoffmann eliminations of the quaternary tryptamines, and iminium cations from retro-Mannich reactions of the tertiary tryptamines were observed, but it is not clear if the latter species are analysis artifacts. Both ana-

lysis methods, HPLC-UV_{260} and ESI MS, are more sensitive for these types of compounds compared to the test ligands: UV_{260} detection used in the HPLC analysis overestimates the real amount of aromatically substituted impurities due to their additional chromophore.
ESI MS with positive ionization overestimates signals of the permanently charged quaternary species, as judged from comparison with the HPLC-UV_{260} data. It should also be noted that some of the compounds with the most prominent high dose-response, 3,5-Me-PE-NMT (**273**) and 2,5-Me-PE-NMT (**271**), had ESI MS signals of the putative quaternary impurities barely above the background signal. Additionally, alkylamines synthesized by a different route exhibited comparable effects in another study [69].



53 Quaternary Tryptamines (M_{quat}^+)

54 3-Vinylindoles (vinylindole)

55 Schiff Bases (M_{imine}^+)

Figure 56: Trace impurities or analysis artifacts detected by ESI MS.

The following compounds could be detected by ESI MS in many of the tested ligands: the quaternary tryptamines **53** (M_{quat}^+) originating from over-alkylation, 3-vinylindoles **54** (vinylindole) from Hoffmann elimination of quaternary tryptamines, and the Schiff bases of structure **55** (M_{imine}^+) from a retro-Mannich reaction of tertiary tryptamines. It is not clear whether the latter species are analysis artifacts.

Non-competitive modulation

A hypothesis about the mechanism of the high-dose activation must explain the following two conflicting observations: On the one hand the effect is dependent on the 5-HT_{2A} receptor as demonstrated by the experiments in wild-type cells, but on the other hand the effect is independent of activation or inhibition by classical receptor ligands, as shown by the antagonist and co-application experiments.

In a recent publication biphasic dose-response curves similar to those obtained in the current work were obtained for the beta-blockers pindolol and alprenolol at β_1-adrenergic receptors in a [^{3}H]cAMP accumulation assay [26]. In other functional assays using alkaline phosphatase

and luciferase as reporter genes it was shown that the activation in these cells by several compounds was resistant to inhibition by classical antagonists such as CGP 20712A. As an explanation the existence of an independent second agonistic binding site of the β_1 receptor has been postulated, at which classical agonists like pindolol and alprenolol, as well as classical antagonists like carvedilol or CGP 12177, activate the receptor at higher concentrations. Indeed, the existence of "allosteric", "non-competitive", "regulatory", or "modulatory" binding sites, separated from the classical ligand binding sites, have been demonstrated for many G-protein coupled receptors (for reviews see: [55, 236]) (Table 5, Figure 57).

5-HT receptor modulators

Several modulators of 5-HT receptors have been described. The tetra-peptide 5-HT-moduline at picomolar concentrations increased 5-HT (**6**) binding to 5-HT_{1B} and 5-HT_{1D} receptors, but decreased the number of receptors [249]. The lipophilic compound oleamide (oleic acid amide) increased 5-HT (**6**) signaling through 5-HT_{1A} [38], 5-HT_{2A} [38, 138, 276], and 5-HT_{2C} [138] receptors and decreased 5-HT (**6**) signaling through 5-HT_7 receptors [38, 127, 276]. Remarkably, oleamide potentiated 5-HT_{2A} mediated responses up to 170%, similar to maximal values obtained in the current study [138]. However, the relevance of the effects of oleamide under physiological conditions recently has been questioned [68]. The amphiphilic compound PNU-69176E positively modulated the 5-HT_{2C} receptor in a subtype selective manner [139]. Amphipathic lipidic compounds such as oleic acid, lysophosphatidylcholine, and the detergent CHAPS (3-[(3-cholamidopropyl)-dimethylammonio]-propane sulfonic acid) have been shown to modulate the 5-HT_{7A} receptor [11].

Table 5: Selected modulators of G-protein coupled receptors.

Legend: ↑: positive modulation; ↓: negative modulation. For a review see: [55].

Neurotransmitter	Receptor	Modulator
-	all GPCR	Na^+ ↓, SCH-202676 ↓ [73]
Adenosine	A_1	PD 81,723 ↑, PD 117,975, ATL525 ↑[74]
	A_{2A}	amilorides
	A_3	VU5455, VU8504
Noradrenaline	α_1	amilorides, benzodiazepines
	α_{2A}, α_{2B}	amiloride ↓
	α_{2D}	agmatine
Adrenaline	β_1	pindolol ↑, alprenolol ↑, carvedilol ↑, CGP 12177 ↑
Calcium	CaR	NPS 467, NPS 568, L-amino acids
Chemokine	CXCR3	IP-10, I-TAC
	CCR5, CXCR4	trichosanthin
	CCR1, CCR3	UCB35625
Dopamine	D_1	Zn^{2+}
	D_2, D_4	amilorides, Zn^{2+}
	D_2	Pro-Leu-Gly-amide (LPG) and analogs [66, 196, 268]
Endothelin	ET_A	Aspirin, salicylic acid
GABA	$GABA_B$	CGP7930, CGP13501
Glutamate	$mGluR_1$	CPCCOEt, Ro 01-6128 [156], Ro 67-7476 ↑ [156], Ro 67-4853 ↑ [156], Bay36-7629
	$mGluR_5$	MPEP, CPPHA [213]
Muscarinic acetylcholine	m_1 - m_5	gallamine ↓, alcuronium ↓, brucines ↑, dimethyl-W48. staurosporine↑, strychnine ↓
Neurokinin	NK1	heparin
Purine	P_{2Y1}	2,2'-pyridylsatogen tosylate
Prostaglandin	PGE_2	L-171837 ↓
5-HT	$5\text{-}HT_{1B/1D}$	5-HT-moduline ↓ (binding sites), ↑ (affinity) [249]
	$5\text{-}HT_{2A}$	oleamide ↑ [38, 138, 276], *N*-cyclopropyl-oleamide↓ [38]
	$5\text{-}HT_{2C}$	oleamide ↑ [138], PNU-69176E ↑↑ [139]
	$5\text{-}HT_{1A}$	oleamide ↑ [38], *N*-cyclopropyl-oleamide ↓ [38]
	$5\text{-}HT_3$	Δ9-THC ↓ [2]
	$5\text{-}HT_7$	oleamide ↓ [38, 127, 276]
	$5\text{-}HT_{7A}$	amphipathic lipids [11]

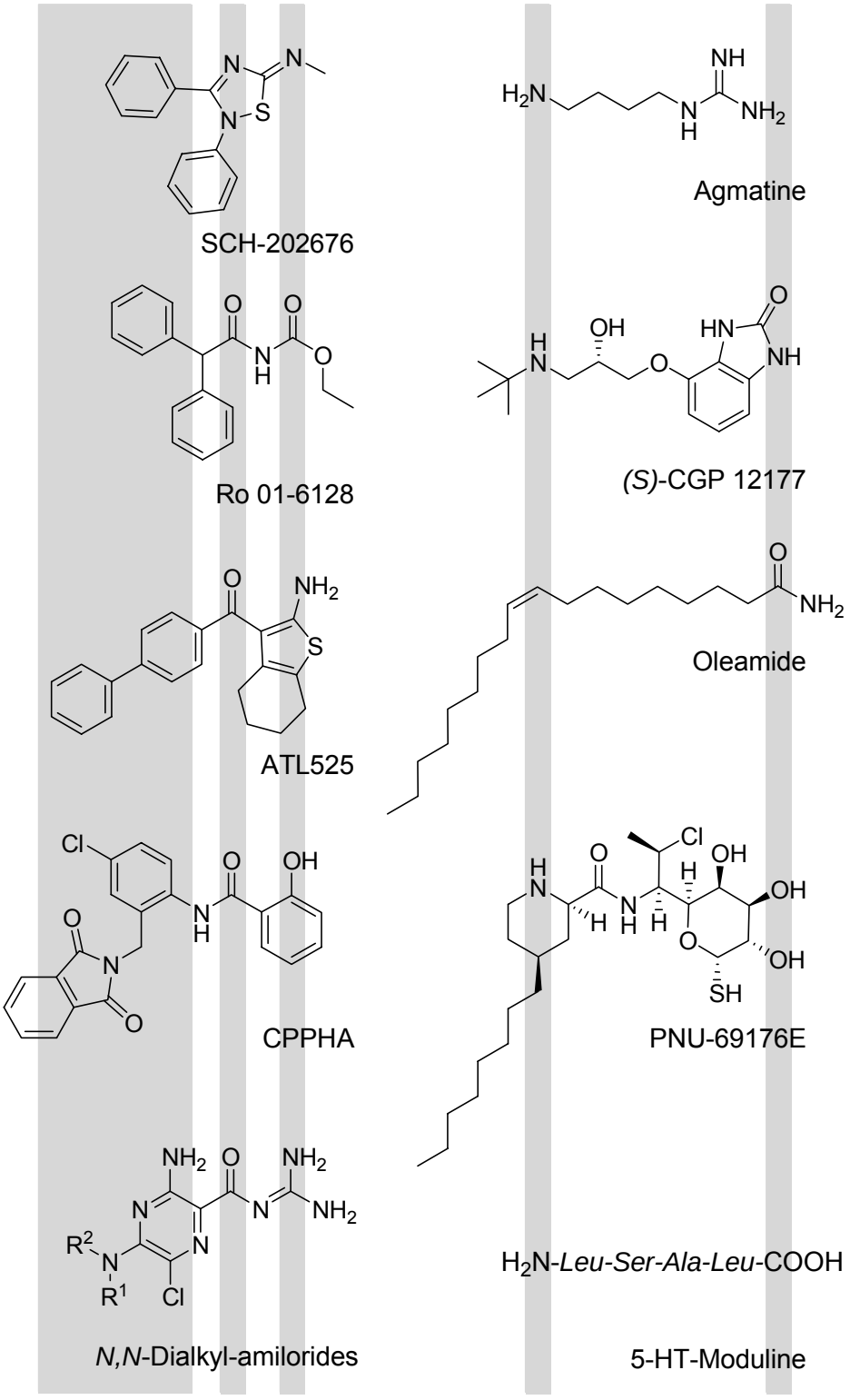
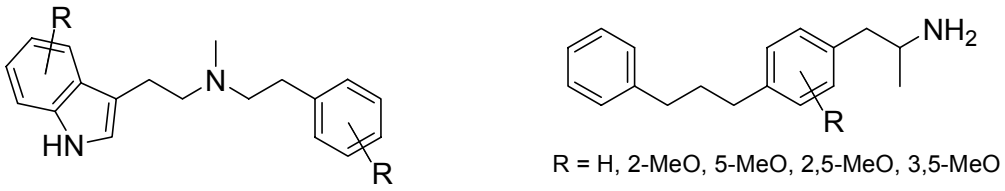


Figure 57: Selected chemical structures of receptor modulators.

SCH-202676 (non-specific), Ro 01-6128 (mGlu1), ATL525 (A_1), CPPHA ($mGluR_5$), 5-(*N,N*-dialkyl)-amilorides (α, D), agmatine (α_{2D}), *(S)*-CGP 12177 (β_1), oleamide (5-HT), PNU-69176E (5-HT_{2C}), and 5-HT-moduline (5-$HT_{1B/1D}$). The gray shading indicates common structural elements.

The activation of G-protein coupled receptors through allosteric or non-competitive binding sites in the absence of ligands for the classical agonist binding site, as seen in this study, has also been observed before. For two different classes of positive modulators of the metabotropic glutamate receptor mGluR1, a relationship between receptor expression level and activation in the absence of the endogenous ligand glutamate was observed. Although the modulators caused an activation of cells with a high receptor expression, even in the absence of a classical agonist, they did not activate the cells on their own at low receptor expression levels or in native cells [156]. The different maximal high-dose activation levels observed for different batches of cells in the current study could accordingly be explained by variations in receptor expression. Indeed, the measured radioactivity in the PI turnover assays under full 5-HT (**6**) activation conditions varied between different experiments by a factor of up to three.

A related effect was observed in another study of a series of 5-HT_{2A} ligands with low-nanomolar affinity and only minor functional response in PI turnover assays at concentrations below 1 µM, indicative of antagonistic or weak partial agonistic activity. However, at concentrations of 10 µM these compounds caused a strong activation of up to 109% of that of 10 µM 5-HT. Additionally, these activations were only partially blocked by 10 µM ketanserin (**48**), similar to experiments from the current study [69] (Figure 58).



56

Figure 58: Chemical structures of putative 5-HT_{2A} receptor modulators.

The general structure of compounds from this study and from another study [69] showing similar high-dose and over-maximal responses in IP accumulation assays at the 5-HT_{2A} receptor.

Reciprocal allosteric modulation in receptor dimers

Dose-response curve with a Hill-factors above unity, as seen for the high-dose responses from the current study, have not been observed previously for receptor mediated stimulation of PLC. Such steep curves are usually indicative of cooperativity between similar binding

sites. There is broad evidence for the homo- and hetero-dimerization of G-protein coupled receptors as discussed above. Receptor dimerization with reciprocal allosteric modulation of the dimerization partners would explain cooperativity. In this model the high-dose activating compounds bind to 5-HT_{2A} receptor homodimers at a non-classical binding site. The binding results in isomerization into an active receptor conformation and subsequent G-protein activation independent of the classical agonist binding mechanism. Additionally, a conformational shift is transmitted to the dimerization partner, where the affinity for the modulator increases, a phenomenon called "reciprocal allosteric modulation".

Pharmacological relevance

In summary, several tested compounds exerted a complex effect on the 5-HT_{2A} receptor. At low concentrations they bound to the classical binding site as partial agonists or antagonists. However, at higher concentrations they also bound to a non-competitive modulatory binding site and activated the receptor. This activation was independent of ligand binding to the classical binding site. This multiple action is a remarkable and new phenomenon, not previously recognized for 5-HT_{2A} receptors. It might be possible to separate both mechanisms by chemical modification of the compounds in order to get pure allosteric or non-competitive activators and inhibitors of the receptor with negligible affinity for the classical binding site. As described above, the 5-HT_{2A} receptor has a key role in current drugs to treat schizophrenia [192]. Negative modulators of this receptor might have a similar antischizophrenic profile in combination with reduced side effects caused by a full blockade of the receptors. It is also possible that non-competitive or allosteric activators might be of value as an adjunct in a neuroleptic therapy in a way that the response to small concentrations of 5-HT (**6**) is decreased by the conventional 5-HT_{2A} antagonist, but the response to higher concentrations is increased by the positive modulator (i.e. shifting the dose-response curve to the right and stretching it vertically). It has indeed been predicted that the characterization of allosteric ligand interaction sites might lead to the identification of compounds with improved selectivity and efficacy [236]. The compounds from this study could serve as a starting point for the exploration of this new binding site of the 5-HT_{2A} receptor.

Another interesting question is that of the physiological relevance of this modulatory binding site of the 5-HT_{2A} receptor. It is possible that a natural ligand for this site exists, comparable to the endogenous 5-HT_1 receptor modulator 5-HT-moduline. The synthesis, transport, or degradation of such an endogenous modulator could provide new pharmacological targets.

Alleged "high affinity" 5-HT_{2A} receptor ligand

During the ongoing pharmacological characterization of the compounds from this study it became apparent that all benzyl or phenethyl substituted tryptamines were antagonists or weak partial agonists. Moreover, no dramatic subtype-selectivities or 5-HT_{2A} receptor affini-

ties were measured. This was unexpected because in a previous study exceptional high binding affinities and possible agonistic activities at the 5–HT_{2A} receptor have been reported for compounds like *N*-(4-bromobenzyl)-5-methoxytryptamine oxalate (**19**) (compound number 33 in: [112]). This substance is also commercially available (Tocris), being described as a "very potent and selective ligand at 5-HT_{2A} receptors" with a claimed affinity for the 5-HT_{2A} receptor of 5 nM ([^{3}H]ketanserin label) and 0.1 nM ([^{125}I]DOI label]) [1].

In order to verify the published results, the synthesis of **19** was reproduced, closely following the published procedure. The identity of the final oxalate salt was confirmed by ^{1}H NMR, ^{13}C NMR, and ESI MS. The desbromo analog could be detected as an impurity even after repeated recrystallizations by HPLC-UV_{260} and ESI MS. ESI MS analysis of the intermediate amide *N*-(4-bromobenzoyl)-5-methoxytryptamine (**359**) also showed signals of the respective desbromo analog, making it most probable that this impurity was introduced with the reagent 4-bromobenzoylchloride (Sigma-Aldrich).

The *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) was then subjected to the binding assays. With a K_i value of 534 nM (n = 4, ±45 nM) against [^{3}H]ketanserin, the measured binding affinity at the 5-HT_{2A} receptor was in sharp contrast to the reported value of 5.2 nM. The 5-HT_{2C} binding affinity was determined to be 394 nM (n = 3, ±19 nM), four-fold lower than the published value of 100 nM. At the 5-HT_{1A} receptor the compound had an affinity of 21 nM (n = 3, ±1.2 nM), tenfold lower than that of the reference compounds 5-MeO-tryptamine and 5-MeO-NMT.

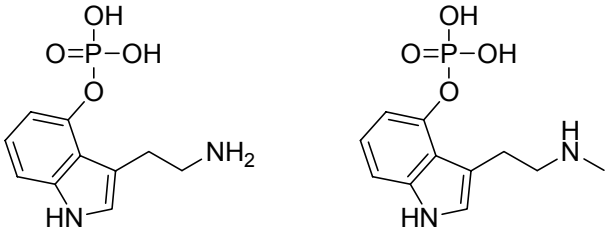
The ratio of affinities obtained from binding experiments using antagonists versus agonists as radioligands has been shown to generally correlate with agonist activity at 5-HT_{2A} receptors [77, 262]. For **19** the mentioned study reported a [^{3}H]ketanserin to [^{125}I]DOI affinity ratio of 52, indicative of full agonist properties of this compound, comparable to 5-methoxytryptamine. However, the IP accumulation data from the current work did not detect any significant agonistic activity at a concentration of 1 µM (n = 2, ±0 %) at rat-5HT_{2A} receptor transfected cells.

However, the 5-HT_{2A} and 5-HT_{2C} affinities from the current study are similar to the reported affinities of the 4-chlorobenzyl and 4-iodobenzyl analogs of **19** [112], as well as to the *N*-methyl-*N*-benzyl and *N*-methyl-*N*-(4-bromobenzyl) analogs from the current work. In fact, high 5-HT_{2A} affinities close to the reported value of *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) have so far only been seen for long-chain 4-alkylated methoxy substituted amphetamines from that laboratory, e.g. DOHx (2,5-dimethoxy-4-hexylphenyl)-2-amino-propane, K_i [^{3}H]ketanserin = 2.5 nM, K_i [^{125}I]DOI = 0.1 nM) or 3,5-dimethoxy-4-(3-phenylpropyl)-phenyl-2-amino-propane (**56**, R = 2,3-MeO) (Figure 58) (K_i [^{3}H]ketanserin = 4 nM). All of these compounds were either antagonists or weak partial agonists [69, 203, 254].

The experimental conditions of the radioreceptor binding assays in the cited publication are nearly identical to those used in the current study. Most notably, in both studies the same species variants of the receptors, the same cell lines, and the same radioligand have been used. It seems highly unlikely that the small differences in the assay protocol (e.g. incubation times of 60 min instead of 30 min) could be responsible for the observed huge discrepancies. These results force the conclusion that the published report is in error. Either the compound that was tested was not in fact the correct one, or else a serious flaw existed in their pharmacological analyses.

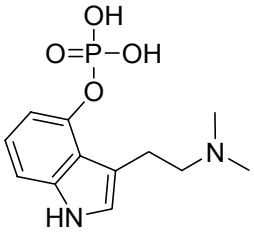
Summary of the aeruginascin project

Inocybe aeruginascens is a hallucinogenic mushroom that has caused several unintentional intoxications due to its vague similarity to a common edible mushroom species [24, 70]. In addition to the known psychoactive alkaloids psilocin (**7**) and psilocybin (**3**) (Figure 59), a new compound of unknown structure and pharmacology, but with very similar TLC staining characteristics and a similar UV spectrum has been described. This compound has been named aeruginascin (**4**) by Gartz [87, 90]. Several unsuccessful attempts to isolate larger amounts of sufficiently pure aeruginascin (**4**) for structure determination by J. Gartz and in the group of H. Laatsch were hampered by its high water solubility [90, 117] and, possibly, by its chemical sensitivity. It was the aim of this project to solve the structure of this natural product. Due to the limited amount of *Inocybe aeruginascens* available an extract of this mushroom was initially compared in TLC experiments to several synthetic reference compounds that included norbaeocystin (**1**) and baeocystin (**2**), their dephosphorylation products, and various other tryptamine derivatives. Unfortunately, none of these compounds was identical to aeruginascin (**4**).

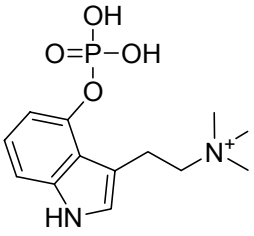


Norbaeocystin (**1**)

Baeocystin (**2**)



Psilocybin (**3**)



Aeruginascin (**4**)

Figure 59: Chemical structures of the *Psilocybe* alkaloids and of aeruginascin.

Chemical structures of the *Psilocybe* alkaloids norbaeocystin (**1**), baeocystin (**2**), and psilocybin (**3**). The structure of the non-basic alkaloid-like compound aeruginascin (**4**) has been elucidated in this study. The compounds are ordered by increasing number of methyl substituents on the amino-group.

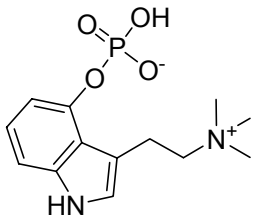
Aeruginascin isolation

From a new batch of mushrooms provided by J. Gartz a small amount of aeruginascin (**4**) was isolated by silica gel column chromatography and Sephadex size exclusion chromatography. This sample was a sufficient quantity for ^{1}H NMR measurements. These experiments unexpectedly suggested a quaternary trimethylammonium structure (Figure 20). Additional ^{13}C NMR, ^{31}P NMR, UV, ESI MS, and high resolution ESI-FTICR MS experiments confirmed that aeruginascin (**4**) is indeed the quaternary trimethylammonium analog **4** of psilocybin (**3**) (Figure 59). As a final proof aeruginascin (**4**) was synthesized from baeocystin (**1**) in an one-step reaction using methyl iodide as reagent. Indeed, this synthetic compound was identical in all respects to the isolated material.

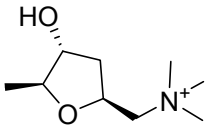
With this new alkaloid-like natural compound the homologous series of phosphorylated *Psilocybe* alkaloids, differing only in the number of *N*-methyl groups, is finally complete. This series consists of norbaeocystin (**1**) (-NH_2), baeocystin (**2**) (-NHMe), psilocybin (**3**) (-NMe_2), and now aeruginascin (**4**) (-N^+Me_3), ordered by increasing number of N-methyl groups (Figure 59). Aeruginascin (**4**) has a remarkable molecular similarity to muscarine (**35**), a mushroom toxin often found in other *Inocybe* species (Figure 60, Figure 61). It is possible that the final methylation steps in the biosyntheses of both compounds are catalyzed by the same methyltransferase enzyme.

Toxicology of aeruginascin

The human pharmacology and toxicology of this new compound has not yet been determined. However, several unintentional intoxications with *Inocybe aeruginascens* have been reported and this mushroom is consumed for its hallucinogenic effects. Due to the quaternary ammonium group it is unlikely that aeruginascin (**4**) is able to pass the blood-brain barrier, a requirement for hallucinogenic effects in human. However, aeruginascin (**4**) might have profound peripheral effects. Aeruginascin (**4**) is assumed to undergo a rapid metabolism into its dephosphorylation product **31** by analogy with the known *Psilocybe* alkaloids. This metabolite has a striking similarity to the peripherally acting 5-HT_3 receptor agonist 5-HTQ (**37**) (Figure 25).



Aeruginascin (**4**)



Muscarine (**35**)

Figure 60: Chemical structures of aeruginascin and muscarine.

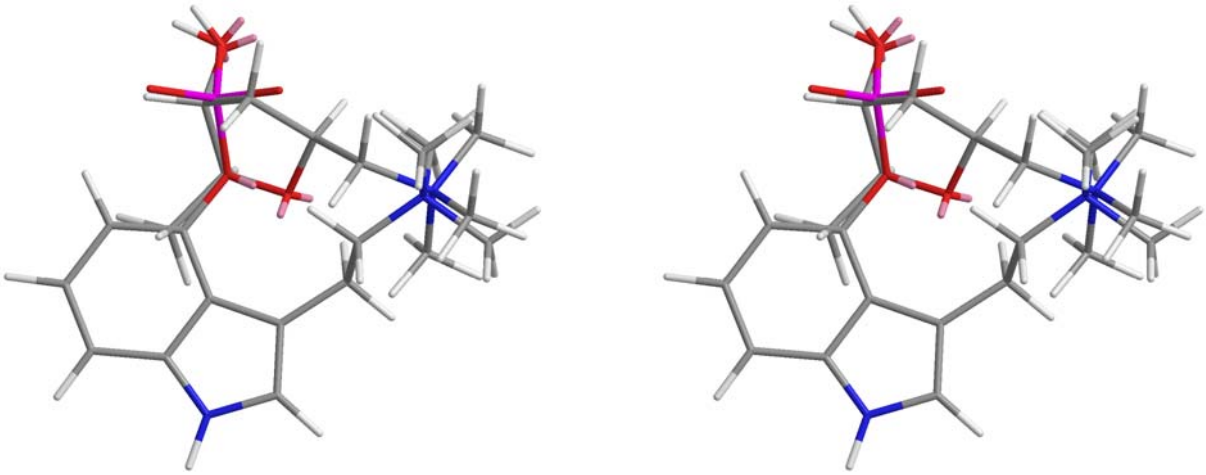


Figure 61: Superposition of aeruginascin and muscarine.

In this stereoscopic view aeruginascin (**4**) and muscarine (**35**) have been superimposed in their minimal energy conformations. The 2-methyl-tetrahydrofuran-3-ol ring of muscarine (**35**) and the phosphate group aeruginascin (**4**) are isosteric and have nearly identical molecular volumes.

New 4-hydroxytryptamine synthesis

During the structure elucidation of aeruginascin (**4**) the *Psilocybe* alkaloids norbaeocystin (**1**) and baeocystin (**2**) were needed as reference compounds. Moreover, it was initially planned to synthesize larger amounts of 4-hydroxylated tryptamines as potential serotonin receptor ligands. Current synthetic approaches to this class of compounds start with the relatively expensive 4-hydroxyindole. Therefore, a new alternative synthetic strategy has been investigated. *Exo*-methylene-tetrahydrofuranone **60** was reacted with Schiff bases and the resulting

3-substituted tetrahydrobenzofuranones gave the 3-substituted tetrahydroindolones on ammonolysis. All these reactions steps have been partially optimized and gave good yields. Unfortunately, the final aromatization could not be accomplished and this synthesis had to be abandoned in order to proceed with the main project.

Instead, baeocystin (**2**) and norbaeocystin (**1**) were synthesized by the classical Speeter-Anthony route followed by phosphorylation using the recently described tetrabenzylpyrophosphate procedure [121, 208, 257].

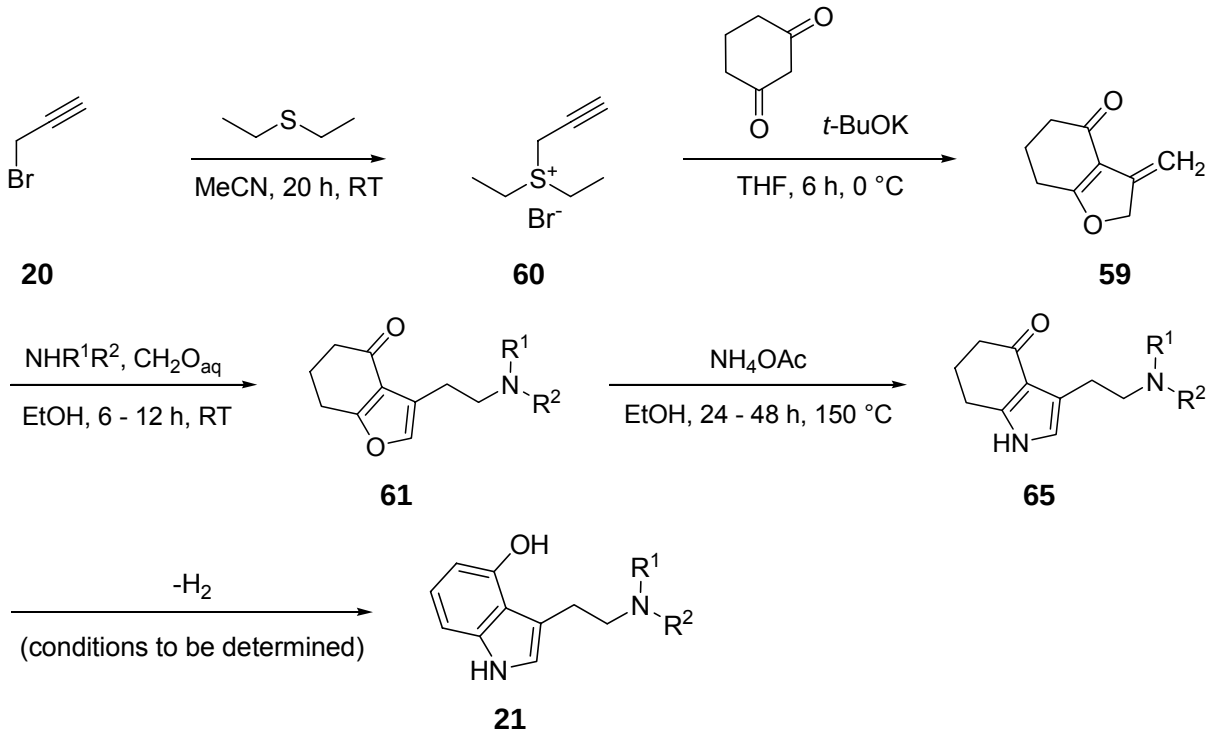


Figure 62: New 4-hydroxytryptamine synthesis.

This promising new synthesis of 4-hydroxytryptamines has been successfully investigated, but conditions for the final aromatization step have not yet been identified.

Summary of the tryptamine project

Hallucinogenic compounds like LSD (**12**) or mescaline, as well as the above mentioned *Psilocybe* alkaloids psilocin (**7**) and psilocybin (**3**) (Figure 59), exert their effects by interaction with 5-HT_{2A} receptors located on nerve cells in the brain. This receptor also has a key role in current drugs to treat schizophrenia [192] and has been implicated in the action of the widely used analgesic drug paracetamol (acetaminophen) [250, 267]. 5-HT_{2A} receptor agonists

are also effective in lowering intraocular pressure after topical application [188] [189]. The 5-HT_{2A} receptor belongs to a group of three closely related 5-HT_2 receptors, consisting of the 5-HT_{2A}, the 5-HT_{2B}, and the 5-HT_{2C} subtypes. There exist subtype selective antagonists for each of these 5-HT_2 receptors, as well as 5-HT_{2B} and 5-HT_{2C} receptor selective agonists. However, no 5-HT_{2A} receptor selective agonist has yet been described. Selective 5-HT_{2A} receptor agonists would be of great importance in the current research on the neurophysiological mechanism of hallucinogenic action and as potential pharmaceuticals. Additionally, such compounds would be valuable in validating and refining existing molecular models of the 5-HT_{2A} receptor [51].

Project description

The structural requirements for high 5-HT_{2A} receptor affinities in the three main families of ligands, the phenethylamines (Figure 6), the lysergamides (Figure 7), and the tryptamines (Figure 8), are relatively well known. However, not much information is available on the effects of *N*-terminal substitutions in tryptamines. In one earlier published study exceptionally high 5-HT_{2A} receptor binding affinities were reported for certain *N*-benzyl analogs of 5-methoxytryptamine (**358**), including the 4-bromobenzyl compound **19** (Figure 65) [112]. In the current work the influence of a broader range of structurally diverse extended *N*-terminal substituents on the affinity of *N*-methyltryptamine and 5-methoxy-*N*-methyltryptamine was examined. In addition to 5-HT_{2A} receptor affinity, the ligands were also tested for 5-HT_{2C} and 5-HT_{1A} receptor affinity in order to identify potentially subtype-selective ligands. Moreover, all tested receptor subtypes are important pharmacological targets and have been associated with the mechanism of hallucinogenic compounds. The compounds were also tested for agonist activity in IP accumulation tests.

Ligand synthesis

The ligands were synthesized by reaction of *N*-methyltryptamine with the appropriate alkyl iodides in the presence of diisopropylethylamine in acetonitrile. Most of the required alkyl iodides were synthesized from carboxylic acids by reduction with borane in THF to the primary alcohol and subsequent halogenation using a reagent system consisting of triphenylphosphine, iodine, and imidazole in methylene chloride. The final tertiary tryptamines were isolated as their hydrogen oxalate salts (Figure 28). The substituents were selected from the following compound classes: substituted benzyl, substituted phenethyl (PE), arylethyl, straight chain alkyl, substituted or branched alkyl, and carbonylalkyl (Figure 63).

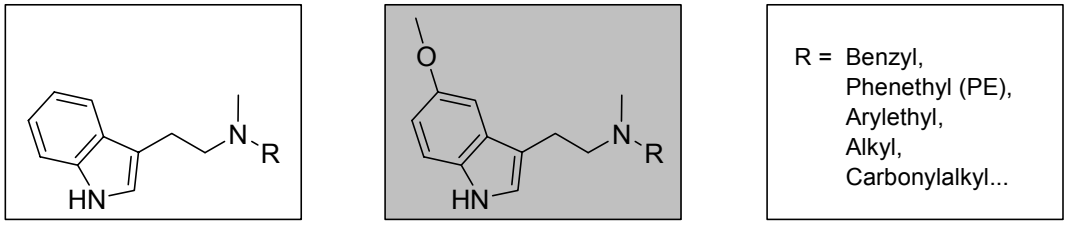


Figure 63: Chemical structures of the tested tryptamines.

N-methyltryptamine (NMT) and 5-methoxy-*N*-methyltryptamine (5-MeO-NMT) *N*-substituted with a broad range of structurally diverse groups were tested at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors.

Binding affinities

Although many ligands had high affinities for the receptors tested, the 5-HT_{2A} receptor selectivities were low for most compounds. Subnanomolar 5-HT_{1A} receptor affinities were measured for the 5-MeO-NMT (**208**) derivatives 2-Cl-PE (**260**), 2,5-Me-PE (**272**), 3-Me-PE (**238**), 3-Br-PE (**268**), (5-MeO-indolyl)-ethyl (**286**), *n*-octyl (**344**), and 3-cyclohexylpropyl (**314**). Ethylene-bis(5-MeO-NMT) (**303**) had a 5-HT_{1A} receptor affinity of 1.9 nM and a remarkable 900-fold selectivity over the 5-HT_{2A} receptor.

5-HT_{2A} receptor affinities around 10 nM were seen for the NMT (**212**) derivatives 2-Me-PE (**235**), 2-Cl-PE (**259**), 3-Me-PE (**237**), 3,5-Me-PE (**273**), (1-naphthyl)-ethyl (**289**), (3-indolyl)-ethyl (**283**), and *n*-octyl (**343**), and the 5-MeO-NMT (**208**) derivatives 2-F-PE (**256**), 2-Cl-PE (**260**), 3-Cl-PE (**262**), 3-Br-PE (**268**), 3,5-Me-PE, (3-indolyl)-ethyl (**274**), and 3-(phenylsulfanyl)-propyl (**326**). 3-(phenylsulfanyl)-propyl-NMT (**325**) had the highest 5-HT_{2A} affinity (1.8 nM). 5-HT_{2C} receptor affinities were usually similar to 5-HT_{2A} values.

In 5-HT_{2A} IP accumulation assays partial agonistic activity with EC_{50} values below 100 nM was seen for the NMT (**212**) derivatives 2,5-MeO-PE (**275**), 3,4-MeO (**277**), 3-AcO-PE (**243**), and (5-MeO-3-indolyl)-ethyl (**284**), and the 5-MeO-NMT (**208**) derivatives 3,4-MeO-PE (**278**), (3-indolyl)-ethyl (**284**), and (5-MeO-3-indolyl)-ethyl (**286**).

Non-competitive modulation

At lower concentrations most compounds exhibited antagonist or partial agonist effects at the 5-HT_{2A} receptor. However, at concentrations above 1 µM several compounds had an unexpected second steep component of their response with a Hill-slope of 2, sometimes reaching activation levels greater than that of 5-HT (Figure 64). In a series of careful experiments it was demonstrated that this effect was not caused by activation of other receptors, by a direct action on second messenger pathways, or by affecting receptor internalization. Instead, the

most plausible explanation, derived from these data, is a non-competitive modulation of the 5-HT_{2A} receptor through a new regulatory binding site. Currently available 5-HT_{2A} agonists and antagonists bind to partially overlapping sites of the receptor. In contrast, allosteric and non-competitive modulators bind to an independent and distinct site. They therefore do not directly compete with the binding of classical ligands, but instead exert an indirect influence on the activation state of the receptor and on the classical binding site.

The observed steep curve of the high-dose response is an indicator of cooperativity between similar binding sites. A similar effect is seen in the classical example of allosteric modulation, the cooperative oxygen binding to the tetrameric protein hemoglobin. Indeed, it is well known that many G-protein receptors can form dimeric complexes and a reciprocal modulation in these dimers has been demonstrated. The effect observed in the current study is therefore most probably the result of cooperativity between the two modulatory binding sites in a dimeric receptor complex.

In summary, several tested compounds exerted a complex effect on the 5-HT_{2A} receptor:

- At low concentrations they bound to the classical binding site as partial agonists or antagonists.
- At higher concentrations they also bound to a non-competitive modulatory binding site and activated the receptor. This activation was independent of ligand binding to the classical binding site.

This multiple action is a remarkable and new phenomenon, not previously recognized for 5-HT_{2A} receptors.

Future prospects

It might be possible to separate both mechanisms by chemical modification of the compounds in order to obtain pure allosteric or non-competitive activators and inhibitors of the receptor with negligible affinity for the classical binding site. As described above, the 5-HT_{2A} receptor has a key role in current drugs to treat schizophrenia [192]. Negative modulators of this receptor might have a similar antischizophrenic profile but with reduced side effects compared to drugs that produce a full blockade of the receptor. It is also possible that allosteric and non-competitive activators might be of value as an adjunct in a neuroleptic therapy in a way that the response to small concentrations of 5-HT (**6**) is decreased by the conventional 5-HT_{2A} antagonist, but the response to higher concentrations is increased by the positive modulator (i.e. shifting the dose-response curve to the right and stretching it vertically). It has indeed been predicted that the characterization of allosteric ligand interaction sites might lead to the identification of compounds with improved selectivity and efficacy [236]. The compounds from this study could serve as a starting point for the exploration of this new binding site at the 5-HT_{2A} receptor.

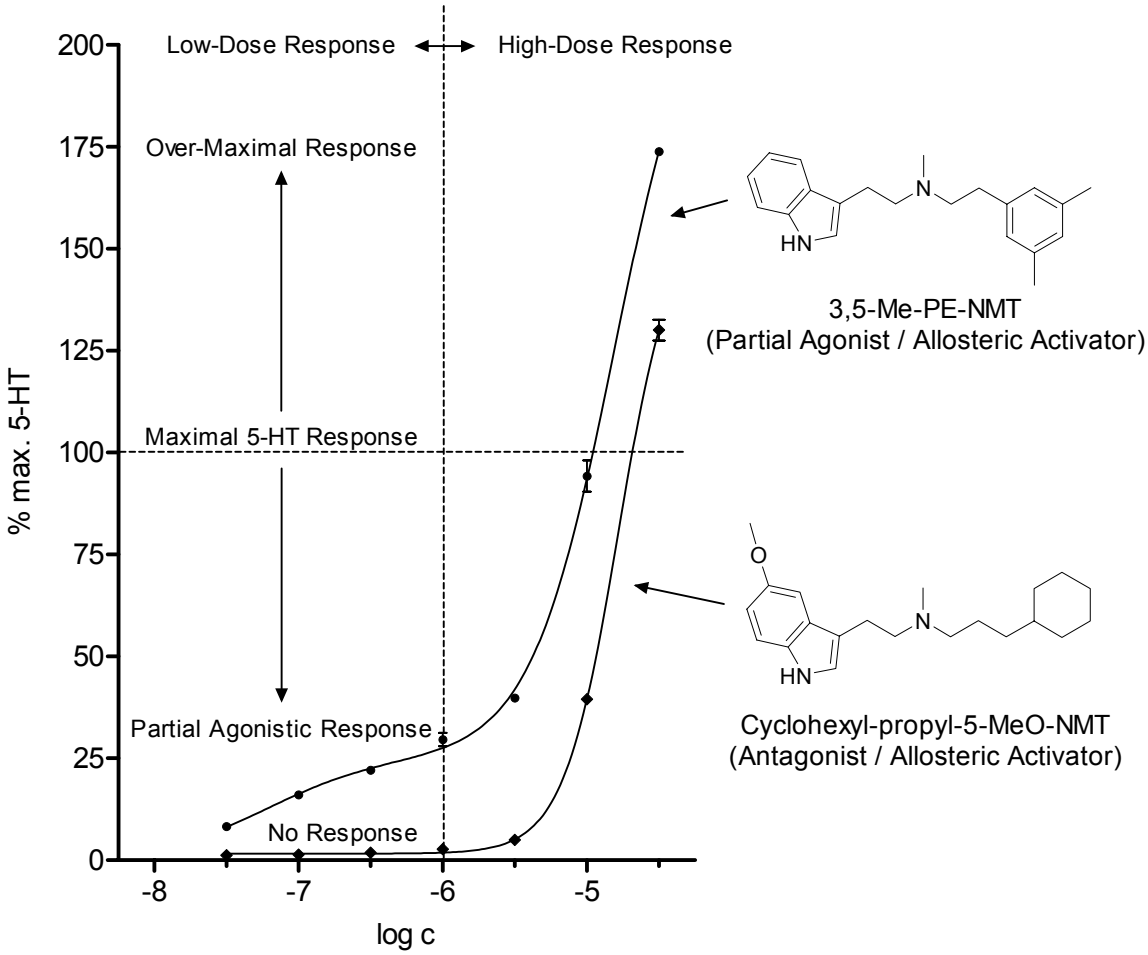


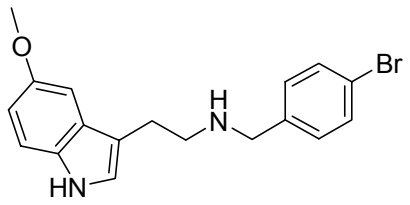
Figure 64: Biphasic dose-response curves.

Biphasic dose-response curves of the 5-HT_{2A} receptor ligands cyclohexylpropyl-5-MeO-NMT (**314**) and 3,5-Me-PE-NMT (**273**). At lower concentrations 3,5-Me-PE-NMT (**273**) elicited a partial agonistic response whereas cyclohexylpropyl-5-MeO-NMT (**314**) did not elicit a response at all. However, at concentrations above 1 µM both compounds show a dramatic over-maximal stimulation of up to 175% that of 5-HT. Moreover, this high-dose response has a slope clearly above unity. Both compounds are most probably non-competitive modulators / activators of the 5-HT_{2A} receptor at higher concentrations in addition to their relatively high affinity for the classical binding site.

Another interesting question is that of the physiological relevance of this modulatory binding site of the 5-HT_{2A} receptor. It is possible that natural ligands for this site exist, comparable to the endogenous 5-HT_1 receptor modulator 5-HT-moduline. The synthesis, transport, or degradation of such an endogenous modulator could provide new interesting pharmacological targets.

Alleged "high affinity" 5-HT$_{2A}$ receptor ligand

During the ongoing pharmacological characterization of the compounds from this study it became apparent that most compounds tested were antagonists or weak partial agonists at submicromolar concentrations. Moreover, no dramatic subtype-selectivities or 5-HT$_{2A}$ receptor affinities were measured. This result was unexpected because in a study reported in the literature an exceptionally high binding affinity, high subtype selectivity, and probable agonistic activity were reported for *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) [112] (Figure 65). In order to verify these published results this compound was synthesized and subjected to the binding and functional assays. In sharp contrast to the reported K_i value of 5.2 nM, in our hands *N*-(4-bromobenzyl)-5-methoxytryptamine (**19**) had only a relatively low 5-HT$_{2A}$ receptor binding affinity of 534 nM. Moreover, the compound was devoid of agonist activity, in marked contrast to the published data. Because of these unexpected findings, particular care was taken to reproduce our data and to confirm the structural identity of the compound. This finding is of special interest, because this compound is commercially available, being described as a very potent and selective 5-HT$_{2A}$ ligand [1]. This result forces the conclusion that the published report is in error. Either the compound that was tested was not in fact the correct one, or else a serious flaw existed in their pharmacological analyses.



19

Figure 65: Alleged 5-HT$_{2A}$ receptor ligand.

This commercially available *N*-alkylated tryptamine has been described as a very potent 5-HT$_{2A}$ receptor ligand with putative agonist activity [112]. However, in the current study, and after careful and detailed experiments, this compound surprisingly proved to be to be a low affinity weak antagonist.

Experimental Part

Materials and Methods

Pharmacological methods

Cell culture

Cells lines were grown in an incubator at 37 °C and 5% CO_2 in 75 cm^2 tissue culture flasks for propagation, in 150 mm diameter × 15 mm tissue culture Petri dishes for radioreceptor assay membrane preparations, and in 24-well tissue culture plates (24 × 2 cm^2) for PI turn-over assays. Cells were passaged after reaching a confluency of about 95% by washing with PBS, detaching with PBS containing 0.05% trypsin and 0.53 mM EDTA (Gibco / BRL, 10 × solution), and dilution of the resulting suspension with fetal calf serum containing medium. The cells were not maintained beyond 30 passages.

5-HT_{1A} receptor cell line CHO-h5-HT_{1A} ("CHO-1A"): Chinese hamster ovary cells stably expressing the human 5-HT_{1A} receptor, provided by Christopher Harber (Christopher.L.Harber@am.pnu.com). Medium: DMEM (Sigma), 10% fetal calf serum, 2 mM L-glutamine, 50 U/l penicillin, 50 µg/l streptomycin, 9 U/l Hygromycin B, 300 mg/l G-418 (Geneticin).

5-HT_{2A} receptor cell line A549-h5-HT_{2A} ("A20"): A549 human lung carcinoma cells stably expressing the human 5-HT_{2A} receptor, provided by Dr. Ulrike Weyer-Czernilofsky (pcz@bender.co.at). Medium: RPMI, 10% dialyzed fetal calf serum, 2 mM L-glutamine, 50 U/l penicillin, 50 µg/l streptomycin, 9 U/l hygromycin B, 300 mg/l G-418 (Geneticin).

Wild type cell line A549: human lung carcinoma cell line (ATCC). Medium: RPMI, 10% dialyzed fetal calf serum, 2 mM L-glutamine, 50 U/l penicillin, 50 µg/l streptomycin.

5-HT_{2A} receptor cell line NIH-3T3-r5-HT_{2A} ("GF-6"): NIH-3T3 mouse fibroblasts stably expressing the rat 5-HT_{2A} receptor, provided by Dr. David Julius (D. Julius et al. PNAS 87: 928 1190). Medium: DMEM (Sigma), 10% dialyzed fetal calf serum, 2 mM L-glutamine, 50 U/l penicillin, 50 µg/l streptomycin, 300 mg/l G-418 (Geneticin).

5-HT_{2C} receptor cell line P0 NIH-3T3-r5-HT_{2C} ("P0"): NIH-3T3 mouse fibroblasts stably expressing the rat 5-HT_{2A} receptor (gift from Dr. David Julius, et al. Science, 244: 1057 1989). Medium: DMEM (Sigma), 10% dialyzed fetal calf serum, 2 mM L-glutamine, 50 U/l penicillin, 50 µg/l streptomycin, 300 mg/l G-418 (Geneticin).

PBS (8 g/l NaCl, 0.2 g/l KCl, 0.2 g/l KH_2PO_4, 1.15 g Na_2HPO_4) was prepared from a 10 × stock solution and adjusted to pH 7.4 with diluted hydrochloric acid or diluted sodium hydroxide solution.

Membrane preparations

Cells were grown in 150 mm diameter × 15 mm tissue culture Petri dishes until they reached 90% confluency, the medium was aspirated, the cells were washed with PBS, and incubated in serum-free, unsupplemented, and phenol red reduced Opti-MEM medium (Gibco / BRL) for 5 h. Cells were scraped off with a cell-scraper, transferred into 50 ml conical tubes on ice, and centrifuged for 5 min at 3000 rpm at 0 °C (Allegra 6R centrifuge, Beckmann). The supernatant was decanted, the pellet was resuspended in ice-cold PBS, and aliquots of 1 ml were transferred into 1.5 ml microcentrifuge tubes on ice. The membranes were pelleted for 2 to 5 min at maximum speed in a benchtop centrifuge (Labnet Z180M, Hermle) located within a cold room. The supernatant was decanted and the tubes were immediately frozen at -80 °C. These membrane preparations could be used for 6 to 12 months without noticeable change of binding parameters.

Receptor binding experiments

Test compounds were dissolved in DMSO at a concentration of 10 mM and were stored at -20 °C. Each binding experiment typically consisted of ten different concentrations of the test compound as duplicates, and each experiment was repeated at least three times from at least two different stocks of the test compounds.

A serial dilution from this stock was prepared in binding buffer (0.1 mM EDTA, 10 mM $MgCl_2$, 50 mM Tris, pH 7.4). A mixture of the test compound, 1 nM of the radioligand, and cell homogenate (about 50 mg protein) in a total volume of 500 µl binding buffer in 1.2 ml PE tubes in racks of 96 (Marsh Bio Products) was incubated for 60 min at room temperature. The suspension was filtered through 96-well filter plates with bonded GF/B filters (Unifilter-96, Whatman GF/B, Packard) using a 96-well harvester (Packard). To reduce non-specific binding the filters were pre-soaked for 50 min in an aqueous solution of 0.3% poly-(ethylene-imine) (PEI, Sigma). The filters were rapidly washed with ice-cold washing buffer (10 mM Tris, 150 mM NaCl) and dried overnight. 40 µl scintillation cocktail (Microscint O, Packard) was added into each filter-well, and the sealed filter plate was counted in a plate reader (TopCount, Packard).

The following radioligands were used: [propyl-2,3-ring-1,2,3-^{3}H]8-OH-DPAT (5-HT_{1A}, specific activity ~135 Ci/mmol, NET929, NEN USA), [ethylene-^{3}H]ketanserin hydrochloride (5-HT_{2A}, specific activity ~63 Ci/mmol, NET791, NEN USA), and [N^{6-}methyl-^{3}H]mesulergine (5-HT_{2C}, specific activity ~74 Ci/mmol, TRK845, Amersham USA).

Non-specific binding was determined in the presence of 10 µM serotonin (5-HT_{1A}), 10 µM ketanserin (**48**) or cinanserin (5-HT_{2A}), or 10 µM mianserin (5-HT_{2C}). Total counts were determined by spotting 20% the added amount of radioligand solution directly onto the processed filter plates. Total binding was determined in the absence of cold ligands.

Binding curves were analyzed using GraphPad-Prism (GraphPad Software) and standard spreadsheet programs.

PI turnover assays

Cells grown in 24-well tissue culture plates (24 × 2 cm^2) were washed with PBS and the cells were incubated for 12 - 18 h with serum- and inositol-free CMRL-1066 medium (Gibco / BRL) containing 1.0 µCi/ml [2-^{3}H]inositol (Amersham, TRK317). 10 µM pargyline, 10 mM LiCl, and, if needed, the antagonists were added and the cells were pre-incubated for 15 min. The test compounds in PBS were then added and the plates were incubated for 30 min at 37 °C. The medium was aspirated on ice and the cells were permeabilized by addition of 300 µl per well of 10 mM formic acid. The plates were kept at 4 °C overnight. [^{3}H]Phosphoinositides were separated by adsorption on Dowex 1 anion exchange resin (strongly basic styrene-DVB gel) in columns of 10 mm diameter × 30 mm height using gravity elution [33]. The content of the wells was pipetted onto the column and the column was equilibrated with 15 ml equilibrium buffer (10 mM D-*myo*-inositol, 3 M ammonium formate). After the column was washed with 15 ml washing buffer (5 mM sodium tetraborate, 10 mM ammonium formate), the [^{3}H]phosphoinositides were eluted with 2 ml elution buffer (1 M ammonium formate, 10 mM formic acid) into plastic scintillation vials. 18 ml scintillation cocktail (EcoLite(+), IGN) was added, and the eluted radioactivity was quantified using a scintillation counter (Beckman). The columns could be reused by washing with 5 ml rejuvenation buffer (3 M ammonium formate, 0.1 M formic acid) and 15 ml equilibrium buffer. Experimental data were analyzed using GraphPad-Prism (GraphPad Software). Data from wells of the outer border of the plates were excluded from analysis if they showed systematically decreased values. The data from each plate was standardized separately to the 10 µM 5-HT (**6**) and to the background response. Monophasic curves were fitted against the sigmoidal (or logistic) dose-response model $y = \frac{max}{1+10^{(\log(EC_{50})-x)\cdot slope}}$, biphasic curves were fitted against the overlay of two independent curves $y = \frac{max_1}{1+10^{(\log(EC_{50_1})-x)\cdot slope_1}} + \frac{max_2}{1+10^{(\log(EC_{50_2})-x)\cdot slope_2}}$ where y is the standardized activation, max is the maximal standardized activation, EC_{50} is the concentration of half-maximal stimulation, $slope$ is the Hill-slope factor of the activation curve, and x is the ligand concentration.

Chemical syntheses

Analytical equipment

^{1}H NMR: Varian VXR-200 (200 MHz, routine spectra, Göttingen), Bruker ARX-300 (300 MHz, routine spectra, Purdue), Varian UNITY-300 (300 MHz, Göttingen), Varian INOVA-500 (500 MHz, Göttingen), or Varian INOVA-600 (600 MHz, Göttingen). — **^{13}C NMR:** Varian

Mercury-200 (50.3 MHz), Varian UNITY-300 (75.5 MHz), Bruker AMX-300 (75.5 MHz), Varian INOVA-500 (125.7 MHz) or Varian INOVA-600 (151 MHz). — **^{31}P NMR:** Varian Mercury-200 (81 MHz). — **TLC:** Polygram SIL G/UV$_{254}$ 200 µm on polyester (Macherey-Nagel & Co, Germany). — **Column chromatography:** silica gel for flash-chromatography 30 - 60 µm (J. T. Baker, Germany). — **Size exclusion chromatography:** Sephadex G-10 (Pharmacia). — **UV:** Perkin-Elmer Lambda 15 UV/VIS spectrophotometer. — **IR:** Perkin-Elmer RX I FT-IR spectrometer, Perkin-Elmer Spectrum 5.0 analysis software. — **EI MS:** Finnigan MAT 95 mass spectrometer system at 70 eV. — **ESI MS:** Finnigan LCQ mass spectrometer system, positive ionization. — **Melting points:** Mettler FP61 apparatus. Melting points / decomposition temperatures were not measured for zwitterionic compounds and salts. — **HPLC:** Degasser DG-1310 (Degasys), two HPLC pumps PU-987, mixing unit, auto-sampler AS-1555 with 100 µl sample loop, multiple wavelength diode array detector MD-910 with an analytical cell, Borwin-PDA 1.0 analysis software (all from Jasco, Germany).

NMR

^{1}H NMR spectra are referenced to tetramethylsilane (TMS, δ = 0) if not stated otherwise. ^{13}C NMR spectra are referenced to the solvent signal of DMSO-d_6 (δ = 39.50) if not stated otherwise. NMR spectra abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), sept (septuplet), m (other multiplet), br (broad), J (coupling constant), C_q (quaternary carbon).

HPLC

Column: Nucleosil, 7 µm, C_6H_5, 230 × 4.6 mm. Detection: 220 nm, 260 nm, 200 - 350 nm. Eluent A: dH_2O, 5% MeOH, 4 g/l Tris-HCl, 100 µl/l H_3PO_4 85%, pH 4. Eluent B: MeOH, 5% dH_2O, 4 g/l, Tris-HCl, 100 µl/l H_3PO_4 85%, pH 4. Standard gradient: 20 min 30% B to 90% B, 5 min 90% B, 1 min 90% B to 30% B, 14 min 30% B. Gradient B for lipophilic compounds: 15 min 50% B, 5 min 50% B to 90% B, 20 min 90% B, 1 min 90% B to 50% B, 14 min 50% B. Peak intensities are listed as the percentage of the total area under the curve at a wavelength of 260 nm ("%total AUC_{260}").

Chemical Experiments

4-Hydroxytryptamines: Ene synthesis route

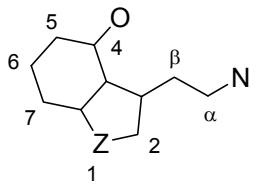


Figure 66: Ene synthesis: compound numbering scheme.

Benzyl-ethoxymethyl-methylamine (57)

A mixture of 61.2 g benzyl-methylamine (121.2 g/mol, d 0.939, 65.17 ml, 505.0 mmol, 1.2 eq), 82.9 g dry K_2CO_3 (138.2 g/mol, 60.0 mmol, 0.14 eq), and 58 ml ethanol (46.07 g/mol, d 0.789, 45.76 g, 993.3 mmol, 2.3 eq) in a round-bottom flask equipped with a drying tube in an ice-bath was magnetically stirred for 5 min. 12.9 g paraformaldehyde (30.03 g/mol, 429.6 mmol, 1 eq) was added and stirring was continued for 15 min at room temperature. The inorganic salt was filtered off and excess ethanol was distilled off on a rotary evaporator. 46.22 g benzyl-ethoxymethyl-methylamine ($C_{11}H_{17}NO$, 179.26 g/mol, 257.8 mmol, 60%) was distilled under oil pump vacuum in a micro-distillation bridge as a clear oil at 65 °C. The yield in a similar reaction on a 40 mmol scale was 67%.

(*N*-Benzyl-*N*-methyl-*N*-methylene)-iminium chloride (Eschenmoser's salt) (58)

44.82 g benzyl-ethoxymethyl-methylamine (179.26 g/mol, 250.0 mmol, 1 eq) (**57**) was added dropwise to a solution of freshly distilled 29.4 ml trichloromethylsilane (149.5 g/mol, 250.0 mmol, d 1.273, 37.4 g, 1 eq) in 100 ml acetonitrile in a round bottom flask with magnetic stirring and cooling in an ice bath. A white precipitate formed and the mixture was stirred for 30 min under cooling. 100 ml dried ether was added, the precipitate was filtered off, washed with 100 ml dry ether, and dried in a desiccator under vacuum, yielding 41.5 g benzyl-methyl-methylene-ammonium chloride ($C_9H_{12}ClN$, 169.7 g/mol, 244.5 mmol, 98%) as a white hygroscopic salt.

Diethyl-prop-2-ynyl-sulfonium bromide (59)

A solution of 43.1 ml diethylsulfide (90.18 g/mol, d 0.836, 36.03 g, 400.0 mmol, 1 eq) and 44.6 ml 3-bromopropyne (propargyl bromide, 119.0 g/mol, 80%, d 1.335, 400 mmol, 47.58 g,

1 eq) in 80 ml dried acetonitrile in a brown light-protected round bottom flask equipped with a drying tube filled with $CaCl_2$ were stirred at room temperature for 22 h. Dried diethyl ether was added under stirring until no further clouding occurred. The product crystallized as a white powder and was filtered off, washed with dry diethyl ether, and dried under vacuum to yield 63.1 g diethyl-prop-2-ynyl-sulfonium bromide ($C_7H_{13}BrS$, 209.2 g/mol, 301.6 mmol, 75%) as a moisture-sensitive white powder.

3-Methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (60)

20 g Cyclohexane-1,3-dione (112.1 g/mol, 178.4 mmol, 1 eq) in 200 ml dried THF was added dropwise over 20 min to a solution of 24 g potassium *tert.*-butoxide (*t*-BuOK, 112.2 g/mol, 213.9 mmol, 1.2 eq) in 500 ml dry THF under vigorous magnetic stirring at room temperature. The resulting suspension was stirred for another 20 min at room temperature and was cooled in an ice bath. 62.9 g diethyl-prop-2-ynyl-sulfonium bromide (209.0 g/mol, 301.0 mmol, 1.5 eq) was added in one portion and stirring was continued at room temperature for 6:30 h. The mixture was diluted with 1000 ml H_2O and subsequently extracted with 750 ml, 250 ml, 200 ml, and 200 ml diethyl ether. The combined organic phases were dried over K_2CO_3 + $MgSO_4$ and evaporated, yielding a reddish liquid. This crude product was subjected to vacuum liquid chromatography (VLC) by adsorption on top of a tightly packed silica gel column of 9.4 cm diameter and 5 cm height in a 500 ml glass fritted Buchner funnel and subsequent elution with 150 ml of hexane (fraction 1), hexane / ethyl acetate (50 + 50, fraction 2), hexane / ethyl acetate (20 + 80, fraction 3), hexane / ethyl acetate (90 + 10, fraction 4), ethyl acetate, ethyl acetate / methanol (99 + 1, fraction 5), ethyl acetate / methanol (98 + 2, fraction 6), ethyl acetate / methanol (97 + 4, fraction 7) each. Fractions testing positive for the product by TLC were evaporated and the product crystallized spontaneously as slightly yellow sandy, table-salt-like crystals with adherent reddish oily impurities. These byproducts could be effectively removed by repeated pressing between paper tissues. The yield of the product was 8.17 g (fraction 4), 8.19 g (fraction 5), and 1.21 g (fraction 6), resulting in a combined yield of 17.4 g of 3-methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one ($C_9H_{10}O_2$, 150.2 g/mol, 115.8 mmol, 65%). Upon storage at room temperature or upon refluxing in acetonitrile this compound slowly decomposes, most probably into 3-methyl-6,7-dihydro-5*H*-benzofuran-4-one.

TLC (ethyl acetate / triethylamine, 99 + 1; R_f): 0.66 (product, Ehrlich: purple without heating), 0.73 (byproduct, Ehrlich: purple), 0.83 (byproduct, Ehrlich: red). Detection by UV_{254} absorption and Ehrlich's reagent.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.28): δ = 5.65 (t, 3.0 Hz, 1 H, H-β), 5.06 (dd, 3 Hz, 3 Hz, 2 H, H_2-2), 4.83 (t, 2.5 Hz, 1 H, H-β), 2.55 (t, J = 6.5 Hz, 2 H, H_2-7), 2.40 (t, J = 6.5 Hz, 2 H, H-5), 2.07 (tt, J = J' = 6.5 Hz, 2 H, H-6).

3-[2-(Benzyl-methylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (from Eschenmoser's salt) (61)

17.0 g 3-Methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (150.2 g/mol, 113.2 mmol, 1 eq) and 3.93 ml triethylamine (101.1 g/mol, d 0.728, 2.864 g, 28.3 mmol, 0.25 eq) were dissolved in 200 ml dried acetonitrile in a 500 ml round-bottom flask with magnetic stirring. 28.81 g benzyl-methyl-methylene-ammonium chloride (169.7 g/mol, 169.7 mmol, 1.5 eq) was added all at once. The temperature rose moderately and the reaction flask was cooled in an ice bath for 10 min. Then the flask was kept at room temperature for 10 min and the solvent was evaporated on a rotary evaporator. The remaining residue was dissolved in 200 ml H_2O + 2 ml conc. HCl and extracted with 200 ml ethyl acetate. The organic phase was re-extracted with 50 ml H_2O + 0.5 ml HCl and then with 50 ml brine. The combined aqueous phases were basified to pH 12 with sodium hydroxide solution and the resulting suspension was subsequently extracted with 200 ml, 50 ml, and 50 ml ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator, and the resulting product was further dried under oil pump vacuum, yielding 30.6 g 3-[2-(benzyl-methylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one ($C_{18}H_{21}NO_2$, 283.4 g/mol, 108.0 mmol, 95%) as a clear yellow oil at room temperature which freezes very slowly at -20 °C.

TLC (ethyl acetate / triethylamine, 99 + 1): R_f = 0.66 (educt, Ehrlich: purple without heating), 0.61 (product, Ehrlich: red). Detection by UV_{254} absorption and Ehrlich's reagent.

^1H NMR (300 MHz, CD_3OD, $\delta_{solvent}$ = 3.30 (reference), compound as its hydrogen oxalate): δ = 7.53 - 7.44 (m, 5 H, C_6H_5), 7.43 (s, 1 H, H-2), 4.88 (s, 3 H, N^+-CH_3), 4.38 (s, 2 H, CH_2-Ph), 3.38 (t, J = 8.0 Hz, 2 H, H_2-α), 3.07 (t, 2 H, H_2-β), 2.87 (t, J = 6.5 Hz, 2 H, H-7), 2.46 (t, J = 6.5 Hz, 2 H, H_2-5), 2.15 (tt, J = J' = 6.5 Hz, 2 H, H-6).

EI MS: *m/z* (%) = 134.1 (100%) $[CH_2$-$N(CH_3)$-CH_2-$C_6H_5]$·+, 91.0 (92%) $[CH_2$-$C_6H_5]^+$, 149.1 (7%) [M - CH_2-$N(CH_3)$-CH_2-$C_6H_5]$·+, 283.2 (3%) $[M]^+$, 192.1 (2%) [M - CH_2-$C_6H_5]^{\cdot+}$, 163.1 (2%) [M - $N(CH_3)$-CH_2-$C_6H_5]^+$.

3-[2-(Dialkylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (general procedure using formalin as reagent) (62 - 64)

A mixture of 3-methylene-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (150.2 g/mol, 1 eq), the respective dialkylamine (1.1 eq), acetic acid (60.06 g/mol, d 1.049, 1.1 eq), and formaldehyde solution (30.03 g/mol, 35%, d 1.08, 1.2 eq) in ethanol (4 ml/mmol) was let stand at room temperature until TLC-analysis indicated complete conversion. The solvent was evaporated on a rotary evaporator and the mixture was dissolved in H_2O, acidified with diluted hydrochloric acid, extracted twice with ethyl acetate, and the aqueous solution basified with diluted sodium hydroxide solution. The product was extracted twice with ethyl acetate, the combined organic phases were dried over $MgSO_4$, and the solvent was evaporated on a ro-

tary evaporator. The resulting crude product was kept under oil pump vacuum and could be purified by silica column chromatography.

The following compounds were prepared using this procedure (dialkylamine, reaction conditions, yield of crude product): 3-[2-(benzyl-methylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (**62**) (benzyl-methylamine, 0.67 mmol, 5 h, not isolated); 3-[2-(dibutyl-amino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (**63**) (dibutyl-amine, 6.67 mmol, 30 h, 48%); 3-[2-(cyclohexylmethylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (**64**) (cyclohexyl-methylamine, 6.67 mmol, 48 h, 87%).

3-[2-(Benzyl-methylamino)-ethyl]-1,5,6,7-tetrahydroindol-4-one (65)

A mixture of 10 g 3-[2-(benzyl-methylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one (283.4 g/mol, 35.30 mmol, 1 eq) and 13.6 g ammonium acetate (77.08 g/mol, 176.4 mmol) in 167 ml pure ethanol in a sealed glass ampul (⅔ filled) was heated for 24 h to 150 °C in an electrical oven in a metal tube as an explosion shield. After cooling and opening the ampoule (no overpressure was observed) the solvent was evaporated on a rotary evaporator, the residue was dissolved in water, acidified to pH 3 - 4 with hydrochloric acid, and extracted twice with dichloromethane. The aqueous layer was basified with sodium hydroxide solution to pH 12 and extracted twice with dichloromethane, the combined organic phases were evaporated on a rotary evaporator, and the residue was further dried under oil pump vacuum overnight, yielding 8.7 g crude 3-[2-(benzyl-methylamino)-ethyl]-1,5,6,7-tetrahydroindol-4-one ($C_{18}H_{22}N_2O$, 283.36 g/mol, 30.70 mmol, 87%) as a light brown amorphous solid. The use of aqueous ammonia instead of ammonium acetate or the use of 95% ethanol instead of pure ethanol reduced the reaction rate considerably.

TLC (ethyl acetate / triethylamine, 99 + 1): R_f = 0.48 (educt, Ehrlich: red), 0.20 (product, Ehrlich: violet). Detection by UV_{254} absorption and Ehrlich's reagent.

EI MS: *m/z* (%) = 134.1 (100%) $[CH_2\text{-}N(CH_3)\text{-}CH_2\text{-}C_6H_5]^+$, 91.1 (83%) $[CH_2\text{-}C_6H_5]^+$, 191.2 (16%) $[M - CH_2\text{-}C_6H_5]^{\cdot+}$, 148.1 (7%) $[M - CH_2\text{-}N(CH_3)\text{-}CH_2\text{-}C_6H_5]^{\cdot+}$, 282.2 (6%) $[M]^+$.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 8.42 (s br, 1 H, H-1), 7.39 - 7.20 (m, 5 H, C_6H_5), 6.45 (s, 1 H, H-2), 3.65 (s, 2 H, CH_2-Ph), 3.01 (t, J = 7.5 Hz, 2 H, H_2-α), 2.81 - 2.70 (m, 4 H, H_2-β, H_2-7), 2.44 (t, J = 6.5 Hz, 2 H, H_2-5), 2.33 (s, 3 H, N-CH_3), 2.07 (tt, J = J' = 6.5 Hz, 2 H, H-6).

Putative 1,2,3,5-tetrahydro-1-methylpyrrolo[4,3,2-*de*]quinoline (66)

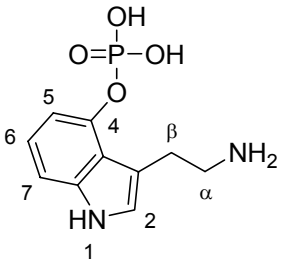
A few milligrams of 3-[2-(benzyl-methylamino)-ethyl]-6,7-dihydro-5*H*-benzofuran-4-one, benzoic acid, and Pd/C 5% in 5 ml tetraline were heated to reflux under a slow stream of N_2 for 30 min. The reaction mixture was diluted with ethyl acetate and the catalyst was filtered off and the solvents were evaporated on a rotary evaporator and then under oil pump

vacuum. Putative 1,2,3,5-tetrahydro-1-methylpyrrolo[4,3,2-*de*]quinoline ($C_{11}H_{12}N_2O$, 172.2 g/mol) was isolated by preparative TLC (silica gel; ethyl acetate / NEt_3, 99 + 1).

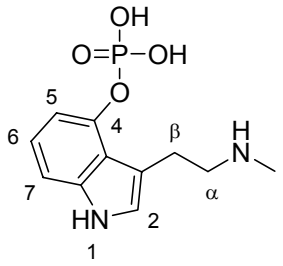
TLC: ethyl acetate / acetic acid (99 + 1), R_f = 0.73. Two-dimensional TLC: 1. ethyl acetate / conc. HCl (100 + 0.1), R_f = 0.12; 2. ethyl acetate / triethylamine (99 + 1), R_f = 0.79. Ehrlich color reaction: blue.

EI MS: *m/z* (%) = 172.2 (100%) $[M]^+$, 157.2 (13%) $[M - CH_3]^+$.

Synthesis of baeocystin and norbaeocystin



Norbaeocystin (**1**)



Baeocystin (**2**)

Figure 67: Structures and numbering scheme of norbaeocystin and baeocystin.

4-Acetoxyindole (acetic acid indol-4-yl ester) (67)

To 15.25 g 4-benzyloxyindole (223 g/mol, 68.39 mmol, 1 eq) in 200 ml acetone was added 20 ml acetic acid anhydride (21.6 g, d 1.08, 102.09 g/mol, 211.6 mmol, 3.1 eq), 0.5 g finely powdered LiCl (42.39 g/mol, 11.80 mmol, 0.17 eq), and 0.5 g catalyst (Pd/C, 10%, oxidic form). The mixture was vigorously shaken at room temperature and standard pressure under H_2 for 16 h until the gas uptake ceased. TLC analysis of the reaction mixture indicated an incomplete conversion of about 50 - 75%. The catalyst was filtered off, 1.0 g of fresh catalyst together with 10 ml acetic acid (60.05 g/mol, d 1.049, 9.53 g, 158.7 mmol, 2.3 eq) and 10 ml triethylamine (101.19 g/mol, d 0.728, 13.7 g, 135.7 mmol, 2.0 eq) as catalysts were added, and the hydrogenation was continued for another 2:30 h until the gas uptake ceased. Further 0.5 g of the catalyst was added and the mixture was shaken for another 1 h. The catalyst was filtered off, the solvent was removed on a rotary evaporator, and the resulting dark oil was dissolved in 150 ml of diethyl ether, washed with 2 × 200 ml H_2O, dried over Na_2SO_4, and filtered. The dark coloration could not be removed by shaking with 1 g of silica gel and subsequent filtration. The solvent was removed on a rotary evaporator. The crude product crystallized at room temperature and was further dried for 9 h at 50 °C under oil pump vacuum, yielding 4-acetoxyindole (11.19 g, $C_{10}H_9NO_2$, 175.19 g/mol, 63.87 mmol, 93%) as a

light green crystal mass. The product from this reaction was used without further purification in the next step. The crude product from a previous reaction has been purified by silica gel column chromatography with diethyl ether / *n*-hexane (80 + 20) as eluent.

TLC (diethyl ether / *n*-hexane, 50 + 50): R_f = 0.52 (product, Ehrlich: pink, dark violet after heating, brown upon storage), 0.69 (educt, Ehrlich: sky-blue after heating, blue-gray upon storage), 0.55 (4-hydroxyindole, Ehrlich: green, greenish brown upon storage). Detection by UV_{254} absorption and Ehrlich's reagent.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 8.28 (s br, 1 H, H-1), 7.23 (d, J = 6 Hz, 1 H, H-5), 7.14 (dd, J = J' = 8 Hz, 1 H, H-6), 7.12 (d, J = 3 Hz, 1 H, H-2), 6.85 (dd, J = 7.5 Hz, 0.5 Hz, 1 H, H-7), 6.42 (dd, J = 2.5 Hz, 2.5 Hz, 1 H, H-3), 2.39 (s, 3 H, CH_3-COO).

4-Acetoxyindol-3-yl-glyoxylic acid chloride (acetic acid 3-chlorooxalyl-indol-4-yl ester) (68)

To a stirred solution of 10.0 g (175.2 g/mol, 57.08 mmol) 4-acetoxyindole in 100 ml diethyl ether was added 14.5 g (126.9 g/mol, d 1.5, 9.7 ml, 114.2 mmol) oxalyl chloride dropwise under cooling in an ice bath. The solution was allowed to warm to room temperature and stirring was continued for 1 h. The orange product was filtered off, and washed with cold diethyl ether, dried under vacuum, and further dried under oil pump vacuum, yielding 13.02 g of a crystalline orange powder. Another 0.64 g of the product was obtained by combining the filtrates and washing solutions and concentration on a rotary evaporator. The combined yield of 4-acetoxyindol-3-yl-glyoxylchloride as a moisture-sensitive fine yellow-orange powder was 13.66 g ($C_{12}H_8ClNO_4$, 265.7 g/mol, 51.4 mmol, 90%).

4-Acetoxy-*N*-methyl-*N*-benzyl-indol-3-yl-glyoxylamide (acetic acid 3-(benzyl-methylaminooxalyl)-indol-4-yl ester) (69)

A solution of 10.34 g methyl-benzylamine (121.18 g/mol, d 0.94, 11.0 ml, 85.3 mmol, 4.5 eq) in 100 ml diethyl ether was added dropwise to a slurry of 5.00 g 4-acetoxyindol-3-yl-glyoxyl-chloride (265.7 g/mol, 18.82 mmol, 1.0 eq) in 200 ml diethyl ether under stirring. The mixture was filtered and the filter cake was washed with ether and dissolved in dichloromethane. This solution was washed with H_2O, dried over $MgSO_4$, and evaporated on a rotary evaporator. The crystalline mass was recrystallized from 20 ml ethyl acetate, yielding 3.22 g of the product. Another 0.964 g was obtained from concentration of the mother liquor. The total yield of 4-acetoxy-*N*-methyl-*N*-benzyl-indol-3-yl-glyoxylamide was 4.19 g ($C_{20}H_{18}N_2O_4$, 350.37 g/mol, 11.95 mmol, 63%).

TLC (two conformers): R_f = 0.50 / 0.25 (ethyl acetate / triethylamine, 99 + 1), 0.72 / 0.48 (ethyl acetate / acetic acid, 99 + 1), 0.96 / 0.96 (ethyl acetate / methanol (50 + 50), 0.16 / 0.16 (diethyl ether / triethylamine, 99 + 1), 0.3 (isopropanol / acetic acid / H_2O, 70 + 20 + 10).

The product is Ehrlich's negative, detection by UV_{254} absorption or by Dragendorff's reagent (bright orange).

4-Hydroxy-*N*-methyl-*N*-benzyltryptamine (3-[2-(benzyl-methylamino)-ethyl]-indol-4-ol) (70)

4-Acetoxy-*N*-methyl-*N*-benzyl-indol-3-yl-glyoxylamide (3.50 g, 350.4 g/mol, 9.99 mmol) in 50 ml dioxane was added dropwise to a refluxing suspension of 8.0 g $LiAlH_4$ powder (37.96 g/mol, 210.8 mmol, 21 eq) in 100 ml dioxane. The mixture was refluxed for 3 h and cooled to room temperature. The reaction was terminated in a 2 l round-bottom flask by careful addition of THF / H_2O (95 + 5), saturated $MgSO_4$ solution, and H_2O, subsequently. Diatomaceous earth was added to the mixture, the slurry filtered through a bed of diatomaceous earth, and the filter cake was washed with 1 l THF. The pooled solutions were evaporated on a rotary evaporator, the resulting oil was redissolved in ethyl acetate, dried over $MgSO_4$, evaporated, and redissolved in THF. 0.5 ml concentrated HCl solution was added, resulting in a viscous precipitate which did not crystallize overnight at 4 °C. Therefore, the THF was decanted, and the product partitioned between 150 ml H_2O / NH_4OH (99 + 1) and 100 ml ethyl acetate. The aqueous phase was re-extracted with 50 ml ethyl acetate, the organic phases pooled, dried over $MgSO_4$, filtered through a short layer of silica gel, and evaporated, yielding 2.40 g of 4-hydroxy-*N*-methyl-*N*-benzyltryptamine ($C_{18}H_{20}N_2O$, 280.37 g/mol, 8.56 mmol, 86%) as a slightly brown clear oil after 2 d under oil pump vacuum. In a previous experiment the resulting base has been purified by silica gel column chromatography using isopropanol / acetic acid / H_2O (70 + 20 + 10) as eluent.

TLC (isopropanol / acetic acid / H_2O, 70 + 20 + 10): R_f = 0.76 (product; Keller + Dragendorff: gray); 0.30 (reactant, Keller + Dragendorff: bright orange). Detection by UV_{254} absorption or staining with Ehrlich's, Keller's, or Dragendorff's reagent. Double staining first with Keller's reagent and then with Dragendorff's reagent has been used to detect the reactant and the product on the same TLC sheet.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (s br, 1 H, H-1), 7.38 - 7.18 (m, 5 H, C_6H_5), 7.06 (dd, J = J' = 8 Hz, 1 H, H-6), 6.86 (dd, J = 8 Hz, 1 Hz, 1 H, H-2), 6.86 (d, J = 8 Hz, 1 H, H-7), 6.62 (dd, J = 7.5 Hz, 0.5 Hz, 1 H, H-5), 3.65 (s, 2 H, H_2-1), 3.13 - 2.97 (m, 2 H, H_2-α), 2.82 - 2.71 (m, 2 H, H_2-β), 2.35 (s, 3 H, N-CH_3).

4-Phosphoryloxy-*N*-methyl-*N,N*-dibenzyltryptamine monobenzyl ester (71)

4-Hydroxy-*N*-methyl-*N*-benzyltryptamine base (533 mg, 280.37 g/mol, 1.90 mmol, 1 eq) was dried under oil pump vacuum for 30 min at 150 °C and dissolved in 50 ml dry THF (freshly distilled from Na wire) in an oven-dried three-neck 100 ml round-bottom flask equipped with a gas inlet, a quickfit-mounted long Pasteur pipette, a rubber septum, and a magnetic stirring bar. 112 mg diisopropylamine (dried over calcium hydride) (101.19 g/mol, d 0.722, 81 µl,

1.11 mmol, 0.58 eq) in 50 ml dry THF was added. The flask was cooled in a dry ice / acetone bath and 1.05 ml of a fresh solution of *n*-butyllithium in *n*-hexane (2.36 M, 2.47 mmol, 1.3 eq) was added dropwise with a syringe while stirring magnetically under a slow stream of N_2. The faintly yellow solution became pale green and after 5 min of stirring 1.30 g tetrabenzylpyrophosphate (TBPP, 538.5 g/mol, 2.41 mmol, 1.27 eq) was added all at once. The solution became turbid and the dry ice / acetone bath was replaced by an ice / salt bath. The solution turned clear and, over a period of 30 min, became a white suspension. After 2 h of continuous stirring 30 ml of a concentrated solution of NH_4Cl in water was added, the mixture was transferred to a separatory funnel, and the minimum amount of water (about 1.5 ml) was added until the suspension became a clear two-phase mixture. The upper THF layer was separated and dried with $MgSO_4$. The aqueous bottom layer was extracted twice with 40 ml ethyl acetate each, the combined extracts dried with $MgSO_4$, pooled with the THF phase, and evaporated, leaving a slightly yellow oil, probably the quaternary monobenzyl ester of the 4-phosphoryloxy-*N,N*-dibenzyl-*N*-methyltryptamine [121] [257].

4-Phosphoryloxy-*N*-methyltryptamine (baeocystin, phosphoric acid mono-[3-(2-methylamino-ethyl)-indol-4-yl] ester) (2)

This crude product was subjected to a catalytical debenzylation in 75 ml MeOH with 0.5 g Pd/C (10%) hydrogenation catalyst in a 250 ml round-bottom flask in a shaking apparatus under H_2 at room temperature and standard pressure. The rapid hydrogen uptake ceased after less than 2 h. TLC analysis of the mixture showed two products, probably baeocystin (**2**) and its benzyl ester. The mixture was vigorously stirred under H_2 for further 16 h until TLC analysis showed a single product. The reaction mixture was filtered through a thin layer of diatomaceous earth and was evaporated to leave a clear, slightly yellow oil.

This oil was chromatographed by dissolving it in 50 ml methanol / 1% acetic acid and adsorption onto 4 g flash silica gel. The solvent was evaporated and the adsorbed product placed on top of a flash column filled with 16 g flash silica gel (height 5 cm, diameter 2.5 cm). The product was eluted with methanol / 1% acetic acid. The fractions testing positive for the product by TLC were pooled and evaporated. To remove traces of acetic acid, 15 ml xylene was added and evaporated three times. The resulting product was redissolved in methanol, and transferred into a 10 ml test tube with a glass-ground joint. The solvent was evaporated on a rotary evaporator without a water bath to prevent over-boiling. The product fell out as a gum-like substance. Oil pump vacuum was carefully applied to prevent excessive foaming in the beginning. The resulting product was scraped off, powdered, and held at oil pump vacuum for 8 hours at 90 °C (water bath) and for a further 2.5 days at room temperature, yielding baeocystin ($C_{11}H_{15}N_2O_4P$, 270.22 g/mol) as a fluffy beige powder. This product was recrystallized from H_2O (1 ml / 100 mg), subsequently washed with H_2O (0.2 ml / 100 mg), ethanol, and acetone, and dried under oil pump vacuum.

TLC: R_f = 0.49 (n-BuOH / AcOH / H_2O, 2 + 1 + 1), 0.46 (n-BuOH / AcOH / H_2O, 24 + 10 + 10), 0.12 (n-PrOH / NH_3 6%, 5 + 2), 0.55 (n-BuOH / AcOH / *i*-PrOH / H_2O, 8 + 2 + 3 + 5), 0.54 (n-BuOH / AcOH / *i*-PrOH / H_2O, 8 + 2 + 1 + 5), 0.22 (n-PrOH / NH_3 28%, 5 + 3), 0.51 (n-PrOH / AcOH / H_2O, 10 + 3 + 3), 0.83 (MeOH / H_2O / NH_3 28%, 70 + 30 + 0.2), 0.69 (MeOH / H_2O / formic acid, 80 + 20 + 0.2). Detection by Ehrlich's reagent (purple, violet after storage). (See Table 2).

^{1}H NMR (300 MHz, D_2O / acetic acid, $\delta_{solvent}$ = 4.87): δ = 7.32 (d, J = 8 Hz, 1 H, H-7), 7.26 (s, 1 H, H-2), 7.22 (dd, J = J' = 8 Hz, 1 H, H-6), 7.07 (d, J = 8 Hz, 1 H, H-5), 3.46 - 3.39 (m, 2 H, H_2-α), 3.17 - 3.10 (m, 2 H, H_2-β), 2.75 (s, 3 H, N-CH_3), 2.100 (s, CH_3COOH, reference).

4-Acetoxy-*N,N*-dibenzyl-indol-3-yl-glyoxylamide (acetic acid 3-dibenzylaminooxalyl-indol-4-yl ester) (72)

Essentially the same procedure as above for the preparation of 4-acetoxy-*N*-methyl-*N*-benzyl-indol-3-yl-glyoxylamide was followed. 5.00 g 4-acetoxyindolylglyoxyl$\alpha\alpha\alpha$chloride (265.7 g/mol, 18.82 mmol) was treated with 16.83 g dibenzylamine (197.28 g/mol, d 1.02, 16.5 ml, 85.3 mmol, 4.5 eq). The product was recrystallized from 100 ml ethyl acetate and a second fraction was collected after evaporation of the mother liquor, yielding 7.00 g 4-acetoxy-*N,N*-dibenzyl-indol-3-yl-glyoxylamide ($C_{26}H_{22}N_2O_4$, 426.5 g/mol, 16.4 mmol, 87%).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 9.81 (s br, 1 H, H-1), 7.70 (d, 2.5 Hz, 1 H, H-2), 7.42 - 7.22 (m, 10 H, 2 C_6H_5), 7.11 (t, 7.5 Hz, 1 H, H-6), 7.05 (d, J = 7.5 Hz, 1 H, H-7), 6.89 (dd, J = 7.5 Hz, 2.5 Hz, 1 H, H-5), 4.56 (s, 2 H, N-CH_2), 4.36 (s, 2 H, N-CH_2), 2.36 (s, 3 H, CH_3COO-).

4-Hydroxy-*N,N*-dibenzyltryptamine (3-(2-dibenzylamino-ethyl)-indol-4-ol) (73)

Essentially the same procedure as above for the $LiAlH_4$ reduction to 4-hydroxy-*N*-methyl-*N*-benzyltryptamine was used. 6.0 g 4-acetoxy-*N,N*-dibenzyl-indol-3-yl-glyoxylamide (426.47 g/mol, 14.07 mmol) was reacted with 10.0 g $LiAlH_4$ (37.96 g/mol, 263.5 mmol, 19 eq). 1.8 g oxalic acid dihydrate (126.07 g/mol, 14.28 mmol, 1.0 eq) in THF was added to the crude base in THF to a final volume of 50 ml, resulting in a gelatinous precipitate. 0.5 ml concentrated HCl solution was added and a white suspension formed. After 1 h at 4 °C the mixture was filtered, the filter cake was washed 50 ml THF, and the combined organic phases evaporated and dried under oil pump vacuum, yielding 4.66 g of 4-hydroxy-*N*-methyl-*N*-benzyltryptamine hydrochloride ($C_{24}H_{24}N_2O$, 382.93 g/mol, 11.86 mmol, 84%) as an amorphous white powder. The free base was liberated by partitioning between H_2O / NH_4OH (99 + 1) and ethyl acetate, re-extraction of the aqueous phase, drying over $MgSO_4$, evaporation, and drying under oil pump vacuum at elevated temperature.

TLC (diethyl ether): R_f = 0.77 (4-hydroxy-*N,N*-dibenzyltryptamine, Ehrlich: dark blue after modest heating, UV_{254} absorption, spots are turning brown over 2 d), 0.40 (4-acetoxy-*N,N*-dibenzyl-indol-3-yl-glyoxylamide, Ehrlich: negative, UV_{254} absorption).

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 7.79 (s br, 1 H, H-1), 7.39 - 7.18 (m, 10 H, 2 C_6H_5), 7.06 (t, 7.5 Hz, 1 H, H-6), 6.84 (d, J = 8 Hz, 1 H, H-7), 6.71 (d, J = 2 Hz, 1 H, H-2), 6.65 (d, J = 8 Hz, 1 H, H-5), 3.74 (s, 4 H, 2 *N*-CH_2), 2.90 - 2.76 (m, 4 H, H_2-α,β).

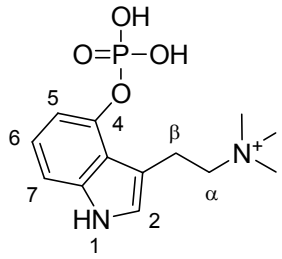
4-Phosphoryloxytryptamine (norbaeocystin, phosphoric acid mono-[3-(2-aminoethyl)-indol-4-yl] ester) (1)

The above procedure for the phosphorylation and deprotection of baeocystin (**2**) was followed closely. 500 mg of 4-hydroxy-*N,N*-dibenzyltryptamine base (356.5 g/mol, 1.40 mmol, 1 eq), 60 mg diisopropylamine (101.19 g/mol, d 0.722, 79 µl, 1.09 mmol, 0.78 eq), 0.77 ml *n*-butyllithium in *n*-hexane (2.36 M, 1.82 mmol, 1.3 eq), and 959 mg tetrabenzylpyrophosphate (TBPP, 538.5 g/mol, 2.41 mmol, 1.27 eq) were reacted, yielding 1.42 g of a light yellow oil, probably the monobenzyl ester of *N,N*-dibenzylbaeocystin. After catalytic debenzylation for 2 h and subsequent chromatography 248 mg (346.3 g/mol, 51% yield) of norbaeocystin-monobenzyl ester was obtained as a white amorphous powder. 216 mg (346.3 g/mol, 624 mol) of norbaeocystin monobenzyl ester was further debenzylated under the same conditions for another 20 h. After chromatography 64 mg of norbaeocystin ($C_{10}H_{13}N_2O_4P$, 256.2 g/mol, 40% yield from the monobenzyl ester) was obtained as a white amorphous powder.

TLC: R_f = 0.60 (n-BuOH / AcOH / H_2O, 2 + 1 + 1), 0.56 (n-BuOH / AcOH / H_2O, 24 + 10 + 10), 0.13 (n-PrOH / NH_3 6%, 5 + 2), 0.64 (n-BuOH / AcOH / *i*-PrOH / H_2O, 8 + 2 + 3 + 5), 0.60 (n-BuOH / AcOH / *i*-PrOH / H_2O, 8 + 2 + 1 + 5), 0.18 (n-PrOH / NH_3 28%, 5 + 3), 0.64 (n-PrOH / AcOH / H_2O, 10 + 3 + 3), 0.93 (MeOH / H_2O / NH_3 28%, 70 + 30 + 0.2), 0.74 (MeOH / H_2O / formic acid, 80 + 20 + 0.2). Detection by Ehrlich's reagent (purple, violet after storage). (See Table 2).

^1H NMR (300 MHz, D_2O / acetic acid, $\delta_{solvent}$ = 4.77): δ = 7.37 (d, J = 8 Hz, 1 H, H-7), 7.31 (s, 1 H, H-2), 7.27 (dd, J = 7.5 Hz, 7.5 Hz, 1 H, H-6), 7.13 (d, J = 7.5 Hz, 1 H, H-5), 3.49 - 3.42 (m, 2 H, H_2-α), 3.31 - 3.24 (m, 2 H, H_2-β), 2.100 (s, CH_3COOH, reference).

Aeruginascin: Isolation, synthesis, and spectroscopic data



Aeruginascin (**4**)

Figure 68: Structure and numbering scheme of aeruginascin.

TLC

Developed TLC sheets were stained by immersion in Ehrlich's reagent (identical to Van Urk's reagent; 8% conc. hydrochloric acid and 1% *p*-dimethylaminobenzaldehyde (DMBA) in MeOH) and subsequent heating in a stream of hot air.

For TLC of dephosphorylation products an aeruginascin-enriched extract, a psilocybin-enriched extract, baeocystin (**2**), or norbaeocystin (**1**) were dissolved in 0.1 M NH_4Cl buffer of pH 9.8 and incubated with alkaline phosphatase (Sigma) at room temperature for several hours. The reaction was acidified with acetic acid and immediately analyzed by TLC.

Aeruginascin by isolation

Throughout the isolation procedure the water bath temperature for the evaporation of solvents on a rotary evaporator was kept at or below 45 °C to prevent possible degradation of the product.

Fruiting bodies of *Inocybe aeruginascens* were collected and identified by J. Gartz, air-dried at temperatures not exceeding 45 °C, and stored at 4 °C. References were deposited in the herbarium of the University of Leipzig (Germany). 9.5 g *Inocybe aeruginascens* carpophores were further dried under oil pump vacuum overnight, finely powdered in a mortar, and transferred into a glass-fritted Buchner funnel. The material was subsequently extracted by applying a weak vacuum with 70 ml cyclohexane, 100 ml ethyl acetate, 100 ml ethanol, 50 ml ethanol / formic acid (100 + 0.2), 20 ml ethanol, 200 ml methanol / H_2O / formic acid (80 + 20 + 0.2; pH ~ 3.5), and 100 ml methanol / H_2O (60 + 40). The methanol / H_2O / formic acid extract tested positive for psilocybin (**3**) and aeruginascin (**4**) by TLC and was concentrated under reduced pressure on a rotary evaporator. The concentrated solution was adsorbed on

10 g silica gel and the mixture was further dried in the rotary evaporator, yielding a fine brown powder.

A short but wide silica column of 130 mm length and 60 mm diameter was prepared, the adsorbed extract was placed on top of the column, and the column was eluted with methanol / H_2O / formic acid (80 + 20 + 0.2). Fractions of about 4 ml were collected and tested by TLC. Fractions 10 - 14 were positive for psilocybin (**3**) and fractions 16 - 32 were positive for aeruginascin. The aeruginascin (**4**) containing fractions were concentrated, adsorbed on 5 g silica, and evaporated, resulting in a fine powder.

A second taller silica column of 280 mm length and 17 mm diameter was prepared. The adsorbed fraction was placed on top of the column and the column was eluted with methanol / H_2O / formic acid (80 + 20 + 0.2). Fractions of about 4 ml were collected and tested by TLC. Fractions 13 - 17 were positive for aeruginascin (**4**) and were pooled and evaporated, yielding 64.5 mg of a slightly brown clear thick oil which partly crystallized into a cream-white amorphous solid (possibly due to crystallization of leached-out silica).

A third silica column of 280 mm length and 17 mm diameter was prepared and the previous fraction was eluted with methanol / H_2O / 28% aqueous ammonia (70 + 30 + 0.2). Fractions of about 8 ml were collected and tested by TLC. Fractions 8 - 15 were positive for aeruginascin (**4**) and were pooled and evaporated, yielding 8.9 mg of a brown residue.

The residue was dissolved in H_2O and eluted from a Sephadex G-10 column of 500 mm length and 11 mm diameter with H_2O. Fractions of about 2 ml were collected and tested for UV absorption at 267 nm. The positive fractions 17 - 19 were pooled and evaporated, yielding 4.6 mg of a clear residue.

Synthetic aeruginascin (trimethyl-[2-(4-phosphonooxyindol-3-yl)-ethyl]-ammonium) (4)

10 mg baeocystin (**2**) (270.22 g/mol, 37.01 µmol, 1 eq) was dissolved in 250 µl H_2O and mixed with 25 µl methyl iodide (141.94 g/mol, d 2.28, 57 mg, 402 µmol, 11 eq) and 20 µl diisopropyl-ethylamine (129.25 g/mol, d 0.742, 14.8 mg, 114.8 µmol, 3.1 eq) in a microreaction tube. Methanol was added dropwise in order to get a homogenous solution. The mixture was kept at 50 °C for 60 min. The solvents and reagents were removed on a rotary evaporator and the crude product was purified using the procedure described above for the isolation of aeruginascin, starting with methanol / H_2O / aqueous ammonia column chromatography.

^{1}H NMR (formic acid, final NMR conditions)

^{1}H NMR of isolated aeruginascin (**4**) (600 MHz, D_2O / 7% formic acid, $\delta_{solvent}$ = 4.87): δ = 8.257 (s, HCOOH, reference), 7.29 (d, J = 8 Hz, 1 H, H-7), 7.25 (s, 1 H, H-2), 7.18 (dd, J =

J' = 8 Hz, 1 H, H-6), 7.06 (d, J = 8 Hz, 1 H, H-5), 3.64 - 3.61 (m, 2 H, H_2-α), 3.46 - 3.42 (m, 2 H, H_2-β), 3.23 (s, 9 H, $N^+(CH_3)_3$).

^{1}H NMR synthetic aeruginascin (**4**) (600 MHz, D_2O / 7% formic acid, $\delta_{solvent}$ = 4.88): δ = 8.257 (s, HCOOH, reference), 7.29 (d, J = 8 Hz, 1 H, H-7), 7.24 (s, 1 H, H-2), 7.17 (dd, J = J' = 8 Hz, 1 H, H-6), 7.06 (d, J = 8 Hz, 1 H, H-5), 3.65 - 3.60 (m, 2 H, H_2-α), 3.45 - 3.40 (m, 2 H, H_2-β), 3.23 (s, 9 H, $N^+(CH_3)_3$).

^{1}H NMR (formic acid / methanol)

^{1}H NMR of isolated aeruginascin (**4**) (500 MHz, D_2O / 3% formic acid / 3% methanol, $\delta_{solvent}$ = 4.81): δ = 8.257 (s, HCOOH, reference), 7.27 (d, J = 8 Hz, 1 H, H-7), 7.24 (s, 1 H, H-2), 7.17 (dd, J = J' = 8 Hz, 1 H, H-6), 7.08 (d, J = 7.5 Hz, 1 H, H-5), 3.37 (s, CH_3OD).

^{1}H NMR of synthetic aeruginascin (**4**) (500 MHz, D_2O / 3% formic acid / 3% methanol, $\delta_{solvent}$ = 4.79): δ = 8.257 (s, HCOOH, reference), 7.28 (d, J = 8 Hz, 1 H, H-7), 7.24 (s, 1 H, H-2), 7.18 (ddd, J = 8 Hz, 8 Hz, 1.5 Hz, 1.5 Hz, 1 H, H-6), 7.06 (d, J = 7.5 Hz, 1 H, H-5), 3.62 (t, J = 8 Hz, 2 H, H_2-α), 3.42 (t, J = 8 Hz, 2 H, H_2-β), 3.21 (s, CH_3OD).

^{1}H NMR (unbuffered)

^{1}H NMR of isolated aeruginascin (**4**) (500 MHz, D_2O, $\delta_{solvent}$ = 4.67): δ = 8.46 (s br, $HCOO^-$), 7.19 (s, 1 H, H-2), 7.19 (d, J = 7.5 Hz, 1 H, H-7), 7.15 (dd, J = 7.5 Hz, 7.5 Hz, 1 H, H-6), 7.10 (d, J = 7 Hz, 1 H, H-5), 3.64 (t, J = 8 Hz, 2 H, H_2-α), 3.43 (t, J = 8 Hz, 2 H, H_2-β), 3.19 (s, 9 H, $N^+(CH_3)_3$).

^{1}H NMR of synthetic aeruginascin (**4**) (500 MHz, D_2O, $\delta_{solvent}$ = 4.67): δ = 8.49 (s br, 1 H, $HCOO^-$), 7.25 (d, J = 8 Hz, 1 H, H-7), 7.17 (s, 1 H, H-2), 7.15 (dd, J = J' = 8 Hz, 1 H, H-6), 7.04 (d, J = 7.5 Hz, 1 H, H-5), 3.55 - 3.50 (m, 2 H, H_2-α), 3.37 - 3.32 (m, 2 H, H_2-β), 3.14 (s, 9 H, $N^+(CH_3)_3$).

^{1}H NMR (triethylamine)

^{1}H NMR of synthetic aeruginascin (**4**) (500 MHz, D_2O / 3% NEt_3, $\delta_{solvent}$ = 4.63, $\delta_{triethylamine}$ = 2.60, 1.00): δ = 8.39 (s br, $HCOO^-$), 7.11 (s, 1 H, H-2), 7.10 - 7.07 (m, 3 H, H-5,6,7), 3.65 - 3.27 (m, 2 H, H_2-α), 3.42 - 3.37 (m, 2 H, H_2-β), 3.15 (s, 9 H, $N^+(CH_3)_3$).

^{13}C NMR

^{13}C-APT NMR of isolated aeruginascin (**4**) (126 MHz, D_2O, methanol, $\delta_{solvent}$ = 4.86): δ = 124.3 (CH-2), 123.7 (CH-6), 109.6 (CH-3), 107.3 (CH-5), 68.7 (CH_2-1'), 54.1 (3 CH_3-N^+), 21.1 (CH_2-2').

^{13}C NMR of isolated aeruginascin (**4**) (151 MHz, D_2O / 3% formic acid / 3% methanol): δ = 166.76 (CH-HCOOD), 165.29 (CH-HCOOH), 49.86 (CH_3-methanol, reference), 139.68 (C_q-7b), 124.91 (CH-2), 123.45 (CH-6), 119.49 (C_q-3b), 109.85 (CH-3), 108.53 (CH-5), 68.71 (CH_2-1'), 54.09 (3 CH_3-N^+), 21.31 (CH_2-2').

^{13}C NMR of synthetic aeruginascin (**4**) (151 MHz, D_2O / 3% formic acid / 3% methanol): δ = 166.68 (CH-HCOOD), 165.49 (CH-HCOOH), 49.89 (CH_3-methanol, reference), 146.84 (C_q-4), 139.55 (C_q-7b), 125.09 (CH-2), 123.49 (CH-6), 119.35 (C_q-3b), 109.93 (CH-3), 108.75 (CH-5), 68.52 (CH_2-1'), 54.09 (3 CH_3-N^+), 21.18 (CH_2-2').

^{31}P NMR

^{31}P NMR of isolated aeruginascin (**4**) (81 MHz, D_2O): δ = 0.7 (br s, R-OPO_3D_2).

^{31}P NMR of baeocystin (**2**) (81 MHz, D_2O): δ = 2.8 (s, R-OPO_3D_2).

UV

UV of isolated aeruginascin (**4**) (H_2O): λ (ε) = 219 (8254), 267 (1589), 282 (sh), 288 nm (1008, sh).

UV of synthetic aeruginascin (**4**) (H_2O): λ (ε) = 219 (14339), 267 (2550), 282 (sh), 288 nm (1637, sh).

UV of norbaeocystin (**1**) (H_2O): λ (ε) = 219 (11067), 267 (1932), 282 (sh), 288 nm (1226, sh).

UV of baeocystin (**2**) (H_2O): λ (ε) = 219 (8189), 267 (1523), 282 (sh), 288 nm (970, sh).

MS

ESI MS of isolated aeruginascin (**4**) (H_2O / methanol): *m/z* (%) = 299.2 (100%) $[M]^+$, 321.2 (52%) $[M - H + Na]^+$, 597.3 (18%) $[2M + H]^+$, 619.3 (17%) $[2M + Na]^+$, 219.1 (16%) $[M - PO_3H]^+$, 160.2 (15%) $[M - PO_3H - N(CH_3)_3 + H]^+$, 337.1 (12%) $[M - H + K]^+$, 240.0 (10%) $[M - N(CH_3)_3 + H]^+$, 635.1 (7%) $[2M + K]^+$.

ESI MS of isolated aeruginascin (**4**) (D_2O): *m/z* (%) = 323.3 (100%) $[M - 3H + 2D + Na]^+$, 623.3 (30%) $[2M - 6H + 5D + Na]^+$, 221.2 (15%) $[M - PO_3H - 2H + 2D]^+$.

ESI FT-ICR MS of isolated aeruginascin (**4**) (*m/z* = 299.1, H_2O): *m/z* = 299.115477. Kindly measured by Dietmar Schmidt (dietmar.schmidt@uni-tübingen.de, Abt. Prof. Jung, Institute of Organic Chemistry, University of Tübingen, Germany).

Synthesis of alcohols

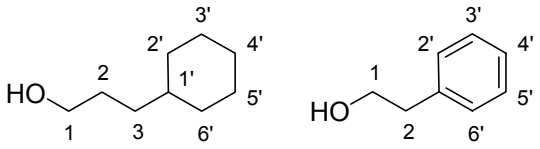


Figure 69: General numbering scheme for intermediate alcohols.

General procedure A: Alcohols by reduction of carboxylic acids with BH_3

A 1 M solution of BH_3 THF complex in dry THF (4.16 ml, 4.16 mmol, 1.5 eq) was added with a syringe to a stirred solution of the carboxylic acid (2.76 mmol, 1 eq) in 10 ml dry THF in a 50 ml two-neck round bottom flask equipped with a calcium chloride drying tube and a rubber septum in an ice / water bath. An exothermic reaction took place after which the ice bath was removed and the mixture was stirred at room temperature for at least 1 h or overnight. The reaction was terminated by careful dropwise addition 0.5 ml conc. hydrochloric acid. After the H_2 evolution had ceased, the reaction was stirred for another 15 min art room temperature and was basified with conc. ammonia. The solvent was evaporated on a rotary evaporator and the resulting aqueous mixture diluted with H_2O and extracted twice with 50 ml ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator. The product was further dried under oil pump vacuum for several hours.

General procedure B: Alcohols by reduction of carboxylic acids, esters, or acid chlorides with $LiAlH_4$

A solution of the carboxylic acid, the ester, or the acid chloride (33.74 mmol, 1.0 eq) in 50 ml dry THF was added dropwise to a refluxing, magnetically stirred slurry of 1.92 g $LiAlH_4$ (37.95 g/mol, 50.61 mmol, 1.5 eq) in 25 ml dry THF in a 100 ml two-necked round bottom flask equipped with a reflux condenser and a dropping funnel. The reaction was held at reflux for 3 h, terminated by dropwise addition of 5 ml saturated $MgSO_4$ solution, and filtered through a layer of diatomaceous earth. The filtrate was evaporated on a rotary evaporator, the residue partitioned between H_2O and ethyl acetate, and the aqueous phase re-extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator. The product was further dried under oil pump vacuum for several hours.

Cyclopropylmethanol (74)

Cyclopropylmethanol (0.97 g, C_4H_8O, 72.06 g/mol, 13.45 mmol, 40%) was obtained from 2.90 g cyclopropanecarboxylic acid (86.09 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

Cyclopentylmethanol (75)

Cyclopentylmethanol ($C_6H_{12}O$, 100.16 g/mol) was obtained From 5.00 g cyclopentanecarboxylic acid (114.14 g/mol, 43.8 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.29): δ = 3.50 (d, J = 7 Hz, 2 H, H_2-1), 2.21 - 1.96 (m, 2 H, H-2'$_{eq}$,5'$_{eq}$), 1.96 - 1.92 (m, 6 H, H-1', OH, H_2-3',4'), 1.42 - 1.11 (m, 2 H, H-2'$_{ax}$,5'$_{ax}$).

Cyclohexylmethanol (76)

Cyclohexylmethanol ($C_{12}H_{14}O$, 114.19 g/mol) was obtained from 5.00 g cyclohexanecarboxylic acid (128.17 g/mol, 39.0 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.28): δ = 3.43 (d, J = 6.5 Hz, 2 H, H_2-1), 1.89 - 1.59 (m, 6 H, H-2'$_{eq}$,6'$_{eq}$,3'$_{eq}$,5'$_{eq}$,4'$_{eq}$, -OH-1), 1.59 - 1.34 (m, 1 H, H-1'), 1.34 - 1.07 (m, 3 H, H-3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.07 - 0.80 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

Adamantan-1-yl-methanol (77)

Adamantan-1-yl-methanol ($C_{11}H_{18}O$, 166.26 g/mol) was obtained from 1.09 g adamantane-1-carboxylic acid (180.24 g/mol, 7.07 mmol) by general procedure B ($LiAlH_4$).

(1*H*-Pyrrol-2-yl)-methanol (78)

(1*H*-Pyrrol-2-yl)-methanol (1.13 g, C_5H_7NO, 97.05 g/mol, 11.64 mmol, 64%, impurities detected by ^{1}H NMR) was obtained from 2.02 g 1*H*-pyrrole-2-carboxylic acid (111.10 g/mol, 18.2 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 8.46 (s br, 1 H, H-1'), 6.73 - 6.66 (m, 1 H, H-5'), 6.19 - 6.07 (m, 2 H, H-3',4'), 4.55 (s, 2 H, H_2-1), 1.86 (s br, 1 H, -OH-1).

(5-Methylthiophen-2-yl)-methanol (79)

(5-Methylthiophen-2-yl)-methanol (2.42 g, $C_6H_8O_5$, 128.20 g/mol, 18.91 mmol, 90%, impurities detected by ^{1}H NMR) was obtained from 3.00 g 5-methylthiophene-2-carboxylic acid (142.18 g/mol, 21.1 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 6.78 (d, J = 3 Hz, 1 H, H-3'), 6.60 (d, J = 3 Hz, 1 H, H-4'), 4.71 (s, 2 H, H_2-1), 2.46 (s, 3 H, -CH_3-5'), 1.91 (s br, 1 H, -OH-1).

(2-Methylphenyl)-ethanol (80)

(2-Methylphenyl)-ethanol (2.60 g, $C_9H_{12}O$, 136.20 g/mol, 19.05 mmol, 95%) from 3.00 g (2-methylphenyl)-acetic acid (150.17 g/mol, 20.0 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.17 - 7.13 (m, 4 H, H-3'-6'), 3.82 (t, J = 7.0 Hz, 2 H, H_2-1), 2.89 (t, J = 7.0 Hz, 2 H, H_2-2), 2.33 (s, 3 H, -CH_3-2'), 1.61 (s, 1 H, -OH-1).

(3-Methylphenyl)-ethanol (81)

(3-Methylphenyl)-ethanol (2.55 g, $C_9H_{12}O$, 136.20 g/mol, 18.69 mmol, 94%) was obtained from 3.00 g (3-methylphenyl)-acetic acid (150.17 g/mol, 20.0 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 7.22 - 7.14 (m, 1 H, H-5'), 7.08 - 6.97 (m, 3 H, H-6',2',4'), 3.82 (t, J = 6.5 Hz, 2 H, H_2-1), 2.81 (t, J = 6.5 Hz, 2 H, H_2-2), 2.33 (s, 3 H, -CH_3-3'), 1.70 (s, 1 H, -OH-1).

(4-Methylphenyl)-ethanol (82)

(4-Methylphenyl)-ethanol (2.63 g, $C_9H_{12}O$, 136.20 g/mol, 19.28 mmol, 96%) was obtained from 3.00 g (4-methylphenyl)-acetic acid (150.17 g/mol, 20.0 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.12 - 7.11 (m, 4 H, H-2',3',5',6'), 3.82 (t, J = 6.5 Hz, 2 H, H_2-1), 2.82 (t, J = 6.5 Hz, 2 H, H_2-2), 2.32 (s, 3 H, -CH_3-4'), 1.57 (s br, 1 H, -OH-1).

Biphenyl-4-yl-ethanol (83)

Biphenyl-4-yl-ethanol (0.80 g, $C_{12}H_{14}O$, 198.27 g/mol, 4.01 mmol, 93%) was obtained from 0.919 g biphenyl-4-yl-acetic acid (212.24 g/mol, 4.33 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.63 - 7.51 (m, 4 H, H-2'',6'',3',5'), 7.49 - 7.26 (m, 5 H, H-3'',5'', H-4'',2',6'), 3.91 (t, J = 6.5 Hz, 2 H, H_2-1), 2.92 (t, J = 6.5 Hz, 2 H, H_2-2), 1.55 (s, 1 H, -OH-1).

(2-Hydroxyphenyl)-ethanol (84)

(2-Hydroxyphenyl)-ethanol (1.07 g, $C_8H_{10}O$, 138.17 g/mol, 7.74 mmol, 118% crude yield) was obtained as water-soluble fine white crystals after from 1.00 g (2-hydroxyphenyl)-acetic acid (152.15 g/mol, 6.57 mmol) by general procedure A (BH_3). Extraction of the product from the reaction mixture with 4 × 20 ml ethyl acetate.

^{1}H NMR (300 MHz, MeOH-d_4, $\delta_{solvent}$ = 4.86, 3.300 (reference)): δ = 7.06 (d, J = 7.5 Hz, 1 H, H-6'), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-4'), 6.74 (d, J = 7.5 Hz, 1 H, H-3'), 6.72

(ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-5'), 3.73 (t, J = 7 Hz, 2 H, H_2-1), 2.82 (t, J = 7 Hz, 2 H, H_2-2).

(3-Hydroxyphenyl)-ethanol (85)

(3-Hydroxyphenyl)-ethanol (1.58 g, $C_8H_{10}O$, 138.17 g/mol, 11.44 mmol, 87%) was obtained as water-soluble fine white crystals from 2.00 g (3-hydroxyphenyl)-acetic acid (152.15 g/mol, 13.14 mmol) by general procedure A (BH_3) with vigorous stirring of the reaction mix for 2 h until the gum-like precipitate had disappeared. Extraction of the product from the reaction mixture with 4 × 20 ml ethyl acetate.

^{1}H NMR (300 MHz, MeOH-d_4, $\delta_{solvent}$ = 4.85, 3.300 (reference)): δ = 7.07 (td, J = 7.5 Hz, 0.5 Hz, 1 H, H-5'), 6.70 - 6.64 (m, 2 H, H-2',4'), 6.60 (td, J = 8 Hz, 2.5 Hz, 1 Hz, 1 H, H-6'), 3.71 (t, J = 7 Hz, 2 H, H_2-1), 2.73 (t, J = 7 Hz, 2 H, H_2-2).

(4-Hydroxyphenyl)-ethanol ($LiAlH_4$) (86)

(4-Hydroxyphenyl)-ethanol (1.26 g, 138.17 g/mol, 9.12 mmol, 28%) was obtained as a water-soluble fine white powder after crystallization of the dark yellow viscous oil from $CHCl_3$ from 5.00 g (4-hydroxyphenyl)-acetic acid (152.15 g/mol, 32.9 mmol) by general procedure B ($LiAlH_4$).

(4-Hydroxyphenyl)-ethanol (BH_3) (86)

(4-Hydroxyphenyl)-ethanol (0.92 g, $C_8H_{10}O$, 138.17 g/mol, 6.67 mmol, 101% crude yield, impurities detected by ^{1}H NMR) was obtained after extraction from the reaction mixture with 4 × 20 ml ethyl acetate as water-soluble fine white crystals from 1.00 g (4-hydroxyphenyl)-acetic acid (152.15 g/mol, 6.57 mmol) by general procedure A (BH_3) with vigorous stirring of the reaction mix for 2 h until the gum-like precipitate had disappeared.

^{1}H NMR (300 MHz, MeOH-d_4, $\delta_{solvent}$ = 4.87, 3.300 (reference)): δ = 7.02 (d, J = 8.5 Hz, 2 H, H-2',6'), 6.69 (d, J = 8.5 Hz, 2 H, H-3',5'), 3.67 (t, J = 7 Hz, 2 H, H_2-1), 2.70 (t, J = 7 Hz, 2 H, H_2-2).

(2-Methoxyphenyl)-ethanol (88)

(2-Methoxyphenyl)-ethanol ($C_9H_{12}O_2$, 152.20 g/mol) was obtained from (2-methoxyphenyl)-acetic acid (3.00 g 166.17 g/mol, 18.1 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.21 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-4'), 7.15 (dd, J = 7 Hz, 1.5 Hz, 1 H, H-6'), 6.89 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'), 6.85 (d, J = 8.5 Hz, 1 H, H-3', 3.81 (s, 3 H, -OCH_3-2'), 3.80 (t, J = 6.5 Hz, 2 H, H_2-1), 2.89 (t, J = 6.5 Hz, 2 H, H_2-2), 1.97 (s, 1 H, -OH-1).

(3-Methoxyphenyl)-ethanol (89)

(3-Methoxyphenyl)-ethanol (2.42 g, $C_9H_{12}O_2$, 152.20 g/mol, 15.90 mmol, 88%) was obtained from 3.00 g (3-methoxyphenyl)-acetic acid (166.17 g/mol, 18.1 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 7.26 - 7.18 (m, 1 H, H-5'), 6.85 - 6.74 (m, 3 H, H-6',2',4'), 3.79 (s, 3 H, -OCH_3-3'), 3.84 (t, J = 6.5 Hz, 2 H, H_2-1), 2.83 (t, J = 6.5 Hz, 2 H, H_2-2), 1.83 (s, 1 H, -OH-1).

(4-Methoxyphenyl)-ethanol (90)

(4-Methoxyphenyl)-ethanol (2.69 g, $C_9H_{12}O_2$, 152.20 g/mol, 17.67 mmol, 59%) was obtained from 5.00 g (4-methoxyphenyl)-acetic acid (166.17 g/mol, 30.09 mmol) by general procedure B ($LiAlH_4$) using diethyl ether instead of THF. The at room temperature oily crystal mass solidified at 4 °C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.14 (d, J = 8.5 Hz, 2 H, H-2',6'), 6.85 (d, J = 8.5 Hz, 2 H, H-3',5'), 3.79 (s, 3 H, -OCH_3-4'), 3.81 (t, J = 6.5 Hz, 2 H, H_2-1), 2.80 (t, J = 6.5 Hz, 2 H, H_2-2), 1.61 (s, 1 H, -OH-1).

(2-Nitrophenyl)-ethanol (91)

(2-Nitrophenyl)-ethanol (1.68 g, $C_8H_9NO_3$, 167.16 g/mol, 10.05 mmol, 90%) was obtained from 2 g (2-nitrophenyl)-acetic acid (181.15 g/mol, 11.04 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 7.92 (dd, J = 8 Hz, 1 Hz, 1 H, H-3'), 7.55 (td, J = 7.5 Hz, 1 Hz, 1 H, H-5'), 7.46 - 7.33 (m, 2 H, H-6',4'), 3.93 (t, J = 6.5 Hz, 2 H, H_2-1), 3.16 (t, J = 6.5 Hz, 2 H, H_2-2), 1.89 (s br, 1 H, -OH-1).

(3-Nitrophenyl)-ethanol (92)

(2-Nitrophenyl)-ethanol (1.81 g, $C_8H_9NO_3$, 167.16 g/mol, 10.83 mmol, 78%) was obtained as yellow-orange crystals from 0.50 g (3-nitrophenyl)-acetic acid (181.15 g/mol, 2.76 mmol) by general procedure A (BH_3). Recrystallization from diethyl ether / hexane.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 8.12 (s, 1 H, H-2'), 8.10 (d, J = 8.5 Hz, 1 H, H-4'), 7.59 (d, J = 7.5 Hz, 1 H, H-6'), 7.48 (t, J = 7.5 Hz, 1 H, H-5'), 3.94 (t, J = 6.5 Hz, 2 H, H_2-1), 2.99 (t, J = 6.5 Hz, 2 H, H_2-2), 1.64 (s br, 1 H, -OH-1).

(4-Nitrophenyl)-ethanol (93)

(4-Nitrophenyl)-ethanol ($C_8H_9NO_3$, 167.16 g/mol) was obtained from 4.96 g (4-nitrophenyl)-acetic acid (181.15 g/mol, 27.4 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 8.17 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.41 (d, J = 8.5 Hz, 2 H, H-2',6'), 3.93 (t, J = 6.5 Hz, 2 H, H_2-1), 2.98 (t, J = 6.5 Hz, 2 H, H_2-2), 1.52 (s br, 1 H, -OH-1).

(2-Fluorophenyl)-ethanol (94)

(2-Fluorophenyl)-ethanol (2.14 g, C_8H_9FO, 140.16 g/mol, 15.25 mmol, 87%) was obtained from 2.71 g (2-fluorophenyl)-acetic acid (154.14 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 - 7.14 (m, 2 H, 2 Ar-H), 7.14 - 6.96 (m, 2 H, 2 Ar-H), 3.84 (t, J = 6.5 Hz, 2 H, H_2-1), 2.90 (t, J = 6.5 Hz, 2 H, H_2-2), 1.80 (s, 1 H, -OH-1).

(3-Fluorophenyl)-ethanol (95)

(3-Fluorophenyl)-ethanol (2.25 g, C_8H_9FO, 140.16 g/mol, 16.07 mmol, 91%) was obtained from 2.71 g (3-fluorophenyl)-acetic acid (154.14 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.33 - 7.19 (m, 1 H, H-5'), 7.03 - 6.86 (m, 3 H, H-6',2',4'), 3.83 (t, J = 6.5 Hz, 2 H, H_2-1), 2.84 (t, J = 6.5 Hz, 2 H, H_2-2), 1.77 (s, 1 H, -OH-1).

(2-Chlorophenyl)-ethanol (96)

(2-Chlorophenyl)-ethanol (2.06 g, C_8H_9ClO, 156.62 g/mol, 13.17 mmol, 75%) was obtained from 3.00 g (2-chlorophenyl)-acetic acid (170.59 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.41 - 7.33 (m, 1 H, H-3'), 7.33 - 7.11 (m, 3 H, H-4',5',6'), 3.88 (t, J = 6.5 Hz, 2 H, H_2-1), 3.02 (t, J = 6.5 Hz, 2 H, H_2-2), 1.59 (s br, 1 H, -OH-1).

(3-Chlorophenyl)-ethanol (97)

(3-Chlorophenyl)-ethanol (2.56 g, C_8H_9ClO, 156.62 g/mol, 16.33 mmol, 93%) was obtained from 3.00 g (3-chlorophenyl)-acetic acid (170.59 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.26 - 7.20 (m, 3 H, H-2',5',4'), 7.14 - 7.07 (m, 1 H, H-6'), 3.85 (t, J = 6.5 Hz, 2 H, H_2-1), 2.84 (t, J = 6.5 Hz, 2 H, H_2-2), 1.56 (s, 1 H, -OH-1).

(4-Choro-phenyl)-ethanol (98)

(4-Choro-phenyl)-ethanol (2.59 g, C_8H_9ClO, 156.62 g/mol, 16.51 mmol, 94%) was obtained from 3.00 g (4-choro-phenyl)-acetic acid (170.59 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.15 (d, J = 8.5 Hz, 2 H, H-2',6'), 3.82 (t, J = 6.5 Hz, 2 H, H_2-1), 2.82 (t, J = 6.5 Hz, 2 H, H_2-2), 1.62 (s, 1 H, -OH-1).

(2-Bromophenyl)-ethanol (99)

(2-Bromophenyl)-ethanol (2.60 g, C_8H_9BrO, 201.07 g/mol, 12.91 mmol, 73%) was obtained from 3.78 g (2-bromophenyl)-acetic acid (215.04 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.54 (d, J = 8 Hz, 1 H, H-3'), 7.26 - 7.22 (m, 2 H, H-5',6'), 7.12 - 7.02 (m, 1 H, H-4'), 3.84 (t, J = 7 Hz, 2 H, H_2-1), 3.00 (t, J = 6.5 Hz, 2 H, H_2-2), 1.93 (s, 1 H, -OH-1).

(3-Bromophenyl)-ethanol (100)

(3-Bromophenyl)-ethanol (1.66 g, C_8H_9BrO, 201.07 g/mol, 8.28 mmol, 94%) was obtained from 1.89 g (3-bromophenyl)-acetic acid (215.04 g/mol, 8.79 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.41 - 7.32 (m, 2 H, H-2',4'), 7.19 - 7.14 (m, 2 H, H-5',6'), 3.83 (t, J = 6.5 Hz, 2 H, H_2-1), 2.82 (t, J = 6.5 Hz, 2 H, H_2-2), 1.67 (s, 1 H, -OH-1).

(4-Bromophenyl)-ethanol (101)

(4-Bromophenyl)-ethanol (3.39 g, C_8H_9BrO, 201.07 g/mol, 16.87 mmol, 96%) was obtained from 3.78 g (4-bromophenyl)-acetic acid (215.04 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.41 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.08 (d, J = 8.5 Hz, 2 H, H-2',6'), 3.79 (t, J = 6.5 Hz, 2 H, H_2-1), 2.79 (t, J = 6.5 Hz, 2 H, H_2-2), 1.85 (s, 1 H, -OH-1).

(2,5-Dimethylphenyl)-ethanol (102)

(2,5-Dimethylphenyl)-ethanol (2.52 g, $C_{10}H_{14}O$, 150.22 g/mol, 16.80 mmol, 92%) was obtained from 3.00 g (2,5-dimethylphenyl)-acetic acid (164.20 g/mol, 18.3 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.22): δ = 7.04 (d, J = 7.5 Hz, 1 H, H-3'), 6.97 (s, 1 H, H-6'), 6.94 (d, J = 7.5 Hz, 1 H, H-4'), 3.79 (t, J = 7 Hz, 2 H, H_2-1), 2.84 (t, J = 7 Hz, 2 H, H_2-2), 2.29 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 1.71 (s, 1 H, -OH-1).

(3,5-Dimethylphenyl)-ethanol (103)

(3,5-Dimethylphenyl)-ethanol ($C_{10}H_{14}O$, 150.22 g/mol) was obtained as a clear oil from 0.80 g (3,5-dimethylphenyl)-acetic acid (164.20 g/mol, 6.09 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 6.87 (s, 1 H, H-4'), 6.84 (s, 2 H, H-2',6'), 3.82 (t, J = 6.5 Hz, 2 H, H_2-1), 2.78 (t, J = 6.5 Hz, 2 H, H_2-2), 2.29 (s, 6 H, -CH_3-3',5'), 1.59 (s, 1 H, -OH-1).

(3,4-Dihydroxyphenyl)-ethanol (104)

(3,4-Dihydroxyphenyl)-ethanol ($C_8H_{10}O_3$, 182.22 g/mol) was obtained as a clear gray-greenish glass-like solid from 2.50 g (3,4-dihydroxyphenyl)-acetic acid (168.15 g/mol, 14.9 mmol) by general procedure A (BH_3).

^{1}H NMR (300 MHz, MeOH-d_4, $\delta_{solvent}$ = 4.88, $\delta_{reference}$ = 3.300): δ = 6.66 (d, J = 8 Hz, 1 H, H-5'), 6.64 (d, J = 2 Hz, 1 H, H-2'), 6.51 (dd, J = 8 Hz, 2 Hz, 1 H, H-6'), 3.66 (t, J = 7.5 Hz, 2 H, H_2-1), 2.65 (t, J = 7.5 Hz, 2 H, H_2-2).

(4-Hydroxy-3-methoxyphenyl)-ethanol (105)

(4-Hydroxy-3-methoxyphenyl)-ethanol (0.33 g, $C_9H_{12}O_3$, 168.20 g/mol, 1.94 mmol, 39%) was obtained as a clear brownish oil from 0.900 g (4-hydroxy-3-methoxyphenyl)-acetic acid (182.17 g/mol, 4.94 mmol) by general procedure A (BH_3). Loss due to spilling.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.86 (d, J = 8.5 Hz, 1 H, H-5'), 6.73 (s, 1 H, H-2'), 6.72 (d, J = 6.5 Hz, 1 H, H-6'), 3.88 (s, 3 H, -OCH_3-3'), 3.81 (t, J = 6.5 Hz, 2 H, H_2-1), 2.80 (t, J = 6.5 Hz, 2 H, H_2-2).

(2,5-Dimethoxyphenyl)-ethanol (106)

(2,5-Dimethoxyphenyl)-ethanol ($C_{10}H_{14}O_3$, 182.22 g/mol) was obtained from 3.00 g (2,5-dimethoxyphenyl)-acetic acid (196.20 g/mol, 15.3 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.82 - 6.68 (m, 3 H, H-3',4',6'), 3.81 (t, J = 6.5 Hz, 2 H, H_2-1), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.87 (t, J = 6.5 Hz, 2 H, H_2-2), 1.97 (s, 1 H, -OH-1).

(3,4-Dimethoxyphenyl)-ethanol (107)

(3,4-Dimethoxyphenyl)-ethanol (4.70 g, $C_{10}H_{14}O_3$, 182.22 g/mol, 27.79 mmol, 96%) was obtained as white crystalline solid from 5.27 g (3,4-dimethoxyphenyl)-acetic acid (196.20 g/mol, 26.9 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 6.86 - 6.74 (m, 3 H, H-2',5',6'), 3.88 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.83 (t, J = 6.5 Hz, 2 H, H_2-1), 2.81 (t, J = 6.5 Hz, 2 H, H_2-2), 1.66 (s, 1 H, -OH-1).

(3,5-Dimethoxyphenyl)-ethanol (108)

(3,5-Dimethoxyphenyl)-ethanol ($C_{10}H_{14}O_3$, 182.22 g/mol) was obtained as a clear oil from 0.736 g (3,5-dimethoxyphenyl)-acetic acid (196.20 g/mol, 3.75 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.39 (d, J = 2 Hz, 2 H, H-2',6'), 6.34 (t, J = 2 Hz, 1 H, H-4'), 3.85 (t, J = 6.5 Hz, 2 H, H_2-1), 3.78 (s, 6 H, 2 OCH_3), 2.81 (t, J = 6.5 Hz, 2 H, H_2-2), 1.55 (s, 1 H, -OH-1).

(2,4-Dichlorophenyl)-ethanol (109)

(2,4-Dichlorophenyl)-ethanol (2.57 g $C_8H_8Cl_2O$, 191.06 g/mol, 13.44 mmol, 76%) was obtained from 3.60 g (2,4-dichlorophenyl)-acetic acid (205.04 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.38 (d, J = 1 Hz, 1 H, H-3'), 7.21 - 7.18 (m, 2 H, H-5',6'), 3.85 (t, J = 6.5 Hz, 2 H, H_2-1), 2.97 (t, J = 6.5 Hz, 2 H, H_2-2), 1.67 (s, 1 H, -OH-1).

(2,6-Dichlorophenyl)-ethanol (110)

(2,6-Dichlorophenyl)-ethanol (0.72 g, 191.06 g/mol, 3.76 mmol, 21%) was obtained from 3.60 g (2,6-dichlorophenyl)-acetic acid (205.04 g/mol, 17.6 mmol) by general procedure A (BH_3).

(2,6-Dichlorophenyl)-ethanol (BH_3, forced conditions) (110)

(2,6-Dichlorophenyl)-ethanol (2.09 g, $C_8H_8Cl_2O$, 191.06 g/mol, 10.94 mmol, 90%) was obtained as white crystals which sublimed under membrane-pump vacuum (around 20 mm Hg = 26.7 hPa) at 70 °C from 2.50 g (2,6-dichlorophenyl)-acetic acid (205.04 g/mol, 12.2 mmol) by general procedure A (BH_3) refluxing the reaction mixture for 2 h, addition of the conc. HCl, and further refluxing for 30 min.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.29 (d, J = 8 Hz, 2 H, H-3',5'), 7.10 (t, J = 8 Hz, 1 H, H-4'), 3.88 (t, J = 7 Hz, 2 H, H_2-1), 3.26 (t, J = 7 Hz, 2 H, H_2-2), 1.55 (s, 1 H, -OH-1).

(3,4-Dichlorophenyl)-ethanol (112)

(3,4-Dichlorophenyl)-ethanol (2.63 g, $C_8H_8Cl_2O$, 191.06 g/mol, 13.77 mmol, 78%) was obtained from 3.60 g (3,4-dichlorophenyl)-acetic acid (205.04 g/mol, 17.6 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.36 (d, J = 8.5 Hz, 1 H, H-5'), 7.33 (d, J = 2.5 Hz, 1 H, H-2'), 7.06 (dd, J = 8 Hz, 2 Hz, 1 H, H-6'), 3.83 (t, J = 6.5 Hz, 2 H, H_2-1), 2.81 (t, J = 6.5 Hz, 2 H, H_2-2), 1.66 (s, 1 H, -OH-1).

(Indol-3-yl)-ethanol (113)

(Indol-3-yl)-ethanol (3.43 g, $C_{10}H_{11}NO$, 161.20 g/mol, 21.28 mmol, 15%) was obtained as a white crystalline solid from 30.00 g (indol-3-yl)-oxo-acetyl chloride (indolylglyoxylchloride) (207.61 g/mol, 144.5 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.21): δ = 8.09 (s br, 1 H, H-1'), 7.60 (d, J = 7.5 Hz, 1 H, H-4'), 7.31 (d, J = 7 Hz, 1 H, H-7'), 7.19 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-6'), 7.11 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-5'), 6.98 (s, 1 H, H-2'), 3.87 (t, J = 6.5 Hz, 2 H, H_2-1), 3.00 (t, J = 6.5 Hz, 2 H, H_2-2), 1.77 (s br, 1 H, -OH-1).

5-Methoxyindol-3-yl)-ethanol (114)

(5-Methoxyindol-3-yl)-ethanol (6.92 g, $C_{11}H_{13}NO$, 191.23 g/mol, 36.19 mmol, 79%) was obtained as a slightly brown oil after repeated extractions of the filter cake from 10.73 g (5-methoxyindol-3-yl)-oxo-acetic acid methyl ester (5-methoxyindolylglyoxylic acid methyl ester) (233.22 g/mol, 46.0 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 8.00 (s br, 1 H, H-1'), 7.24 (d, J = 4.5 Hz, 1 H, H-7'), 7.05 (s, 1 H, H-2'), 7.04 (s, 1 H, H-4'), 6.87 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'), 3.89 (t, J = 6.5 Hz, 2 H, H_2-1), 3.86 (s, 3 H, -OCH_3-5'), 3.00 (t, J = 6.5 Hz, 2 H, H_2-2), 1.65 (s br, 1 H, -OH-1).

Naphthalen-1-yl-ethanol (115)

Naphthalen-1-yl-ethanol (4.25 g, $C_{12}H_{12}O$, 172.23 g/mol, 24.68 mmol, 92%) was obtained as a colorless oil from 5.00 g naphthalen-1-yl-acetic acid (186.21 g/mol, 26.9 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.22): δ = 8.07 - 7.99 (m, 1 H, H-8'), 7.88 - 7.81 (m, 1 H, H-5'), 7.73 (dd, J = 7.5 Hz, 1.5 Hz, 1 H, H-4'), 7.56 - 7.31 (m, 4 H, H-7',6',3',2'), 3.95 (t, J = 6.5 Hz, 2 H, H_2-1), 3.32 (t, J = 6.5 Hz, 2 H, H_2-2), 1.67 (s, 1 H, -OH-1).

Naphthalen-2-yl-ethanol (116)

Naphthalen-2-yl-ethanol (4.36 g, $C_{12}H_{12}O$, 172.23 g/mol, 25.31 mmol, 94%) was obtained as white crystalline solid from 5.00 g naphthalen-2-yl-acetic acid (186.21 g/mol, 26.9 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.86 - 7.75 (m, 3 H, H-5',4',8'), 7.67 (s, 1 H, H-1'), 7.52 - 7.31 (m, 3 H, H-7',6',3'), 3.92 (t, J = 6.5 Hz, 2 H, H_2-1), 3.01 (t, J = 6.5 Hz, 2 H, H_2-2), 1.58 (s br, 1 H, -OH-1).

2,2-Diphenylethanol (117)

2,2-Diphenylethanol ($C_{14}H_{14}O$, 198.26 g/mol) was obtained from 7.16 g diphenylacetic acid (212.24 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 - 7.15 (m, 10 H, 2 C_6H_5), 4.18 (td, 3 H, H_2-1, H-2), 1.57 (s, 1 H, -OH-1).

2,2-Dimethylpropanol (118)

2,2-Dimethylpropan-1-ol (neopentyl alcohol) (1.97 g, $C_5H_{12}O$, 88.15 g/mol, 22.35 mmol, 22.35 mmol, 66%) was obtained from 4.07 g 2,2-dimethylpropionyl chloride (pivaloyl chloride) (120.58 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

3-Cyclohexylpropan-1-ol (119)

3-Cyclohexylpropan-1-ol (4.27 g, $C_9H_{18}O$, 142.25 g/mol, 30.02 mmol, 89%) was obtained from 5.27 g 3-cyclohexylpropionic acid (156.22 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 3.61 (t, J = 6.5 Hz, 2 H, H_2-1), 1.79 - 1.49 (m, 8 H, H-2'$_{eq}$,6'$_{eq}$,3'$_{eq}$,5'$_{eq}$,4'$_{eq}$, H_2-2, -OH-1), 1.34 - 1.08 (m, 6 H, H-1', H_2-3, H-3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.04 - 0.76 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

3-Phenylpropan-1-ol (120)

3-Phenylpropan-1-ol (3.96 g, $C_9H_{12}O$, 136.19 g/mol, 29.08 mmol, 86%) was obtained from 5.00 g 3-phenylacrylic acid (*trans*-cinnamic acid) (148.16 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 - 7.07 (m, 5 H, C_6H_5), 3.64 (t, J = 6.5 Hz, 2 H, H_2-1), 2.69 (t, J = 7.5 Hz, 2 H, H_2-3), 2.04 (s, 1 H, -OH-1), 1.87 (tt, J = J' = 7 Hz, 2 H, H_2-2).

3-(2,5-Dimethoxyphenyl)-propan-1-ol (121)

3-(2,5-Dimethoxyphenyl)-propan-1-ol ($C_{11}H_{16}O_3$, 196.24 g/mol) was obtained from 3-(2,5-dimethoxyphenyl)-propionic acid (210.23 g/mol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.81 - 6.65 (m, 3 H, H-3',4',6'), 3.78 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.58 (t, J = 6 Hz, 2 H, H_2-1), 2.69 (t, J = 7.5 Hz, 2 H, H_2-3), 2.17 (s br, 1 H, -OH-1), 1.83 (tt, J = J' = 7 Hz, 2 H, H_2-2).

3-(3,4,5-Trimethoxyphenyl)-propan-1-ol (122)

3-(3,4,5-Trimetoxyphenyl)-propan-1-ol (2.49 g, $C_{12}H_{18}O_4$, 226.28 g/mol, 11.02 mmol, 88%) was obtained from 3.00 g 3-(3,4,5-trimethoxyphenyl)-propionic acid (240.25 g/mol, 12.5 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 6.42 (s, 2 H, H-2',6'), 3.85 (s, 6 H, -OCH_3-3',5'), 3.82 (s, 3 H, -OCH_3-4'), 3.69 (t, J = 6.5 Hz, 2 H, H_2-1), 2.66 (t, J = 7.5 Hz, 2 H, H_2-3), 1.89 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.59 (s, 1 H, -OH-1).

3-(Indol-3-yl)-propan-1-ol (123)

3-(Indol-3-yl)-propan-1-ol (2.85 g, $C_{11}H_{13}NO$, 175.10 g/mol, 16.29 mmol, 97%) was obtained from 3.19 g 3-(indol-3-yl)-propionic acid (189.21 g/mol, 16.9 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.97 (s br, 1 H, H-1'), 7.61 (d, J = 7.5 Hz, 1 H, H-4'), 7.34 (d, J = 8 Hz, 1 H, H-7'), 7.19 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-6'), 7.11 (ddd, J = 7 Hz, 7 Hz, 1.5 Hz, 1 H, H-5'), 6.97 (s, 1 H, H-2'), 3.72 (t, J = 6.5 Hz, 2 H, H_2-1), 2.86 (t, J = 7.5 Hz, 2 H, H_2-3), 1.99 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.54 (s br, 1 H, -OH-1).

2,2-Diphenylpropanol (124)

2,2-Diphenylpropanol (7.02 g, $C_{15}H_{16}O$, 208.27 g/mol, 33.68 mmol, 100%) was obtained from 7.63 g 2,2-diphenylpropionic acid (226.27 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34 - 7.15 (m, 10 H, 2 C_6H_5), 4.08 (s, 2 H, H_2-1), 1.70 (s, 3 H, H_3-3), 1.70 (s, 1 H, -OH-1).

3-Phenylsulfanyl-propan-1-ol (125)

3-Phenylsulfanyl-propan-1-ol ($C_9H_{12}OS$, 168.26 g/mol) was obtained from 6.22 g 3-phenylsulfanyl-propionic acid (184.24 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 - 7.13 (m, 5 H, C_6H_5), 3.76 (t, J = 6 Hz, 2 H, H_2-1), 3.04 (t, J = 7 Hz, 2 H, H_2-3), 1.89 (tt, J = J' = 6.5 Hz, 2 H, H_2-2), 1.72 (s, 1 H, -OH-1).

2-Ethylbutan-1-ol (126)

2-Ethylbutan-1-ol ($C_6H_{14}O$, 102.17 g/mol) was obtained from 3.92 g 2-ethylbutyric acid (116.16 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.28): δ = 3.55 (d, J = 5 Hz, 2 H, H_2-1), 1.69 (s, 1 H, -OH-1), 1.46 - 1.27 (m, 5 H, H-2, 2 H_2-3), 0.90 (t, J = 7 Hz, 6 H, 2 H_3-4).

3,3-Dimethylbutan-1-ol (127)

3,3-Dimethylbutan-1-ol ($C_6H_{14}O$, 102.17 g/mol) was obtained from 3.92 g 3,3-dimethylbutyric acid (116.16 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

4-Phenylbutan-1-ol (128)

4-Phenylbutan-1-ol (4.84 g, $C_{10}H_{14}O$, 146.19 g/mol, 33.13 mmol, 98%) was obtained from 5.54 g 4-phenylbutyric acid (164.20 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 - 7.10 (m, 5 H, C_6H_5), 3.61 (td, J = 6.5 Hz, 1 Hz, 2 H, H_2-1), 2.62 (t, J = 7 Hz, 2 H, H_2-4), 1.92 (s, 1 H, -OH-1), 1.77 - 1.48 (m, 4 H, H_2-3,2).

4-(Indol-3-yl)-butan-1-ol (129)

4-(Indol-3-yl)-butan-1-ol (0.94 g, $C_{12}H_{15}NO$, 189.12 g/mol, 4.97 mmol, 15%) was obtained as a clear red oil from 6.86 g 4-(indol-3-yl)-butyric acid (203.24 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.95 (s br, 1 H, H-1'), 7.60 (d, J = 7.5 Hz, 1 H, H-4'), 7.34 (d, J = 8 Hz, 1 H, H-7'), 7.18 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-5'), 7.10 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-6'), 6.96 (s, 1 H, H-2'), 3.67 (t, J = 6.5 Hz, 2 H, H_2-1), 2.79 (t, J = 7 Hz, 2 H, H_2-4), 1.88 - 1.57 (m, 4 H, H_2-2,3), 1.50 (s br, 1 H, -OH-1).

2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctan-1-ol (130)

2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctan-1-ol ($C_8H_3F_{15}O$, 400.08 g/mol) was obtained from 10.00 g perfluorooctanoic acid (2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid) (414.10 g/mol, 24.1 mmol) by general procedure B ($LiAlH_4$). No reaction of 6.00 g perfluorooctanoic acid (414.07 g/mol, 14.5 mmol) by general procedure A (BH_3).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 4.09 (t, J = 13.5 Hz, 2 H, H_2-1), 2.37 (s br, 1 H, -OH-1).

Tetradecan-1-ol (131)

Tetradecan-1-ol (5.64 g, $C_{14}H_{30}O$, 214.39 g/mol, 26.31 mmol, 78%) was obtained from 8.33 g tetradecanoyl chloride (246.82 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.63 (t, J = 6.5 Hz, 2 H, H_2-1), 1.64 - 1.40 (m, 2 H, H_2-2), 1.40 - 1.21 (m, 22 H, H_2-3-13), 1.02 (s br, 1 H, -OH-1), 0.88 (t, J = 6.5 Hz, 3 H, H_3-14).

Icosan-1-ol (132)

Icosan-1-ol ($C_{20}H_{42}O$, 298.55 g/mol) was obtained from 11.49 g icosanoic acid ethyl ester (340.58 g/mol, 33.7 mmol) by general procedure B ($LiAlH_4$).

Synthesis of alkyl halides

General procedure C: Iodides by reaction of alcohols with PPh_3 / imidazole / iodine

To 3.16 g triphenylphosphine (PPh_3) (262.29 g/mol, 12.06 mmol, 1.30 eq) and 0.85 g imidazole (68.08 g/mol, 12.5 mmol, 1.35 eq) in 25 ml dichloromethane in a 50 ml round bottom flask equipped with a capillary was added 3.06 g iodine (253.81 g/mol, 12.06 mmol, 1.30 eq) under stirring. During the next few minutes a slightly exothermic reaction took place during which the iodine was consumed and a bright yellow slurry in a clear yellow solution formed. The flask was moved into an ice / water bath and a solution of the alcoholic educt in 10 ml dichloromethane was added all at once under stirring. The yellow precipitate disappeared during a slightly exothermic reaction and imidazole hydrochloride fell out as a white flocculent precipitate over 5 minutes. The mixture was stirred at room temperature for at least 1 h or overnight.

3 ml methanol was added and stirring was continued for 30 min. The solution was extracted with 40 ml H_2O and the organic phase vigorously shaken and extracted with 40 ml of a sodium hydrogen sulfite ($NaHSO_3$) solution acidified with hydrochloric acid. The organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator. During this evaporation triphenylphosphine oxide crystallized as a white mass. The crude product was transferred into a 25 ml beaker, homogenized with 3 ml diethyl ether, and filtered through a miniature conical Buchner funnel by applying vacuum. The filter cake was washed with 2 × 3 ml diethyl ether, leaving pure white triphenylphosphine oxide. The filtrate was evaporated on a rotary evaporator under membrane pump vacuum and later under oil pump vacuum, leaving the product as a light yellow to brown oil or crystalline mass. Sometimes more triphenylphosphine oxide crystallized from liquid products upon storage at 4 °C which could be removed by a second filtration of the undissolved oil. The amount of triphenylphosphine oxide impurity was calculated from ^1H NMR spectra. The crude yields as well as the yields corrected for the triphenylphosphine oxide content ("corr. yield") are given. The products were stored at 4 °C in the dark. Liquid products were kept over a small amount of copper powder. The crude products were used without further purification in the next reaction.

General procedure D: Bromides by reaction of alcohols with PPh_3 / imidazole / bromine

Bromides were synthesized analogous to the synthesis of iodides from alcohols by replacing iodine with equimolar amounts of bromine, added slowly as a solution in dichloromethane.

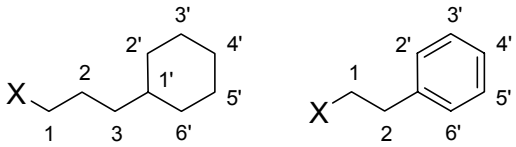


Figure 70: General numbering scheme for intermediate alkyl halides.

(Iodomethyl)-cyclopropane (133)

(Iodomethyl)-cyclopropane (C_4H_7I, 182.00 g/mol, 5% PPh_3O) was obtained from 0.670 g cyclopropylmethanol (**74**) (72.11 g/mol, 9.29 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 3.14 (d, J = 8 Hz, 2 H, H_2-1), 1.44 - 1.17 (m, 1 H, H-1'), 0.90 - 0.76 (m, 2 H, H-2'$_{trans}$,3'$_{trans}$), 0.37 - 0.25 (m, 2 H, H_2-2'$_{cis}$,3'$_{cis}$).

(Iodomethyl)-cyclopentane (134)

(Iodomethyl)-cyclopentane (2.66 g, $C_6H_{11}I$, 210.06 g/mol, 12.66 mmol, 69%, 2% PPh_3O, 68% corr. yield) was obtained as a yellow oil from 1.85 g cyclopentylmethanol (**75**) (100.16 g/mol, 18.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.21 (d, J = 7 Hz, 2 H, H_2-1), 2.18 (dtt, J = J' = J'' = 7.5 Hz, 1 H, H-1'), 1.96 - 1.76 (m, 2 H, H-2'$_{eq}$,5'$_{eq}$), 2.99 - 2.85 (m, 4 H, H_2-3',4'), 1.35 - 1.13 (m, 2 H, H-2'$_{ax}$,5'$_{ax}$).

(Iodomethyl)-cyclohexane (135)

(Iodomethyl)-cyclohexane (3.22 g, $C_7H_{13}I$, 224.08 g/mol, 14.36 mmol, 78%, 2% PPh_3O, 76% corr. yield, impurities detected by ^{1}H NMR) was obtained as a yellow oil from 2.11 g cyclohexylmethanol (**76**) (114.19 g/mol, 18.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.10 (d, J = 6.5 Hz, 2 H, H_2-1), 1.95 - 1.53 (m, 5 H, H-2'$_{eq}$,6'$_{eq}$,3'$_{eq}$,5'$_{eq}$,4'$_{eq}$), 1.53 - 1.11 (m, 4 H, H-1',3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.11 - 0.82 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

1-Iodomethyl-adamantane (136)

1-Iodomethyl-adamantane (0.47 g, $C_{10}H_{17}I$, 276.16 g/mol, 1.70 mmol, 34%, 4% PPh_3O, 32% corr. yield) was obtained from 0.843 g adamantan-1-yl-methanol (**77**) (166.26 g/mol, 5.07 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.02 (s, 2 H, H_2-1), 2.03 - 1.89 (tqu, 3 H, 3 H-3'), 1.62 (d, J = 2.5 Hz, 6 H, 3 H_2-4'), 1.52 (d, J = 2.5 Hz, 6 H, 3 H_2-2').

2-Iodomethyl-5-methylthiophene (impure) (137)

2-Iodomethyl-5-methylthiophene (1.25 g, C_6H_7IS, 238.09 g/mol, 5.24 mmol, 52%, 50% PPh_3O, 26% corr. yield, impurities detected by ^1H NMR) was obtained from 1.28 g (5-methylthiophen-2-yl)-methanol (**79**) (128.19 g/mol, 10 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.77 (d, J = 3 Hz, 1 H, H-3'), 6.60 (d, J = 2.5 Hz, 1 H, H-4'), 4.57 (s, 2 H, H_2-1), 2.46 (s, 3 H, -CH_3-5').

2-Iodomethyl-tetrahydrofuran (138)

2-Iodomethyl-tetrahydrofuran (2.88 g, C_5H_9IO, 213.04 g/mol, 13.51 mmol, 61%, 4% PPh_3O, 59% corr. yield) was obtained as a slightly yellow oil from 2.25 g (tetrahydrofuran-2-yl)-methanol (102.13 g/mol, 22.0 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.29): δ = 4.08 - 3.75 (m, 3 H, H_2-1, H-2'), 3.26 - 3.19 (m, 2 H, H_2-5'), 2.21 - 1.18 (m, 3 H, H_2-3', H-3'$_{eq}$), 1.18 - 1.57 (m, 1 H, H-3'$_{ax}$).

Chloroacetic acid methyl ester (139)

Chloroacetic acid (15.00 g, 94.50 g/mol, 158.7 mmol) and 0.5 g (4-toluene)-sulfonic acid (172.20 g/mol, 2.90 mmol) in 50 ml methanol were refluxed for 3 h, the solvent was removed on a rotary evaporator, and the resulting liquid was distilled under oil pump vacuum, yielding 6.23 g chloroacetic acid methyl ester ($C_3H_5ClO_2$, 108.52 g/mol, 57.41 mmol, 36%, bp 132 - 133 °C (oil pump vacuum)) as a clear colorless liquid.

2-Chloro-*N,N*-diethylacetamide (140)

To 5.00 g chloroacetyl chloride (112.94 g/mol, 44.3 mmol) in 100 ml diethyl ether was added 6.48 g diethylamine (73.14 g/mol, 88.54 mmol) in diethyl ether dropwise under stirring. After the addition the resulting slurry was stirred for 10 min at room temperature, the organic phase extracted with 100 ml water, 100 ml diluted hydrochloric acid, 100 ml diluted $NaHCO_3$ solution, and with 2 × 100 ml H_2O. The organic phase was dried over $MgSO_4$, the solvent was removed on a rotary evaporator, and the resulting oil was kept under membrane pump vacuum at 60 °C for 30 min, yielding 1.21 g 2-chloro-*N,N*-diethylacetamide ($C_6H_{12}ClNO$, 149.62 g/mol, 8.09 mmol, 18%).

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.28): δ = 4.06 (s, 2 H, H_2-1), 3.47 - 3.31 (m, 4 H, 2 *N*-CH_2), 1.24 (t, J = 7 Hz, 3 H, $C_{(Z)}H_3$), 1.15 (t, J = 7 Hz, 3 H, $C_{(E)}H_3$).

(2-Iodoethyl)-benzene (141)

(2-Iodoethyl)-benzene (3.67 g, C_8H_9I, 232.06 g/mol, 15.8 mmol, 96%, 6% PPh_3O, 92% corr. yield) was obtained from 2.00 g 2-phenylethanol (122.16 g/mol, 16.4 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 - 7.15 (m, 5 H, C_6H_5), 3.40 - 3.28 (m, 2 H, H_2-1), 3.24 - 3.12 (m, 2 H, H_2-2).

2-Methyl-1-(2-iodoethyl)-benzene (142)

2-Methyl-1-(2-iodoethyl)-benzene (4.10 g, $C_9H_{11}I$, 246.09 g/mol, 16.65 mmol, 97%, 4% PPh_3O, 93% corr. yield) was obtained from 2.35 g (2-methylphenyl)-ethanol (**80**) (136.19 g/mol, 17.3 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 7.20 - 7.09 (m, 4 H, H-3',4',5',6'), 3.35 - 3.12 (m, 4 H, H_2-1,2), 2.31 (s, 3 H, -CH_3-2').

3-Methyl-1-(2-iodoethyl)-benzene (143)

3-Methyl-1-(2-iodoethyl)-benzene (3.69 g, $C_9H_{11}I$, 246.09 g/mol, 14.98 mmol, 86%, 4% PPh_3O, 83% corr. yield) was obtained from 2.37 g (3-methylphenyl)-ethanol (**81**) (136.19 g/mol, 17.4 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.20 (dd, J = J' = 8 Hz, 1 H, H-5'), 7.11 - 6.94 (m, 3 H, H-6',2',4'), 3.38 - 3.28 (m, 2 H, H_2-1), 3.18 - 3.07 (m, 2 H, H_2-2), 2.34 (s, 3 H, -CH_3-3').

4-Methyl-1-(2-iodoethyl)-benzene (144)

4-Methyl-1-(2-iodoethyl)-benzene (4.15 g, $C_9H_{11}I$, 246.09 g/mol, 16.84 mmol, 92%, 4% PPh_3O, 88% corr. yield) was obtained from 2.50 g (4-methylphenyl)-ethanol (**82**) (136.19 g/mol, 18.4 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.22): δ = 7.12 (d, 8.5 Hz, 2 H, H-3',5'), 7.06 (d, 8.5 Hz, 2 H, H-2',6'), 3.37 - 3.26 (m, 2 H, H_2-1), 3.18 - 3.07 (m, 2 H, H_2-2), 2.31 (s, 3 H, -CH_3-4').

4-(2-Iodoethyl)-biphenyl (145)

4-(2-Iodoethyl)-biphenyl ($C_{14}H_{13}I$, 308.16 g/mol, 11% PPh_3O) was obtained from 2-biphenyl-4-yl-ethanol (**83**) (198.26 g/mol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62 - 7.23 (m, 9 H, $C_{12}H_9$ + PPh_3O), 3.38 (t, 7.5 Hz, 2 H, H_2-1), 3.22 (t, 7.5 Hz, 2 H, H_2-2).

2-Hydroxy-1-(2-iodoethyl)-benzene (146)

2-Hydroxy-1-(2-iodoethyl)-benzene (C_8H_9IO, 248.06 g/mol, 48% PPh_3O) was obtained from 0.830 g (2-hydroxyphenyl)-ethanol (**84**) (138.16 g/mol, 6.01 mmol) by general procedure C. The compound is not soluble in diethyl ether

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.11 - 6.99 (m, 2 H, H-6',4'), 6.88 - 6.74 (m, 2 H, H-5',3'), 3.44 - 3.33 (m, 2 H, H_2-1), 3.24 - 3.13 (m, 2 H, H_2-2).

3-Hydroxy-1-(2-iodoethyl)-benzene (147)

3-Hydroxy-1-(2-iodoethyl)-benzene (C_8H_9IO, 248.06 g/mol, 49% PPh_3O) was obtained from 1.57 g (3-hydroxyphenyl)-ethanol (**85**) (138.16 g/mol, 11.36 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.10 (t, J = 8 Hz, 1 H, H-5'), 6.78 (dd, J = 8 Hz, 2 Hz, 2 H, H-2'), 6.72 - 6.62 (m, 2 H, H-4',6'), 3.24 (t, J = 7.5 Hz, 2 H, H_2-1), 3.03 (t, J = 8 Hz, 2 H, H_2-2).

4-Hydroxy-1-(2-iodoethyl)-benzene (148)

4-Hydroxy-1-(2-iodoethyl)-benzene (C_8H_9IO, 248.06 g/mol, 47% PPh_3O) was obtained as a diethyl ether-insoluble dark yellow oil containing triphenylphosphine oxide crystals from 1.07 g (4-hydroxyphenyl)-ethanol (**86**) (138.17 g/mol, 7.74 mmol) by general procedure C.

^{1}H NMR (300 MHz, MeOH-d_4, $\delta_{solvent}$ = 4.78, 3.300 (reference)): δ = 6.91 (d, J = 8.5 Hz, 2 H, H-2',6'), 6.59 (d, J = 8.5 Hz, 2 H, H-3',5'), 3.24 - 3.18 (t, 2 H, H_2-1 + solvent), 2.92 (t, J = 7.5 Hz, 2 H, H_2-2).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.01 (d, 8.5 Hz, 2 H, H-2',6'), 6.81 (d, 8.5 Hz, 2 H, H-3',5'), 3.29 (t, 7.5 Hz, 2 H, H_2-1), 3.08 (t, 7.5 Hz, 2 H, H_2-2).

4-Hydroxy-3-methoxy-1-(2-iodoethyl)-benzene (149)

4-Hydroxy-3-methoxy-1-(2-iodoethyl)-benzene (C_8H_9IO, 278.09 g/mol) was obtained from 0.326 g (4-hydroxy-3-methoxyphenyl)-ethanol (**86**) (104.15 g/mol, 3.13 mmol) by general procedure C.

2-Methoxy-1-(2-iodoethyl)-benzene (150)

2-Methoxy-1-(2-iodoethyl)-benzene (3.73 g, $C_9H_{11}IO$, 261.99 g/mol, 14.24 mmol, 92%, 7% PPh_3O, 86% corr. yield) was obtained from 2.35 g (2-methoxyphenyl)-ethanol (**88**) (152.19 g/mol, 15.4 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.24 (ddd, J = 8 Hz, 8 Hz, 1.5 Hz, 1 H, H-4'), 7.12 (dd, J = 7.5 Hz, 1 Hz, 1 H, H-6'), 6.89 (t, 7.5 Hz, 1 H, H-5'), 6.85 (d, 8.5 Hz, 1 H, H-3'), 3.82 (s, 3 H, -OCH_3-2'), 3.36 (t, J = 7.5 Hz, 2 H, H_2-1), 3.18 (t, J = 7.5 Hz, 2 H, H_2-2).

3-Methoxy-1-(2-iodoethyl)-benzene (151)

3-Methoxy-1-(2-iodoethyl)-benzene (3.29 g, $C_9H_{11}IO$, 261.99 g/mol,12.54 mmol, 87%, 6% PPh_3O, 82% corr. yield) was obtained from 2.20 g (3-methoxyphenyl)-ethanol (**89**) (152.19 g/mol, 14.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 7.23 (t, J = 8 Hz, 1 H, H-5'), 6.84 - 6.71 (m, 3 H, H-6',2',4'), 3.80 (s, 3 H, -OCH_3-3'), 3.34 (t, 7.5 Hz, 2 H, H_2-1), 3.15 (t, 7.5 Hz, 2 H, H_2-2).

4-Methoxy-1-(2-iodoethyl)-benzene (152)

4-Methoxy-1-(2-iodoethyl)-benzene (3.73 g, $C_9H_{11}IO$, 262.09 g/mol, 14.23 mmol, 87%, 11% PPh_3O, 77% corr. yield) was obtained as a slightly yellow oil from 2.49 g (4-methoxyphenyl)-ethanol (**90**) (152.19 g/mol, 16.37 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.11 (d, J = 8.5 Hz, 2 H, H-2',6'), 6.85 (d, J = 8.5 Hz, 2 H, H-3',5'), 3.79 (s, 3 H, -OCH_3-4'), 3.31 (t, 7.5 Hz, 2 H, H_2-1), 3.11 (t, 7.5 Hz, 2 H, H_2-2).

4-Dimethylamino-1-(2-iodoethyl)-benzene (153)

4-Dimethylamino-1-(2-iodoethyl)-benzene ($C_{10}H_{14}IN$, 275.13 g/mol) was obtained as a complex dark mixture from 0.500 g (4-dimethylamino-phenyl)-ethanol (165.23 g/mol, 3.03 mmol) by general procedure C. The crude product was not worked up.

2-Nitro-1-(2-iodoethyl)-benzene (154)

2-Nitro-1-(2-iodoethyl)-benzene (2.72 g, $C_8H_8INO_2$, 277.06 g/mol, 9.82 mmol, 109%, 18% PPh_3O, 89% corr. yield) was obtained as an off-white crystalline compound melting slightly above room temperature from 1.5 g (2-nitrophenyl)-ethanol (**91**) (167.16 g/mol, 8.97 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.99 (d, J = 8 Hz, 1 H, H-3'), 7.74 - 7.36 (m, 3 H, H-5',6',4' + PPh_3O), 3.46 (s br, 4 H, H_2-1,2).

3-Nitro-1-(2-iodoethyl)-benzene (155)

0.54 g 3-nitro-1-(2-iodoethyl)-benzene ($C_8H_8INO_2$, 277.06 g/mol, 1.95 mmol, 96%, 13% PPh_3O, 84% corr. yield) was obtained from 0.338 g (3-nitrophenyl)-ethanol (**92**) (167.16 g/mol, 2.02 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 8.14 (ddd, J = 7 Hz, 7 Hz, 2.5 Hz, 1 H, H-4'), 8.10 (s, 1 H, H-2'), 7.73 - 7.44 (m, 2 H, H-6',5' + PPh_3O), 3.10 - 3.24 (2m, 4 H, H_2-1,2).

4-Nitro-1-(2-iodoethyl)-benzene (156)

4-Nitro-1-(2-iodoethyl)-benzene ($C_8H_8INO_2$, 277.06 g/mol, 25% PPh_3O) was obtained from 1.67 g (4-nitrophenyl)-ethanol (**93**) (167.16 g/mol, 9.99 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 8.20 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.39 (d, J = 8.5 Hz, 2 H, H-2',6'), 3.32 (t, 7.5 Hz, 2 H, H_2-1), 3.12 (t, 7.5 Hz, 2 H, H_2-2).

2-Fluoro-1-(2-iodoethyl)-benzene (157)

2-Fluoro-1-(2-iodoethyl)-benzene (C_8H_8FI, 250.05 g/mol, 6% PPh_3O) was obtained from 2.92 g (2-fluorophenyl)-ethanol (**94**) (140.15 g/mol, 20.8 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.32 - 6.97 (m, 4 H, H-3',4',5',6'), 3.42 - 3.31 (m, 2 H, H_2-1), 3.27 - 3.16 (m, 2 H, H_2-2).

3-Fluoro-1-(2-iodoethyl)-benzene (158)

3-Fluoro-1-(2-iodoethyl)-benzene (4.11 g, C_8H_8FI, 250.05 g/mol, 16.43 mmol, 115%, 9% PPh_3O, 106% corr. yield) was obtained as a yellow oil from 2.00 g (3-fluorophenyl)-ethanol (**95**) (140.15 g/mol, 14.3 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.30 (dd, J = J' = 7 Hz, 1 H, H-5'), 7.03 - 6.85 (m, 3 H, H-6',2',4'), 3.40 - 3.29 (m, 2 H, H_2-1), 3.23 - 3.11 (m, 2 H, H_2-2).

4-Fluoro-1-(2-iodoethyl)-benzene (159)

4-Fluoro-1-(2-iodoethyl)-benzene (4.01 g, C_8H_8FI, 250.05 g/mol, 16.04 mmol, 86%, 8% PPh_3O, 79% corr. yield) was obtained as a yellow oil from 2.60 g (4-fluorophenyl)-ethanol (140.15 g/mol, 18.6 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.21 - 7.10 (m, 2 H, H-2',6'), 7.06 - 6.94 (m, 2 H, H-3',5'), 3.38 - 3.28 (m, 2 H, H_2-1), 3.20 - 3.09 (m, 2 H, H_2-2).

2-Chloro-1-(2-iodoethyl)-benzene (160)

2-Chloro-1-(2-iodoethyl)-benzene (C_8H_8ClI, 266.51 g/mol, 8% PPh_3O) was obtained from 1.89 g (2-chlorophenyl)-ethanol (**96**) (156.61 g/mol, 12.1 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 - 7.06 (m, 4 H, H-3',5',6',4'), 3.50 - 3.16 (m, 4 H, H_2-1,2).

3-Chloro-1-(2-iodoethyl)-benzene (161)

3-Chloro-1-(2-iodoethyl)-benzene (C_8H_8ClI, 266.51 g/mol, 9% PPh_3O) was obtained from 2.30 g (3-chlorophenyl)-ethanol (**97**) (156.61 g/mol, 14.7 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 - 6.90 (m, 4 H, H-2',5',4',6'), 3.50 - 2.95 (m, 4 H, H_2-1,2).

4-Chloro-1-(2-iodoethyl)-benzene (162)

4-Chloro-1-(2-iodoethyl)-benzene (3.41 g, C_8H_8ClI, 266.51 g/mol, 12.78 mmol, 83%, 10% PPh_3O, 75% corr. yield) was obtained from 2.40 g (4-chlorophenyl)-ethanol (**98**) (156.61 g/mol, 15.3 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.11 (d, J = 8 Hz, 2 H, H-2',6'), 3.31 (t, 7.5 Hz, 2 H, H_2-1), 3.13 (t, 7.5 Hz, 2 H, H_2-2).

2-Bromo-1-(2-iodoethyl)-benzene (163)

2-Bromo-1-(2-iodoethyl)-benzene (C_8H_8BrI, 310.06 g/mol, 8% PPh_3O) was obtained from 2.30 g (2-bromophenyl)-ethanol (**99**) (201.06 g/mol, 11.4 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.5 Hz, 1 H, H-3'), 7.28 - 7.20 (m, 2 H, H-5',6'), 7.18 - 7.07 (m, 1 H, H-4'), 3.51 - 3.15 (m, 4 H, H_2-1,2).

3-Bromo-1-(2-iodoethyl)-benzene (164)

3-Bromo-1-(2-iodoethyl)-benzene (C_8H_8BrI, 310.06 g/mol, 9% PPh_3O) was obtained from 2.02 g (3-bromophenyl)-ethanol (**100**) (201.06 g/mol, 10.0 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39 - 7.11 (m, 4 H, H-2',4',5',6'), 3.50 - 2.95 (m, 4 H, H_2-1,2).

4-Bromo-1-(2-iodoethyl)-benzene (165)

4-Bromo-1-(2-iodoethyl)-benzene (C_8H_8BrI, 310.06 g/mol, 13% PPh_3O) was obtained from 3.12 g (4-bromophenyl)-ethanol (**101**) (201.06 g/mol, 15.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.44 (d, J = 8 Hz, 2 H, H-3',5'), 7.06 (d, J = 8 Hz, 2 H, H-2',6'), 3.32 (t, 7.5 Hz, 2 H, H_2-1), 3.12 (t, 7.5 Hz, 2 H, H_2-2).

2,5-Dimethyl-1-(2-iodoethyl)-benzene (166)

2,5-Dimethyl-1-(2-iodoethyl)-benzene (3.55 g, $C_{10}H_{13}I$, 260.11 g/mol, 13.66 mmol, 93%, 3% PPh_3O, 90% corr. yield) was obtained from 2.20 g (2,5-dimethylphenyl)-ethanol (**102**) (150.22 g/mol, 14.6 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 7.07 - 6.92 (m, 3 H, H-3',4',6'), 3.33 - 3.22 (m, 2 H, H_2-1), 3.22 - 3.08 (m, 2 H, H_2-2), 2.30 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3).

3,5-Dimethyl-1-(2-iodoethyl)-benzene (167)

3,5-Dimethyl-1-(2-iodoethyl)-benzene (0.83 g, $C_{10}H_{13}I$, 260.11 g/mol, 3.19 mmol, 32%, 5% PPh_3O, 30% corr. yield) was obtained as an amber oil from 1.50 g (3,5-dimethylphenyl)-ethanol (**103**) (150.22 g/mol, 9.99 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 6.90 (s, 1 H, H-4'), 6.80 (s, 2 H, H-2',6'), 3.32 (t, J = 8 Hz, 2 H, H_2-1), 3.09 (t, J = 8 Hz, 2 H, H_2-2), 2.30 (s, 6 H, -CH_3-3',5').

2,5-Dimethoxy-1-(2-iodoethyl)-benzene (168)

2,5-Dimethoxy-1-(2-iodoethyl)-benzene (4.20 g, $C_{10}H_{13}IO_2$, 292.11 g/mol, 111%, 11% PPh_3O, 99% corr. yield) was obtained from 2.35 g (2,5-dimethoxyphenyl)-ethanol (**106**) (182.22 g/mol, 12.9 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 6.77 (2d, J = 2 Hz, 2 H, H-3',4'), 6.72 (d, J = 1.5 Hz, 1 H, H-6'), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.35 (t, 7.5 Hz, 2 H, H_2-1), 3.15 (t, 7.5 Hz, 2 H, H_2-2).

3,4-Dimethoxy-1-(2-iodoethyl)-benzene (169)

3,4-Dimethoxy-1-(2-iodoethyl)-benzene (6.13 g, $C_{10}H_{13}IO_2$, 292.12 g/mol, 20.98 mmol, 101%, 8% PPh_3O, 93% corr. yield) was obtained as a slightly yellow oil from 3.79 g (3,4-dimethoxyphenyl)-ethanol (**107**) (182.22 g/mol, 20.8 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.82 (d, J = 8 Hz, 1 H, H-5'), 6.73 (d, J = 8 Hz, 1 H, H-6'), 6.71 (s, 1 H, H-2'), 3.88 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.33 (t, J = 7.5 Hz, 2 H, H_2-1), 3.11 (t, J = 7.5 Hz, 2 H, H_2-2).

3,5-Dimethoxy-1-(2-iodoethyl)-benzene (170)

3,5-Dimethoxy-1-(2-iodoethyl)-benzene (0.95 g, $C_{10}H_{13}IO_2$, 292.11 g/mol, 3.5 mmol, 105% crude yield, 31% PPh_3O, 72% corr. yield) was obtained as a clear oil from 0.57 g (3,5-dimethoxyphenyl)-ethanol (**108**) (182.22 g/mol, 3.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.40 - 6.32 (m, 3 H, H-2',4',6'), 3.79 (s, 6 H, 2 OCH_3), 3.34 (t, 7.5 Hz, 2 H, H_2-1), 3.11 (t, 7.5 Hz, 2 H, H_2-2).

2,6-Dimethoxy-1-(2-iodoethyl)-benzene (171)

2,6-Dimethoxy-1-(2-iodoethyl)-benzene (2.02 g, $C_{10}H_{13}IO_2$, 292.11 g/mol, 6.92 mmol, 84%) was obtained from 1.5 g (2,6-dimethoxyphenyl)-ethanol (182.22 g/mol, 8.23 mmol) by general procedure C.

2,4-Dichloro-1-(2-iodoethyl)-benzene (172)

2,4-Dichloro-1-(2-iodoethyl)-benzene ($C_8H_7Cl_2I$, 300.95 g/mol, 10% PPh_3O) was obtained from 2.30 g (2,4-dichlorophenyl)-ethanol (**109**) (191.05 g/mol, 12.0 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 (d, J = 1.5 Hz, 1 H, H-3'), 7.21 - 7.17 (2d, 2 H, H-5',6'), 3.48 - 3.11 (m, 4 H, H_2-1,2).

3,4-Dichloro-1-(2-iodoethyl)-benzene (173)

3,4-Dichloro-1-(2-iodoethyl)-benzene ($C_8H_7Cl_2I$, 300.95 g/mol, 12% PPh_3O) was obtained from 2.35 g (3,4-dichlorophenyl)-ethanol (**112**) (191.05 g/mol, 12.3 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (d, J = 8 Hz, 1 H, H-5'), 7.28 (d, J = 2 Hz, 1 H, H-2'), 7.03 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'), 3.49 - 3.34 (m, 2 H, H_2-1), 3.34 - 2.94 (m, 2 H, H_2-2).

2,6-Dichloro-1-(2-iodoethyl)-benzene (174)

No reaction of 3.45 g (2,6-dichlorophenyl)-ethanol (**110**) (191.06 g/mol, 18.1 mmol) using general procedure C as indicated by NMR analysis.

3-(2-Iodoethyl)-indole (175)

3-(2-Iodoethyl)-indole (34.21 g, $C_{10}H_{10}NI$, 271.10 g/mol, 126.19 mmol, 81%) was obtained from 25.00 g (indol-3-yl)-ethanol (**113**) (161.20 g/mol, 155.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 8.00 (s br, 1 H, H-1'), 7.58 (d, J = 7 Hz, 1 H, H-4'), 7.37 (d, J = 7.5 Hz, 1 H, H-7'), 7.17 (2dd, J = J' = 8 Hz, 2 H, H-5',6'), 7.08 (d, J = 2 Hz, 1 H, H-2'), 3.50 - 3.28 (m, 4 H, H_2-1,2).

3-(2-Iodoethyl)-5-methoxyindole (176)

3-(2-Iodoethyl)-5-methoxyindole (7.16 g, $C_{11}H_{12}INO$, 301.12 g/mol, 23.78 mmol, 91%) was obtained as a light brown oil which crystallized at room temperature from 5.00 g 2-(5-methoxyindol-3-yl)-ethanol (**114**) (191.23 g/mol, 26.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.93 (s br, 1 H, H-1'), 7.24 (d, J = 9 Hz, 1 H, H-7'), 7.04 (s, 1 H, H-2'), 6.99 (d, J = 2 Hz, 1 H, H-4'), 6.86 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'), 3.86 (s, 3 H, -OCH_3-5'), 3.48 - 3.24 (m, 4 H, H_2-1,2).

1-(2-Iodoethyl)-naphthalene (177)

1-(2-Iodoethyl)-naphthalene (6.10 g, $C_{12}H_{11}I$, 282.12 g/mol, 21.62 mmol, 98%, 3% PPh_3O, 95% corr. yield) was obtained as a slightly yellow oil from 3.81 g naphthalen-1-yl-ethanol (**115**) (172.22 g/mol, 22.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.22): δ = 7.99 - 7.73 (m, 3 H, H-8',5',4'), 7.58 - 7.30 (m, 4 H, H-7',6',3',2'), 3.63 (t, 7.5 Hz, 2 H, H_2-1), 3.44 (t, 7.5 Hz, 2 H, H_2-2).

2-(2-Iodoethyl)-naphthalene (178)

2-(2-Iodoethyl)-naphthalene (3.39 g, $C_{12}H_{11}I$, 282.12 g/mol, 12.01 mmol, 54%, 10% PPh_3O, 49% corr. yield) was obtained as a slightly yellow oil from 3.81 g naphthalen-2-yl-ethanol (**116**) (172.22 g/mol, 22.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.86 - 7.75 (m, 3 H, H-5',4',8'), 7.64 (s, 1 H, H-1'), 7.51 - 7.42 (m, 2 H, H-7',6'), 7.30 (dd, J = 8.5 Hz, 1.5 Hz, 1 H, H-3'), 3.50 - 3.26 (m, 4 H, H_2-1,2).

2-Diphenyl-1-iodoethane (179)

2,2-Diphenyl-1-iodoethane (3.06 g, $C_{14}H_{13}I$, 308.16 g/mol, 9.94 mmol, 99%, 18% PPh_3O, 81% corr. yield) was obtained from 2.00 g 2,2-diphenylethanol (**117**) (198.26 g/mol, 10.1 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 - 7.19 (m, 10 H, 2 C_6H_5), 4.34 (t, J = 8 Hz, 1 H, H-2), 3.74 (d, J = 8 Hz, 2 H, H_2-1).

1-Iodo-2-nitroethane (180)

1-Iodo-2-nitroethane ($C_2H_4INO_2$, 200.96 g/mol, 23% PPh_3O) was obtained from 2-nitroethanol (91.07 g/mol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 4.77 (t, J = 6.5 Hz, 2 H, H_2-2), 3.81 (t, J = 6.5 Hz, 2 H, H_2-1).

2-Iodoethanol (181)

2-Chloroethanol (24.00 g, 80.51 g/mol, d 1.20, 20 ml, 298.1 mmol) and 89.36 g sodium iodide (149.89 g/mol, 896 mmol, 3.3 eq) were refluxed in 100 ml acetone in the presence of 100 mg copper powder in a weakly exothermic reaction. The acetone was evaporated on a rotary evaporator, 200 ml H_2O was added, and the product extracted with 3 × 75 ml dichloromethane. The solvent was evaporated on a rotary evaporator and the resulting liquid was distilled under membrane pump vacuum with a drilled fine copper wire placed in the condenser, yielding 22.49 g 2-iodoethanol (C_2H_5IO, 171.96 g/mol, 130.61 mmol, 44%) as the fraction distilling at 75 - 77 °C as a clear colorless liquid that was stored at 4 °C over copper powder.

1-Chloro-2-iodoethane (182)

1-Chloro-2-iodoethane (C_2H_4ClI, 190.41 g/mol, 15% PPh_3O) was obtained from 2-chloroethanol (80.51 g/mol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.87 - 3.76 (m, 2 H, H_2-1), 3.46 - 3.26 (m, 2 H, H_2-2-Cl).

2,2,2-Trichloroethanol iodination

No reaction of 2.77 g 2,2,2-Trichloroethanol (149.4 g/mol, 18.54 mmol) using the standard general procedure C as well as with the same reaction in refluxing toluene.

3-Bromo-*N,N*-diethylpropionamide (183)

To 5.00 g 3-bromopropionyl chloride (171.42 g/mol, 29.2 mmol) in 100 ml diethyl ether was added 4.27 g diethylamine (73.14 g/mol, 58.33 mmol) in diethyl ether dropwise under stirring.

After the addition the resulting slurry was stirred for 10 min at room temperature, the organic phase was extracted with 100 ml water, 100 ml diluted hydrochloric acid, 100 ml diluted NH_3 solution, and with 2 × 100 ml H_2O. The organic phase was dried over $MgSO_4$, the solvent removed on a rotary evaporator, and the resulting oil was kept under membrane pump vacuum at room temperature for 10 min, yielding 3.09 g 3-bromo*N,N*-diethylpropionamide ($C_7H_{14}BrNO$, 208.10 g/mol, 14.85 mmol, 51%).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.28): δ = 3.68 (t, J = 7.5 Hz, 2 H, H_2-1), 3.42 (q, J = 7 Hz, 2 H, *N*-C(*Z*)H_2), 3.30 (q, J = 7 Hz, 2 H, *N*-C(*E*)H_2), 2.90 (t, J = 7 Hz, 2 H, H_2-2), 1.20 (t, J = 7 Hz, 3 H, C(*Z*)H_3), 1.13 (t, J = 7 Hz, 3 H, C(*E*)H_3).

1-Iodo-2-methylpropane (184)

1-Iodo-2-methylpropane (0.84 g, C_4H_9I, 184.02 g/mol, 4.59 mmol, 21%) was obtained as a slightly yellow oil from 1.63 g 2-methylpropan-1-ol (isobutanol) (74.07 g/mol, 22.0 mmol) by general procedure C.

1-Iodo-2,2-dimethylpropane (185)

1-Iodo-2,2-dimethylpropane ($C_5H_{11}I$, 198.05 g/mol, 5% PPh_3O) was obtained from 1.63 g 2,2-dimethylpropan-1-ol (**118**) (neopentyl alcohol) (88.15 g/mol, 18.49 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.16 (s, 2 H, H_2-1), 1.07 (s, 9 H, 3 CH_3).

(3-Iodopropyl)-cyclohexane (186)

(3-Iodopropyl)-cyclohexane (3.34 g, $C_9H_{17}I$, 252.14 g/mol, 13.24 mmol, 63%, 1% PPh_3O, 62% corr. yield) was obtained as an amber oil from 2.63 g 3-cyclohexylpropan-1-ol (**119**) (124.24 g/mol, 21.2 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.17 (t, J = 7 Hz, 2 H, H_2-1), 1.93 - 1.54 (m, 7 H, H-2'$_{eq}$,6'$_{eq}$,3'$_{eq}$,5'$_{eq}$,4'$_{eq}$, H_2-2), 1.35 - 1.07 (m, 6 H, H-1', H_2-3, H-3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.01 - 0.76 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

(3-Bromopropyl)-benzene (187)

(3-Bromopropyl)-benzene (3.44 g, $C_9H_{11}Br$, 246.09 g/mol, 75%) was obtained from 2.52 g 3-phenylpropan-1-ol (**120**) (136.19 g/mol, 18.5 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36 - 7.15 (m, 5 H, C_6H_5), 3.40 (t, J = 6.5 Hz, 2 H, H_2-1), 2.78 (t, J = 7.5 Hz, 2 H, H_2-3), 2.17 (tt, J = J' = 7 Hz, 2 H, H_2-2).

(3-Iodopropyl)-benzene (188)

(3-Iodopropyl)-benzene ($C_9H_{11}I$, 246.09 g/mol, 7% PPh_3O) was obtained from 3-phenylpropan-1-ol (**120**) (136.19 g/mol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 7.35 - 7.14 (m, 5 H, C_6H_5), 3.17 (t, J = 7 Hz, 2 H, H_2-1), 2.72 (t, J = 7.5 Hz, 2 H, H_2-3), 2.13 (tt, J = J' = 7 Hz, 2 H, H_2-2).

(3-Bromopropenyl)-benzene (189)

(3-Bromopropenyl)-benzene (3.44 g, C_9H_9Br, 197.07 g/mol, 17.4 mmol, 94%, 11% PPh_3O, 84% corr. yield) was obtained from 2.49 g 3-phenylprop-2-en-1-ol (134.18 g/mol, 18.5 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.44 - 7.21 (m, 5 H, C_6H_5), 6.65 (d, J = 16 Hz, 1 H, H-3), 6.39 (dt, J = 15.5 Hz, 7.5 Hz, 1 H, H-2), 4.16 (d, J = 7.5 Hz, 2 H, H_2-1).

(3-Iodopropenyl)-benzene (190)

(3-Iodopropenyl)-benzene (1.42 g, C_9H_9I, 244.07 g/mol, 5.81 mmol, 31%, 7% PPh_3O, 29% corr. yield) was obtained as an unstable, brown, and at room temperature rapidly darkening oil from 2.49 g 3-phenylprop-2-en-1-ol (134.18 g/mol, 18.5 mmol) by general procedure C.

2,5-Dimethoxy-1-(3-iodopropyl)-benzene (191)

2,5-Dimethoxy-1-(3-iodopropyl)-benzene (2.19 g, $C_{11}H_{15}IO_2$, 306.14 g/mol, 7.15 mmol, 89%, 19% PPh_3O, 72% corr. yield) was obtained as a brown oil from 1.57 g 3-(2,5-dimethoxyphenyl)-propan-1-ol (**121**) (196.24 g/mol, 8.00 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.80 - 6.70 (m, 3 H, H-3',4',6'), 3.77 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.18 (t, J = 7 Hz, 2 H, H_2-1), 2.69 (t, J = 7.5 Hz, 2 H, H_2-3), 2.11 (tt, J = J' = 7 Hz, 2 H, H_2-2).

3,4,5-Trimethoxy-1-(3-Iodopropyl)-benzene (192)

3,4,5-Trimethoxy-1-(3-Iodopropyl)-benzene (2.26 g, $C_{12}H_{17}IO_3$, 314.14 g/mol, 7.18 mmol, 78%, 14% PPh_3O, 67% corr. yield) was obtained as a yellow viscous oil from 2.08 g 3-(3,4,5-trimethoxyphenyl)-propan-1-ol (**122**) (226.27 g/mol, 9.19 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 6.42 (s, 2 H, H-2',6'), 3.86 (s, 6 H, -OCH_3-3',5'), 3.83 (s, 3 H, -OCH_3-4'), 3.18 (t, J = 7 Hz, 2 H, H_2-1), 2.68 (t, J = 7 Hz, 2 H, H_2-3), 2.11 (tt, J = J' = 7 Hz, 2 H, H_2-2).

3-(4-Iodobutyl)-indole (193)

3-(4-Iodobutyl)-indole (1.89 g, $C_{12}H_{14}IN$, 299.15 g/mol, 6.3 mmol, 142% crude yield) was obtained from 0.84 g 4-(Indol-3-yl)-butan-1-ol (**123**) (189.25 g/mol, 4.44 mmol) by general procedure C and purified by silica gel column chromatography (ethyl acetate).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 8.26 (s br, 1 H, H-1'), 7.73 - 7.40 (m, 1 H, H-4' + PPh_3O), 7.33 (d, J = 7.5 Hz, 1 H, H-7'), 7.17 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-6'), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1 H, H-5'), 6.96 (s, 1 H, H-2'), 3.21 (t, J = 6.5 Hz, 2 H, H_2-1), 2.78 (t, J = 7 Hz, 2 H, H_2-4), 2.00 - 1.73 (m, 4 H, H_2-2,3).

(3-Bromopropylsulfanyl)-benzene (194)

(3-Bromopropylsulfanyl)-benzene ($C_9H_{11}BrS$, 231.15 g/mol, 7% PPh_3O) was obtained as a clear oil from 1.23 g 3-phenylsulfanyl-propan-1-ol (**125**) (168.26 g/mol, 7.31 mmol) by general procedure D (PPh_3 / imidazole / Br_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42 - 7.14 (m, 5 H, C_6H_5), 3.32 (t, J = 7.0 Hz, 2 H, H_2-1), 3.03 (t, J = 7 Hz, 2 H, H_2-3), 2.10 (tt, J = J' = 7.0 Hz, 2 H, H_2-2).

(3-Iodopropylsulfanyl)-benzene (195)

(3-Iodopropylsulfanyl)-benzene (5.05 g, $C_9H_{11}IS$, 278.25 g/mol, 18.16 mmol, 98%, 9% PPh_3O, 89% corr. yield) was obtained as an amber oil from 3.12 g 3-phenylsulfanyl-propan-1-ol (**125**) (168.26 g/mol, 18.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 - 7.14 (m, 5 H, C_6H_5), 3.52 (t, J = 6.5 Hz, 2 H, H_2-1), 3.07 (t, J = 7 Hz, 2 H, H_2-3), 2.14 (tt, J = J' = 6.5 Hz, 2 H, H_2-2).

1-Chloro-3-iodopropane (196)

1-Chloro-3-iodopropane (C_3H_6ClI, 204.44 g/mol, 7%PPh_3O) was obtained from 3-Iodopropan-1-ol (185.99 g/mol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.65 (t, J = 7 Hz, 2 H, H_2-3-Cl), 3.33 (t, J = 6.5 Hz, 2 H, H_2-1), 2.23 (tt, J = J' = 6.5 Hz, 2 H, H_2-2).

1-Iodobutane (197)

Commercial 1-iodobutane (C_4H_9I, 184.02 g/mol) stored for several years was redistilled and used.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.20 (t, J = 7 Hz, 2 H, H_2-1), 1.81 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.43 (tq, J = 9 Hz, 2 H, H_2-3), 0.92 (t, J = 7.5 Hz, 3 H, H_3-4).

3-Iodomethyl-pentane (198)

3-Iodomethyl-pentane ($C_6H_{13}I$, 212.07 g/mol, 4% PPh_3O) was obtained from 1.89 g 2-ethylbutan-1-ol (**126**) (102.17 g/mol, 18.5 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.28 (d, J = 4.5 Hz, 2 H, H_2-1), 1.52 - 1.21 (m, 4 H, 2 H_2-3), 1.10 - 0.93 (m, 1 H, H-2), 0.87 (t, J = 7.5 Hz, 6 H, 2 H_3-4).

(4-Iodobutyl)-benzene (199)

(4-Iodobutyl)-benzene (4.28 g, $C_{10}H_{13}I$, 260.11 g/mol, 16.45 mmol, 89%, 4% PPh_3O, 85% corr. yield) was obtained as a brown oil from 2.78 g 4-phenylbutan-1-ol (**128**) (150.22 g/mol, 18.5 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.34 - 7.12 (m, 5 H, C_6H_5), 3.19 (t, J = 6.5 Hz, 2 H, H_2-1), 2.63 (t, J = 7.5 Hz, 2 H, H_2-4), 1.94 - 1.64 (m, 4 H, H_2-2,3).

1-Iodopentane (200)

1-Iodopentane (3.26 g, $C_5H_{11}I$, 198.05 g/mol, 16.46 mmol, 75%, 3% PPh_3O, 73% corr. yield) was obtained as a slightly yellow oil from 1.94 g pentan-1-ol (88.15 g/mol, 22.0 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.27): δ = 3.19 (t, J = 7 Hz, 2 H, H_2-1), 1.92 - 1.74 (m, 2 H, H_2-2), 1.45 - 1.21 (m, 4 H, H_2-3,4), 0.91 (t, J = 7 Hz, 3 H, H_3-5).

1-Iodooctane (201)

1-Iodooctane (3.19 g, $C_8H_{17}I$, 240.13 g/mol, 13.28 mmol, 81%, 2% PPh_3O, 79% corr. yield) was obtained as a slightly yellow oil from 2.13 g octanol (130.23 g/mol, 16.37 mmol) by general procedure C.

^1H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.19 (t, J = 7 Hz, 2 H, H_2-1), 1.82 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.49 - 1.20 (m, 10 H, H_2-3-7), 0.88 (t, J = 6.5 Hz, 3 H, H_3-8).

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-Pentadecafluoro-8-iodooctane (202)

No reaction of 5.16 g 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctan-1-ol (400.08 g/mol, 128.74 mmol) using general procedure C. A similar reaction in refluxing toluene yielded a solution of 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoro-8-iodooctane (**130**) ($C_8H_2F_{15}I$, 509.98 g/mol) in toluene.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.62 (t, J = 17 Hz, 2 H, H_2-1).

1-Iodotetradecane (203)

1-Iodotetradecane (4.09 g, $C_{14}H_{29}I$, 324.29 g/mol, 12.62 mmol, 68%, 1% PPh_3O, 67% corr. yield) was obtained from 3.97 g tetradecan-1-ol (**131**) (214.39 g/mol, 18.5 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.18 (t, J = 7 Hz, 2 H, H_2-1), 1.82 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.38 - 1.21 (m, 22 H, H_2-3-13), 0.88 (t, J = 6.5 Hz, 3 H, H_3-14).

1-Iodooctadecane (204)

1-Iodooctadecane (6.83 g, $C_{18}H_{37}I$, 380.40 g/mol, 17.97 mmol, 82%, 2% PPh_3O, 80% corr. yield) was obtained as a white waxy substance from 5.96 g octadecan-1-ol (270.49 g/mol, 22.0 mmol) by general procedure C.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 3.19 (t, J = 7 Hz, 2 H, H_2-1), 1.82 (tt, J = J' = 7 Hz, 2 H, H_2-2), 1.48 - 1.12 (m, 30 H, H_2-3-17), 0.88 (t, J = 6.5 Hz, 3 H, H_3-18).

Synthesis of *N*-alkyl-*N*-methyltryptamines

Benzyl-(4,4-diethoxybutyl)-methylamine (205)

A mixture of 50 g 4-chloro-1,1-diethoxybutane (180.67 g/mol, 276 mmol, 1 eq), 100 ml methyl-benzylamine (121.18 g/mol, d 0.939, 93.9 g, 775 mmol, 2.8 eq, bp 184 - 189 °C), 76 g K_2CO_3 (138.21 g/mol, 550 mmol, 2.0 eq), and 4.6 g KI (166.01 g/mol, 28 mmol, 0.1 eq) in 200 ml acetonitrile was refluxed under a slow stream of nitrogen for 2 h. The reaction mixture was filtered through a glass fritted funnel and the filter cake washed twice with acetonitrile. The organic phases were pooled and the solvent was evaporated on a rotary evaporator. The resulting oil was distilled under oil pump vacuum. The first fractions consisted of 69 g (569 mmol, 2.1 eq) recovered methyl-benzylamine. The fractions from 116 - 119 °C at 1 mm Hg gave 56.1 g of pure benzyl-(4,4-diethoxybutyl)-methylamine ($C_{16}H_{27}NO_2$, 265.38 g/mol, 211 mmol, 77%) as a colorless oil.

TLC (diethyl ether / *n*-hexane, 50 + 50): R_f = 0.95 (educt), 0.50 (product). Detection by double staining first with 2,4-dinitrophenylhydrazine in MeOH / conc. HCl 75 + 25 (yellow spots), then Dragendorff's reagent for amines (red product spot).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.26): δ = 7.34 - 7.28 (m, 5 H, H-arom), 4.48 (t, J = 4.5 Hz, 1 H, H-1), 3.72 - 3.38 (m, 6 H, 2 O-CH_2, N-CH_2), 2.40 (t, J = 6.5 Hz, 2 H, H_2-4-N), 2.20 (s, 3 H, N-CH_3), 1.68 - 1.55 (m, 4 H, H_2-2,3), 1.20 (t, J = 7 Hz, 6 H, 2 CH_3).

5-Methoxy-*N*-benzyl-*N*-methyltryptamine (Benzyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine) (206)

A 4% (w/w) solution of 12.6 ml sulfuric acid (98.07 g/mol, d 1.84, 23.29 g, 238 mmol, 2.7 eq) in 580 ml H_2O was heated to 60 °C under a slow stream of nitrogen in a 2 l round-bottom flask equipped with a dropping funnel, a gas inlet, and a magnetic stirrer. 15.25 g 4-methoxyphenylhydrazine (174.63 g/mol, 87.33 mmol, 1.0 eq) was dissolved in the solution, and 23.17 g benzyl-(4,4-diethoxybutyl)-methylamine (**205**, 265.38 g/mol, 87.33 mmol, 1.0 eq) was added dropwise over 15 min not letting the temperature rise above 60 °C. The mixture was then slowly heated to 70 °C over 20 min and held at 70 °C for 60 min. The mixture was cooled to room temperature, basified with diluted sodium hydroxide solution, and extracted twice with ethyl acetate. The addition of conc. ammonia solution did help to dissolve the precipitate in the organic phase. The combined solvent phases were dried ($MgSO_4$) and evaporated on a rotary evaporator. The resulting thick brown oil with a faint liquorice-like smell crystallized upon standing and was recrystallized from dichloromethane, resulting in 20.65 g of 5-methoxy-*N*-methyl-*N*-benzyltryptamine ($C_{19}H_{22}N_2O$, 294.38 g/mol, 70.15 mmol, 80%) as an off-white powder.

In a similar experiment the acetal was added to an 85 °C hot solution and the mixture was heated under reflux for 60 min. The product was obtained in a yield of only 40% after re-crystallization.

^{1}H NMR (base, 300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.59 (s br, 1 H, H-1'''), 7.36 - 7.21 (m, 5 H, H-2'-6'), 7.20 (d, J = 8.5 Hz, 1 H, H-7'''), 7.08 (d, J = 1 Hz, 1 H, H-4'''), 6.87 (d, J = 2 Hz, 1 H, H-2'''), 6.68 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.70 (s, 3 H, -OCH_3-5'''), 3.56 (s, 2 H, H_2-1), 2.84 (t, J = 8 Hz, 2 H, H_2-1''), 2.62 (t, J = 8 Hz, 2 H, H_2-2''), 2.26 (s, 3 H, N-CH_3).

^{13}C NMR (base, 50.3 MHz, APT, DMSO-d_6): δ = 152.8 (C_q-5'''), 139.1 (C_q-1'), 131.3 (C_q-7b'''), 128.6 (CH-3',5'), 128.0 (CH-2',6'), 127.4 (C_q-3b'''), 126.7 (CH-4'), 123.0 (CH-2'''), 112.2 (C_q-3'''), 111.8 (CH-7'''), 110.9 (CH-6'''), 100.0 (CH-4'''), 61.3 (CH_2-1), 57.3 (CH_2-1''), 55.3 (OCH_3-5'''), 41.8 (CH_3-N), 22.7 (CH_2-2'').

IR (KBr): $\tilde{\nu}$ = 3418, 3089, 3033, 2997, 2949, 1824, 1693, 1629, 1579, 1489, 1469, 1438, 1375, 1354, 1329, 1305, 1268, 1235, 1207, 1173, 1131, 1112, 1062, 1027, 966, 911, 848, 795, 743, 700, 481 cm^{-1}.

5-Methoxy-*N*-benzyl-*N*-methyltryptamine hydrogen oxalate (Benzyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (207)

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.74 (s br, 1 H, H-1'''), 7.52 - 7.38 (m, 5 H, H-2'-6'), 7.24 (d, J = 8.5 Hz, 1 H, H-7'''), 7.15 (s, 1 H, H-4'''), 6.94 (s, 1 H, H-2'''), 6.72 (dd, J = 8.5 Hz, 1.5 Hz, 1 H, H-6'''), 4.13 (sb, 2 H, H_2-1), 3.74 (s, 3 H, -OCH_3-5'''), 3.13 - 2.97 (m, 4 H, H_2-1,2), 2.63 (s, 3 H, N^+-CH_3).

IR (KBr): $\tilde{\nu}$ = 3401, 3044, 2990, 2938, 2830, 2668,1666, 1643, 1587, 1488, 1458, 1372, 1326, 1218, 1110, 1082, 1065, 1029, 923, 831, 801, 742, 700, 618, 504 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 220 (425%) sh, 275 (100%), 270 (97%) sh, 291 (84%), 296 (81%) sh, 307 (54%) sh.

HPLC: R_t (%total AUC_{260}) = 5.5 (oxalic acid), 16.1 (97.8%), 19.8 (1.5%), 21.5 min (0.6%).

ESI MS: *m/z* (%) = 295.2 (100%) $[M + H]^+$.

5-Methoxy-*N*-methyltryptamine ([2-(5-Methoxyindol-3-yl)-ethyl]-methylamine) (208)

19.05 g 5-methoxy-*N*-methyl-*N*-benzyltryptamine (**206**, 294.39 g/mol, 64.71 mmol) was dissolved in 500 ml warm ethanol. 0.6 g used Pd/C (10%) catalyst was added, vigorously mixed, and filtered off. 2.0 g of fresh Pd/C (10%) catalyst was added and the mixture hydrogenated in a shaking apparatus at room temperature and normal room pressure until the hydrogen uptake ceased. The catalyst was filtered off, the filtrate evaporated on a rotary evaporator, and the residue dissolved in 200 ml ethyl acetate. The product was subsequently

extracted with 200 ml of 2% hydrochloric acid and 50 ml H_2O. The combined aqueous phases were basified with concentrated NaOH solution and subsequently re-extracted with 150 ml and 50 ml of dichloromethane. The organic phases were pooled, dried over $MgSO_4$, and evaporated on a rotary evaporator. The product was further dried under oil pump vacuum, resulting in 11.47 g of [2-(5-methoxyindol-3-yl)-ethyl]-methylamine ($C_{12}H_{16}N_2O$, 204.27 g/mol, 56.15 mmol, 87%) as an off-white crystalline mass. The product was stored at -20 °C.

5-Methoxy-*N*-methyltryptamine hydrogen oxalate
([2-(5-Methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (209)

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'), 7.18 (d, 2 Hz, 1 H, H-4'), 7.06 (d, 2.5 Hz, 1 H, H-2'), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'), 3.77 (s, 3 H, -OCH_3-5'), 3.15 (t, 7.5 Hz, 2 H, H_2-1), 2.98 (t, 7.5 Hz, 2 H, H_2-2), 2.60 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (C_q-7b'''), 127.0 (C_q-3b'''), 123.9 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 108.9 (C_q-3'''), 100.1 (CH-4'''), 55.4 (OCH_3-5'''), 48.6 (CH_2-1''), 32.4 (CH_3-N^+), 21.6 (CH_2-2'').

IR (KBr): $\tilde{\nu}$ = 3422, 3317, 2959, 2848, 2794, 2440, 2350, 2300, 1720, 1703, 1631, 1458, 1406, 1340, 1280, 1230, 1113, 1012, 823, 767, 744, 721, 606, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 275 (100%), 292 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.9 (oxalic acid), 9.0 min (99.6%).

ESI MS: *m/z* (%) = 499.0 (9%) [2M + oxalic acid + H]$^+$, 409.0 (22%) [2M + H]$^+$, 205.0 (100%) [M + H]$^+$, 174.2 (22%) [5-MeO-vinylindole + H]$^+$.

***N*-Benzyl-*N*-methyltryptamine**
(Benzyl-[2-(indol-3-yl)-ethyl]-methylamine) (210)

N-Methyl-*N*-benzyltryptamine was prepared from phenylhydrazine (**205**, 174.63 g/mol, mmol, 1.0 eq) and benzyl-(4,4-diethoxybutyl)-methylamine (265.38 g/mol, 87.33 mmol, 1.0 eq) analogous to the preparation of 5-methoxy-*N*-methyl-*N*-benzyltryptamine (**206**) above, yielding *N*-methyl-*N*-benzyltryptamine ($C_{18}H_{20}N_2$, 264.16 g/mol).

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.23): δ = 8.01 (s br, 1 H, H-1'''), 7.54 (d, J = 7.5 Hz, 1 H, H-4'''), 7.38 - 7.25 (m, 6 H, H-7''',2'-6'), 7.17 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.08 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.98 (s, 1 H, H-2'''), 3.62 (s, 2 H, H_2-1), 3.13 - 2.97 (m, 2 H, H_2-1''), 2.83 - 2.71 (m, 2 H, H_2-2''), 2.34 (s, 3 H, N-CH_3).

N-Methyltryptamine
([2-(Indol-3-yl)-ethyl]-methylamine) (211)

13.88 g *N*-methyl-*N*-benzyltryptamine (**210**, 264.16 g/mol, 52.54 mmol) was debenzylated analogous to the preparation of 5-methoxy-*N*-methyltryptamine (**208**) above, yielding [2-(indol-3-yl)-ethyl]-methylamine ($C_{11}H_{14}N_2$, 174.24 g/mol) as an off-white waxy crystalline mass after distillation under oil pump vacuum. The product was stored at -20 °C

N-Methyltryptamine hydrogen oxalate
([2-(Indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (212)

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'), 7.57 (d, J = 8 Hz, 1 H, H-4'), 7.37 (d, J = 8 Hz, 1 H, H-7'), 7.22 (d, J = 2.5 Hz, 1 H, H-2'), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'), 3.20 - 3.10 (m, 2 H, H_2-1), 3.10 - 2.97 (m, 2 H, H_2-2), 2.60 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.9 (C_q-oxalate), 136.3 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.0 (CH-4'''), 111.5 (CH-7'''), 109.1 (C_q-3'''), 48.7 (CH_2-1''), 32.4 (CH_3-N^+), 21.6 (CH_2-2'').

IR (KBr): $\tilde{\nu}$ = 3422, 3317, 2958, 2847, 2794, 2439, 2300, 1720, 1703, 1631, 1458, 1405, 1340, 1280, 1230, 1113, 1012, 933, 823, 766, 720, 605, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>500%), 266 (85%) sh, 273 (96%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 8.3 min (99.8%).

ESI MS: *m/z* (%) = 499.2 (28%) $[2M + oxalic\ acid + H]^+$, 349.2 (14%) $[2M + H]^+$, 189.2 (16%), 175.1 (100%) $[M + H]^+$, 144.2 (49%) [vinylindole + H]$^+$.

General procedure E: *N*-alkyl-*N*-methyltryptamine and *N*-alkyl-*N*-methyl-5-methoxy-tryptamines

587.5 µmol alkyl halide (1.2 eq), 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.6 µmol, 1.0 eq) or 100 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.6 µmol, 1.0 eq), and 150 µl diisopropyl-ethylamine (129.25 g/mol, d 0.742, 111.3 mg, 861.1 mmol, 1.8 eq) in 4 ml acetonitrile in a glass-stoppered reaction tube were mixed and kept at room temperature overnight. 100 µl acetic acid anhydride (102.09 g/mol, d 1.082, 108.2 mg, 10.60 mmol, 22 eq) was added and the reaction was kept for another 1 h at room temperature. The mixture was partitioned between 40 ml dichloromethane and 40 ml diluted sodium hydroxide solution by vigorous agitation for 4 min, and the organic layer was dried over $MgSO_4$ and evaporated. The residue was further evaporated under oil pump vacuum for 30 min at room temperature and 5 min at 100 °C. The residue was dissolved in 2 ml THF, 2 ml of a 4 mM solution of oxalic acid dihydrate in THF (290 g/mol, 1.6 eq) was added, and the reaction flask was kept at or below 4 °C for at least 60 min after crystallization. The precipitate was filtered off in a miniature conical Buchner funnel using vacuum, washed with a small amount of cold THF, and was recrystallized from the minimum amount of THF. The final [2-(indol-3-yl)-ethyl]-methyl-alkylamine hydrogen oxalate salts were dried under oil pump vacuum at 60 °C in a drying oven for 24 h. All reactions were followed by TLC (MeOH / NET_3, 99 + 1; staining with Ehrlich's reagent).

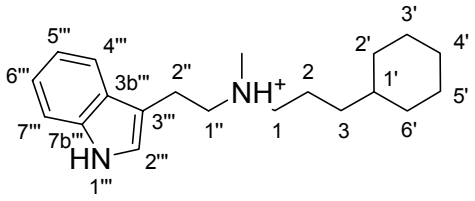
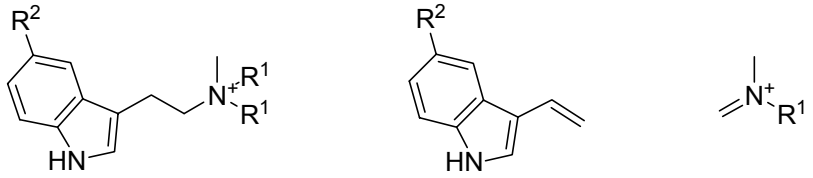


Figure 71: General numbering scheme for *N*-substituted *N*-methyltryptamine.



53 (M_{quat}^+) **54** (vinylindole) **55** (M_{imine}^+)

Figure 72: MS spectra abbreviations for trace impurities and analysis artifacts.

N-Cyclopropylmethyl-*N*-methyltryptamine hydrogen oxalate (Cyclopropylmethyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (213)

N-Cyclopropylmethyl-*N*-methyltryptamine hydrogen oxalate ($C_{15}H_{20}N_2 \cdot C_2H_2O_4$, 318.37 g/mol) was obtained from 176.0 mg iodomethyl-cyclopropane (**133**, 182 g/mol, 61%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3394, 3270 sh, 3007, 2918, 2850, 2697, 1717, 1617, 1457, 1425, 1205, 1104, 1025, 1012, 998, 941, 740, 720, 704, 468 cm^{-1}.

UV (H_2O): λ (%max_A) = 217 (> 400%), 264 (86%) sh, 273 (97%), 279 (100%), 287 nm (85%).

HPLC: R_t (%total AUC_{260}) = 4.8 (oxalic acid), 9.8 (3.7%), 11.6 (90.2%), 15.1 (0.9%), 16.5 min (5.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (s, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 4 Hz, 1 H, H-5'''), 3.37 - 3.27 (m, 2 H, H_2-1''), 3.16 - 3.05 (m, 4 H, H_2-1,2''), 2.88 (s, 3 H, N^+-CH_3), 1.18 - 1.04 (m, 1 H, H-1'), 0.63 (J = 7 Hz, 2 H, H-2',3'), 0.38 (d, J = 4.5 Hz, 2 H, H-2',3').

ESI MS: *m/z* (%) = 547.1 (5%) [2M + oxalic acid + H]$^+$, 283.2 (86%) [M_{quat}]$^+$, 229.2 (100%) [M + H]$^+$, 144.2 (25%) [vinylindole + H]$^+$.

N-Cyclopropylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Cyclopropylmethyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (214)

N-Cyclopropylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{16}H_{22}N_2O \cdot C_2H_2O_4$, 348.39 g/mol) was obtained as a non-crystallizing mass from 176.0 mg iodomethyl-cyclopropane (**133**, 182 g/mol, 61%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-Cyclopentylmethyl-_N_-methyltryptamine hydrogen oxalate (Cyclopentylmethyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (215)

_N_-Cyclopentylmethyl-_N_-methyltryptamine hydrogen oxalate ($C_{17}H_{24}N_2 \cdot C_2H_2O_4$, 346.42 g/mol) was obtained from 129.7 mg iodomethyl-cyclopentane (**134**, 210.06 g/mol, 95%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3405, 3273, 3048, 2949, 2866, 2706, 1702, 1636, 1458, 1413, 1355, 1280, 1213, 1104, 1012, 928, 737, 720, 705, 616, 486 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.6 (3.9%), 16.6 min (95.9%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.32 - 3.23 (m, 2 H, H_2-1''), 3.15 - 3.06 (m, 4 H, H_2-1,2''), 2.83 (s, 3 H, N^+-CH_3), 2.24 (dtt, J = J' = J'' = 7.5 Hz, 1 H, H-1'), 1.86 - 1.73 (m, 2 H, H-3',6'), 1.68 - 1.45 (m, 4 H, H_2-4',5'), 1.30 - 1.16 (m, 2 H, H-3',6').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 60.0 (CH_2-1), 55.9 (CH_2-1''), 39.7 (CH_3-N^+), 34.9 (CH-1'), 30.6 (CH_2-2',5'), 24.6 (CH_2-3',4'), 19.7 (CH_2-2'').

ESI MS: _m/z_ (%) = 626.8 (%) $[2M + HCl + H]^+$, 603.0 (7%) $[2M + oxalic\ acid + H]^+$, 257.2 (100%) $[M + H]^+$.

_N_-Cyclopentylmethyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate (Cyclopentylmethyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (216)

_N_-Cyclopentylmethyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{18}H_{26}N_2O \cdot C_2H_2O_4$, 376.45 g/mol) was obtained from 129.7 mg iodomethyl-cyclopentane (**134**, 210.06 g/mol, 95%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3265, 3041, 2954, 2868, 2691, 1718, 1625, 1487, 1465, 1280, 1214, 1030, 926, 792, 721, 709, 637, 504 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (> 400%), 276 (100%), 295 (85%) sh, 305 (62%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 11.5 (1.3%), 15.4 (0.6%), 17.1 (94.2%), 20.8 (0.9%), 23.1 min (2.2%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz,

2 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.32 - 3.22 (m, 2 H, H_2-1''), 3.12 - 3.02 (m, 4 H, H_2-1,2''), 2.83 (s, 3 H, N^+-CH_3), 2.24 (dtt, J = J' = J'' = 7.5 Hz, 1 H, H-1'), 1.89 - 1.76 (m, 2 H, H-3',6'), 1.68 - 1.46 (m, 4 H, H_2-4',5'), 1.31 - 1.15 (m, 2 H, H-3',6').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 60.1 (CH_2-1''), 55.8 (CH_2-1), 55.4 (OCH_3-5'''), 39.8 (CH_3-N^+), 34.9 (CH-1'), 30.6 (CH_2-2',5'), 24.6 (CH_2-3',4'), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 663.2 (3%) $[2M + \text{oxalic acid} + H]^+$, 369.4 (15%) $[M_{quat}]^+$, 287.4 (100%) $[M + H]^+$.

N-Cyclohexylmethyl-*N*-methyltryptamine hydrogen oxalate (Cyclohexylmethyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (217)

N-Cyclohexylmethyl-*N*-methyltryptamine hydrogen oxalate ($C_{18}H_{26}N_2 \cdot C_2H_2O_4$, 360.45 g/mol) was obtained from 138.6 mg iodomethyl-cyclohexane (**135**, 224.08 g/mol, 95%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3229, 2929, 2855, 2689, 1720, 1592, 1459, 1406, 1280, 1198, 1104, 1010, 734, 720, 620, 497, 465 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 267 (87%) sh, 272 (96%), 280 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.5 (3.3%), 16.4 (0.6%), 18.1 min (96.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (s, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.30 - 3.20 (m, 2 H, H_2-1''), 3.14 - 3.05 (m, 2 H, H_2-2''), 2.93 (d, J = 6 Hz, 2 H, H_2-1), 2.80 (s, 3 H, N^+-CH_3), 1.81 - 1.57 (m, 6 H, H-2'$_{eq}$-6'$_{eq}$,1'$_{ax}$), 1.33 - 1.08 (m, 3 H, H-3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.04 - 0.86 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 61.2 (CH_2-1), 56.2 (CH_2-1''), 40.0 (CH_3-N^+), 32.7 (CH-1'), 30.2 (CH_2-2',6'), 25.5 (CH_2-4'), 24.9 (CH_2-3',5'), 19.7 (CH_2-2'').

ESI MS: *m/z* (%) = 631.0 (57%) $[2M + \text{oxalic acid} + H]^+$, 577.1 (8%) $[2M + HCl + H]^+$, 271.2 (100%) $[M + H]^+$.

N-Cyclohexylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Cyclohexylmethyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (218)

N-Cyclohexylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{19}H_{28}N_2O \cdot C_2H_2O_4$, 390.47 g/mol) was obtained from 138.6 mg iodomethyl-cyclohexane (**135**, 224.08 g/mol,

95%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3418, 3234, 2929, 2855, 2682, 1719, 1587, 1623, 1488, 1451, 1405, 1280, 1216, 1117, 1069, 1031, 925, 828, 802, 721, 640, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 227 (>300%) sh, 275 (100%), 295 (83%) sh, 307 (54%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 16.5 (1.2%), 18.1 (95.7%), 21.9 (0.5%), 23.4 min (1.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2.5 Hz, 1 H, H-4'''), 7.08 (s, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.28 - 3.19 (m, 2 H, H_2-1''), 3.10 - 3.02 (m, 2 H, H_2-2''), 2.93 (d, J = 6.5 Hz, 2 H, H_2-1), 2.81 (s, 3 H, N^+-CH_3), 1.81 - 1.56 (m, 6 H, H-2'$_{eq}$-6'$_{eq}$,1'$_{ax}$), 1.32 - 1.08 (m, 3 H, H-3'$_{ax}$,5'$_{ax}$,4'$_{ax}$), 1.03 - 0.87 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 61.2 (CH_2-1), 56.1 (CH_2-1''), 55.4 (OCH_3-5'''), 40.1 (CH_3-N^+), 32.8 (CH-1'), 30.2 (CH_2-2',6'), 25.5 (CH_2-4'), 24.9 (CH_2-3',5'), 19.7 (CH_2-2'').

ESI MS: *m/z* (%) = 691.6 (6%) $[2M + oxalic\ acid + H]^+$, 637.7 (5%) $[2M + HCl + H]^+$, 301.3 (100%) $[M + H]^+$.

N-(Tetrahydrofuran-2-ylmethyl)-*N*-methyltryptamine hydrogen oxalate ((Tetrahydrofuran-2-ylmethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (219)

N-(Tetrahydrofuran-2-ylmethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{16}H_{22}N_2O \cdot C_2H_2O_4$, 348.39 g/mol) was obtained as a non-crystallizing mass from 138.7 mg 2-iodomethyl-tetrahydrofuran (**138**, 212.03 g/mol, 89%, 584.7 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-(Tetrahydrofuran-2-ylmethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((Tetrahydrofuran-2-ylmethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (220)

N-(Tetrahydrofuran-2-ylmethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{25}H_{56}N_2O_2 \cdot C_2H_2O_4$, 378.42 g/mol) was obtained as a non-crystallizing mass from 138.7 mg 2-iodomethyl-tetrahydrofuran (**138**, 212.03 g/mol, 89%, 584.7 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-(4-Bromobenzyl)-_N_-methyltryptamine hydrogen oxalate ((4-Bromobenzyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (221)

_N_-(4-Bromobenzyl)-_N_-methyltryptamine hydrogen oxalate ($C_{18}H_{19}BrN_2 \cdot C_2H_2O_4$, 433.3 g/mol) was obtained from 123.3 mg 4-bromo-1-bromomethyl-benzene (249.93 g/mol, 100%, 493.3 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3394, 3049, 2862, 2668, 1919, 1717, 1635, 1458, 1215,1073, 1013, 930, 841, 804, 746, 705, 466 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (735%), 266 (93%) sh, 272 (99%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 18.7 (98.5%), 24.7 min (0.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.92 (s br, 1 H, H-1'''), 7.63 (d, J = 8 Hz, 2 H, H-3',5'), 7.48 (d, J = 8 Hz, 1 H, H-4'''), 7.45 (d, J = 8 Hz, 2 H, H-2''',6'''), 7.35 (d, J = 8 Hz, 1 H, H-7'''), 7.19 (s, 1 H, H-2'''), 7.08 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 6.98 (dd, J = J' = 7 Hz, 1 H, H-5'''), 4.16 (s, 2 H, H_2-1), 3.10 (s, 4 H, H_2-1''',2'''), 2.64 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.0 (C_q-oxalate), 153.1 (C_q-5'''), 132.6 (CH-3',5'), 131.7 (C_q-1'), 131.5 (CH-2',6'), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.7 (CH-2'''), 122.2 (C_q-4'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.4 (C_q-3'''), 100.0 (CH-4'''), 58.1(CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.4 (CH_3-N^+), 20.4 (CH_2-2'').

ESI MS: _m/z_ (%) = 776.8 (6%) [[^{79}Br]M + [^{81}Br]M + oxalic acid + H]$^+$, 345.1 (100%) [^{81}[Br]M + H]$^+$, 343.1 (39%) [[^{79}Br]M + H]$^+$, 214 (7%) [[^{81}Br]M_{imine}], 212.0 (7%) [[^{79}Br]M_{imine}].

_N_-(4-Bromobenzyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((4-Bromobenzyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (222)

_N_-(4-Bromobenzyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate (43.1 mg $C_{19}H_{21}BrN_2O \cdot C_2H_2O_4$, 463.32 g/mol, 19%) was obtained from 123.3 mg 4-bromo-1-bromomethyl-benzene (249.93 g/mol, 100%, 493.3 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3405, 3327, 3026, 2937, 2829, 2593, 1714, 1624, 1487, 1457, 1409, 1280, 1215, 1130, 1105, 1074, 1050, 1013, 923, 845, 803, 721, 643, 502, 457 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>600%), 268 (92%) sh, 274 (98%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 18.5 min (99.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.77 (s br, 1 H, H-1'''), 7.65 (d, J = 8 Hz, 2 H, H-3',5'), 7.48 (d, J = 8 Hz, 2 H, H-2',6'), 7.25 (d, J = 8 Hz, 1 H, H-7'''), 7.16 (s, 1 H, H-4'''), 6.97 (s, 1 H, H-2'''), 6.73 (d, J = 8 Hz, 1 H, H-6'''), 4.22 (s, 2 H, H_2-1), 3.76 (s, 3 H, -OCH_3-5'''), 3.24 - 3.00 (m, 4 H, H_2-1''',2'''), 2.68 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 745.1 (25%) [[^{79}Br]M + [^{81}Br]M + H]$^+$, 836.8 (7%) [2M + oxalic acid + H]$^+$, 743.1 (14%) [2[^{80}Br]M + H]$^+$, 743.1 (17%) [2[^{79}Br]M + H]$^+$, 541.0 (4%) [M_{quat}]$^+$, 375.1 (95%) [[^{81}Br]M + H]$^+$, 373.1 (100%) [[^{79}Br]M + H]$^+$, 214.0 (11%) [[^{81}Br]M_{imine}], 212.0 (7%) [[^{79}Br]M_{imine}], 174.2 (10%) [5-MeO-vinylindole + H]$^+$.

_N_-(3-methyl-but-2-enyl)-_N_-methyltryptamine hydrogen oxalate ((3-Methyl-but-2-enyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (223)

N-(3-Methyl-but-2-enyl)-*N*-methyltryptamine hydrogen oxalate ($C_{16}H_{22}N_2 \cdot C_2H_2O_4$, 332.39 g/mol) was obtained as a non-crystallizing mass from 87.6 mg 1-bromo-3-methyl-but-2-ene (149.03 g/mol, 100%, 587.8 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

_N_-(3-methyl-but-2-enyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((3-methyl-but-2-enyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (224)

N-(3-Methyl-but-2-enyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{17}H_{24}N_2O \cdot C_2H_2O_4$, 362.42 g/mol) was obtained as a non-crystallizing mass from 87.6 mg 1-bromo-3-methyl-but-2-ene (149.03 g/mol, 100%, 587.8 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-Cyanomethyl-_N_-methyltryptamine hydrogen oxalate (Cyanomethyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (225)

N-Cyanomethyl-*N*-methyltryptamine hydrogen oxalate ($C_{13}H_{15}N_3 \cdot C_2H_2O_4$, 303.31 g/mol) was obtained as a non-crystallizing mass from 44.4 mg chloroacetonitrile (75.5 g/mol, 100%, 588.1 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

2,3,4,9-Tetrahydro-6-methoxy-2-methyl-1_H_-pyrido[3,4-b]indole (6-Methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline hydrogen oxalate) (226)

Crude 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline hydrogen oxalate ($C_{15}H_{18}N_2O_5 \cdot C_2H_2O_4$, 334.32 g/mol) was obtained unexpectedly as a fine brown powder from 44.4 mg chloroacetonitrile (75.5 g/mol, 100%, 588.1 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3258, 3030, 2955, 2834, 2728, 1718, 1633, 1488, 1458, 1313, 1286, 1210, 1150, 1029, 957, 903, 844, 800, 708, 619, 476 cm^{-1}.

UV (H_2O): λ (%max_A) = 221 (357%) sh, 272 (100%), 285 (80%) sh, 291 (74%) sh, 306 (45%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 10.5 (97.3%), 16.5 min (1.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.85 (s br, 1 H, H-1'''), 7.24 (d, J = 9 Hz, 1 H, H-7'''), 6.94 (d, J = 2 Hz, 1 H, H-4'''), 6.73 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 4.27 (s, 2 H, H_2-1), 3.75 (s, 3 H, -OCH_3-5'''), 3.43 - 3.33 (m, 2 H, H_2-1''), 2.96 - 2.84 (m, 2 H, H_2-2''), 2.87 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 477.9 (7%), 432.9 (17%) $[2M + H]^+$, 346.1 (11%) $[M_2 + Na]^+$, 324.2 (71%) $[M_2 + H]^+$, 262.1 (8%), 217.1 (100%) $[M + H]^+$, 174.2 (33%).

N-Methoxycarbonylmethyl-*N*-methyltryptamine hydrogen oxalate ({[2-(Indol-3-yl)-ethyl]-methylamino}-acetic acid methyl ester hydrogen oxalate) (227)

N-Methoxycarbonylmethyl-*N*-methyltryptamine hydrogen oxalate ($C_{14}H_{18}N_2O_2 \cdot C_2H_2O_4$, 336.34 g/mol) was obtained from 63.8 mg chloroacetic acid methyl ester (**139**, 108.52 g/mol, 100%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3402, 3262, 2958, 2856, 2618, 1764, 1638, 1459, 1431, 1405, 1367, 1341, 1314, 1281, 1218, 1103, 1019, 769, 745, 720, 709, 494 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%), 271 (95%) sh, 278 (100%), 280 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 10.5 (99.0%), 14.8 min (0.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.40 (s br, 1 H, H-1'''), 7.54 (d, J = 8 Hz, 1 H, H-4'''), 7.35 (d, J = 8 Hz, 1 H, H-7'''), 7.19 (d, J = 1 Hz, 1 H, H-2'''), 7.07 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 6.99 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.83 (s, 2 H, H_2-1), 3.69 (s, 3 H, $COOCH_3$), 3.14 - 3.04 (m, 2 H, H_2-1''), 3.04 - 2.93 (m, 2 H, H_2-2''), 2.67 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 168.3 (C_q-2), 163.3 (C_q-oxalate), 136.2 (C_q-7b'''), 126.9 (C_q-3b'''), 123.0 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 110.3 (C_q-3'''), 56.4 (CH_2-1), 55.8 (CH_2-1''), 51.8 (CH_3-COOMe), 41.0 (CH_3-N^+), 21.1 (CH_2-2'').

ESI MS: *m/z* (%) = 247.1 (100%) $[M + H]^+$.

N-Methoxycarbonylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ({[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-acetic acid methyl ester hydrogen oxalate) (228)

N-Methoxycarbonylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{15}H_{20}N_2O_3 \cdot C_2H_2O_4$, 366.37 g/mol) was obtained from 63.8 mg chloroacetic acid methyl

ester (**139**, 108.52 g/mol, 100%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3309, 3047, 2959, 2835, 2670, 1754, 1626, 1489, 1442, 1405, 1281, 1217, 1179, 1105, 1063, 1030, 924, 805, 720, 703, 639, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (435%), 275 (100%), 295 (82%) sh, 307 (52%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 11.2 min (98.9%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.72 (s br, 1 H, H-1'''), 7.23 (d, J = 8.5 Hz, 1 H, H-7'''), 7.14 (d, J = 2 Hz, 1 H, H-4'''), 7.03 (d, J = 2 Hz, 1 H, H-2'''), 6.72 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.83 (s, 2 H, H_2-1), 3.77 (s, 3 H, -OCH_3-5'''), 3.69 (s, 3 H, $COOCH_3$), 3.12 - 3.01 (m, 2 H, H_2-1''), 3.01 - 2.90 (m, 2 H, H_2-2''), 2.67 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 168.4 (C_q-2), 163.3 (C_q-oxalate), 153.0 (C_q-5'''), 131.4 (C_q-7b'''), 127.2 (C_q-3b'''), 123.5 (CH-2'''), 112.0 (CH-7'''), 111.1 (CH-6'''), 110.0 (C_q-3'''), 100.2 (CH-4'''), 56.3 (CH_2-1), 55.8 (CH_2-1''), 55.4 (OCH_3-5'''), 51.8 (CH_3-COOMe), 41.0 (CH_3-N^+), 21.2 (CH_2-2'').

ESI MS: *m/z* (%) = 574.9 (11%) $[2M + oxalic\ acid + H]^+$, 299.1 (6%) $[M + Na]^+$, 277.1 (100%) $[M + H]^+$, 174.2 (16%) $[5\text{-MeO-vinylindole} + H]^+$.

N-tert.-Butoxycarbonylmethyl-*N*-methyltryptamine hydrogen oxalate ({[2-(Indol-3-yl)-ethyl]-methylamino}-acetic acid *tert.*-butyl ester hydrogen oxalate) (229)

IR (KBr): $\tilde{\nu}$ = 3404, 3253, 2983, 2935, 2625, 1744, 1603, 1459, 1404, 1371, 1280, 1157, 1012, 948, 879, 837, 741, 720, 610, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 272 (96%) sh, 278 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.8 (3.4%), 16.1 min (96.3%).

N-tert.-Butoxycarbonylmethyl-*N*-methyltryptamine hydrogen oxalate (97 mg, $C_{17}H_{24}N_2O_2 \cdot C_2H_2O_4$, 378.42 g/mol, 54%) was obtained from 114.6 mg iodoacetic acid *tert.*-butyl ester (242.05 g/mol, 100%, 473.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.55 (d, J = 8 Hz, 1 H, H-4'''), 7.35 (d, J = 8 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-2'''), 7.08 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 6.99 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.78 (s, 2 H, H_2-1), 3.17 - 3.05 (m, 2 H, H_2-1''), 3.05 - 2.95 (m, 2 H, H_2-2''), 2.70 (s, 3 H, N^+-CH_3), 1.45 (s, 9 H, $C(CH_3)_3$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 166.6 (C_q-2), 163.6 (C_q-oxalate), 136.2 (C_q-7b'''), 126.8 (C_q-3b'''), 123.0 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5

(CH-7'''), 110.0 (C_q-3'''), 82.2 (C_q-*tert.*-butyl), 56.4 (CH_2-1), 56.3 (CH_2-1''), 40.8 (CH_3-N^+), 27.6 (CH_3-*tert.*-butyl), 20.8 (CH_2-2'').

ESI MS: *m/z* (%) = 311.2 (19%) $[M + Na]^+$, 289.2 (100%) $[M + H]^+$.

N-tert.-Butoxycarbonylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ({[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-acetic acid *tert.*-butyl ester hydrogen oxalate) (230)

N-tert.-butoxycarbonylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (125.4 mg, $C_{18}H_{26}N_2O_3 \cdot C_2H_2O_4$, 408.45 g/mol, 65%) was obtained from 114.6 mg iodoacetic acid *tert.*-butyl ester (242.05 g/mol, 100%, 473.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3411, 3252, 2939, 2608, 1740, 1625, 1586, 1488, 1458, 1406, 1370, 1281, 1218, 1156, 1110, 1028, 925, 832, 802, 755, 720, 639, 499, 461 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 275 (100%), 293 (82%), 305 (58%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 10.8 (4.6%), 16.1 min (95.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.74 (s br, 1 H, H-1'''), 7.24 (d, J = 8.5 Hz, 1 H, H-7'''), 7.14 (d, J = 2 Hz, 1 H, H-4'''), 7.03 (d, J = 2 Hz, 1 H, H-2'''), 6.73 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.77 (s, 2 H, H_2-1), 3.77 (s, 3 H, -OCH_3-5'''), 3.15 - 3.06 (m, 2 H, H_2-1''), 3.00 - 2.92 (m, 2 H, H_2-2''), 2.70 (s, 3 H, N^+-CH_3), 1.45 (s, 9 H, $C(CH_3)_3$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 166.6 (C_q-2), 163.6 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (C_q-7b'''), 127.1 (C_q-3b'''), 123.6 (CH-2'''), 112.1 (CH-7'''), 111.1 (CH-6'''), 109.8 (C_q-3'''), 100.2 (CH-4'''), 82.2 (C_q-*tert.*-butyl), 56.4 (CH_2-1), 56.2 (CH_2-1''), 55.4 (OCH_3-5'''), 40.8 (CH_3-N^+), 27.6 (CH_3-*tert.*-butyl), 20.9 (CH_2-2'').

ESI MS: *m/z* (%) = 659.0 (14%) $[2M + Na]^+$, 341.1 (23%) $[M + Na]^+$, 319.1 (100%) $[M + H]^+$.

N-(Carbamoylmethyl)-*N*-methyltryptamine hydrogen oxalate (2-{[2-(Indol-3-yl)-ethyl]-methylamino}-acetamide hydrogen oxalate) (231)

103.4 mg *N*-Carbamoylmethyl-*N*-methyltryptamine hydrogen oxalate ($C_{13}H_{17}N_3O \cdot C_2H_2O_4$, 321.33 g/mol, 55%) was obtained from 108.7 mg 2-iodoacetamide (184.96 g/mol, 100%, 587.7 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3403, 3319, 3045, 2942, 2860, 2400, 1700, 1619, 1458, 1416, 1342, 1280, 1212, 1096, 1011, 949, 877, 794, 749, 720, 707, 602, 497 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>400%), 265 (82%) sh, 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 8.2 min (99.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.90 (s br, 1 H, H-1'''), 7.82 (s br, 1 H, CONH), 7.57 (d, J = 7.5 Hz, 2 H, H-4''', CONH), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.21 (d, J = 2 Hz, 1 H, H-2'''), 7.06 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.74 (s, 2 H, H_2-1), 3.27 - 3.16 (m, 2 H, H_2-1''), 3.10 - 3.01 (m, 2 H, H_2-2''), 2.78 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 167.5 (C_q-2), 164.1 (C_q-oxalate), 136.3 (C_q-7b'''), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.5 (C_q-3'''), 56.7 (CH_2-1), 56.4 (CH_2-1''), 41.0 (CH_3-N^+), 20.5 (CH_2-2'').

ESI MS: *m/z* (%) = 485.1 (74%) $[2M + Na]^+$, 254.3 (23%) $[M + Na]^+$, 232.2 (100%) $[M + H]^+$.

N-(Carbamoylmethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate (2-{[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-acetamide hydrogen oxalate) (232)

84.9 mg *N*-Carbamoylmethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{14}H_{19}N_3O_2 \cdot C_2H_2O_4$, 351.35 g/mol, 41%) was obtained from 108.7 mg 2-iodoacetamide (184.96 g/mol, 100%, 587.7 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3387, 3314, 3167, 2950, 2655, 1702, 1635, 1487, 1464, 1441, 1417, 1357, 1311, 1208, 1177, 1111, 1082, 1026, 801, 706, 602, 488 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 262 (69%) sh, 268 (89%) sh, 275 (100%), 293 (82%) sh, 295 (81%) sh, 307 (52%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.2 (99.2%), 17.0 min (0.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.84 (s br, 1 H, CONH), 7.57 (s br, 1 H, CONH), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.16 (d, J = 1 Hz, 1 H, H-4'''), 7.06 (d, J = 1.5 Hz, 1 H, H-2'''), 6.73 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.76 (s, 2 H, H_2-1), 3.26 - 3.16 (m, 2 H, H_2-1''), 3.07 - 2.98 (m, 2 H, H_2-2''), 2.79 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 167.5 (C_q-2), 164.2 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (C_q-7b'''), 127.1 (C_q-3b'''), 123.7 (CH-2'''), 112.2 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 56.7 (CH_2-1), 56.2 (CH_2-1''), 55.4 (OCH_3-5'''), 41.0 (CH_3-N^+), 20.5 (CH_2-2'').

ESI MS: *m/z* (%) = 545.3 (23%) $[2M + Na]^+$, 284.1 (7%) $[M + Na]^+$, 262.1 (100%) $[M + H]^+$, 173.9 (3%) [5-MeO-vinylindole + H]$^+$.

N-(2-Phenethyl)-*N*-methyltryptamine hydrogen oxalate ((2-Phenethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (233)

N-(2-Phenethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{22}N_2 \cdot C_2H_2O_4$, 368.43 g/mol) was obtained from 149.0 mg 1-(2-iodoethyl)-benzene (**141**, 232.06 g/mol, 91%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3396, 3018, 2937, 2858, 2676, 1718, 1701, 1618, 1458, 1358, 1340, 1280, 1182, 951, 879, 783, 746, 721, 703, 618, 586, 496 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>600%), 264 (80%) sh, 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.1 (5.1%), 17.3 min (94.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.35 - 7.25 (m, 5 H, H-2'-6'), 7.24 (d, J = 2.5 Hz, 1 H, H-2'''), 7.10 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.37 - 3.25 (m, 4 H, H_2-1'',1), 3.16 - 3.07 (m, 2 H, H_2-2''), 3.04 - 2.95 (m, 2 H, H_2-2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 137.3 (C_q-1'), 136.2 (C_q-7b'''), 128.7 (CH-3',5'), 128.5 (CH-2',6'), 126.7 (C_q-3b'''), 126.6 (CH-4'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 56.0 (CH_2-1), 55.4 (CH_2-1''), 39.3 (CH_3-N^+), 29.7 (CH_2-2), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 647.1 (3%) $[2M + oxalic\ acid + H]^+$, 279.2 (100%) $[M + H]^+$.

N-(2-Phenethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2-Phenethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (234)

N-[2-Phenethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{24}N_2O \cdot C_2H_2O_4$, 398.45 g/mol) was obtained from 149.0 mg 1-(2-iodoethyl)-benzene (**141**, 232.06 g/mol, 91%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3401, 3236, 3031, 2940, 2691, 1719, 1623, 1488, 1456, 1280, 1216, 1108, 1062, 1028, 953, 927, 836, 801, 754, 720, 700, 637, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (> 400%) sh, 267 (88%) sh, 272 (98%) sh, 275 (100%), 295 (83%) sh, 307 (52%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 17.8 (98.0%), 23.9 min (1.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.39 - 7.23 (m, 5 H, H-2'-6'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.10 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.36 - 3.25 (m, 4 H, H_2-1'',1), 3.12 - 2.95 (m, 4 H, H_2-2'',2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.9 (C_q-oxalate), 153.1 (C_q-5'''), 137.3 (C_q-1'), 131.4 (C_q-7b'''), 128.7 (CH-3',5'), 128.5 (CH-2',6'), 127.1 (C_q-3b'''), 126.6 (CH-4'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 56.0 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.2 (CH_3-N^+), 29.6 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 707.5 (23%) $[2M + \text{oxalic acid} + H]^+$, 413.3 (14%) $[M_{quat}]^+$, 309.2 (100%) $[M + H]^+$.

N-[2-(2-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2-Methylphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (235)

N-[2-(2-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2 \cdot C_2H_2O_4$, 382.45 g/mol) was obtained from 155.7 mg 2-methyl-1-(2-iodoethyl)-benzene (**142**, 246.09 g/mol, 93%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3410, 3294, 3053, 2925, 2878, 2681, 1720, 1702, 1632, 1459, 1341, 1279, 1223, 1110, 1011, 966, 933, 817, 747, 721, 707, 486 cm^{-1}.

UV (H_2O): λ (%max_A) = 216 (>600%), 272 (99%), 278 (100%), 280 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 17.6 (2.3%), 19.3 min (97.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.61 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 2 Hz, 1 H, H-2'''), 7.22 - 7.13 (m, 4 H, H-3',4',5',6'), 7.10 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.39 - 3.30 (m, 2 H, H_2-1''), 3.25 - 3.16 (m, 2 H, H_2-1), 3.16 - 3.07 (m, 2 H, H_2-2''), 3.02 - 2.98 (m, 2 H, H_2-2), 2.92 (s, 3 H, N^+-CH_3), 2.31 (s, 3 H, -CH_3-2').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.3 (C_q-oxalate), 136.2 (C_q-7b'''), 136.0 (C_q-1'), 135.5 (C_q-2'), 130.2 (CH-3'), 129.2 (CH-6'), 126.72 (C_q-3b'''), 126.69 (CH-4'), 126.0 (CH-5'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 55.5 (CH_2-1''), 55.1 (CH_2-1), 39.3 (CH_3-N^+), 27.4 (CH_2-2), 20.0 (CH_2-2''), 18.7 (Ph-CH_3-2').

ESI MS: *m/z* (%) = 675.4 (6%) $[2M + \text{oxalic acid} + H]^+$, 621.5 (5%) $[2M + HCl + H]^+$, 293.3 (100%) $[M + H]^+$.

N-[2-(2-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2-Methylphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (236)

N-[2-(2-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O \cdot C_2H_2O_4$, 412.48 g/mol) was obtained from 155.7 mg 2-methyl-1-(2-iodoethyl)-benzene (**142**, 246.09 g/mol, 93%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3386, 3243, 3025, 2940, 1718, 1629, 1489, 1303, 1215, 1110, 1062, 1029, 949, 927, 833, 799, 755, 697, 639, 468 cm^{-1}.

UV (H_2O): λ (%max_A) = 208 (>500%), 266 (87%) sh, 274 (100%), 288 (85%) sh, 295 (81%) sh, 307 (53%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 19.2 (98.7%), 25.1 min (1.0%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 9 Hz, 1 H, H-7'''), 7.21 - 7.12 (m, 4 H, H-3',4',5',6'), 7.20 (d, J = 2 Hz, 1 H, H-4'''), 7.10 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.37 - 3.28 (m, 2 H, H_2-1'), 3.25 - 3.15 (m, 2 H, H_2-1), 3.13 - 3.04 (m, 2 H, H_2-2''), 3.03 - 2.92 (m, 2 H, H_2-2), 2.91 (s, 3 H, N^+-CH_3), 2.31 (s, 3 H, -CH_3-2').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 136.0 (C_q-1'), 135.5 (C_q-2'), 131.3 (C_q-7b'''), 130.2 (CH-3'), 129.2 (CH-6'), 127.1 (C_q-3b'''), 126.7 (CH-4'), 126.0 (CH-5'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.40 (OCH_3-5'''), 55.37 (CH_2-1''), 55.1 (CH_2-1), 39.3 (CH_3-N^+), 27.3 (CH_2-2), 20.1 (CH_2-2''), 18.7 (Ph-CH_3-2').

ESI MS: *m/z* (%) = 735.6 (18%) $[2M + oxalic\ acid + H]^+$, 681 (3%) $[2M + HCl + H]^+$, 441.5 (6%) $[M_{quat}]^+$, 323.3 (100%) $[M + H]^+$.

N-[2-(3-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3-Methylphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (237)

N-[2-(3-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2 \cdot C_2H_2O_4$, 382.45 g/mol) was obtained from 156.2 mg 3-methyl-1-(2-iodoethyl)-benzene (**143**, 246.09 g/mol, 93%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3408, 3257, 3021, 2947, 2861, 2690, 1719, 1701, 1609, 1457, 1419, 1341, 1280, 1173, 1014, 944, 799, 773, 749, 721, 703, 591, 582, 488 cm^{-1}.

HPLC: R_t (%total AUC_{260}) = 4.7 (oxalic acid), 8.8 (1.0%), 18.0 min (99.0%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.95 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 2.5 Hz, 1 H, H-2'''), 7.21 (dd, J = J' = 7 Hz, 1 H, H-5'), 7.12 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.09 - 7.03 (m, 3 H, H-2',4',6'), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.37 - 3.22 (m, 4 H, H_2-1,1''), 3.15 - 3.06 (m, 2 H, H_2-2''), 2.98 - 2.85 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3), 2.29 (s, 3 H, -CH_3-3').

ESI MS: *m/z* (%) = 293.2 (100%) $[M + H]^+$, 162.1 (9%) $[M_{imine}]^+$.

N-[2-(3-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate

([2-(3-Methylphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (238)

N-[2-(3-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O \cdot C_2H_2O_4$, 412.48 g/mol) was obtained from 156.2 mg 3-methyl-1-(2-iodoethyl)-benzene (**143**, 246.09 g/mol, 93%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3443, 3265, 3018, 2939, 2690, 1703, 1637, 1487, 1458, 1325, 1281, 1215, 1186, 1112, 1063, 1030, 936, 924, 799, 720, 700, 613, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 216 (>500%) sh, 220 (480%) sh, 268 (91%) sh, 274 (100%), 295 (80%) sh, 306 (56%) sh.

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 19.5 min (99.8%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.26 (d, J = 9 Hz, 1 H, H-7'''), 7.23 - 7.17 (m, 2 H, H-4''',2'), 7.11 - 7.03 (m, 3 H, H-4',5',6'), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.36 - 3.21 (m, 4 H, H_2-1,1''), 3.12 - 3.01 (m, 2 H, H_2-2''), 2.99 - 2.85 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3), 2.28 (s, 3 H, -CH_3-2').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 153.1 (C_q-5'''), 137.6 (C_q-3'), 137.2 (C_q-1'), 131.3 (C_q-7b'''), 129.3 (CH-2'), 128.4 (CH-5'), 127.2 (CH-4'), 127.1 (C_q-3b'''), 125.7 (CH-6'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.3 (CH-4'''), 56.1 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.4 (CH_3-N^+), 29.7 (CH_2-2), 20.8 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 323.2 (100%) $[M + H]^+$.

***N*-[2-(4-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Methylphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (239)**

N-[2-(4-Methylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2 \cdot C_2H_2O_4$, 382.45 g/mol) was obtained from 156.2 mg 4-methyl-1-(2-iodoethyl)-benzene (**144**, 246.09 g/mol, 93%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3397, 3280, 3026, 2936, 2861, 2695, 1718, 1702, 1636, 1517, 1458, 1341, 1280, 1186, 1107, 1033, 813, 742, 720, 703, 489 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>700%), 263 (82%) sh, 273 (100%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.5 (0.7%), 19.1 min (99.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.19 - 7.12 (m, 4 H, H-2',3',5',6'), 7.10 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.37 - 3.22 (m, 4 H, H_2-1,1''), 3.15 - 3.06 (m, 2 H, H_2-2''), 2.98 - 2.85 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3), 2.27 (s, 3 H, -CH_3-4).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.2 (C_q-7b'''), 135.6 (C_q-1'), 134.1 (C_q-4'), 129.0 (CH-3',5'), 128.5 (CH-2',6'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 56.2 (CH_2-1), 55.4 (CH_2-1''), 39.3 (CH_3-N^+), 29.3 (CH_2-2), 20.5 (Ph-CH_3-4'), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 697 (8%) $[2M + oxalic\ acid + Na]^+$, 675 (3%) $[2M + oxalic\ acid + H]^+$, 621 (4%) $[2M + HCl + H]^+$, 293.1 (100%) $[M + H]^+$.

N-[2-(4-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Methylphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (240)

N-[2-(4-Methylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O \cdot C_2H_2O_4$, 412.48 g/mol) was obtained from 156.2 mg 4-methyl-1-(2-iodoethyl)-benzene (**144**, 246.09 g/mol, 93%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3415, 3286, 3026, 2941, 2682, 1719, 1702, 1625, 1516, 1488, 1406, 1280, 1215, 1177, 1108, 1033, 808, 721, 707, 642, 501 cm^{-1}.

UV (H_2O): λ (%max_A) = 217 (>500%), 267 (89%) sh, 273 (100%), 276 (98%) sh, 296 (78%) sh, 305 (58%) sh.

HPLC: R_t (%total AUC_{260}) = 5.9 (oxalic acid), 19.4 min (99.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.13 - 7.11 (m, 4 H, H-2',3',5',6'), 7.09 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.35 - 3.21 (m, 4 H, H_2-1,1''), 3.12 - 3.01 (m, 2 H, H_2-2''), 2.98 - 2.84 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3), 2.27 (s, 3 H, -CH_3-4).

^{13}C NMR (75.5 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 153.1 (C_q-5'''), 135.6 (C_q-1'), 134.1 (C_q-4'), 131.3 (C_q-7b'''), 129.0 (CH-3',5'), 128.5 (CH-2',6'), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 56.2 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.4 (CH_3-N^+), 29.3 (CH_2-2), 20.5 (Ph-CH_3-4'), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 735.6 (6%) $[2M + oxalic\ acid + H]^+$, 681 (3%) $[2M + HCl + H]^+$, 323.4 (100%) $[M + H]^+$.

_N_-(2-Biphenyl-4-yl-ethyl)-_N_-methyltryptamine hydrogen oxalate ((2-Biphenyl-4-yl-ethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (241)

_N_-(2-Biphenyl-4-yl-ethyl)-_N_-methyltryptamine hydrogen oxalate ($C_{25}H_{26}N_2 \cdot C_2H_2O_4$, 444.52 g/mol) was obtained from 211.7 mg 4-(2-iodoethyl)-biphenyl (**145**, 308.16 g/mol, 86%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3396, 3027, 2928, 2859, 2686, 1718, 1618, 1487, 1458, 1418, 1341, 1280, 1181, 1011, 943, 840, 765, 753, 721, 703, 489, 426 cm^{-1}.

UV (methanol): λ (%max_A) = 207 (>200%), 219 (185%) sh, 253 (100%), 283 (37%) sh, 289 nm (27%).

HPLC: R_t (%total AUC_{260}) = 13.6 (oxalic acid), 15.0 (5.9%), 23.4 (93.5%), 29.9 min (0.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.68 - 7.60 (m, 5 H, H-4''',2*,6*,3',5'), 7.46 (dd, J = J' = 7.5 Hz, 2 H, H-3*,5*), 7.38 (d, J = 8 Hz, 2 H, H-2', 6'), 7.38 (d, J = 8 Hz, 1 H, H-4*), 7.38 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.39 - 3.30 (m, 4 H, H_2-1'',1), 3.19 - 3.10 (m, 2 H, H_2-2''), 3.10 - 3.01 (m, 2 H, H_2-2), 2.92 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 139.8 (C_q-1'), 138.5 (C_q-1*), 136.6 (C_q-4'), 136.2 (C_q-7b'''), 129.3 (CH-3*,5*), 128.8 (CH-2',6'), 127.2 (CH-4*), 126.74 (CH-2*,6*), 126.71 (C_q-3b'''), 126.5 (CH-3',5'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.5 (CH-7'''), 109.4 (C_q-3'''), 56.0 (CH_2-1), 55.4 (CH_2-1''), 39.3 (CH_3-N^+), 29.3 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: _m/z_ (%) = 798.8 (12%) $[2M + \text{oxalic acid} + H]^+$, 355.2 (100%) $[M + H]^+$, 224.2 (9%) $[M_{imine}]^+$.

_N_-(2-Biphenyl-4-yl-ethyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((2-Biphenyl-4-yl-ethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (242)

_N_-(2-Biphenyl-4-yl-ethyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{26}H_{28}N_2O \cdot C_2H_2O_4$, 474.55 g/mol) was obtained from 211.7 mg 4-(2-iodoethyl)-biphenyl (**145**, 308.16 g/mol, 86%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3414, 3029, 2929, 2678, 1718, 1701, 1626, 1487, 1280, 1215, 1177, 1061, 1031, 939, 926, 829, 802, 764, 721, 699, 495 cm^{-1}.

UV (methanol): λ (%max_A) = 210 (>200%) sh, 223 (126%) sh, 229 (107%) sh, 243 (86%) sh, 261 (91%) sh, 264 (85%) sh, 270 (69%) sh, 275 nm (56%) sh.

HPLC: R_t (%total AUC_{260}) = 10.3 (oxalic acid), 13.5 (0.6%), 15.3 (2.9%), 23.2 min (95.1%).

HPLC (gradient B): R_t (%total AUC_{260}) = 10.3 (oxalic acid), 13.5 (0.6%), 15.3 (2.9%), 23.2 min (95.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.65 (d, J = 7 Hz, 2 H, H-2*,6*), 7.63 (d, J = 7 Hz, 2 H, H-3',5'), 7.46 (t, J = 7.5 Hz, 2 H, H-3*,5*), 7.38 (d, J = 8 Hz, 2 H, H-2', 6'), 7.38 (d, J = 8 Hz, 1 H, H-4*), 7.26 (d, J = 7.5 Hz, 1 H, H-7'''), 7.20 (d, J = 2 Hz, 1 H, H-4'''), 7.11 (d, J = 2 Hz, 1 H, H-2'''), 6.75 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.34 - 3.26 (m, 4 H, H_2-1'',1), 3.14 - 2.98 (m, 4 H, H_2-2'',2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 139.8 (C_q-1'), 138.5 (C_q-1*), 136.7 (C_q-4'), 131.3 (C_q-7b'''), 129.3 (CH-3*,5*), 128.8 (CH-2',6'), 127.2 (CH-4*), 127.1 (C_q-3b'''), 126.7 (CH-2*,6*), 126.5 (CH-3',5'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.3 (C_q-3'''), 100.3 (CH-4'''), 56.1 (CH_2-1), 55.5 (CH_2-1''), 55.4 (OCH_3-5'''), 39.8 (CH_3-N^+), 29.5 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 565.2 (5%) $[M_{quat}]^+$, 385.2 (100%) $[M + H]^+$, 224.2 (9%) $[M_{imine}]^+$.

N-[2-(3-Acetoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3-Acetoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (243)

N-[2-(3-Acetoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate (A) ($C_{19}H_{22}N_2O \cdot C_2H_2O_4$, 384.43 g/mol) was obtained from 315.0 mg 3-hydroxy-1-(2-iodoethyl)-benzene (**147**, 248.06 g/mol, 46%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E. The product contained *N*-[2-(3-hydroxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate as an impurity after prolonged storage (signals B in the spectra below).

IR (KBr): $\tilde{\nu}$ = 3415, 3293, 3044, 2942, 2861, 2711, 1739, 1615, 1459, 1375, 1211, 1148, 1014, 942, 790, 742, 696, 591, 468 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%), 268 (92%) sh, 272 (98%), 278 (100%), 280 (99%) sh, 288 nm (75%).

HPLC: R_t (%total AUC_{260}) = 5.9 (oxalic acid), 10.3 (1.4%), 15.2 (53.5%), 17.9 min (44.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (t, J = 8 Hz, 1 H, H-5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.17 (d, J = 8 Hz, 1 H, H-6'), 7.09 (dd, J = J' = 8 Hz, 1 H, H-6'''), 7.07 (s, 1 H, H-2'), 7.02 (d, J = 8 Hz, 1 H, H-2'), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.69 (s, 1 H, H-2'$_B$, minor peak), 6.67 (d, J' = 7.5 Hz, 1 H, H-3'$_B$, minor peak), 3.35 - 3.23 (m, 4 H, H_2-1,1''), 3.15 - 3.06 (m, 2 H, H_2-2''), 3.05 - 2.96 (m, 2 H, H_2-2), 2.88 (s, 3 H, N_B^+-CH_3, minor peak), 2.86 (s, 3 H, N^+-CH_3), 2.27 (s, 3 H, H_3-OAc).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 169.0 (C_q-OAc_A), 164.8 (C_q-oxalate), 157.6 (C_q-3'$_B$), 150.6 (C_q-3'$_A$), 139.2 (C_q-1'$_B$), 138.7 (C_q-1'$_A$), 136.2 (C_q-7b'''), 129.44 (CH-5'B), 129.41 CH-5'$_A$), 126.7 (C_q-3b'''), 126.2 (CH-6'A), 123.2 (CH-2'''), 122.0 (CH-6'$_B$), 121.1 (CH-5'''), 120.0 (CH-2'$_A$), 119.1 (CH-4'$_A$), 118.4 (CH-6'''), 118.2 (CH-4'''), 115.7 (CH-2'$_B$), 113.6 (CH-2'$_B$), 109.6 (C_q-3'''$_B$), 109.4 (C_q-3'''$_A$), 56.1 (CH_2-1$_B$), 55.9 (CH_2-1$_A$), 55.5 (CH_2-1''$_A$),55.4 (CH_2-1''$_B$), 39.3 (CH_3-N^+), 29.8 (CH_2-2$_B$), 29.5 (CH_2-2$_A$), 20.7 (CH_3-OAc_A), 20.1 (CH_2-2''$_A$), 19.9 (CH_2-2''$_B$).

ESI MS: *m/z* (%) = 337.3 (100%) $[M_A + H]^+$, 295.2 (28%) $[M_B + H]^+$.

N-[2-(3-Acetoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3-Hydroxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (244)

N-[2-(3-Acetoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{26}N_2O_3 \cdot C_2H_2O_4$, 456.49 g/mol) was obtained as a non-crystallizing mass from 315.0 mg 3-hydroxy-1-(2-iodoethyl)-benzene (**147**, 248.06 g/mol, 46%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(2-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2-Methoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (245)

N-[2-(2-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2O \cdot C_2H_2O_4$, 398.45 g/mol) was obtained as an amorphous brownish powder from 170.3 mg 2-methoxy-1-(2-iodoethyl)-benzene (**150**, 262.09 g/mol, 90%, 587.5 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3417, 3315, 3045, 2937, 2688, 1720, 1702, 1636, 1496, 1459, 1357, 1341, 1281, 1247, 1107, 1028, 961, 755, 721, 497 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 219 (>500%), 262 (70%) sh, 268 (91%) sh, 272 (99%), 277 (100%), 288 nm (65%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.9 (1.3%), 19.7 min (98.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.61 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.30 - 7.19 (m, 3 H, H-2''',4',6'), 7.11 (ddd, J = 7 Hz, 7 Hz, 0.5 Hz, 1 H, H-6'''), 7.05 - 6.98 (m, 2 H, H-3',5'), 6.91 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.81 (s, 3 H, OCH_3), 3.38 - 3.28 (m, 2 H, H_2-1''), 3.28 - 3.19 (m, 2 H, H_2-1), 3.16 - 3.06 (m, 2 H, H_2-2''), 3.01 - 2.92 (m, 2 H, H_2-2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 157.1 (C_q-2'), 136.2 (C_q-7b'''), 130.1 (CH-6'), 128.3 (CH-4'), 126.7 (C_q-3b'''), 124.9 (C_q-1'), 123.2 (CH-2'''), 121.1 (CH-5'''),

120.4 (CH-5'), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 110.9 (CH-3'), 109.3 (C_q-3'''), 55.3 (OCH_3-2'), 55.1 (CH_2-1''), 54.4 (CH_2-1), 39.4 (CH_3-N^+), 24.5 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 706.9 (8%) [2M + oxalic acid + H]$^+$, 443.0 (1%) $[M_{quat}]^+$, 309.2 (100%) [M + H]$^+$, 178.6 (4%) $[M_{imine}]^+$.

N-[2-(2-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2-Methoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (246)

N-[2-(2-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4$, 428.49 g/mol) was obtained as an amorphous brownish powder from 170.3 mg 2-methoxy-1-(2-iodoethyl)-benzene (**150**, 262.09 g/mol, 90%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3321, 3048, 2935, 2697, 1724, 1702, 1627, 1495, 1465, 1280, 1248, 1218, 1119, 1081, 1027, 962, 927, 820, 797, 755, 710, 624, 560, 478 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>400%), 273 (100%), 276 (100%), 293 (63%), 296 (61%) sh, 306 (43%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 19.5 (98.9%), 26.5 min (0.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.83 (s br, 1 H, H-1'''), 7.26 (d, J = 9 Hz, 1 H, H-7'''), 7.24 (m, 2 H, H-6',4'), 7.19 (s, 1 H, H-4'''), 7.11 (d, J = 1 Hz, 1 H, H-2'''), 7.00 (d, J = 8 Hz, 1 H, H-3'), 6.91 (dd, J = J' = 7 Hz, 1 H, H-5'), 6.74 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.80 (s, 3 H, OCH_3), 3.77 (s, 3 H, -OCH_3-5'''), 3.37 - 3.19 (m, 4 H, H_2-1,1''), 3.13 - 3.03 (m, 2 H, H_2-2''), 3.03 - 2.93 (m, 2 H, H_2-2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 157.0 (C_q-2'), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 130.1 (CH-6'), 128.2 (CH-4'), 127.0 (C_q-3b'''), 124.9 (C_q-1'), 123.8 (CH-2'''), 120.4 (CH-5'), 112.1 (CH-7'''), 111.2 (CH-6'''), 110.9 (CH-3'), 109.0 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.3 (OCH_3-2'), 55.0 (CH_2-1''), 54.4 (CH_2-1), 39.4 (CH_3-N^+), 24.5 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 767.5 (33%) [2M + oxalic acid + H]$^+$, 473.4 (7%) $[M_{quat}]^+$, 339.2 (100%) [M + H]$^+$.

N-[2-(3-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3-Methoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (247)

N-[2-(3-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2O \cdot C_2H_2O_4$, 398.45 g/mol) was obtained from 169.8 mg 3-methoxy-1-(2-iodoethyl)-benzene (**151**,

262.09 g/mol, 91%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3396, 3285, 3030, 2943, 2861, 2691, 1719, 1604, 1458, 1356, 1341, 1263, 1100, 1038, 1012, 961, 879, 743, 720, 699, 478 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 265 (82%) sh, 272 (99%), 242 (98%) sh, 278 (100%), 288 nm (68%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.8 (3.0%), 18.8 (95.8%), 22.0 min (0.5%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (t, J = 8 Hz, 1 H, H-5'), 7.24 (s, 1 H, H-2'''), 7.10 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.89 - 6.79 (m, 3 H, H-2',4',6'), 3.75 (s, 3 H, OCH_3), 3.36 - 3.25 (m, 4 H, H_2-1,1''), 3.15 - 3.06 (m, 2 H, H_2-2''), 3.00 - 2.92 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 159.4 (C_q-3'), 138.9 (C_q-1'), 136.2 (C_q-7b'''), 129.5 (CH-5'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 120.9 (CH-6'), 118.4 (CH-6'''), 118.2 (CH-4'''), 114.4 (CH-2'), 112.01 (CH-4'), 111.4 (CH-7'''), 109.4 (C_q-3'''), 56.1 (CH_2-1), 55.5 (CH_2-1''), 54.9 (OCH_3-3'), 39.8 (CH_3-N^+), 29.9 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 706.9 (8%) $[2M + oxalic\ acid + H]^+$, 309.2 (100%) $[M + H]^+$, 178.6 (4%) $[M_{imine}]^+$.

N-[2-(3-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3-Methoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (248)

N-[2-(3-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4$, 428.49 g/mol) was obtained as a non-crystallizing mass from 169.8 mg 3-methoxy-1-(2-iodoethyl)-benzene (**151**, 262.09 g/mol, 91%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(4-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Methoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (249)

N-[2-(4-Methoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2O \cdot C_2H_2O_4$, 398.45 g/mol) was obtained from 184.8 mg 4-methoxy-1-(2-iodoethyl)-benzene (**152**, 262.09 g/mol, 83%, 587.3 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3392, 3269, 2997, 2940, 2836, 2689, 1717, 1700, 1612, 1513, 1457, 1419, 1405, 1341, 1302, 1279, 1246, 1181, 1110, 1034, 959, 829, 748, 720, 704, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (566%), 266 (86%) sh, 271 (98%) sh, 275 (100%), 278 (100%), 281 (98%) sh, 288 (71%) sh.

HPLC: R_t (%total AUC_{260}) = 6.7 (oxalic acid), 18.9 min (99.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.51): δ = 10.97 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (s, 1 H, H-2'''), 7.20 (d, J = 7.5 Hz, 2 H, H-3',5'), 7.10 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.89 (d, J = 7 Hz, 2 H, H-2',6'), 3.73 (s, 3 H, -OCH_3-4'), 3.37 - 3.20 (m, 4 H, H_2-1,1''), 3.16 - 3.06 (m, 2 H, H_2-2''), 2.97 - 2.86 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.3 (C_q-oxalate), 158.0 (C_q-1'), 136.2 (C_q-7b'''), 129.6 (CH-1',6'), 129.1 (C_q-1'), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 113.9 (CH-3',5'), 111.4 (CH-7'''), 109.4 (C_q-3'''), 56.3 (CH_2-1), 55.4 (CH_2-1''), 55.0 (OCH_3-4'), 39.4 (CH_3-N^+), 28.9 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 309.2 (100%) $[M + H]^+$, 178.2 (9%) $[M_{imine}]^+$.

N-[2-(4-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Methoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (250)

N-[2-(4-Methoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4$, 428.49 g/mol) was obtained from 184.8 mg 4-methoxy-1-(2-iodoethyl)-benzene (**152**, 262.09 g/mol, 83%, 587.3 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3286, 2938, 2835, 2690, 1718, 1614, 1514, 1487, 1303, 1248, 1215, 1177, 1109, 1061, 1028, 924, 827, 800, 704, 638, 595, 456 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (467%), 274 (100%), 282 (89%) sh, 294 (67%) sh, 307 nm (42%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 18.6 (97.6%), 24.9 min (1.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.79 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.20 (d, J = 2.5 Hz, 1 H, H-4'''), 7.19 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.08 (d, J = 2.5 Hz, 1 H, H-2'''), 6.89 (d, J = 8.5 Hz, 2 H, H-2',6'), 6.75 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.73 (s, 3 H, -OCH_3-4'), 3.35 - 3.18 (m, 4 H, H_2-1,1''), 3.10 - 3.01 (m, 2 H, H_2-2''), 2.96 - 2.83 (m, 2 H, H_2-2), 2.86 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 766.9 (21%) $[2M + \text{oxalic acid} + H]^+$, 473.2 (10%) $[M_{quat}]^+$, 339.2 (100%) $[M + H]^+$.

N-(2-Nitroethyl)-*N*-methyltryptamine hydrogen oxalate ((2-Nitroethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (251)

N-(2-Nitroethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{13}H_{17}N_3O_2 \cdot C_2H_2O_4$, 337.33 g/mol) was obtained as a non-crystallizing mass from 177.0 mg 1-bromo-2-nitroethane (**154**, 153.96 g/mol, 51%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-(2-Nitroethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2-Nitroethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (252)

N-(2-Nitroethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{14}H_{19}N_3O_3 \cdot C_2H_2O_4$, 367.35 g/mol) was obtained as a non-crystallizing mass from 177.0 mg 1-bromo-2-nitroethane (**154**, 153.96 g/mol, 51%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(4-Nitrophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Nitrophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (253)

N-[2-(4-Nitrophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate (40.5 mg, $C_{19}H_{21}N_3O_2 \cdot C_2H_2O_4$, 413.42 g/mol, 17%) was obtained as a fine yellow powder from 224.5 mg 4-nitro-1-(2-iodoethyl)-benzene (**156**, 277.06 g/mol, 73%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3397, 3275, 3043, 2858, 2693, 1929, 1719, 1635, 1518, 1458, 1347, 1280, 1216, 1108, 1011, 857, 745, 720, 696, 620, 478 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (272%), 271 (99%) sh, 277 (100%), 288 (82%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.8 (3.6%), 17.0 min (95.4%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.92 (s br, 1 H, H-1'''), 8.20 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.58 (2d, J = 8.5 Hz, 3 H, H-4''',2',6'), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.34 - 3.18 (m, 4 H, H_2-1,1''), 3.17 - 3.01 (m, 4 H, H_2-2,2''), 2.82 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 324.2 (100%) $[M + H]^+$, 193.1 (14%) $[M_{imine}]^+$.

N-[2-(4-Nitrophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Nitrophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (254)

N-[2-(4-Nitrophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate (40.3 mg, $C_{20}H_{23}N_3O_3 \cdot C_2H_2O_4$, 443.45 g/mol, 15%) was obtained as a fine yellow powder from 224.5 mg 4-nitro-1-(2-iodoethyl)-benzene (**156**, 277.06 g/mol, 73%, 587.5 µmol) and

100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3397, 3039, 2944, 2832, 2682, 1719, 1626, 1607, 1519, 1488, 1347, 1212, 1176, 1109, 1060, 1030, 939, 925, 859, 802, 746, 696, 630, 480 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>200%), 274 (100%), 296 (65%) sh, 307 (39%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 17.3 min (99.5%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.78 (s br, 1 H, H-1'''), 8.20 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.58 (d, J = 8.5 Hz, 2 H, H-2',6'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.08 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.36 - 3.20 (m, 4 H, H_2-1,1''), 3.19 - 3.09 (m, 2 H, H_2-2), 3.09 - 3.00 (m, 2 H, H_2-2''), 2.84 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.3 (C_q-oxalate), 153.1 (C_q-5'''), 146.3 (C_q-4'), 145.9 (C_q-1'), 131.3 (C_q-7b'''), 130.1 (CH-2',6'), 127.1 (C_q-3b'''), 123.7 (CH-2'''), 123.5 (CH-3',5'), 112.1 (CH-7'''), 111.1 (CH-6'''), 109.4 (C_q-3'''), 100.3 (CH-4'''), 55.6 (CH_2-2), 55.5 (CH_2-2''), 55.4 (OCH_3-5'''), 39.6 (CH_3-N^+), 29.8 (CH_2-1), 20.3 (CH_2-1'').

ESI MS: *m/z* (%) = 354.3 (100%) $[M + H]^+$.

N-[2-(2-Fluorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2-Fluorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (255)

N-[2-(2-Fluorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}FN_2 \cdot C_2H_2O_4$, 386.42 g/mol) was obtained from 198.1 mg 2-fluoro-1-(2-iodoethyl)-benzene (**157**, 250.05 g/mol, 74%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3423, 3397, 3278, 3038, 2943, 2862, 2682, 1720, 1702, 1617, 1493, 1458, 1419, 1341, 1280, 1230, 1184, 1010, 942, 877, 846, 788, 772, 752, 720, 704, 668, 618, 584, 534, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 261 (84%) sh, 268 (100%), 272 (97%) sh, 280 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.9 (4.3%), 18.5 min (95.5%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.42 - 7.28 (m, 2 H, H-6',5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (s, 1 H, H-2'''), 7.25 - 7.15 (m, 2 H, H-3',4'), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.35 - 3.22 (m, 4 H, H_2-1,1''), 3.15 - 2.99 (m, 4 H, H_2-2'',2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 160.4 (d, J = 244 Hz, C_q-2'), 136.2 (C_q-7b'''), 131.1 (d, J = 4 Hz, CH-6'), 129.0 (d, J = 8 Hz, CH-4'), 126.7 (C_q-3b'''), 124.6

(d, J = 3 Hz, CH-5'), 124.1 (d, J = 16 Hz, C_q-1'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 115.2 (d, J = 22 Hz, CH-3'), 111.4 (CH-7'''), 109.4 (C_q-3'''), 55.5 (CH_2-1''), 54.6 (CH_2-1), 39.4 (CH_3-N^+), 23.3 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 683.6 (13%) $[2M + \text{oxalic acid} + H]^+$, 629 (3%) $[2M + HCl + H]^+$, 297.2 (100%) $[M + H]^+$.

N-[2-(2-Fluorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2-Fluorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (256)

N-[2-(2-Fluorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}FN_2O \cdot C_2H_2O_4$, 416.44 g/mol) was obtained from 198.1 mg 2-fluoro-1-(2-iodoethyl)-benzene (**157**, 250.05 g/mol, 74%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3416, 3306, 3040, 2956, 2681, 1718, 1629, 1586, 1492, 1457, 1406, 1281, 1219, 1184, 1125, 1065, 1029, 926, 840, 802, 769, 720, 706, 641, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 262 (81%) sh, 268 (99%), 275 (100%), 279 (97%) sh, 293 (82%), 306 (56%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 18.4 min (99.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.42 - 7.28 (m, 2 H, H-6',5'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.25 - 7.15 (m, 2 H, H-3',4'), 7.19 (d, J = 2.5 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.35 - 3.22 (m, 4 H, H_2-1,1''), 3.11 - 2.99 (m, 4 H, H_2-2'',2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.2 (C_q-oxalate), 160.4 (d, J = 244 Hz, C_q-2'), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 131.1 (d, J = 5 Hz, CH-6'), 128.9 (d, J = 8 Hz, CH-4'), 127.1 (C_q-3b'''), 124.6 (d, J = 4 Hz, CH-5'), 124.1 (d, J = 15 Hz, C_q-1'), 123.8 (CH-2'''), 115.2 (d, J = 22 Hz, CH-3'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.42 (CH_2-1''), 55.39 (OCH_3-5'''), 54.6 (CH_2-1), 39.8 (CH_3-N^+), 23.4 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 742.9 (14%) $[2M + \text{oxalic acid} + H]^+$, 449.2 (4%) $[M_{quat}]^+$, 327.2 (100%) $[M + H]^+$, 174.2 (6%) [5-MeO-vinylindole + H]$^+$, 166.1 (85) $[M_{imine}]^+$.

N-[2-(4-Fluorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Fluorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (257)

N-[2-(4-Fluorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}FN_2 \cdot C_2H_2O_4$, 386.42 g/mol) was obtained from 172.1 mg 4-fluoro-1-(2-iodoethyl)-benzene (**158**, 250.05 g/mol, 100%, 688.3 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E. Recrystallization from a small amount of THF.

IR (KBr): $\tilde{\nu}$ = 3395, 3277 sh, 3040, 2924, 2858, 2694, 1721, 1610, 1513, 1459, 1427, 1341, 1280, 1224, 1177, 1018, 942, 836, 756, 721, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%), 256 (60%) sh, 264 (88%) sh, 270 (100%), 277 (95%) sh, 280 (96%), 288 nm (81%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.8 (2.4%), 17.5 (97.0%), 26.8 min (0.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8.5 Hz, 1 H, H-7'''), 7.33 (t, J = 8 Hz, 5.5 Hz, 2 H, H-2',6'), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.16 (dd, J = J' = 9 Hz, 2 H, H-3',5'), 7.10 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.36 - 3.23 (m, 4 H, H_2-1,1''), 3.15 - 3.06 (m, 2 H, H_2-2''), 3.03 - 2.94 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 161.1 (d, J = 242 Hz, C_q-4'), 136.2 (C_q-7b'''), 133.5 (d, J = 3 Hz, C_q-1), 130.6 (d, J = 8 Hz, CH-2',6'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 115.2 (d, J = 21 Hz, CH-3',5'), 111.5 (CH-7'''), 109.4 (C_q-3'''), 56.0 (CH_2-1), 55.4 (CH_2-1''), 39.3 (CH_3-N^+), 28.8 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 297.3 (100%) $[M + H]^+$.

***N*-[2-(4-Fluorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Fluorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (258)**

N-[2-(4-Fluorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}FN_2O \cdot C_2H_2O_4$, 416.44 g/mol) was obtained from 172.1 mg 4-fluoro-1-(2-iodoethyl)-benzene (**158**, 250.05 g/mol, 100%, 688.3 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3433, 3216, 3044, 2944, 2719, 1702, 1625, 1512, 1488, 1463, 1216, 1179, 1103, 1030, 962, 924, 832, 803, 720, 701, 550, 496, 469 cm^{-1}.

UV (H_2O): λ (%max_A) = 210 (>400%) sh, 264 (85%) sh, 270 (100%), 276 (96%) sh, 294 (79%), 306 (54%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 17.6 (99.0%), 22.8 min (0.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.33 (t, J = 8 Hz, 5.5 Hz, 2 H, H-2',6'), 7.25 (d, J = 9 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.16 (dd, J = J' = 9 Hz, 2 H, H-3',5'), 7.10 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.35 - 3.22 (m, 4 H, H_2-1,1''), 3.13 - 2.94 (m, 4 H, H_2-2'',2), 2.87 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 161.0 (d, J = 243 Hz, C_q-4'), 153.1 (C_q-5'''), 133.5 (d, J = 3 Hz, C_q-1), 131.3 (C_q-7b'''), 130.6 (d, J = 8 Hz, CH-2',6'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 115.2 (d, J = 21 Hz, CH-3',5'), 112.0 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.3 (CH-4'''), 56.0 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.3 (CH_3-N^+), 28.9 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 743 (8%) $[2M + \text{oxalic acid} + H]^+$, 449 (4%) $[M_{quat}]^+$, 327.4 (100%) $[M + H]^+$.

N-[2-(2-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2-Chlorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (259)

N-[2-(2-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}ClN_2 \cdot C_2H_2O_4$, 402.87 g/mol) was obtained from 177.8 mg 2-chloro-1-(2-iodoethyl)-benzene (**160**, 266.51 g/mol, 100%, 667.1 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3267, 3048, 2861, 2682, 1719, 1634, 1476, 1458, 1357, 1341, 1280, 1202, 1102, 1053, 1011, 937, 746, 721, 705, 682, 468 cm^{-1}.

UV (H_2O): λ (%max_A) = 222 (>400%), 268 (92%) sh, 273 (98%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.8 (2.2%), 19.6 min (97.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.20): δ = 10.98 (s br, 1 H, H-1'''), 7.61 (d, J = 8 Hz, 1 H, H-4'''), 7.49 - 7.40 (m, 2 H, H-3',5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.34 - 7.29 (m, 2 H, H-6',4'), 7.24 (d, J = 1.5 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.37 - 3.19 (m, 4 H, H_2-1'',1), 3.19 - 3.08 (m, 4 H, H_2-2'',2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 135.0 (C_q-1'), 133.0 (C_q-2'), 131.2 (CH-6'), 129.3 (CH-3'), 128.7 (CH-4'), 127.5 (CH-5'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.5 (CH-7'''), 109.5 (C_q-3'''), 55.5 (CH_2-1''), 54.3 (CH_2-1), 39.8 (CH_3-N^+), 27.7 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 714.7 (6%) $[2[^{35}Cl]M + \text{oxalic acid} + H]^+$, 315.1 (33%) $[[^{37}Cl]M + H]^+$, 313.1 (100%) $[[^{35}Cl]M + H]^+$, 182.1 (10%) $[[^{35}Cl]M_{imine}]^+$.

N-[2-(2-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2-Chlorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (260)

N-[2-(2-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}ClN_2O \cdot C_2H_2O_4$, 432.9 g/mol) was obtained from 177.8 mg 2-chloro-1-(2-iodoethyl)-

benzene (**160**, 266.51 g/mol, 100%, 667.1 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3445, 3261, 3012, 2945, 2687, 2624, 1720, 1625, 1487, 1442, 1405, 1280, 1214, 1186, 1103, 1053, 1030, 925, 802, 756, 720, 700, 682, 638, 497 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%) sh, 267 (90%) sh, 274 (100%), 280 (94%) sh, 293 (79%), 305 (56%) sh.

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 19.7 min (99.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.49 - 7.40 (m, 2 H, H-3',5'), 7.37 - 7.29 (m, 2 H, H-6',4'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2.5 Hz, 1 H, H-4'''), 7.10 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.36 - 3.19 (m, 4 H, H_2-1'',1), 3.19 - 3.03 (m, 4 H, H_2-2'',2), 2.90 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 134.8 (C_q-1'), 133.0 (C_q-2'), 131.3 (CH-6'), 131.2 (C_q-7b'''), 129.3 (CH-3'), 128.7 (CH-4'), 127.5 (CH-5'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 54.2 (CH_2-1''), 39.4 (CH_3-N^+), 27.6 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 776.7 (7%) [2[^{35}Cl]M + oxalic acid + H]$^+$, 720.7 (6%) [2[^{35}Cl]M + HCl + H]$^+$, 345.1 (33%) [[^{37}Cl]M + H]$^+$, 343.1 (100%) [[^{35}Cl]M + H]$^+$, 182.1 (9%) [[^{35}Cl]M_{imine}]$^+$.

N-[2-(3-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3-Chlorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (261)

N-[2-(3-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}ClN_2 \cdot C_2H_2O_4$, 402.87 g/mol) was obtained from 181.7 mg 3-Chloro-1-(2-iodoethyl)-benzene (**161**, 266.51 g/mol, 100%, 681.8 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3391, 3270, 3046, 2924, 2862, 2682, 1718, 1636, 1458, 1430, 1356, 1340, 1281, 1208, 1102, 1011, 942, 874, 784, 744, 698, 474 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%), 266 (90%) sh, 273 (98%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.6 (5.6%), 19.2 min (94.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.95 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.42 - 7.31 (m, 4 H, H-7''',2',4',5'), 7.28 - 7.22 (m, 2 H, H-2''',6'), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.31 - 3.22 (m, 4 H, H_2-1'',1), 3.13 - 3.04 (m, 2 H, H_2-2''), 3.03 - 2.95 (m, 2 H, H_2-2'), 2.84 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 140.2 (C_q-1'), 136.2 (C_q-7b'''), 133.0 (C_q-3'), 130.2 (CH-2'), 128.6 (CH-5'), 127.5 (CH-4'), 126.7 (C_q-3b'''), 126.5 (CH-6'),

123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.6 (C_q-3'''), 55.9 (CH_2-1), 55.6 (CH_2-1''), 39.6 (CH_3-N^+), 29.5 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 718.6 (11%) [[^{35}Cl]M + [^{37}Cl]M + oxalic acid + H]$^+$, 715.6 (18%) [2[^{35}Cl]M + oxalic acid + H]$^+$, 315.2 (38%) [[^{37}Cl]M + H]$^+$, 313.3 (100%) [[^{35}Cl]M + H]$^+$.

N-[2-(3-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3-Chlorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (262)

N-[2-(3-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}ClN_2O \cdot C_2H_2O_4$, 432.9 g/mol) was obtained from 181.7 mg 3-chloro-1-(2-iodoethyl)-benzene (**161**, 266.51 g/mol, 100%, 681.8 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3445, 3266, 3020, 2945, 2682, 1720, 1625, 1487, 1280, 1215, 1186, 1102, 1063, 1030, 924, 799, 721, 695, 685, 498 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 219 (>500%) sh, 267 (87%) sh, 269 (92%) sh, 275 (100%), 279 (95%) sh, 294 (80%), 306 (54%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 19.1 min (99.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.42 - 7.32 (m, 3 H, H-2',4',5'), 7.25 (2d, J = 8.5 Hz, 2 H, H-7''',6'), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.10 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.34 - 3.25 (m, 4 H, H_2-1'',1), 3.12 - 2.97 (m, 4 H, H_2-2'',2), 2.87 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 140.0 (C_q-1'), 133.1 (C_q-3'), 131.3 (C_q-7b'''), 130.3 (CH-2'), 128.6 (CH-5'), 127.5 (CH-4'), 127.1 (C_q-3b'''), 126.6 (CH-6'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.7 (CH_2-1), 55.40 (OCH_3-5'''), 55.36 (CH_2-1''), 39.4 (CH_3-N^+), 29.3 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 345.1 (29%) [[^{37}Cl]M + H]$^+$, 343.2 (100%) [[^{35}Cl]M + H]$^+$.

N-[2-(4-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Chlorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (263)

N-[2-(4-Chlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}ClN_2 \cdot C_2H_2O_4$, 402.87 g/mol) was obtained as a non-crystallizing mass from 180.9 mg 4-chloro-1-(2-iodoethyl)-benzene (**162**, 266.51 g/mol, 87%, 587.5 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3394, 3040, 2951, 2861, 2691, 2636, 1720, 1700, 1620, 1494, 1459, 1422, 1340, 1280, 1178, 1096, 1017, 944, 879, 838, 807, 756, 721, 704, 668, 494 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>700%), 266 (88%) sh, 272 (98%), 275 (99%) sh, 278 (100%), 280 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.5 (1.8%), 19.0 min (97.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.40 (d, J = 8.5 Hz, 2 H, H-3',5'), 7.37 (d, J = 8.5 Hz, 1 H, H-7'''), 7.31 (d, J = 8.5 Hz, 2 H, H-2',6'), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.35 - 3.23 (m, 4 H, H_2-1'',1), 3.15 - 3.06 (m, 2 H, H_2-2''), 3.03 - 2.95 (m, 2 H, H_2-2), 2.87 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.4 (C_q-7b'''), 136.2 (C_q-1'), 131.3 (C_q-4'), 130.6 (CH-2',6'), 128.4 (CH-3',5'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 55.8 (CH_2-1), 55.5 (CH_2-1''), 39.4 (CH_3-N^+), 29.1 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 714.6 (3%) [2[^{35}Cl]M + oxalic acid + H]$^+$, 315.1 (32%) [[^{37}Cl]M + H]$^+$, 313.1 (100%) [[^{35}Cl]M + H]$^+$, 182.1 (6%) [[^{35}Cl]M_{imine}]$^+$.

***N*-[2-(4-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Chlorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (264)**

N-[2-(4-Chlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}ClN_2O \cdot C_2H_2O_4$, 432.9 g/mol) was obtained from 180.9 mg 4-chloro-1-(2-iodoethyl)-benzene (**162**, 266.51 g/mol, 87%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

***N*-[2-(2-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2-Bromophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (265)**

N-[2-(2-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}BrN_2 \cdot C_2H_2O_4$, 391.46 g/mol) was obtained as a non-crystallizing mass from 259.8 mg 2-bromo-1-(2-iodoethyl)-benzene (**163**, 208.1 g/mol, 70%, 877.8 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

***N*-[2-(2-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2-Bromophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (266)**

N-[2-(2-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}BrN_2O \cdot C_2H_2O_4$, 421.49 g/mol) was obtained as a non-crystallizing mass from 259.8 mg 2-bromo-1-(2-iodoethyl)-benzene (**163**, 208.1 g/mol, 70%, 877.8 µmol) and

100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(3-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3-Bromophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (267)

N-[2-(3-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}BrN_2 \cdot C_2H_2O_4$, 447.32 g/mol) was obtained from 214.0 mg 3-bromo-1-(2-iodoethyl)-benzene (**164**, 263.96 g/mol, 100%, 810.7 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3388, 3269, 3044, 2928, 2859, 2685, 1718, 1635, 1458, 1426, 1341, 1280, 1205, 1102, 1072, 1011, 961, 940, 880, 846, 782, 744, 721, 692, 669, 458 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>600%), 266 (89%) sh, 271 (97%) sh, 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.6 (5.4%), 20.1 min (94.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.95 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.54 (s, 1 H, H-2'), 7.45 (td, J = 4.5 Hz, 2 Hz, 1 H, H-5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.30 (d, J = 5 Hz, 2 H, H-4',6'), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.32 - 3.22 (m, 4 H, H_2-1'',1), 3.14 - 3.05 (m, 2 H, H_2-2''), 3.04 - 2.94 (m, 2 H, H_2-2), 2.85 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 140.4 (C_q-1'), 136.2 (C_q-7b'''), 131.5 (CH-2'), 130.6 (CH-5'), 129.4 (CH-4'), 127.9 (CH-6'), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.7 (C_q-3'), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.6 (C_q-3'''), 55.8 (CH_2-1), 55.6 (CH_2-1''), 39.8 (CH_3-N^+), 29.4 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 804.7 (10%) [[^{79}Br]M + [^{81}Br]M + oxalic acid + H]$^+$, 750.7 (10%) [[^{79}Br]M + [^{81}Br]M + HCl + H]$^+$, 359.1 (85%) [[^{81}Br]M + H]$^+$, 357.1 (100%) [[^{79}Br]M + H]$^+$, 228.1 (10%) [[^{81}Br]M_{imine}]$^+$, 226 (14%) [[^{79}Br]M_{imine}]$^+$.

N-[2-(3-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3-Bromophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (268)

N-[2-(3-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}BrN_2O \cdot C_2H_2O_4$, 477.35 g/mol) was obtained from 214.0 mg 3-bromo-1-(2-iodoethyl)-benzene (**164**, 263.96 g/mol, 100%, 810.7 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3442, 3267, 3015, 2944, 2832, 2684, 1722, 1625, 1588, 1487, 1441, 1280, 1214, 1186, 1064, 1030, 924, 839, 798, 720, 693, 669, 610, 493 cm^{-1}.

UV (H_2O): λ (%max_A) = 221 (>400%), 267 (87%) sh, 275 (100%), 279 (96%) sh, 294 (81%), 306 (56%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 20.0 min (99.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.54 (s, 1 H, H-2'), 7.46 (td, J = 4.5 Hz, 2 Hz, 1 H, H-5'), 7.30 (d, J = 5 Hz, 2 H, H-4',6'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.34 - 3.25 (m, 4 H, H_2-1'',1), 3.11 - 2.96 (m, 4 H, H_2-2'',2), 2.87 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 140.2 (C_q-1'), 131.5 (CH-2'), 131.3 (C_q-7b'''), 130.6 (CH-5'), 129.5 (CH-4'), 127.9 (CH-6'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 121.7 (C_q-3'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.6 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.3 (CH_3-N^+), 29.2 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 389.1 (90%) [[^{81}Br]M + H]$^+$, 387.1 (100%) [[^{79}Br]M + H]$^+$, 228 (10%) [[^{81}Br]M_{imine}]$^+$, 226.1 (13%) [[^{79}Br]M_{imine}]$^+$, 174.2 (9%) [5-MeO-vinylindole]$^+$.

N-[2-(4-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(4-Bromophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (269)

N-[2-(4-Bromophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{21}BrN_2 \cdot C_2H_2O_4$, 447.32 g/mol) was obtained from 222.7 mg 4-bromo-1-(2-iodoethyl)-benzene (**165**, 263.96 g/mol, 82%, 692.1 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3400, 3252, 2937, 2632, 1719, 1703, 1622, 1489, 1458, 1406, 1281, 1207, 1103, 1012, 963, 814, 745, 721, 500 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>700%), 272 (97%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.5 (3.2%), 19.9 min (96.3%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.52 (d, J = 8 Hz, 2 H, H-3',5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, 8.5 Hz, 2 H, H-2',6'), 7.23 (s, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.32 - 3.21 (m, 4 H, H_2-1'',1), 3.14 - 3.04 (m, 2 H, H_2-2''), 3.01 - 2.92 (m, 2 H, H_2-2), 2.85 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 136.9 (C_q-1'), 136.2 (C_q-7b'''), 131.3 (CH-3',5'), 131.0 (CH-2',6'), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 119.7 (CH-4'), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.5 (C_q-3'''), 55.7 (CH_2-2), 55.5 (CH_2-2''), 39.4 (CH_3-N^+), 29.2 (CH_2-1), 20.0 (CH_2-1'').

ESI MS: *m/z* (%) = 804.6 (5%) [[^{79}Br]M + [^{81}Br]M + oxalic acid + H]$^+$, 359.1 (98%) [[^{81}Br]M + H]$^+$, 357.1 (100%) [[^{79}Br]M + H]$^+$, 228.1 (11%) [[^{81}Br]M$_{imine}$]$^+$, 226 (10%) [[^{79}Br]M$_{imine}$]$^+$.

N-[2-(4-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(4-Bromophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (270)

N-[2-(4-Bromophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{23}BrN_2O \cdot C_2H_2O_4$, 477.35 g/mol) was obtained from 222.7 mg 4-bromo-1-(2-iodoethyl)-benzene (**165**, 263.96 g/mol, 82%, 692.1 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3265, 3002, 2932, 2830, 2716, 2639, 1718, 1608, 1489, 1301, 1215, 1102, 1072, 1031, 1012, 985, 960, 926, 884, 829, 798, 722, 634, 521, 496 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 220 (>500%), 275 (100%), 294 (80%), 306 (55%) sh.

HPLC: R_t (%total AUC$_{260}$) = 5.8 (oxalic acid), 19.8 (98.5%), 24.9 min (0.5%).

^{1}H NMR (300 MHz, DMSO-d$_6$, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.52 (d, J = 8 Hz, 2 H, H-3',5'), 7.25 (2d, J = 8.5 Hz, 3 H, H-7''',2',6'), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH$_3$-5'''), 3.34 - 3.22 (m, 4 H, H$_2$-1'',1), 3.12 - 3.03 (m, 2 H, H$_2$-2''), 3.03 - 2.93 (m, 2 H, H$_2$-2), 2.86 (s, 3 H, N$^+$-CH$_3$).

^{13}C NMR (50.3 MHz, APT, DMSO-d$_6$): δ = 164.8 (C$_q$-oxalate), 153.1 (C$_q$-5'''), 136.8 (C$_q$-1'), 131.34 (C$_q$-7b'''), 131.29 (CH-3',5'), 131.0 (CH-2',6'), 127.1 (C$_q$-3b'''), 123.8 (CH-2'''), 119.7 (CH-4'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C$_q$-3'''), 100.2 (CH-4'''), 55.7 (CH$_2$-2), 55.4 (CH$_2$-2''), 55.3 (OCH$_3$-5'''), 39.3 (CH$_3$-N$^+$), 29.1 (CH$_2$-1), 20.0 (CH$_2$-1'').

ESI MS: *m/z* (%) = 865.5 (5%) [[^{79}Br]M + [^{81}Br]M + oxalic acid + H]$^+$, 389.3 (88%) [[^{81}Br]M + H]$^+$, 387.3 (100%) [[^{79}Br]M + H]$^+$.

N-[2-(2,5-Dimethylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2,5-Dimethylphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (271)

N-[2-(2,5-Dimethylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{26}N_2 \cdot C_2H_2O_4$, 396.48 g/mol) was obtained from 163.2 mg 2,5-dimethyl-1-(2-iodoethyl)-benzene (**166**, 260.11 g/mol, 94%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3392, 3269, 2922, 2865, 2683, 1719, 1636, 1459, 1340, 1281, 1107, 1033, 938, 814, 754, 721, 701, 480 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>600%), 271 (97%) sh, 276 (100%), 280 (96%) sh, 288 nm (78%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.8 (1.5%), 20.8 min (97.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.62 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.08 - 6.93 (m, 4 H, H-3',4',6',5'''), 3.40 - 3.30 (m, 2 H, H_2-1'), 3.24 - 3.09 (m, 4 H, H_2-2'',1), 2.98 - 2.90 (m, 2 H, H_2-2), 2.92 (s, 3 H, N^+-CH_3), 2.25 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 136.2 (C_q-7b'''), 135.1 (C_q-1'), 134.9 (C_q-5'), 132.7 (C_q-2'), 130.1 (CH-6'), 129.9 (CH-3'), 127.3 (CH-4'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.5 (CH-7'''), 109.4 (C_q-3'''), 55.4 (CH_2-1''), 55.1 (CH_2-1), 39.3 (CH_3-N^+), 27.3 (CH_2-2), 20.4 (OCH_3-5'), 20.0 (CH_2-2''), 18.2 (OCH_3-2').

ESI MS: *m/z* (%) = 307.2 (100%) $[M + H]^+$.

N-[2-(2,5-Dimethylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2,5-Dimethylphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (272)

N-[2-(2,5-Dimethylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O \cdot C_2H_2O_4$, 426.51 g/mol) was obtained from 163.2 mg 2,5-dimethyl-1-(2-iodoethyl)-benzene (**166**, 260.11 g/mol, 94%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3410, 3282, 3021, 2943, 2682, 1720, 1702, 1625, 1486, 1280, 1214, 1178, 1105, 1062, 1030, 924, 809, 721, 701, 637, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 217 (>400%), 266 (84%) sh, 270 (93%) sh, 275 (100%), 293 (75%) sh, 296 (72%) sh, 307 (49%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 20.5 min (99.4%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.26 (d, J = 8.5 Hz, 1 H, H-7'''), 7.20 (d, J = 2 Hz, 1 H, H-4'''), 7.11 (d, J = 2 Hz, 1 H, H-2'''), 7.06 (d, J = 7.5 Hz, 1 H, H-3'), 6.99 (s, 1 H, H-6'), 6.96 (d, J = 8 Hz, 1 H, H-4'), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.38 - 3.28 (m, 2 H, H_2-1'), 3.24 - 3.14 (m, 2 H, H_2-1), 3.14 - 3.04 (m, 2 H, H_2-2''), 2.99 - 2.98 (m, 2 H, H_2-2), 2.91 (s, 3 H, N^+-CH_3), 2.25 (s, 3 H, Ar-CH_3), 2.23 (s, 3 H, Ar-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 135.2 (C_q-1'), 134.9 (C_q-5'), 132.7 (C_q-2'), 131.3 (C_q-7b'''), 130.1 (CH-6'), 129.9 (CH-3'), 127.3 (CH-4'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''),

55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 55.1 (CH_2-1), 39.2 (CH_3-N^+), 27.2 (CH_2-2), 20.4 (Ph-CH_3-5'), 20.0 (CH_2-2''), 18.2 (Ph-CH_3-2').

ESI MS: *m/z* (%) = 762.9 (13%) $[2M + \text{oxalic acid} + H]^+$, 337.2 (100%) $[M + H]^+$.

N-[2-(3,5-Dimethylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3,5-Dimethylphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (273)

N-[2-(3,5-Dimethylphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{26}N_2 \cdot C_2H_2O_4$, 396.48 g/mol) was obtained from 165.6 mg 3,5-dimethyl-1-(2-iodoethyl)-benzene (**167**, 260.11 g/mol, 92%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3392, 3293, 3018, 2923, 2862, 2690, 1723, 1608, 1459, 1353, 1280, 1237, 1105, 965, 859, 844, 822, 737, 720, 704, 622, 494 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>600%), 273 (98%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 10.3 (1.9%), 20.9 min (97.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.61 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 6.86 (s, 3 H, H-2',6',4'), 3.37 - 3.21 (m, 4 H, H_2-1,1''), 3.17 - 3.08 (m, 2 H, H_2-2''), 2.96 - 2.86 (m, 5 H, N^+-CH_3, H_2-2), 2.24 (s, 6 H, -CH_3-3',5').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 137.5 (C_q-3',5''), 137.0 (C_q-1'), 136.2 (C_q-7b'''), 128.0 (CH-4'), 126.7 (C_q-3b'''), 126.4 (CH-2',6'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.5 (CH-7'''), 109.4 (C_q-3'''), 56.1 (CH_2-1), 55.3 (CH_2-1''), 39.3 (CH_3-N^+), 29.5 (CH_2-2), 20.8 (Ph-CH_3-3',5'), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 703.0 (13%) $[2M + \text{oxalic acid} + H]^+$, 307.2 (100%) $[M + H]^+$, 176.1 (6%) $[M_{imine}]^+$.

N-[2-(3,5-Dimethylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3,5-Dimethylphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (274)

N-[2-(3,5-Dimethylphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O \cdot C_2H_2O_4$, 426.51 g/mol) was obtained from 165.6 mg 3,5-dimethyl-1-(2-iodoethyl)-benzene (**167**, 260.11 g/mol, 92%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3397, 3293, 3012, 2940, 2686, 1721, 1702, 1609, 1486, 1352, 1281, 1208, 1121, 1063, 1031, 964, 841, 803, 788, 721, 710, 640, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>500%) sh, 266 (84%) sh, 271 (96%) sh, 275 (100%), 296 (78%) sh, 308 (48%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 12.0 (0.9%), 18.1 (0.5%), 20.8 (97.0%), 25.1 min (1.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.88 (s br, 1 H, H-1'''), 7.26 (d, J = 8.5 Hz, 1 H, H-7'''), 7.20 (d, J = 2 Hz, 1 H, H-4'''), 7.11 (d, J = 2 Hz, 1 H, H-2'''), 6.89 - 6.84 (s br, 3 H, H-2',6',4'), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.37 - 3.21 (m, 4 H, H_2-1,1''), 3.13 - 3.04 (m, 2 H, H_2-2''), 2.95 - 2.85 (m, 5 H, N^+-CH_3, H_2-2), 2.24 (2s, 6 H, -CH_3-3',5').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 137.4 (C_q-3',5''), 137.0 (C_q-1'), 131.4 (C_q-7b'''), 128.0 (CH-4'), 127.1 (C_q-3b'''), 126.4 (CH-2',6'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 56.0 (CH_2-1), 55.4 (OCH_3-5'''), 55.2 (CH_2-1''), 39.3 (CH_3-N^+), 29.5 (CH_2-2), 20.7 (Ph-CH_3-3',5'), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 763.6 (12%) $[2M + oxalic\ acid + H]^+$, 709 (4%) $[2M + HCl + H]^+$, 337.2 (100%) $[M + H]^+$.

***N*-[2-(2,5-Dimethoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2,5-Dimethoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (275)**

N-[2-(2,5-Dimethoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4$, 428.48 g/mol) was obtained from 198.8 mg 2,5-dimethoxy-1-(2-iodoethyl)-benzene (**168**, 292.11 g/mol, 86%, 587.5 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3407, 3299, 3004, 2934, 2834, 2698, 1719, 1702, 1636, 1505, 1460, 1280, 1226, 1107, 1045, 962, 877, 807, 745, 721, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>400%), 268 (75%) sh, 273 (86%) sh, 280 (100%) sh, 282 (100%), 288 nm (98%).

HPLC: R_t (%total AUC_{260}) = 5.9 (oxalic acid), 9.9 (2.2%), 20.1 min (97.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.60 (d, J = 7.5 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (ddd, J = 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 6.93 (d, J = 8.5 Hz, 1 H, H-3'), 6.85 (d, J = 2.5 Hz, 1 H, H-6'), 6.81 (dd, J = 8.5 Hz, 3 Hz, 1 H, H-4'), 3.75 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.35 - 3.26 (m, 2 H, H_2-1''), 3.26 - 3.17 (m, 2 H, H_2-1), 3.14 - 3.05 (m, 2 H, H_2-2''), 2.98 - 2.87 (m, 2 H, H_2-2), 2.86 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 153.1 (C_q-5'), 151.2 (C_q-2'), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 126.2 (C_q-1'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''),

118.1 (CH-4'''), 116.4 (CH-3'), 112.3 (CH-4'), 111.9 (CH-6'), 111.5 (CH-7'''), 109.4 (C_q-3'''), 55.8 (OCH_3-2'), 55.3 (OCH_3-5'), 55.2 (CH_2-1''), 54.5 (CH_2-1), 39.6 (CH_3-N^+), 24.7 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 339.2 (100%) $[M + H]^+$.

N-[2-(2,5-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2,5-Dimethoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (276)

N-[2-(2,5-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O_3 \cdot C_2H_2O_4$, 458.5 g/mol) was obtained from 198.8 mg 2,5-dimethoxy-1-(2-iodoethyl)-benzene (**168**, 292.11 g/mol, 86%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3321, 3047, 2950, 2831, 1722, 1703, 1625, 1587, 1505, 1489, 1468, 1308, 1280, 1230, 1183, 1048, 1033, 963, 927, 818, 795, 711, 630, 480 cm^{-1}.

UV (H_2O): λ (%max_A) = 221 (>300%), 274 (90%) sh, 277 (95%) sh, 279 (97%) sh, 282 (98%) sh, 288 (100%), 294 (95%) sh, 297 (87%) sh, 306 (48%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 19.9 min (99.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.26 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2.5 Hz, 1 H, H-4'''), 7.10 (d, J = 2 Hz, 1 H, H-2'''), 6.93 (d, J = 9 Hz, 1 H, H-3'), 6.85 (d, J = 3 Hz, 1 H, H-6'), 6.81 (dd, J = 8.5 Hz, 3 Hz, 1 H, H-4'), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.75 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.36 - 3.19 (m, 4 H, H_2-1,1''), 3.12 - 3.02 (m, 2 H, H_2-2''), 2.99 - 2.89 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.13 (C_q-5'''), 153.10 (C_q-5'), 151.2 (C_q-2'), 131.4 (C_q-7b'''), 127.1 (C_q-3b'''), 126.0 (C_q-1'), 123.8 (CH-2'''), 116.4 (CH-3'), 112.4 (CH-4'), 112.1 (CH-7'''), 111.8 (CH-6'), 111.2 (CH-6'''), 109.0 (C_q-3'''), 100.2 (CH-4'''), 55.8 (OCH_3-2'), 55.4 (OCH_3-5'), 55.3 (OCH_3-5'''), 55.0 (CH_2-1''), 54.3 (CH_2-1), 39.4 (CH_3-N^+), 24.6 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 826.8 (5%) [2M + oxalic acid + H]$^+$, 369.2 (100%) $[M + H]^+$, 208.1 (11%) $[M_{imine}]^+$.

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3,4-Dimethoxyphenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (277)

100.4 mg *N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4$, 428.48 g/mol, 40%) was obtained from 176.9 mg 3,4-dimethoxy-

1-(2-iodoethyl)-benzene (**169**, 292.11 g/mol, 97%, 587.4 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3302, 3003, 2941, 2833, 2691, 1728, 1702, 1619, 1518, 1461, 1341, 1262, 1238, 1159, 1024, 935, 849, 810, 767, 739, 720, 708, 495 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 273 (94%) sh, 278 (100%), 288 (70%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.8 (0.7%), 17.3 (97.4%), 22.2 min (0.6%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 6.91 - 6.86 (m, 2 H, H-5',6'), 6.79 (dd, J = 8 Hz, 1.5 Hz, 1 H, H-2'), 3.75 (t, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.37 - 3.23 (m, 4 H, H_2-1,1''), 3.16 - 3.07 (m, 2 H, H_2-2''), 2.97 - 2.86 (m, 2 H, H_2-2), 2.89 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 148.8 (C_q-3'), 147.6 (C_q-4'), 136.2 (C_q-7b'''), 129.6 (C_q-1'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 120.7 (CH-2'), 118.4 (CH-6'''), 118.2 (CH-4'''), 112.7 (CH-6'), 112.1 (CH-5'), 111.5 (CH-7'''), 109.4 (C_q-3'''), 56.3 (CH_2-1), 55.53 (OCH_3-3'), 55.46 (OCH_3-4'), 55.4 (CH_2-1''), 39.3 (CH_3-N^+), 29.3 (CH_2-2), 19.9 (CH_2-2'').

ESI MS ("E2"): *m/z* (%) = 339.2 (100%) $[M + H]^+$, 503.2 (5%) $[M_{quat}]^+$.

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3,4-Dimethoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (278)

93.8 mg *N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O_3 \cdot C_2H_2O_4$, 458.5 g/mol, 35%) was obtained from 176.9 mg 3,4-dimethoxy-1-(2-iodoethyl)-benzene (**169**, 292.11 g/mol, 97%, 587.4 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3350, 2938, 2835, 2681, 1718, 1626, 1519, 1487, 1452, 1337, 1301, 1265, 1241, 1221, 1159, 1142, 1062, 1026, 939, 923, 851, 808, 766, 720, 695, 641, 484 cm^{-1}.

UV (H_2O): λ (%max_A) = 222 (>300%), 270 (88%) sh, 277 (100%), 285 (86%) sh, 296 (55%) sh, 307 (37%) sh.

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 17.7 (94.9%), 21.8 (1.4%), 23.1 min (3.7%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (s, 1 H, H-4'''), 7.11 (s, 1 H, H-2'''), 6.82 - 6.70 (m, 2 H, H-5',6'), 6.82 - 6.70 (m, 2 H, H-6''', H-2'), 3.78 (s, 3 H, -OCH_3-5'''), 3.75 (t, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.37 -

3.21 (m, 4 H, H_2-1,1''), 3.16 - 3.02 (m, 2 H, H_2-2''), 3.00 - 2.85 (m, 2 H, H_2-2), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 148.8 (C_q-3'), 147.6 (C_q-4'), 131.4 (C_q-7b'''), 129.7 (C_q-1'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 120.7 (CH-2'), 112.7 (CH-6'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 56.3 (CH_2-1), 55.52 (OCH_3-3'), 55.46 (OCH_3-3'), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39.3 (CH_3-N^+), 29.3 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 533.4 (10%) $[M_{quat}]^+$, 369.2 (100%) $[M + H]^+$.

N-[2-(2,6-Dichlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(2,6-Dichlorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (279)

N-[2-(2,6-Dimethoxyphenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{20}Cl_2N_2 \cdot C_2H_2O_4$, 428.48 g/mol) was obtained from 176.9 mg 2,6-dimethoxy-1-(2-iodoethyl)-benzene (**171**, 292.11 g/mol, 97%, 587.5 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3406, 3269, 3057, 2936, 2652, 1720, 1696, 1611, 1438, 1377, 1202, 1088, 1026, 1013, 794, 779, 739, 721, 470 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (753%), 266 (88%) sh, 272 (96%), 275 (97%) sh, 279 (100%), 287 nm (82%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 10.3 (4.4%), 19.2 (1.7%), 21.4 min (94.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.92 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.51 (d, J = 8 Hz, 2 H, H-3',5'), 7.36 (d, J = 7.5 Hz, 1 H, H-7'''), 7.34 (t, J = 8 Hz, 1 H, H-4'), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.08 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7 Hz, 7 Hz, 1 Hz, 1 H, H-5'''), 3.33 - 3.22 (m, 4 H, H_2-1,1''), 3.14 - 3.02 (m, 4 H, H_2-2,2''), 2.85 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 349.1 (56%) $[[^{37}Cl]M + H]^+$, 347.1 (100%) $[[^{35}Cl]M + H]^+$, 313.1 (25%) $[M - HCl + H]^+$, 216.1 (18%) $[M_{imine}]^+$, 182.0 (6%) $[M_{imine} - HCl]^+$.

N-[2-(2,6-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(2,6-Dimethoxyphenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (280)

N-[2-(2,6-Dimethoxyphenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O_3 \cdot C_2H_2O_4$, 458.5 g/mol) was obtained as a non-crystallizing mass from 176.9 mg 2,6-dimethoxy-1-(2-iodoethyl)-benzene (**171**, 292.11 g/mol, 97%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(3,4-Dichlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ([2-(3,4-Dichlorophenyl)-ethyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (281)

N-[2-(3,4-Dichlorophenyl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{19}H_{20}Cl_2N_2 \cdot C_2H_2O_4$, 437.32 g/mol) was obtained from 214.6 mg 3,4-dichloro-1-(2-iodoethyl)-benzene (**173**, 300.95 g/mol, 100%, 713.1 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3447, 3408, 3260, 3042, 2936, 2860, 1719, 1618, 1458, 1405, 1341, 1280, 1184, 1132, 1030, 946, 897, 827, 753, 720, 704, 584, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 272 (96%), 275 (96%), 280 (100%), 288 nm (80%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.8 (3.5%), 20.9 min (95.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.61 (s, 1 H, H-2'), 7.60 (2d, J = 8 Hz, 2 H, H-4''',5'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.30 (d, J = 8 Hz, 1 H, H-6'), 7.24 (d, J = 1 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.34 - 3.24 (m, 4 H, H_2-1'',1), 3.14 - 3.05 (m, 2 H, H_2-2''), 3.05 - 2.96 (m, 2 H, H_2-2), 2.85 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 138.7 (C_q-1'), 136.2 (C_q-7b'''), 130.9 (C_q-3',4'), 130.8 (CH-5'), 130.5 (CH-2'), 129.2 (CH-6'), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 55.5 (CH_2-1,1''), 39.4 (CH_3-N^+), 28.8 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 351.1 (17%) [[^{37}Cl][^{37}Cl]M + H]$^+$, 349.12 (38%) [[^{35}Cl][^{37}Cl]M + H]$^+$, 347.1 (100%) [[^{35}Cl][^{35}Cl]M + H]$^+$.

N-[2-(3,4-Dichlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([2-(3,4-Dichlorophenyl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (282)

N-[2-(3,4-Dichlorophenyl)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{20}H_{22}Cl_2N_2O \cdot C_2H_2O_4$, 467.34 g/mol) was obtained 214.6 mg 3,4-dichloro-1-(2-iodoethyl)-benzene (**173**, 300.95 g/mol, 100%, 713.1 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E. Recrystallization from a larger amount of THF.

IR (KBr): $\tilde{\nu}$ = 3253, 3002, 2939, 2831, 2633, 1720, 1590, 1476, 1403, 1281, 1216, 1131, 1061, 1031, 960, 926, 828, 802, 721, 641, 494 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 274 (100%), 279 (98%) sh, 293 (79%), 306 (55%) sh, 308 (48%) sh.

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 20.9 min (98.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.61 (s, 1 H, H-2'), 7.59 (d, J = 8 Hz, 4 Hz, 1 H, H-5'), 7.30 (dd, J = 8.5 Hz, 1.5 Hz, 1 H, H-6'), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 7.5 Hz, 1 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.33 - 3.23 (m, 4 H, H_2-1'',1), 3.11 - 2.97 (m, 4 H, H_2-2'',2), 2.86 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 138.7 (C_q-1'), 131.4 (C_q-7b'''), 131.0 (C_q-3',4'), 130.8 (CH-5'), 130.5 (CH-2'), 129.3 (CH-6'), 127.1 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.44 (CH_2-1), 55.41 (OCH_3-5'''), 55.38(CH_2-1''), 39.4 (CH_3-N^+), 28.7 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 381 (8%) [[^{37}Cl][^{37}Cl]M + H]$^+$, 379.1 (61%) [[^{35}Cl][^{37}Cl]M + H]$^+$, 377.1 (100%) [[^{35}Cl][^{35}Cl]M + H]$^+$, 218.1 (7%) [[^{35}Cl][^{37}Cl]M_{imine}]$^+$, 216.1 (11%) [[^{35}Cl][^{35}Cl]M_{imine}]$^+$.

N-[2-(Indol-3-yl)-ethyl]-*N*-methyltryptamine hydrogen oxalate (Bis-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (283)

42.4 mg *N*-[2-(Indol-3-yl)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{23}N_3 \cdot C_2H_2O_4$, 407.46 g/mol, 18%) was obtained as a white powder from 159.3 mg 3-(2-iodoethyl)-indole (**175**, 271.10 g/mol, 100%, 587.6 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3402, 3276, 3049, 2926, 2860, 2693, 1718, 1701, 1627, 1458, 1356, 1341, 1233, 1102, 1011, 934, 817, 747, 709, 489 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>500%), 273 (96%), 279 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 6.0 (oxalic acid), 17.1 (0.7%), 18.4 (83.8%), 23.4 (1.3%), 24.5 min (13.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.95 (s br, 2 H, H-1',1'''), 7.59 (d, J = 7.5 Hz, 2 H, H-4',4'''), 7.36 (d, J = 8 Hz, 2 H, H-7',7'''), 7.23 (s, 2 H, H-2',2'''), 7.09 (dd, J = J' = 7.5 Hz, 2 H, H-6',6'''), 7.01 (dd, J = J' = 7.5 Hz, 2 H, H-5',5'''), 3.38 - 3.22 (m, 4 H, H_2-1'',1), 3.16 - 3.03 (m, 4 H, H_2-2,2''), 2.88 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.2 (C_q-7b',7b'''), 126.7 (C_q-3b',3b'''), 123.0 (CH-2',2'''), 121.0 (CH-5',5'''), 118.3 (CH-6',6'''), 118.1 (CH-4',4'''), 111.4 (CH-7',7'''), 109.7 (C_q-3',3'''), 55.7 (CH_2-1,1''), 39.7 (CH_3-N^+), 20.3 (CH_2-2,2'').

ESI MS: *m/z* (%) = 461.4 (53%) [M_{quat}]$^+$, 318.2 (100%) [M + H]$^+$.

_N_-[2-(Indol-3-yl)-ethyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate ([2-(Indol-3-yl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (284)

_N_-[2-(Indol-3-yl)-ethyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate (55.1 mg, $C_{22}H_{25}N_3O \cdot C_2H_2O_4$, 437.49 g/mol, 21%) was obtained from 159.3 mg 3-(2-iodoethyl)-indole (**175**, 271.10 g/mol, 100%, 587.6 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3405, 3178, 3045, 2926, 1609, 1489, 1457, 1288, 1230, 1214, 1178, 1104, 1031, 939, 925, 877, 809, 742 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>300%), 273 (99%) sh, 277 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 18.3 (95.8%), 24.5 min (3.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.89 (s br, 1 H, H-1'''), 10.73 (s br, 1 H, H-1'), 7.56 (d, J = 8 Hz, 1 H, H-4'), 7.35 (d, J = 8 Hz, 1 H, H-7'), 7.24 (d, J = 8.5 Hz, 1 H, H-7'''), 7.20 (d, J = 1.5 Hz, 1 H, H-2'), 7.16 (d, J = 1.5 Hz, 1 H, H-4'''), 7.08 (dd, J = J' = 7.5 Hz, 1 H, H-6'), 7.05 (s, 1 H, H-2'''), 6.99 (dd, J = J' = 7 Hz, 1 H, H-5'), 6.73 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.76 (s, 3 H, -OCH_3-5'''), 3.14 - 2.92 (m, 8 H, H_2-1'',1,2'',2), 2.70 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 153.0 (C_q-5'), 136.1 (C_q-7b'''), 131.3 (C_q-7b'), 127.2 (C_q-3b'), 126.9 (C_q-3b'''), 123.5 (CH-2'), 122.8 (CH-2'''), 120.9 (CH-5'''), 118.2 (CH-6'''), 118.1 (CH-4'''), 111.9 (CH-7'), 111.3 (CH-7'''), 111.0 (CH-6'), 110.7 (C_q-3'''), 110.5 (C_q-3'), 100.2 (CH-4'), 56.5 (CH_2-1), 56.4 (CH_2-1''), 55.3 (OCH_3-5'), 40.4 (CH_3-N^+), 21.2 (CH_2-2,2'').

ESI MS: _m/z_ (%) = 491.5 (5%) $[M_{quat}]^+$, 348.3 (100%) $[M + H]^+$, 174.2 (22%) [5-MeO-vinyl-indole + $H]^+$.

_N_-[2-(5-Methoxyindol-3-yl)-ethyl]-_N_-methyltryptamine hydrogen oxalate ([2-(Indol-3-yl)-ethyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine) (285)

_N_-[2-(5-Methoxy-Indol-3-yl)-ethyl]-_N_-methyltryptamine hydrogen oxalate ($C_{22}H_{25}N_3O \cdot C_2H_2O_4$, 437.49 g/mol) was obtained as a non-crystallizing brown viscous mass from 176.9 mg 3-(2-iodoethyl)-5-methoxyindole (**176**, 301.12 g/mol, 100%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

_N_-[2-(5-Methoxyindol-3-yl)-ethyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate (Bis-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (286)

_N_-[2-(5-Methoxy-Indol-3-yl)-ethyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate (60.7 mg, $C_{23}H_{27}N_3O_2 \cdot C_2H_2O_4$, 467.51 g/mol, 22%) was obtained from 176.9 mg 3-(2-iodoethyl)-

5-methoxyindole (**176**, 301.12 g/mol, 100%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3409, 3229, 3045, 2938, 2720, 1606, 1488, 1295, 1214, 1176, 1062, 1030, 927, 797, 640, 501 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (391%), 275 (100%), 295 (82%) sh, 306 (59%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 11.5 (0.6%), 16.0 (0.5%), 18.9 (92.4%), 24.9 min (5.5%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.73 (s br, 2 H, H-1',1'''), 7.24 (d, J = 9 Hz, 2 H, H-7',7'''), 7.17 (s, 2 H, H-4',4'''), 7.04 (s, 2 H, H-2',2'''), 6.74 (dd, J = 6 Hz, 3 Hz, 2 H, H-6',6'''), 3.76 (s, 6 H, -OCH_3-5''',5'), 3.07 - 2.93 (m, 8 H, H_2-1'',1,2'',2), 2.73 (s, 3 H, N^+-CH_3).

ESI MS: *m/z* (%) = 551.3 (35%) $[M_{quat}]^+$, 378.2 (100%) $[M + H]^+$, 174.2 (10%) [5-MeO-vinyl-indole + H]$^+$.

N-(1-Naphthalen-2-yl-ethyl)-*N*-methyltryptamine hydrogen oxalate ((2-Naphthalen-1-yl-ethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (287)

N-(1-Naphthalen-2-yl-ethyl)-*N*-methyltryptamine hydrogen oxalate (65.1 mg, $C_{23}H_{24}N_2 \cdot C_2H_2O_4$, 418.48 g/mol, 26%) was obtained from 170.9 mg 1-(2-iodoethyl)-naphthalene (**177**, 282.12 g/mol, 97%, 587.6 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3410, 3263, 3045, 2945, 2860, 2684, 1718, 1635, 1458, 1398, 1355, 1280, 1235, 1106, 962, 802, 778, 742, 721, 705, 495 cm^{-1}.

UV (H_2O): λ (%max_A) = 223 (>800%), 262 (66%) sh, 271 (91%), 277 (92%) sh, 281 (100%), 288 nm (77%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 10.0 (1.8%), 21.7 (96.8%), 28.1 min (0.7%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 8.15 (d, J = 8 Hz, 1 H, H-8'), 7.95 (d, J = 8 Hz, 1 H, H-5'), 7.85 (dd, J = 6 Hz, 2.5 Hz, 1 H, H-4'), 7.65 - 7.43 (m, 5 H, H-4''', H-7',6',3',2'), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (s, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.56 - 3.30 (m, 6 H, H_2-1,1'',2), 3.20 - 3.04 (m, 2 H, H_2-2''), 2.98 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 133.5 (C_q-1'), 133.4 (C_q-4b'), 131.2 (C_q-8b'), 128.6 (CH-5'), 127.2 (CH-3'), 126.8 (CH-4'), 126.7 (C_q-3b'''), 126.3 (CH-7'), 125.7 (CH-6'), 125.5 (CH-2'), 123.4 (CH-8'), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.5 (C_q-3'''), 55.6 (CH_2-1), 55.5 (CH_2-1''), 39.4 (CH_3-N^+), 27.0 (CH_2-2), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 483.4 (11%) $[M_{quat}]^+$, 329.2 (100%) $[M + H]^+$.

_N_-(1-Naphthalen-2-yl-ethyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((2-Naphthalen-1-yl-ethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (288)

_N_-(1-Naphthalen-2-yl-ethyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate (77.4 mg, $C_{24}H_{26}N_2O \cdot C_2H_2O_4$, 448.51 g/mol, 29%) was obtained from 170.9 mg 1-(2-iodoethyl)-naphthalene (**177**, 282.12 g/mol, 97%, 587.6 µmol) and 100.0 mg _N_-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3376, 3041, 2947, 2694, 1718, 1626, 1487, 1280, 1215, 1177, 1096, 1063, 1030, 926, 800, 778, 720, 702, 640, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 223 (>600%), 261 (62%) sh, 272 (93%), 277 (95%) sh, 281 (100%), 289 (79%) sh, 293 (77%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 21.6 (97.9%), 24.6 (0.9%), 28.0 min (0.6%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 8.15 (d, J = 7 Hz, 1 H, H-8'), 7.96 (d, J = 8 Hz, 1 H, H-5'), 7.86 (d, J = 6 Hz, 1 H, H-4'), 7.66 - 7.43 (m, 4 H, H-7',6',3',2'), 7.26 (d, J = 8.5 Hz, 1 H, H-7'''), 7.21 (s, 1 H, H-4'''), 7.12 (s, 1 H, H-2'''), 6.74 (d, J = 8.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.57 - 3.31 (m, 6 H, H_2-1,1'',2), 3.18 - 3.05 (m, 2 H, H_2-2''), 2.99 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 133.5 (C_q-1'), 133.4 (C_q-4b'), 131.3 (C_q-7b'''), 131.2 (C_q-8b'), 128.6 (CH-5'), 127.3 (CH-3'), 127.1 (C_q-3b'''), 126.8 (CH-4'), 126.3 (CH-7'), 125.7 (CH-6'), 125.5 (CH-2'), 123.8 (CH-2'''), 123.4 (CH-8'), 112.0 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.3 (CH-4'''), 55.6 (CH_2-1), 55.44 (CH_2-1''), 55.38 (OCH_3-5'''), 39.5 (CH_3-N^+), 27.0 (CH_2-2), 20.1 (CH_2-2'').

ESI MS: _m/z_ (%) = 513 (4%) $[M_{quat}]^+$, 359.2 (100%) $[M + H]^+$.

_N_-(2-Naphthalen-2-yl-ethyl)-_N_-methyltryptamine hydrogen oxalate ((2-Naphthalen-2-yl-ethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (289)

_N_-(2-Naphthalen-2-yl-ethyl)-_N_-methyltryptamine hydrogen oxalate (90.5 mg, $C_{23}H_{24}N_3 \cdot C_2H_2O_4$, 418.48 g/mol, 37%) was obtained from 184.2 mg 2-(2-iodoethyl)-naphthalene (**178**, 282.12 g/mol, 90%, 587.6 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3395, 3253, 3039, 2937, 2856, 2695, 1720, 1619, 1508, 1458, 1417, 1362, 1340, 1280, 1178, 943, 901, 867, 827, 753, 721, 704, 482 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>500%), 264 (85%) sh, 267 (92%) sh, 281 (92%) sh, 287 (76%) sh.

HPLC: R_t (%total AUC_{260}) = 5.5 (oxalic acid), 9.8 (3.5%), 21.3 (93.7%), 27.7 min (2.4%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.93 - 7.83 (m, 3 H, H-5',8',4'), 7.78 (s, 1 H, H-1'), 7.62 (d, J = 7.5 Hz, 1 H, H-4'''), 7.56 - 7.42 (m, 3 H, H-7',6',3'), 7.38 (d, J = 8 Hz, 1 H, H-7'''), 7.25 (d, J = 0.5 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.47 - 3.31 (m, 4 H, H_2-1,1''), 3.24 - 3.09 (m, 4 H, H_2-2,2''), 2.93 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 134.9 (C_q-2'), 133.0 (C_q-8b'), 131.8 (C_q-4b'), 128.0 (CH-3'), 127.4 (CH-5'), 127.2 (CH-8'), 127.2 (CH-4'), 126.9 (CH-1'), 126.7 (C_q-3b'''), 126.1 (CH-7'), 125.6 (CH-6'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 55.9 (CH_2-1), 55.4 (CH_2-1''), 39.4 (CH_3-N^+), 29.9 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 483.3 (26%) $[M_{quat}]^+$, 329.2 (100%) $[M + H]^+$, 198.1 (10%) $[M_{imine}]^+$.

N-(2-Naphthalen-2-yl-ethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2-Naphthalen-2-yl-ethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (290)

N-(2-Naphthalen-2-yl-ethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate (89.9 mg, $C_{24}H_{26}N_2O \cdot C_2H_2O_4$, 448.51 g/mol, 34%) was obtained from 184.2 mg 2-(2-iodoethyl)-naphthalene (**178**, 282.12 g/mol, 90%, 587.6 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3405, 3014, 2945, 2687, 1718, 1626, 1486, 1215, 1174, 1061, 1031, 941, 900, 867, 827, 799, 753, 721, 704, 483 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 269 (94%) sh, 275 (100%), 287 (77%) sh, 308 (31%) sh.

HPLC: R_t (%total AUC_{260}) = 5.5 (oxalic acid), 18.5 (1.1%), 21.5 (96.0%), 27.5 min (2.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.83 (s br, 1 H, H-1'''), 7.95 - 7.80 (m, 3 H, H-5',8',4'), 7.78 (s, 1 H, H-1'), 7.58 - 7.40 (m, 3 H, H-7',6',3'), 7.26 (d, J = 8 Hz, 1 H, H-7'''), 7.21 (s, 1 H, H-4'''), 7.12 (s, 1 H, H-2'''), 6.75 (d, J = 8.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.49 - 3.28 (m, 4 H, H_2-1,1''), 3.28 - 3.03 (m, 4 H, H_2-2,2''), 2.93 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.2 (C_q-oxalate), 153.2 (C_q-5'''), 134.7 (C_q-2'), 133.0 (C_q-8b'), 131.9 (C_q-4b'), 131.4 (C_q-7b'''), 128.1 (CH-3'), 127.5 (CH-5'), 127.3 (CH-8'), 127.2 (CH-4'), 127.1 (C_q-3b'''), 127.0 (CH-1'), 126.2 (CH-7'), 125.6 (CH-6'), 123.9 (CH-2'''), 112.1 (CH-7'''), 111.3 (CH-6'''), 109.0 (C_q-3'''), 100.3 (CH-4'''), 55.8 (CH_2-1), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 39 (CH_3-N^+), 29.7 (CH_2-2), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 806.9 (7%) $[2M + \text{oxalic acid} + H]^+$, 513.2 (11%) $[M_{quat}]^+$, 359.2 (100%) $[M + H]^+$, 198.1 (7%) $[M_{imine}]^+$.

N-(2,2-Diphenylethyl)-*N*-methyltryptamine hydrogen oxalate

((2,2-Diphenylethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (291)

N-(2,2-Diphenylethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{25}H_{26}N_2 \cdot C_2H_2O_4$, 444.52 g/mol) was obtained from 229.5 mg 2,2-diphenyl-1-iodoethane (**179**, 308.16 g/mol, 79%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

***N*-(2,2-Diphenylethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2,2-Diphenylethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (292)**

N-(2,2-Diphenylethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{26}H_{28}N_2O \cdot C_2H_2O_4$, 474.55 g/mol) was obtained as a non-crystallizing mass from 229.5 mg 2,2-diphenyl-1-iodoethane (**179**, 308.16 g/mol, 79%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-2-Cyanoethyl-N-methyltryptamine hydrogen oxalate (2-Cyanoethyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (293)

N-(3-Phenylallyl)-*N*-methyltryptamine hydrogen oxalate ($C_{14}H_{17}N_3 \cdot C_2H_2O_4$, 317.34 g/mol) was obtained from 78.7 mg 3-bromopropionitrile (133.97 g/mol, 100%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3414, 3314, 3050, 2944, 2693, 2253, 1720, 1702, 1621, 1459, 1406, 1232, 1097, 944, 740, 720, 585, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 272 (97%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 8.7 min (99.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.89 (s br, 1 H, H-1'''), 7.57 (d, J = 7.5 Hz, 1 H, H-4'''), 7.35 (d, J = 8 Hz, 1 H, H-7'''), 7.20 (d, J = 2 Hz, 1 H, H-2'''), 7.07 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 6.99 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.13 (t, J = 7 Hz, 2 H, H_2-1), 3.07 - 2.93 (m, 4 H, H_2-1'',2''), 2.89 (t, J = 7 Hz, 2 H, H_2-2), 2.61 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 163.7 (C_q-oxalate), 136.2 (C_q-7b'''), 126.8 (C_q-3b'''), 123.0 (CH-2'''), 121.0 (CH-5'''), 118.7 (C_q-3), 118.3 (CH-6'''), 118.2 (CH-4'''), 111.4 (CH-7'''), 110.1 (C_q-3'''), 56.0 (CH_2-1''), 50.7 (CH_2-1), 39.8 (CH_3-N^+), 20.7 (CH_2-2''), 13.6 (CH_2-2).

ESI MS: *m/z* (%) = 228.1 (100%) $[M + H]^+$, 144.2 (40%) [vinylindole + H]$^+$.

N-2-Cyanoethyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (2-Cyanoethyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (294)

N-(3-Phenylallyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{15}H_{19}N_3O \cdot C_2H_2O_4$, 347.37 g/mol) was obtained from 78.7 mg 3 bromopropionitrile (133.97 g/mol, 100%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3374, 2948, 2836, 2596, 2252, 1720, 1703, 1626, 1487, 1406, 1281, 1214, 1177, 1106, 1063, 1032, 804, 720, 632, 496 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 275 (100%), 293 (81%), 306 (55%) sh.

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.8 (96.8%), 24.9 min (2.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.74 (s br, 1 H, H-1'''), 7.24 (d, J = 8.5 Hz, 1 H, H-7'''), 7.16 (d, J = 2 Hz, 1 H, H-4'''), 7.05 (d, J = 2 Hz, 1 H, H-2'''), 6.73 (dd, J = 5 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.19 (t, J = 7 Hz, 2 H, H_2-1), 3.11 - 2.89 (m, 6 H, H_2-1'',2'',2), 2.65 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 163.9 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.2 (C_q-3b'''), 123.7 (CH-2'''), 118.6 (C_q-3), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.7 (C_q-3'''), 100.2 (CH-4'''), 55.7 (CH_2-1''), 55.4 (OCH_3-5'''), 50.5 (CH_2-1), 39.7 (CH_3-N^+), 20.6 (CH_2-2''), 13.4 (CH_2-2).

ESI MS: *m/z* (%) = 280.1 (10%) $[M + Na]^+$, 258.1 (100%) $[M + H]^+$, 174.2 (16%) [5-MeO-vinylindole + H]$^+$.

N-(2-Acetoxyethyl)-*N*-methyltryptamine hydrogen oxalate (1-Acetoxy-2-{[2-(Indol-3-yl)-ethyl]-methylamino}-ethane hydrogen oxalate) (295)

N-(2-Acetoxyethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{15}H_{20}N_2O_2 \cdot C_2H_2O_4$, 350.37 g/mol) was obtained from 104.1 mg 2-iodoethanol (**181**, 171.96 g/mol, 97%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3321, 2956, 2638, 1740, 1703, 1619, 1459, 1404, 1280, 1230, 1096, 1068, 750, 720, 708, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 271 (95%) sh, 274 (96%), 280 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.5 (oxalic acid), 8.5 (2.6%), 10.3 min (97.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.95 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.22 (d, J = 2.5 Hz, 1 H, H-2'''), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 4.33 (t, J = 5.5 Hz, 2 H, H_2-2''), 3.33 (t, J = 5.5 Hz, 2 H, H_2-1''), 3.30 - 3.20 (m, 2 H, H_2-1''), 3.12 - 3.02 (m, 2 H, H_2-2''), 2.80 (s, 3 H, N^+-CH_3), 2.03 (s, 3 H, H_3-OAc).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 170.0 164.5 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.2 (CH-4'''), 111.5 (CH-7'''), 109.5 (C_q-3'''), 58.7 (CH_2-2), 56.0 (CH_2-1), 53.5 (CH_2-1''), 40.0 (CH_3-N^+), 20.6 (COO-CH_3) 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 283.1 (40%) $[M + Na]^+$, 261.1 (100%) $[M + H]^+$.

N-(2-Hydroxyethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate (2-{[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-ethanol hydrogen oxalate) (296)

N-(2-Hydroxyethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{14}H_{20}N_2O_2 \cdot C_2H_2O_4$, 338.36 g/mol) was obtained as a non-crystallizing mass from 104.1 mg 2-iodoethanol (**181**, 171.96 g/mol, 97%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-[2-(2-Hydroxy-ethoxy)-ethyl]-*N*-methyltryptamine hydrogen oxalate (2-(2-{[2-(Indol-3-yl)-ethyl]-methylamino}-ethoxy)-ethanol) (297)

N-[2-(2-Hydroxy-ethoxy)-ethyl]-*N*-methyltryptamine hydrogen oxalate ($C_{15}H_{22}N_2O_2 \cdot C_2H_2O_4$, 352.38 g/mol) was obtained as a non-crystallizing mass from 130.8 mg 2-(2-chloroethoxy)-ethanol (124.57 g/mol, 1.11 mmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-[2-(2-Hydroxy-ethoxy)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate (2-(2-{[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-ethoxy)-ethanol) (298)

N-[2-(2-Hydroxy-ethoxy)-ethyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{16}H_{24}N_2O_3 \cdot C_2H_2O_4$, 382.41 g/mol) was obtained from 130.8 mg 2-(2-chloroethoxy)-ethanol (124.57 g/mol, 1.11 mmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-(2-Chloroethyl)-*N*-methyltryptamine hydrogen oxalate ((2-Chloroethyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (299)

N-(2-Chloroethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{13}H_{17}ClN_2 \cdot C_2H_2O_4$, 326.78 g/mol) was obtained as a non-crystallizing gel from 142.4 mg 1-chloro-2-iodoethane (**182**, 190.41 g/mol, 79%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-(2-Chloroethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2-Chloroethyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (300)

N-(2-Chloroethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{14}H_{19}ClN_2O \cdot C_2H_2O_4$, 356.8 g/mol) was obtained as a non-crystallizing gel from 142.4 mg 1-chloro-2-iodoethane

(**182**, 190.41 g/mol, 79%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

***N*-(2-Diethylcarbamoylethyl)-*N*-methyltryptamine hydrogen oxalate (*N,N*-Diethyl-3-{[2-(indol-3-yl)-ethyl]-methylamino}-propionamide hydrogen oxalate) (301)**

N-(2-Diethylcarbamoylethyl)-*N*-methyltryptamine hydrogen oxalate ($C_{18}H_{27}N_3O \cdot C_2H_2O_4$, 391.46 g/mol) was obtained as a non-crystallizing oily precipitate from 115.2 mg 3-bromo-*N,N*-diethylpropionamide (**183**, 208.1 g/mol, 100%, 553.6 µmol) and 85.3 mg *N*-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

***N*-(2-Diethylcarbamoylethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate (*N,N*-Diethyl-3-{[2-(5-methoxyindol-3-yl)-ethyl]-methylamino}-propionamide hydrogen oxalate) (302)**

N-(2-Diethylcarbamoylethyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{19}H_{29}N_3O_2 \cdot C_2H_2O_4$, 421.49 g/mol) was obtained from 115.2 mg 3-bromo-*N,N*-diethylpropionamide (**183**, 208.1 g/mol, 100%, 553.6 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E. Recrystallization from a larger amount of THF.

IR (KBr): $\tilde{\nu}$ = 3292, 2974, 2938, 2635, 1720, 1703, 1633, 1488, 1461, 1404, 1279, 1219, 1178, 1148, 1101, 1029, 925, 798, 720, 703, 638, 497 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (>400%) sh, 265 (81%) sh, 268 (90%) sh, 275 (100%), 288 (84%) sh, 294 (81%), 306 (58%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 15.4 min (99.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.10 (d, J = 2.5 Hz, 1 H, H-2'''), 6.73 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.39 - 3.22 (m, 8 H, CON(CH_2)$_2$, H_2-1',1), 3.11 - 3.03 (m, 2 H, H_2-2''), 2.86 (t, J = 7 Hz, 2 H, H_2-2), 2.83 (s, 3 H, N^+-CH_3), 1.11 (t, J = 7 Hz, 3 H, CH_3), 1.01 (t, J = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 168.2 (C_q-3), 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.0 (C_q-3'''), 100.2 (CH-4'''), 55.43 (CH_2-1), 55.39 (OCH_3-5'''), 51.6 (CH_2-1''), 41.2 (CH_2-NEt), 39.7 (CH_3-N^+), 39.4 (CH_2-NEt), 27.0 (CH_2-2), 19.7 (CH_2-2''), 13.9 (CH_3-NEt), 12.9 (CH_3-NEt).

ESI MS: *m/z* (%) = 684.9 (5%) $[2M + Na]^+$, 332.2 (100%) $[M + H]^+$, 174.3 (6%) [5-MeO-vinylindole + H]$^+$.

Ethylene-bis(N-methyl-5-methoxytryptamine) hydrogen oxalate

(N^1,$N^{2'}$-Bis(2-(5-methoxyindol-3-yl)ethyl)-N^1,$N^{2'}$-dimethylethane-1,2-diamine hydrogen oxalate) (303)

Ethylene-bis(*N*-methyl-5-methoxytryptamine) hydrogen oxalate ($C_{26}H_{34}N_4O_2 \cdot C_2H_2O_4$, 524.61 g/mol) was obtained as an amorphous brown powder from 131.6 mg 1-chloro-2-iodoethane (**182**, 190.41 g/mol, 85%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol).

UV (H_2O): λ (%max_A) = 219 (429%), 275 (100%), 292 (84%) sh, 307 (55%) sh.

HPLC: R_t (%total AUC_{260}) = 4.8 (oxalic acid), 14.0 (77.0%), 18.3 min (21.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 9.21 (s br, 2 H, 2 H-1'''), 7.25 (d, J = 8.5 Hz, 2 H, 2 H-7'''), 7.16 (d, J = 2.5 Hz, 2 H, 2 H-4'''), 7.08 (s, 2 H, 2 H-2'''), 6.73 (dd, J = 8.5 Hz, 2.5 Hz, 2 H, 2 H-6'''), 3.76 (s, 6 H, 2 -OCH_3-5'''), 3.27 (s, 4 H, 2 H_2-1), 3.22 - 3.08 (m, 4 H, 2 H_2-1''), 3.08 - 2.97 (m, 4 H, 2 H_2-2''), 2.72 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 163.8 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (2 C_q-7b'''), 127.1 (2 C_q-3b'''), 123.6 (2 CH-2'''), 112.0 (2 CH-7'''), 111.1 (2 CH-6'''), 109.8 (2 C_q-3'''), 100.3 (2 CH-4'''), 56.4 (2 CH_2-1''), 55.4 (2 OCH_3-5'''), 50.8 (2 CH_2-1), 40.2 (2 CH_3-N^+), 20.5 (2 CH_2-2'').

ESI MS: *m/z* (%) = 735.3 (6%) $[M_{quat} + 70]^+$, 665.3 (36%) $[M_{quat}]^+$, 505.3 (16%) $[M + 70 + H]^+$, 435.3 (100%) $[M + H]^+$, 174.2 (7%) [5-MeO-vinylindole + H]$^+$.

ESI MS (negative ionization): *m/z* (%) = 863.6 (100%), 649.0 (84%), 322.1 (65%), 1277.0 (50%), 1278.0 (42%), 843.6 (40%), 804.8 (26%), 313.1 (26%), 559.3 (24%), 864.5 (24%), 447.2 (20%), 534.4 (20%), 1597.0 (20%).

***N*-Allyl-*N*-methyltryptamine hydrogen oxalate**
(Allyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (305)

N-Allyl-*N*-methyltryptamine hydrogen oxalate (84.8 mg, $C_{14}H_{18}N_2 \cdot C_2H_2O_4$, 304.34 g/mol, 47%) was obtained from 71.1 mg 3-bromopropene (120.98 g/mol, 100%, 587.7 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3387, 3250, 2941, 2686, 1720, 1703, 1620, 1458, 1405, 1280, 1194, 1011, 743, 720, 706, 618, 493 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 272 (97%), 280 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 11.5 (97.4%), 14.1 (1.4%), 15.9 (0.5%), 20.7 min (0.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.58 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.05 - 5.89 (ddt, 1 H, H-2), 5.52 (d,

J = 16.5 Hz, 1 H, C(*E*)-3H), 5.48 (d, J = 10 Hz, 1 H, C(Z)-3H), 3.74 (d, J = 7 Hz, 2 H, H_2-1), 3.27 - 3.15 (m, 2 H, H_2-1''), 3.15 - 3.04 (m, 2 H, H_2-2''), 2.76 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 128.3 (CH-2), 126.7 (C_q-3b'''), 124.0 (CH_2-3), 123.1 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 57.3 (CH_2-1), 54.8 (CH_2-1''), 39.0 (CH_3-N^+), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 519.0 (60%) $[2M + oxalic\ acid + H]^+$, 465.1 (11%) $[2M + HCl + H]^+$, 255.2 (26%) $[M_{quat}]^+$, 215.1 (100%) $[M + H]^+$.

N-Allyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Allyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (306)

45.9 mg *N*-Allyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{15}H_{20}N_2O \cdot C_2H_2O_4$, 334.37 g/mol, 23%) was obtained from 71.1 mg 3-bromopropene (120.98 g/mol, 100%, 587.7 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3335, 3038, 2937, 2671, 1722, 1703, 1625, 1487, 1461, 1355, 1310, 1280, 1210, 1177, 1108, 1028, 946, 847, 798, 720, 710, 625, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 270 (94%) sh, 275 (100%), 294 (83%), 307 (53%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 12.3 (98.9%), 16.8 min (0.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.79 (s br, 1 H, H-1'''), 7.25 (d, J = 9 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.06 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 6.04 - 5.89 (ddt, 1 H, H-2), 5.53 (d, J = 17.5 Hz, 1 H, C(*E*)-3H), 5.48 (d, J = 10 Hz, 1 H, C(Z)-3H), 3.77 (s, 3 H, -OCH_3-5'''), 3.73 (d, J = 7 Hz, 2 H, H_2-1), 3.24 - 3.15 (m, 2 H, H_2-1''), 3.09 - 3.00 (m, 2 H, H_2-2''), 2.75 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 128.4 (CH-2), 127.0 (C_q-3b'''), 123.9 (CH_2-3), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.1 (CH-4'''), 57.2 (CH_2-1), 55.4 (OCH_3-5'''), 54.7(CH_2-1''), 39.0 (CH_3-N^+), 20.0 (CH_2-2'').

ESI MS: *m/z* (%) = 245.1 (100%) $[M + H]^+$, 174.2 (6%) [5-MeO-vinylindole + H]$^+$.

N-Propargyl-*N*-methyltryptamine hydrogen oxalate (Prop-2-ynyl-[2-(Indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (307)

N-Propargyl-*N*-methyltryptamine hydrogen oxalate (58.7 mg, $C_{14}H_{16}N_2 \cdot C_2H_2O_4$, 302.33 g/mol, 33%) was obtained from 87.4 mg 3-bromopropyne (118.96 g/mol, 80%, 587.8 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3405, 3281, 3007, 2932, 2621, 2127, 1721, 1620, 1460, 1404, 1359, 1342, 1280, 1211, 1100, 1010, 930,767, 744, 720, 642, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 10.7 min (99.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.89 (s br, 1 H, H-1'''), 7.56 (d, J = 8 Hz, 1 H, H-4'''), 7.35 (d, J = 8 Hz, 1 H, H-7'''), 7.20 (d, J = 2 Hz, 1 H, H-2'''), 7.08 (td, J = 7.5 Hz, 1 Hz, 1 H, H-6'''), 6.99 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.84 (d, J = 2 Hz, 2 H, H_2-1), 3.55 (t, J = 2 Hz, 1 H, H-3), 3.10 - 2.92 (m, 4 H, H_2-1'',2''), 2.63 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.0 (C_q-oxalate), 136.2 (C_q-7b'''), 126.8 (C_q-3b'''), 123.0 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.9 (C_q-3'''), 79.4 (C_q-2), 75.0 (CH-3, inverse peak), 54.8 (CH_2-1''), 44.2 (CH_2-1), 39.8 (CH_3-N^+), 20.8 (CH_2-2'').

ESI MS: *m/z* (%) = 515.6 (5%) [2M + oxalic acid + H]$^+$, 461.4 (2%) [2M + HCl + H]$^+$, 213.2 (100%) [M + H]$^+$.

N-Propargyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Prop-2-ynyl-[2-(5-Methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (308)

N-Propargyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (73.3 mg, $C_{15}H_{18}N_2O \cdot C_2H_2O_4$, 332.35 g/mol, 38%) was obtained as an amorphous brownish powder from 87.4 mg 3-bromopropyne (118.96 g/mol, 80%, 587.8 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3421, 3284, 2922, 2853, 2630, 2125, 1719, 1633, 1485, 1466, 1280, 1214, 1117, 1059, 1024, 925, 867, 797, 720, 707, 635, 502 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 275 (100%), 294 (83%), 305 (59%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 11.5 min (99.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.51): δ = 10.74 (s br, 1 H, H-1'''), 7.24 (d, J = 8.5 Hz, 1 H, H-7'''), 7.08 (d, J = 2.5 Hz, 1 H, H-4'''), 7.04 (s br, 1 H, H-2'''), 6.75 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.87 (s, 2 H, H_2-1), 3.77 (s, 3 H, -OCH_3-5'''), 3.57 (s, 1 H, H-3), 3.11 - 3.00 (m, 2 H, H_2-1''), 3.00 - 2.90 (m, 2 H, H_2-2''), 2.64 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 163.8 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (C_q-7b'''), 127.1 (C_q-3b'''), 123.6 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.7 (C_q-3'''), 100.1 (CH-4'''), 79.1 (C_q-2), 75.2 (CH-3, inverse peak), 55.4 (OCH_3-5'''), 54.7(CH_2-1''), 39.9 (CH_3-N^+), 20.9 (CH_2-2'').

ESI MS: *m/z* (%) = 574.8 (18%) [2M + oxalic acid + H]$^+$, 243.1 (100%) [M + H]$^+$, 174.2 (21%) [5-MeO-vinylindole + H]$^+$.

_N_-Isobutyl-_N_-methyltryptamine hydrogen oxalate (Isobutyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (309)

_N_-Isobutyl-_N_-methyltryptamine hydrogen oxalate ($C_{15}H_{22}N_2 \cdot C_2H_2O_4$, 320.38 g/mol) was obtained from 113.8 mg 1-iodo-2-methylpropane (**184**, 184.02 g/mol, 95%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3394, 3251, 2964, 2683, 1720, 1702, 1623, 1459, 1405, 1280, 1191, 1105, 974, 754, 720, 703, 496 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 271 (95%) sh, 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.7 (4.7%), 13.7 min (94.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.30 - 3.18 (m, 2 H, H_2-1''), 3.18 - 3.05 (m, 2 H, H_2-2''), 2.93 (d, J = 7 Hz, 2 H, H_2-1), 2.80 (s, 3 H, N^+-CH_3), 2.06 (tqq, J = 7 Hz, 1 H, H-2), 0.96 (d, J = 6.5 Hz, 6 H, 2 H_3-3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.4 (C_q-3'''), 62.3 (CH_2-1), 56.3 (CH_2-1''), 39.9 (CH_3-N^+), 23.8 (CH-2), 20.2 (2 CH_3-3), 19.6 (CH_2-2'').

ESI MS: _m/z_ (%) = 551.3 (8%) $[2M + oxalic\ acid + H]^+$, 497.3 (10%) $[2M + HCl + H]^+$, 231.2 (100%) $[M + H]^+$.

_N_-Isobutyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate (Isobutyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (310)

_N_-Isobutyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{16}H_{24}N_2O \cdot C_2H_2O_4$, 350.41 g/mol) was obtained from 113.8 mg 1-iodo-2-methylpropane (**184**, 184.02 g/mol, 95%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3340, 3037, 2961, 2720, 1718, 1628, 1463, 1416, 1306, 1280, 1214, 1178, 1080, 976, 921, 787, 721, 712, 641, 500 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 272 (97%) sh, 275 (100%), 286 (90%) sh, 292 (86%), 296 (83%) sh, 307 (57%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 11.7 (0.5%), 14.0 (95.6%), 16.6 (1.4%), 20.1 min (1.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (s, 1 H, H-4'''), 7.09 (s, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 3.77

(s, 3 H, -OCH_3-5'''), 3.29 - 3.19 (m, 2 H, H_2-1''), 3.12 - 3.01 (m, 2 H, H_2-2''), 2.93 (d, J = 7 Hz, 2 H, H_2-1), 2.80 (s, 3 H, N^+-CH_3), 2.07 (tqq, J = 6.5 Hz, 1 H, H-2), 0.96 (d, J = 6.5 Hz, 6 H, 2 H_3-3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.2 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 62.5 (CH_2-1), 56.3 (CH_2-1''), 55.4 (OCH_3-5'''), 40.1 (CH_3-N^+), 23.9 (CH-2), 20.2 (2 CH_3-3), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 261.2 (100%) $[M + H]^+$, 174.2 (5%) [5-MeO-vinylindole]$^+$.

N-(2,2-Dimethylpropyl)-*N*-methyltryptamine hydrogen oxalate ((2,2-Dimethylpropyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (311)

N-(2,2-Dimethylpropyl)-*N*-methyltryptamine hydrogen oxalate ($C_{16}H_{24}N_2 \cdot C_2H_2O_4$, 348.44 g/mol) was obtained as a non-crystallizing mass from 126.2 mg 1-iodo-2,2-dimethylpropane (**185**, 198.05 g/mol, 92%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-(2,2-Dimethylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2,2-Dimethylpropyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (312)

N-(2,2-Dimethylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{17}H_{26}N_2O \cdot C_2H_2O_4$, 378.46 g/mol) was obtained as a non-crystallizing mass from 126.2 mg 1-iodo-2,2-dimethylpropane (**185**, 198.05 g/mol, 92%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-(3-Cyclohexylpropyl)-*N*-methyltryptamine hydrogen oxalate ((3-Cyclohexylpropyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (313)

N-(3-Cyclohexylpropyl)-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{30}N_2 \cdot C_2H_2O_4$, 388.5 g/mol) was obtained from 153.7 mg (3-iodopropyl)-cyclohexane (**186**, 252.14 g/mol, 96%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3421, 3057, 2924, 2852, 2673, 1719, 1702, 1636, 1459, 1405, 1280, 1233, 1106, 1010, 738, 721, 501 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>300%), 273 (96%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.7 (1.2%), 21.7 min (98.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.31 - 3.21 (m, 2 H, H_2-1''), 3.13 - 2.98 (m,

4 H, H_2-1,2''), 2.79 (s, 3 H, N^+-CH_3), 1.73 - 1.56 (m, 7 H, H_2-2, H-3'$_{eq}$,5'$_{eq}$,4'$_{eq}$,2'$_{eq}$,6'$_{eq}$), 1.22 - 1.15 (m, 6 H, H-1',3'$_{ax}$,5'$_{ax}$,4'$_{ax}$, H_2-3), 0.93 - 0.80 (m, 2 H, H-2'$_{ax}$,6'$_{ax}$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.3 (C_q-3'''), 55.24 (CH_2-1), 55.20 (CH_2-1''), 39.2 (CH_3-N^+), 36.5 (CH-1'), 33.6 (CH_2-3), 32.5 (CH_2-2',6'), 26.0 (CH_2-4'), 25.6 (CH_2-3',5'), 20.8 (CH_2-3), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 687.6 (38%) $[2M + \text{oxalic acid} + H]^+$, 299.2 (100%) $[M + H]^+$.

N-(3-Cyclohexylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((3-Cyclohexylpropyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (314)

N-(3-Cyclohexylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{32}N_2O \cdot C_2H_2O_4$, 418.53 g/mol) was obtained from 153.7 mg (3-iodopropyl)-cyclohexane (**186**, 252.14 g/mol, 96%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3400, 3268, 2924, 2851, 2694, 1719, 1642, 1489, 1448, 1281, 1217, 1103, 1065, 1032, 926, 836, 799, 720, 700, 641, 499 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 221 (437%), 272 (98%) sh, 275 (100%), 292 (84%), 304 (62%) sh, 307 (53%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 21.8 (92.9%), 28.0 min (6.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.09 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.26 - 3.21 (m, 2 H, H_2-1''), 3.10 - 2.99 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.74 - 1.56 (m, 7 H, H_2-2, H-3'$_{eq}$,5'$_{eq}$,4'$_{eq}$,2'$_{eq}$,6'$_{eq}$), 1.29 - 1.10 (m, 6 H, H-1',3'$_{ax}$,5'$_{ax}$,4'$_{ax}$, H_2-3), 0.87 (t, J = 10.5 Hz, 2 H, H-2'$_{ax}$,6'$_{ax}$).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 131.4 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.0 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.09 (CH_2-1), 55.05 (CH_2-1''), 39.1 (CH_3-N^+), 36.5 (CH-1'), 33.6 (CH_2-3), 32.5 (CH_2-2',6'), 26.0 (CH_2-4'), 25.6 (CH_2-3',5'), 20.7 (CH_2-3), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 747 (5%) $[2M + \text{oxalic acid} + H]^+$, 747 (3%) $[2M + HCl + H]^+$, 453.5 (31%) $[M_{quat}]^+$, 329.3 (100%) $[M + H]^+$.

_N_-(3-Phenylpropyl)-_N_-methyltryptamine hydrogen oxalate ((3-Phenylpropyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (315)

_N_-(4-Phenylpropyl)-_N_-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2 \cdot C_2H_2O_4$, 382.45 g/mol) was obtained from 160.2 mg (4-iodopropyl)-benzene (**188**, 246.09 g/mol, 90%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3415, 3264, 3036, 2948, 2699, 1724, 1703, 1622, 1458, 1427, 1183, 1103, 1015, 946, 752, 721, 702, 588, 487 cm^{-1}.

UV (H_2O): λ (%max_A) = 217 (>600%), 272 (96%), 278 (100%) sh, 280 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 18.8 min (99.2%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.58 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.34 - 7.17 (m, 5 H, C_6H_5), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.10 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.32 - 3.23 (m, 2 H, H_2-1''), 3.14 - 3.03 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 2.62 (t, J = 8 Hz, 2 H, H_2-3), 2.04 - 1.90 (m, 2 H, H_2-2).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 140.6 (C_q-1'), 136.2 (C_q-7b'''), 128.3 (CH-3',5'), 128.2 (CH-2',6'), 126.7 (C_q-3b'''), 126.0 (CH-4'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.5 (CH_2-1), 39.3 (CH_3-N^+), 32.0 (CH_2-3), 25.0 (CH_2-2), 19.8 (CH_2-2'').

ESI MS: _m/z_ (%) = 674.9 (6%) $[2M + oxalic\ acid + H]^+$, 411.2 (0.7%) $[M_{quat}]^+$, 293.2 (100%) $[M + H]^+$.

_N_-(3-Phenylpropyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((3-Phenylpropyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (316)

_N_-(4-Phenylpropyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2O \cdot C_2H_2O_4$, 412.48 g/mol) was obtained from 160.2 mg (4-iodopropyl)-benzene (**188**, 246.09 g/mol, 90%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3292, 2946, 2836, 2623, 1965, 1723, 1614, 1489, 1457, 1401, 1203, 1101, 1034, 958, 924, 838, 803, 753, 720, 708, 639, 578, 483 cm^{-1}.

UV (H_2O): λ (%max_A) = 222 (>400%) sh, 268 (90%) sh, 275 (100%), 294 (82%) sh, 300 (70%) sh, 305 (58%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 19.0 (96.8%), 24.9 min (2.2%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.34 - 7.19 (m, 5 H, C_6H_5H), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.07 (d, J = 2 Hz, 1 H,

H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.76 (s, 3 H, -OCH_3-5'''), 3.30 - 3.21 (m, 2 H, H_2-1''), 3.14 - 2.98 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 2.62 (t, J = 7.5 Hz, 2 H, H_2-3), 2.04 - 1.89 (m, 2 H, H_2-2).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 140.7 (C_q-1'), 131.4 (C_q-7b'''), 128.3 (CH-3',5'), 128.2 (CH-2',6'), 127.0 (C_q-3b'''), 126.0 (CH-4'), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.0 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.1 (CH_2-1''), 54.5 (CH_2-1), 39.3 (CH_3-N^+), 32.0 (CH_2-3), 25.1 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 734.9 (9%) $[2M + \text{oxalic acid} + H]^+$, 441.3 (23%) $[M_{quat}]^+$, 323.2 (100%) $[M + H]^+$.

N-(3-Phenylallyl)-*N*-methyltryptamine hydrogen oxalate ((3-Phenylallyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (317)

N-2-Cyanoethyl-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{22}N_2 \cdot C_2H_2O_4$, 380.44 g/mol) was obtained from 131.9 mg (3-bromopropenyl)-benzene (**189**, 197.07 g/mol, 88%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3398, 3032, 2923, 2686, 1719, 1701, 1636, 1458, 1420, 1340, 1281, 1209, 1104, 974, 938, 747, 721, 700, 669, 496 cm^{-1}.

UV (H_2O): λ (%max_A) = 210 (>200%), 216 (221%), 223 (161%) sh, 254 (100%), 283 (34%) sh, 288 nm (28%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 11.4 (24.6%), 17.6 min (75.4%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.96 (s br, 1 H, H-1'''), 7.57 (d, J = 8 Hz, 1 H, H-4'''), 7.51 (d, J = 7 Hz, 2 H, H-2',6'), 7.44 - 7.28 (m, 4 H, H-7''',3',4',5'), 7.24 (d, J = 2.5 Hz, 1 H, H-2'''), 7.08 (ddd, J = 7.5 Hz, 7.5 Hz, 0.5 Hz, 1 H, H-6'''), 6.95 (ddd, J = 7 Hz, 7 Hz, 0.5 Hz, 1 H, H-5'''), 6.85 (d, J = 16 Hz, 1 H, H-3), 6.41 (dt, J = 16 Hz, 7 Hz, 1 H, H-2), 3.89 (d, J = 7 Hz, 2 H, H_2-1), 3.33 - 3.22 (m, 2 H, H_2-1''), 3.16 - 3.07 (m, 2 H, H_2-2''), 2.81 (s, 3 H, N^+-CH_3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.4 (C_q-oxalate), 137.7 (CH-3), 136.2 (C_q-7b'''), 135.6 (CH-1'), 128.6 (CH-3',5'), 128.4 (CH-4'), 126.6 (CH-2',6', C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 119.3 (CH-2), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.4 (C_q-3'''), 56.9 (CH_2-1), 54.8 (CH_2-1''), 39.3 (CH_3-N^+), 20.1 (CH_2-2'').

ESI MS: *m/z* (%) = 670.8 (3%) $[2M + \text{oxalic acid} + H]^+$, 407.2 (33%) $[M_{quat}]^+$, 291.1 (100%) $[M + H]^+$.

_N_-(3-Phenylallyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((3-Phenylallyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (318)

_N_-2-Cyanoethyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{24}N_2O \cdot C_2H_2O_4$, 410.46 g/mol) was obtained as a non-crystallizing mass from 131.9 mg (3-bromopropenyl)-benzene (**189**, 197.07 g/mol, 88%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-[3-(2,5-Dimethylphenyl)-propyl]-_N_-methyltryptamine hydrogen oxalate ([3-(2,5-Dimethylphenyl)-propyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (319)

_N_-[3-(2,5-Dimethylphenyl)-propyl]-_N_-methyltryptamine hydrogen oxalate ($C_{22}H_{28}N_2 \cdot C_2H_2O_4$, 410.51 g/mol) was obtained as a non-crystallizing mass from 179.9 mg 2,5-dimethoxy-1-(3-iodopropyl)-benzene (306.14 g/mol, 81%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

_N_-[3-(2,5-Dimethylphenyl)-propyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate ([3-(2,5-Dimethylphenyl)-propyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (320)

_N_-[3-(2,5-Dimethylphenyl)-propyl]-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{23}H_{30}N_2O \cdot C_2H_2O_4$, 440.53 g/mol) was obtained as a non-crystallizing mass from 179.9 mg 2,5-dimethoxy-1-(3-iodopropyl)-benzene (306.14 g/mol, 81%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-[(3,4,5-Trimethoxyphenyl)-propyl]-_N_-methyltryptamine hydrogen oxalate ([(3,4,5-Trimethoxyphenyl)-propyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (321)

_N_-[4-(3,4,5-Trimethoxyphenyl)-propyl]-_N_-methyltryptamine hydrogen oxalate ($C_{23}H_{30}N_2O_3 \cdot C_2H_2O_4$, 486.56 g/mol) was obtained from 242.6 mg 3,4,5-trimethoxy-1-(4-iodopropyl)-benzene (**192**, 350.19 g/mol, 100%, 692.8 µmol) and 85.3 mg _N_-methyl-tryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3399, 3055, 2942, 2682, 1719, 1591, 1510, 1458, 1422, 1345, 1318, 1240, 1132, 1007, 956, 827, 737, 495 cm^{-1}.

UV (H_2O): λ (%max_A) = 224 (>500%) sh, 266 (88%) sh, 269 (95%) sh, 272 (98%), 275 (99%), 278 (100%), 288 nm (78%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 18.2 min (99.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.58 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 1.5 Hz, 1 H, H-2'''), 7.09 (dd, J = J' =

7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 6.54 (s, 2 H, H-2',6'), 3.76 (s, 6 H, -OCH_3-3',5'), 3.62 (s, 3 H, -OCH_3-4'), 3.32 - 3.21 (m, 2 H, H_2-1''), 3.13 - 3.03 (m, 4 H, H_2-1,2''), 2.82 (s, 3 H, N^+-CH_3), 2.56 (t, J = 7.5 Hz, 2 H, H_2-3), 2.04 - 1.89 (m, 2 H, H-2).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 152.7 (C_q-5'''), 136.3 (C_q-4'), 136.2 (C_q-7b'''), 135.8 (C_q-1'), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 105.6 (C_q-2',6'), 59.9 (OCH_3-4'), 55.8 (OCH_3-5'''), 55.3 (CH_2-1''), 54.5 (CH_2-1), 39.4 (CH_3-N^+), 32.4 (CH_2-3), 25.1 (CH_2-2), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 786.9 (9%) $[2M + Na]^+$, 383.2 (100%) $[M + H]^+$.

***N*-[(3,4,5-Trimethoxyphenyl)-propyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([(3,4,5-Trimethoxyphenyl)-propyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (322)**

N-[4-(3,4,5-Trimethoxyphenyl)-propyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{24}H_{32}N_2O_4 \cdot C_2H_2O_4$, 516.58 g/mol) was obtained from 242.6 mg 3,4,5-trimethoxy-1-(4-iodopropyl)-benzene (**192**, 350.19 g/mol, 100%, 692.8 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E. The viscous mass crystallized after 20 d at 4 °C.

IR (KBr): $\tilde{\nu}$ = 3392, 3043, 2942, 2833, 2702, 1720, 1626, 1592, 1510, 1485, 1458, 1422, 1346, 1318, 1240, 1212, 1178, 1133, 1065, 1034, 1002, 827, 794, 776, 703, 662, 634, 496 cm^{-1}.

UV (H_2O): λ (%max_A) = 274 (100%), 295 (74%) sh, 298 (70%) sh, 307 (49%) sh.

HPLC: R_t (%total AUC_{260}) = 6.0 (oxalic acid), 18.4 (98.2%), 23.1 min (1.3%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.07 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 6.54 (s, 2 H, H-2',6'), 3.76 (s, 9 H, -OCH_3-3',5',5'''), 3.62 (s, 3 H, -OCH_3-4'), 3.30 - 3.21 (m, 2 H, H_2-1''), 3.14 - 2.98 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 2.62 (t, J = 7.5 Hz, 2 H, H_2-3), 2.04 - 1.89 (m, 2 H, H_2-2).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 152.8 (C_q-3',5'), 136.3 (C_q-4'), 135.9 (C_q-1'), 131.4 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 105.6 (C_q-2',6'), 100.2 (CH-4'''), 59.9 (OCH_3-4'), 55.8 (OCH_3-3',5'), 55.4 (OCH_3-5'''), 55.2 (CH_2-1''), 54.5 (CH_2-1), 39.3 (CH_3-N^+), 32.4 (CH_2-3), 25.1 (CH_2-2), 19.9 (CH_2-2'').

ESI MS: *m/z* (%) = 914.6 (37%) $[2M + oxalic\ acid + H]^+$, 824.7 (15%) $[2M + HCl + H]^+$, 621.3 (14%) $[M_{quat}]^+$, 413.2 (100%) $[M + H]^+$.

N-[4-(Indol-3-yl)-butyl]-*N*-methyltryptamine hydrogen oxalate ([4-(Indol-3-yl)-butyl]-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (323)

N-[4-(Indol-3-yl)-butyl]-*N*-methyltryptamine hydrogen oxalate ($C_{23}H_{27}N_3 \cdot C_2H_2O_4$, 435.52 g/mol) was obtained as a non-crystallizing mass from 167.5 mg 3-(4-iodobutyl)-indole (**193**, 299.15 g/mol, 100%, 560.0 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-[4-(Indol-3-yl)-butyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ([4-(Indol-3-yl)-butyl]-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (324)

N-[4-(Indol-3-yl)-butyl]-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{24}H_{29}N_3O \cdot C_2H_2O_4$, 465.54 g/mol) was obtained as a non-crystallizing mass from 167.5 mg 3-(4-iodobutyl)-indole (**193**, 299.15 g/mol, 100%, 560.0 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-(3-Phenylsulfanyl-propyl)-*N*-methyltryptamine hydrogen oxalate ((3-Phenylsulfanyl-propyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (325)

N-(3-Phenylsulfanyl-propyl)-*N*-methyltryptamine hydrogen oxalate ($C_{20}H_{24}N_2S \cdot C_2H_2O_4$, 414.52 g/mol) was obtained from 184.8 mg (3-bromopropylsulfanyl)-benzene (**194**, 231.15 g/mol, 88%, 706.9 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3396, 3018, 3254, 2937, 2859, 2674, 1718, 1458, 1280, 1184, 1097, 953, 812, 746, 721, 703, 620, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>400%), 255 (100%), 260 (93%) sh, 272 (76%) sh, 281 (69%) sh, 288 nm (56%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.9 (1.3%), 13.4 (0.7%), 16.5 (4.6%), 20.4 (83.1%), 22.5 min (10.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.57 (d, J = 8 Hz, 1 H, H-4'''), 7.40 - 7.29 (m, 5 H, H-7''',2',6',3',5'), 7.25 - 7.19 (m, 2 H, H-2''',4'), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.28 - 3.15 (m, 4 H, H_2-1'',1), 3.11 - 3.00 (m, 4 H, H_2-2'',3), 2.78 (s, 3 H, N^+-CH_3), 2.04 - 1.89 (m, 2 H, H_2-2).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 135.5 (C_q-1'), 129.0 (CH-3',5'), 128.3 (CH-2',6'), 126.7 (C_q-3b'''), 125.8 (CH-4'), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.4 (CH_2-1''), 53.7 (CH_2-1), 39.4 (CH_3-N^+), 29.3 (CH_2-3), 23.3 (CH_2-2), 19.8 (CH_2-2'').

ESI MS: *m/z* (%) = 685.0 (5%) $[2M + HCl + H]^+$, 325.3 (100%) $[M + H]^+$.

_N_-(3-Phenylsulfanyl-propyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((3-Phenylsulfanyl-propyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (326)

_N_-(3-Phenylsulfanyl-propyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{21}H_{26}N_2OS \cdot C_2H_2O_4$, 444.54 g/mol) was obtained from 184.8 mg (3-bromopropylsulfanyl)-benzene (**194**, 231.15 g/mol, 88%, 706.9 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3404 3244, 2939, 2703, 1956, 1719, 1586, 1485, 1331, 1301, 1280, 1216, 1023, 826, 802, 743, 721, 691, 639, 498, 460 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (339%) sh, 249 (95%) sh, 253 (100%), 258 (95%) sh, 275 (77%) sh, 296 (53%) sh, 307 (34%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 14.4 (0.6%), 16.7 (8.1%), 20.3 (84.5%), 22.5 min (6.4%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.79 (s br, 1 H, H-1'''), 7.39 - 7.28 (m, 5 H, C_6H_5), 7.25 (d, J = 8.5 Hz, 1 H, H-4'''), 7.16 (m, J = 2 Hz, 1 H, H-4'''), 7.06 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.25 - 3.11 (m, 4 H, H_2-1'',1), 3.07 - 2.96 (m, 4 H, H_2-2'',3), 2.75 (s, 3 H, N^+-CH_3), 2.02 - 1.88 (m, 2 H, H_2-2).

ESI MS: _m/z_ (%) = 798.7 (12%) $[2M + \text{oxalic acid} + H]^+$, 355.1 (100%) $[M + H]^+$.

_N_-(3-Chloropropyl)-_N_-methyltryptamine hydrogen oxalate ((3-Chloropropyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (327)

_N_-(3-Chloropropyl)-_N_-methyltryptamine hydrogen oxalate ($C_{14}H_{19}ClN_2 \cdot C_2H_2O_4$, 340.8 g/mol) was obtained from 133.8 mg 1-chloro-3-iodopropane (**196**, 204.44 g/mol, 90%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

_N_-(3-Chloropropyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ((3-Chloropropyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (328)

_N_-(3-Chloropropyl)-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{15}H_{21}ClN_2O \cdot C_2H_2O_4$, 370.83 g/mol) was obtained from 133.8 mg 1-chloro-3-iodopropane (**196**, 204.44 g/mol, 90%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-(3-Ethoxycarbonylpropyl)-*N*-methyltryptamine hydrogen oxalate (4-{[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-butyric acid ethyl ester hydrogen oxalate) (329)

N-(3-Ethoxycarbonylpropyl)-*N*-methyltryptamine hydrogen oxalate ($C_{17}H_{24}N_2O_2 \cdot C_2H_2O_4$, 378.42 g/mol) was obtained as a non-crystallizing viscous mass from 142.2 mg 4-iodobutyric acid ethyl ester (242.05 g/mol, 100%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

N-(3-Ethoxycarbonylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate (4-{[2-(5-Methoxyindol-3-yl)-ethyl]-methylamino}-butyric acid ethyl ester hydrogen oxalate) (330)

N-(3-Ethoxycarbonylpropyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{18}H_{26}N_2O_3 \cdot C_2H_2O_4$, 408.45 g/mol) was obtained as a non-crystallizing viscous mass from 142.2 mg 4-iodobutyric acid ethyl ester (242.05 g/mol, 100%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

N-Butyl-*N*-methyltryptamine hydrogen oxalate (Butyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (331)

N-Butyl-*N*-methyltryptamine hydrogen oxalate (73.6 mg, $C_{15}H_{22}N_2 \cdot C_2H_2O_4$, 320.38 g/mol, 39%) was obtained as a white powder from 108.1 mg 1-iodobutane (**197**, 184.02 g/mol, 100%, 587.4 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3244, 2962, 2875, 2694, 1720, 1703, 1620, 1459, 1405, 1342, 1280, 1218, 1106, 1012, 934, 878, 746, 720, 500 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>600%), 270 (92%) sh, 273 (95%), 279 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 10.0 (0.8%), 14.2 min (98.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.31 - 3.23 (m, 2 H, H_2-1''), 3.14 - 3.03 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.70 - 1.57 (m, 2 H, H_2-2), 1.32 (tq, J = 7.5 Hz, 2 H, H_2-3), 0.90 (t, J = 7.5 Hz, 3 H, H_3-4).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.7 (CH_2-1), 39.1 (CH_3-N^+), 25.3 (CH_2-2), 19.7 (CH_2-2''), 19.3 (CH_2-3), 13.4 (CH_3-4).

ESI MS: *m/z* (%) = 575.5 (8%) $[2M + oxalic\ acid + Na]^+$, 551.4 (39%) $[2M + oxalic\ acid + H]^+$, 497 (5%) $[2M + HCl + H]^+$, 309.1 (5%) $[M_{quat}]^+$, 231.2 (100%) $[M + H]^+$.

N-Butyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Butyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (332)

N-Butyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (123.9 mg, $C_{16}H_{24}N_2O \cdot C_2H_2O_4$, 350.41 g/mol, 60%) was obtained as an off-white fine powder from 108.1 mg 1-iodobutane (**197**, 184.02 g/mol, 100%, 587.4 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3379, 3248, 2960, 2873, 2835, 2690, 1718, 1626, 1487, 1280, 1214, 1178, 1072, 1031, 927, 858, 796, 721, 701, 636, 499 cm^{-1}.

UV (H_2O): λ (%max_A) = 221 (>400%), 275 (100%), 294 (83%) sh, 296 (81%) sh, 307 (54%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 14.6 (83.1%), 19.6 min (16.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.08 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.30 - 3.20 (m, 2 H, H_2-1''), 3.14 - 3.00 (m, 4 H, H_2-1,2''), 2.80 (s, 3 H, N^+-CH_3), 1.70 - 1.56 (m, 2 H, H_2-2), 1.32 (tq, J = 7.5 Hz, 2 H, H_2-3), 0.91 (t, J = 7.5 Hz, 3 H, H_3-4).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.9 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.2 (CH-4'''), 55.4 (CH_2-1''), 55.2 (OCH_3-5'''), 54.7 (CH_2-1), 39.2 (CH_3-N^+), 25.4 (CH_2-2), 19.8 (CH_2-2''), 19.4 (CH_2-3), 13.4 (CH_3-4).

ESI MS: *m/z* (%) = 317.2 (100%) $[M_{quat}]^+$, 261.2 (64%) $[M + H]^+$, 174.2 (15%) [5-MeO-vinylindole + H]$^+$.

N-(2-Ethylbutyl)-*N*-methyltryptamine hydrogen oxalate ((2-Ethylbutyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (333)

N-(2-Ethylbutyl)-*N*-methyltryptamine hydrogen oxalate ($C_{17}H_{26}N_2 \cdot C_2H_2O_4$, 348.44 g/mol) was obtained from 136.7 mg 3-iodomethyl-pentane (**198**, 212.07 g/mol, 91%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3392, 3232, 2965, 2877, 2690, 1720, 1593, 1459, 1405, 1279, 1197, 1104, 1010, 950, 736, 721, 498 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%) 273 (96%), 280 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.6 (0.5%), 10.8 (2.2%), 16.9 min (97.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.83 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.29 - 3.20 (m, 2 H, H_2-1''), 3.19 - 3.05 (m, 2 H, H_2-2''), 2.95 (d, J = 6.5 Hz, 2 H, H_2-1), 2.80 (s, 3 H, N^+-CH_3), 1.75 - 1.63 (m, 1 H, H-2), 1.46 - 1.27 (dq, 4 H, 2 H_2-3), 0.85 (t, J = 7.5 Hz, 6 H, 2 H_3-4).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.4 (C_q-3'''), 58.7 (CH_2-1), 56.3 (CH_2-1''), 40.1 (CH_3-N^+), 35.5 (CH-2), 22.8 (2 CH_2-3), 19.7 (CH_2-2''), 10.1 (2 CH_3-4).

ESI MS: *m/z* (%) = 607.0 (4%) [2M + oxalic acid + H]$^+$, 553.0 (3%) [2M + HCl + H]$^+$, 259.2 (100%) [M + H]$^+$.

N-(2-Ethylbutyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((2-Ethylbutyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (334)

N-(2-Ethylbutyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{18}H_{28}N_2O \cdot C_2H_2O_4$, 378.46 g/mol) was obtained from 136.7 mg 3-iodomethyl-pentane (**198**, 212.07 g/mol, 91%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3408, 3228, 2964, 2936, 2693, 1719, 1587, 1488, 1460, 1405, 1280, 1218, 1104, 1070, 1031, 926, 828, 802, 758, 721, 641, 499 cm^{-1}.

UV (H_2O): λ (%max$_A$) = 220 (>400%), 269 (93%) sh, 276 (100%), 296 (80%) sh, 305 (59%) sh.

HPLC: R_t (%total AUC_{260}) = 5.9 (oxalic acid), 12.2 (0.9%), 17.1 min (98.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.81 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.08 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.28 - 2.18 (m, 2 H, H_2-1''), 3.10 - 3.03 (m, 2 H, H_2-2''), 2.96 (d, J = 6.5 Hz, 2 H, H_2-1), 2.80 (s, 3 H, N^+-CH_3), 1.76 - 1.64 (m, 1 H, H-2'), 1.47 - 1.26 (dq, 4 H, 2 H_2-3), 0.85 (t, J = 7.5 Hz, 6 H, 2 H_3-4).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.3 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.7 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 58.8 (CH_2-1), 56.2 (CH_2-1''), 55.4 (OCH_3-5'''), 40.2 (CH_3-N^+), 35.5 (CH-2), 22.8 (2 CH_2-3), 19.8 (CH_2-2''), 10.0 (2 CH_3-4).

ESI MS: *m/z* (%) = 667.7 (6%) [2M + oxalic acid + H]+, 613.7 (7%) [2M + HCl + H]$^+$, 289.3 (100%) [M + H]$^+$.

N-(4-Phenylbutyl)-*N*-methyltryptamine hydrogen oxalate

((4-Phenylbutyl)-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (335)

N-(4-Phenylbutyl)-*N*-methyltryptamine hydrogen oxalate ($C_{21}H_{26}N_2 \cdot C_2H_2O_4$, 396.48 g/mol) was obtained from 164.0 mg (4-iodobutyl)-benzene (**199**, 260.11 g/mol, 93%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3397, 3250, 3027, 2942, 2861, 2681, 1719, 1702, 1619, 1458, 1420, 1341, 1280, 1180, 940, 753, 720, 703, 496, 426 cm^{-1}.

UV (H_2O): λ (%max_A) = 217 (>600%), 262 (77%) sh, 267 (90%) sh, 273 (97%), 280 (100%), 288 nm (85%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 20.4 min (99.2%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.58 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.32 - 7.14 (m, 6 H, C_6H_5, H-2'''), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.31 - 3.21 (m, 2 H, H_2-1), 3.16 - 3.03 (m, 4 H, H_2-1,2''), 2.80 (s, 3 H, N^+-CH_3), 2.61 (t, J = 7 Hz, 2 H, H_2-4), 1.75 - 1.53 (m, 4 H, H_2-2,3).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 141.6 (C_q-1'), 136.2 (C_q-7b'''), 128.2 (CH-3',5',2',6'), 126.7 (C_q-3b'''), 125.7 (CH-4'), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.2 (C_q-3'''), 55.2 (CH_2-1''), 54.6 (CH_2-1), 39.2 (CH_3-N^+), 34.4 (CH_2-4), 27.9 (CH_2-3), 23.0 (CH_2-2), 19.7 (CH_2-2'').

ESI MS: *m/z* (%) = 703.6 (6%) $[2M + oxalic\ acid + H]^+$, 439.5 (4%) $[M_{quat}]^+$, 307.4 (100%) $[M + H]^+$.

***N*-(4-Phenylbutyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ((4-Phenylbutyl)-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (336)**

N-(4-Phenylbutyl)-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{22}H_{28}N_2O \cdot C_2H_2O_4$, 426.51 g/mol) was obtained from 164.0 mg (4-iodobutyl)-benzene (**199**, 260.11 g/mol, 93%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3255, 3026, 2936, 2859, 2691, 1718, 1627, 1488, 1455, 1299, 1213, 1175, 1102, 1062, 1027, 924, 832, 800, 750, 699, 634, 453 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (> 400%) sh, 268 (92%) sh, 275 (100%), 293 (83%) sh, 307 (51%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 20.3 (98.7%), 26.4 min (0.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.79 (s br, 1 H, H-1'''), 7.32 - 7.16 (m, 6 H, C_6H_5, H-4'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.06 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz,

2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.25 - 3.14 (m, 2 H, H_2-1), 3.12 - 2.97 (m, 4 H, H_2-1,2''), 2.75 (s, 3 H, N^+-CH_3), 2.60 (t, J = 7 Hz, 2 H, H_2-4), 1.72 - 1.53 (m, 4 H, H_2-2,3).

ESI MS: *m/z* (%) = 763.0 (43%) $[2M + \text{oxalic acid} + H]^+$, 469.3 (4%) $[M_{quat}]^+$, 337.2 (100%) $[M + H]^+$.

N-Pentyl-*N*-methyltryptamine hydrogen oxalate (Pentyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (337)

61.6 mg *N*-Pentyl-*N*-methyltryptamine hydrogen oxalate ($C_{16}H_{24}N_2 \cdot C_2H_2O_4$, 334.41 g/mol, 31%) was obtained as a pearlescent white powder from 116.3 mg 1-iodopentane (**200**, 198.05 g/mol, 100%, 587.2 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E. Recrystallization from diethyl ether.

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.31 - 3.22 (m, 2 H, H_2-1''), 3.13 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.72 - 1.58 (m, 2 H, H_2-2), 1.38 - 1.21 (m, 4 H, H_2-3,4), 0.88 (t, J = 7 Hz, 3 H, H_3-5).

IR (KBr): $\tilde{\nu}$ = 3393, 3268, 3054, 2956, 2932, 2871, 2690, 1720, 1702, 1619, 1458, 1405, 1353, 1279, 1191, 1101, 1026, 1010, 957, 880, 839, 817, 742, 720, 707, 589, 491 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (585%), 272 (96%), 279 (100%), 287 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 9.8 (1.7%), 15.9 (97.5%), 21.9 min (0.6%).

ESI MS: *m/z* (%) = 579.1 (77%) $[2M + \text{oxalic acid} + H]^+$, 245.2 (100%) $[M + H]^+$.

N-Pentyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Pentyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (338)

N-Pentyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{17}H_{26}N_2O \cdot C_2H_2O_4$, 364.44 g/mol) was obtained from 116.3 mg 1-iodopentane (**200**, 198.05 g/mol, 100%, 587.2 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E. Recrystallization from THF / diethyl ether.

IR (KBr): $\tilde{\nu}$ = 3363, 3233, 3043, 2957, 2870, 2830, 2689, 1717, 1700, 1605, 1486, 1460, 1439, 1384, 1353, 1311, 1217, 1175, 1126, 1100, 1074, 1030, 924, 862, 828, 799, 759, 702, 636, 470 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (419%), 274 (100%), 294 (83%) sh, 307 (53%) sh.

HPLC: R_t (%total AUC_{260}) = 5.6 (oxalic acid), 16.2 (90.2%), 21.9 min (9.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.07 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.26 - 3.17 (m, 2 H, H_2-1''), 3.10 - 2.97 (m, 4 H,

H_2-1,2''), 2.77 (s, 3 H, N^+-CH_3), 1.70 - 1.56 (m, 2 H, H_2-2), 1.38 - 1.20 (m, 4 H, H_2-3,4), 0.88 (t, J = 6.5 Hz, 3 H, H_3-5).

ESI MS: *m/z* (%) = 639.0 (20%) $[2M + \text{oxalic acid} + H]^+$, 345.3 (66%) $[M_{quat}]^+$, 275.2 (100%) $[M + H]^+$.

N-Hexyl-*N*-methyltryptamine hydrogen oxalate (Hexyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (339)

N-Hexyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate-*N*-methyltryptamine hydrogen oxalate (65.6 mg, $C_{17}H_{26}N_2 \cdot C_2H_2O_4$, 348.44 g/mol, 32%) was obtained as a pearlescent white powder from 124.6 mg 1-iodohexane (212.07 g/mol, 100%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3473, 3421, 3250, 3046, 2937, 2852, 2691, 1720, 1703, 1621, 1457, 1421, 1340, 1280, 1200, 1098, 1011, 945, 745, 720, 705, 613, 490 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 266 (85%) sh, 271 (94%) sh, 280 (100%), 288 nm (84%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 10.0 (0.6%), 18.1 min (98.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.99 (s br, 1 H, H-1'''), 7.60 (d, J = 8 Hz, 1 H, H-4'''), 7.37 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.32 - 3.23 (m, 2 H, H_2-1''), 3.14 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.71 - 1.57 (m, 2 H, H_2-2), 1.37 - 1.24 (m, 6 H, H_2-3-5), 0.87 (t, J = 6.5 Hz, 3 H, H_3-6).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.5 (C_q-oxalate), 136.2 (C_q-7b'''), 126.6 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.9 (CH_2-1), 39.2 (CH_3-N^+), 25.6 (CH_2-2), 23.2 (CH_2-3), 21.7 (CH_2-4), 19.7 (CH_2-2''), 19.3 (CH_2-5), 13.7 (CH_3-6).

ESI MS: *m/z* (%) = 607.7 (5%) $[2M + \text{oxalic acid} + H]^+$, 259.3 (100%) $[M + H]^+$.

N-Hexyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Hexyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (340)

N-Hexyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate-*N*-methyl-5-methoxytryptamine hydrogen oxalate (62.3 mg, $C_{18}H_{28}N_2O \cdot C_2H_2O_4$, 378.46 g/mol, 28%) was obtained as a white powder from 124.6 mg 1-iodohexane (212.07 g/mol, 100%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-Heptyl-_N_-methyltryptamine hydrogen oxalate
(Heptyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (341)

_N_-Heptyl-_N_-methyltryptamine hydrogen oxalate ($C_{18}H_{28}N_2 \cdot C_2H_2O_4$, 362.46 g/mol) was obtained from 105.2 mg 1-bromoheptane (179.1 g/mol, 100%, 587.5 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3395, 3249, 3015, 2930, 2857, 2691, 1721, 1703, 1637, 1459, 1423, 1341, 1280, 1194, 1104, 940, 753, 720, 703, 494 cm^{-1}.

UV (H_2O): λ (%max_A) = 219 (>500%), 259 (62%) sh, 273 (95%), 279 (100%), 288 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 9.8 (0.9%), 20.2 min (98.9%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.97 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (td, J = 7.5 Hz, 1.5 Hz, 1 H, H-6'''), 7.01 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.32 - 3.22 (m, 2 H, H_2-1''), 3.13 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.70 - 1.57 (m, 2 H, H_2-2), 1.37 - 1.22 (m, 8 H, H_2-3-6), 0.86 (t, J = 6.5 Hz, 3 H, H_3-7).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.1 (CH-5'''), 118.4 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.9 (CH_2-1), 39.2 (CH_3-N^+), 30.9 (CH_2-2), 28.1 (CH_2-3), 26.0 (CH_2-4), 23.3 (CH_2-5), 21.9 (CH_2-6), 19.8 (CH_2-2''), 13.8 (CH_3-7).

ESI MS: _m/z_ (%) = 635.1 (22%) $[2M + oxalic\ acid + H]^+$, 273.2 (100%) $[M + H]^+$.

_N_-Heptyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate
(Heptyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (342)

_N_-Heptyl-_N_-methyl-5-methoxytryptamine hydrogen oxalate ($C_{19}H_{30}N_2O \cdot C_2H_2O_4$, 392.49 g/mol) was obtained as a non-crystallizing mass from 105.2 mg 1-bromoheptane (179.1 g/mol, 100%, 587.5 µmol) and 100.0 mg _N_-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

_N_-Octyl-_N_-methyltryptamine hydrogen oxalate
(Octyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (343)

_N_-Octyl-_N_-methyltryptamine hydrogen oxalate (72.9 mg, $C_{19}H_{30}N_2 \cdot C_2H_2O_4$, 376.49 g/mol, 33%) was obtained as a pearlescent white powder from 141.1 mg 1-iodooctane (**201**, 240.13 g/mol, 100%, 587.6 µmol) and 85.3 mg _N_-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3393, 3242, 2927, 2857, 2685, 1720, 1702, 1619, 1459, 1405, 1341, 1280, 1195, 1105, 942, 753, 721, 703, 668, 501 cm^{-1}.

UV (H_2O): λ (%max_A) = 218 (600%), 271 (95%) sh, 279 (100%), 287 nm (83%).

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 9.7 (0.6%), 21.9 min (98.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (ddd, J = 7 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 0.5 Hz, 1 H, H-5'''), 3.31 - 3.22 (m, 2 H, H_2-1''), 3.13 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.70 - 1.57 (m, 2 H, H_2-2), 1.37 - 1.22 (m, 10 H, H_2-3-7), 0.86 (t, J = 6.5 Hz, 3 H, H_3-8).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.9 (CH_2-1), 39.1 (CH_3-N^+), 31.0 (CH_2-2), 28.39 (CH_2-3), 28.36 (CH_2-4), 26.0 (CH_2-5), 23.2 (CH_2-6), 21.9 (CH_2-7), 19.7 (CH_2-2''), 13.7 (CH_3-8).

ESI MS: *m/z* (%) = 663.6 (23%) $[2M + \text{oxalic acid} + H]^+$, 609.5 (8%) $[2M + HCl + H]^+$, 287.3 (100%) $[M + H]^+$.

N-Octyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Octyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (344)

N-Octyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (97.6 mg, $C_{20}H_{32}N_2O \cdot C_2H_2O_4$, 406.52 g/mol, 41%) was obtained as a pearlescent white powder from 141.1 mg 1-iodooctane (**201**, 240.13 g/mol, 100%, 587.6 µmol) and 100.0 mg *N*-methyl-5-methoxy-tryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr): $\tilde{\nu}$ = 3275, 3032, 2933, 2855, 2691, 1722, 1703, 1631, 1584, 1470, 1406, 1315, 1280, 1263, 1208, 1108, 1029, 838, 791, 720, 710, 638, 492 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (>400%), 275 (100%), 294 (83%), 306 (57%) sh.

HPLC: R_t (%total AUC_{260}) = 5.5 (oxalic acid), 21.5 min (99.1%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.82 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.19 (d, J = 2 Hz, 1 H, H-4'''), 7.08 (d, J = 2.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.5 Hz, 2.5 Hz, 1 H, H-6'''), 3.78 (s, 3 H, -OCH_3-5'''), 3.30 - 3.21 (m, 2 H, H_2-1''), 3.11 - 3.01 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.71 - 1.57 (m, 2 H, H_2-2), 1.34 - 1.22 (m, 10 H, H_2-3-7), 0.86 (t, J = 6.5 Hz, 3 H, H_3-8).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.9 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.0 (C_q-3'''), 100.1 (CH-4'''), 55.4 (CH_2-1''), 55.1 (OCH_3-5'''), 54.9 (CH_2-1), 31.1 (CH_2-2), 28.44 (CH_2-3), 28.38 (CH_2-4), 26.03 (CH_2-5), 23.2 (CH_2-6), 21.9 (CH_2-7), 19.8 (CH_2-2''), 13.4 (CH_3-8).

ESI MS: *m/z* (%) = 723.0 (23%) $[2M + \text{oxalic acid} + H]^+$, 429.3 (7%) $[M_{quat}]^+$, 317.2 (100%) $[M + H]^+$.

N-Dodecyl-*N*-methyltryptamine hydrogen oxalate

(Dodecyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (345)

N-Dodecyl-*N*-methyltryptamine hydrogen oxalate (62.5 mg, $C_{23}H_{38}N_2 \cdot C_2H_2O_4$, 423.60 g/mol, 30%) was obtained from 192.2 mg 1-bromododecane (249.23 g/mol, 771.1 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3392, 3251, 2920, 2853, 2681, 1720, 1702, 1636, 1459, 1421, 1341, 1281, 1188, 1104, 940, 754, 740, 721, 703, 499 cm^{-1}.

UV (methanol): λ (%max_A) = 221(>300%), 268 (87%) sh, 273 (95%), 280 (100%), 289 nm (87%).

HPLC: R_t (%total AUC_{260}) = 12.3 (oxalic acid), 25.1 min (99.5%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.51): δ = 10.97 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 1 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.01 (dd, J = J' = 7.5 Hz, 1 H, H-5'''), 3.32 - 3.22 (m, 2 H, H_2-1''), 3.13 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.70 - 1.56 (m, 2 H, H_2-2), 1.35 - 1.19 (m, **18H**, H_2-3-11), 0.86 (t, J = 6.5 Hz, 3 H, H_3-12).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.2 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.5 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.9 (CH_2-1), 39.2 (CH_3-N^+), 31.2 (CH_2-2), 28.9 (CH_2-3,4), 28.84 (CH_2-5), 28.75 (CH_2-6), 28.6 (CH_2-7), 28.5 (CH_2-8), 26.0 (CH_2-9), 23.3 (CH_2-10), 22.0 (CH_2-11), 19.7 (CH_2-2''), 13.8 (CH_3-12).

ESI MS: *m/z* (%) = 775.0 (44%) $[2M + oxalic\ acid + H]^+$, 721.2 (7%) $[2M + HCl + H]^+$, 343.3 (100%) $[M + H]^+$.

***N*-Dodecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate**
(Dodecyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (346)

N-Dodecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{24}H_{40}N_2O \cdot C_2H_2O_4$, 462.62 g/mol) was obtained from 192.2 mg 1-bromododecane (249.23 g/mol, 771.1 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3408, 3262, 3042, 2925, 2854, 2696, 1718, 1703, 1604, 1488, 1466, 1314, 1280, 1217, 1177, 1106, 1070, 1031, 925, 833, 800, 721, 499 cm^{-1}.

UV (methanol): λ (%max_A) = 224 (>300%), 275 (100%), 291 (77%) sh, 296 (77%), 308 nm (59%).

HPLC: R_t (%total AUC_{260}) = 5.8 (oxalic acid), 26.4 min (99.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.25 (d, J = 8.7 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.07 (d, J = 2 Hz, 1 H, H-2'''), 6.74 (dd, J = 8.8 Hz,

2.3 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.26 - 3.17 (m, 2 H, H_2-1''), 3.09 - 2.97 (m, 4 H, H_2-1,2''), 2.77 (s, 3 H, N^+-CH_3), 1.69 - 1.54 (m, 2 H, H_2-2), 1.30 - 1.21 (m, 18 H, H_2-3-11), 0.85 (t, J = 6.5 Hz, 3 H, H_3-12).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.8 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.7 (CH-2'''), 112.0 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 55.0 (CH_2-1), 39.3 (CH_3-N^+), 31.2 (CH_2-2), 28.9 (CH_2-3,4), 28.8 (CH_2-5), 28.7 (CH_2-6), 28.6 (CH_2-7), 28.5 (CH_2-8), 26.1 (CH_2-9), 23.5 (CH_2-10), 22.0 (CH_2-11), 19.7 (CH_2-2''), 13.8 (CH_3-12).

HPLC (gradient B): R_t (%total AUC_{260}) = 12.7 (oxalic acid), 24.9 min (99.7%).

ESI MS: *m/z* (%) = 835.8 (19%) $[2M + \text{oxalic acid} + H]^+$, 781 (3%) $[2M + HCl + H]^+$, 373.5 (100%) $[M + H]^+$.

N-Tetradecyl-*N*-methyltryptamine hydrogen oxalate (Tetradecyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (347)

N-Tetradecyl-*N*-methyltryptamine hydrogen oxalate ($C_{25}H_{42}N_2 \cdot C_2H_2O_4$, 460.33 g/mol) was obtained from 196.4 mg 1-iodotetradecane (**203**, 324.28 g/mol, 97%, 587.5 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3395, 3259, 2923, 2853, 2685, 1720, 1702, 1636, 1459, 1406, 1340, 1280, 1219, 1106, 753, 741, 721, 704, 499 cm^{-1}.

UV (methanol): λ (%max_A) = 221 (>400%), 268 (87%) sh, 273 (95%), 280 (100%), 289 nm (87%).

HPLC (gradient B): R_t (%total AUC_{260}) = 12.5 (oxalic acid), 14.8 (1.7%), 25.0 (1.0%), 25.9 min (97.0%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.59 (d, J = 8 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.24 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-6'''), 7.00 (ddd, J = 7.5 Hz, 7.5 Hz, 1 Hz, 1 H, H-5'''), 3.31 - 3.32 (m, 2 H, H_2-1''), 3.13 - 3.02 (m, 4 H, H_2-1,2''), 2.81 (s, 3 H, N^+-CH_3), 1.71 - 1.57 (m, 2 H, H_2-2), 1.35 - 1.22 (m, 22 H, H_2-3-13), 0.85 (t, J = 7 Hz, 3 H, H_3-14).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 136.2 (C_q-7b'''), 126.7 (C_q-3b'''), 123.1 (CH-2'''), 121.0 (CH-5'''), 118.3 (CH-6'''), 118.1 (CH-4'''), 111.4 (CH-7'''), 109.3 (C_q-3'''), 55.2 (CH_2-1''), 54.9 (CH_2-1), 39.2 (CH_3-N^+), 31.2 (CH_2-2), 28.94 (CH_2-3,4,5), 28.90 (CH_2-6), 28.8 (CH_2-7), 28.7 (CH_2-8), 28.6 (CH_2-9), 28.5 (CH_2-10), 26.0 (CH_2-11), 23.3 (CH_2-12), 22.0 (CH_2-13), 19.7 (CH_2-2''), 13.8 (CH_3-14).

ESI MS: *m/z* (%) = 831.9 (13%) $[2M + \text{oxalic acid} + H]^+$, 777.8 (5%) $[2M + HCl + H]^+$, 371.6 (100%) $[M + H]^+$.

N-Tetradecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Tetradecyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (348)

N-Tetradecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate ($C_{26}H_{44}N_2O \cdot C_2H_2O_4$, 490.68 g/mol) was obtained from 196.4 mg 1-iodotetradecane (**203**, 324.28 g/mol, 97%, 587.5 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3414, 3300, 3049, 2923, 2853, 1718, 1701, 1610, 1488, 1469, 1313, 1265, 1215, 1176, 1075, 1028, 926, 828, 803, 763, 697, 486 cm^{-1}.

UV (methanol): λ (%max_A) = 218 (>300%), 268 (91%) sh, 275 (100%), 296 (79%), 303 (69%) sh, 308 nm (62%).

HPLC: R_t (%total AUC_{260}) = 13.1 (oxalic acid), 26.0 min (99.7%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 2 Hz, 1 H, H-4'''), 7.07 (d, J = 2 Hz, 1 H, H-2'''), 6.73 (dd, J = 9 Hz, 2.5 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.25 - 3.15 (m, 2 H, H_2-1''), 3.08 - 2.96 (m, 4 H, H_2-1,2''), 2.76 (s, 3 H, N^+-CH_3), 1.71 - 1.55 (m, 2 H, H_2-2), 1.40 - 1.18 (m, 22 H, H_2-3-13), 0.85 (t, J = 7 Hz, 3 H, H_3-14).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.7 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 55.1 (CH_2-1), 39.4 (CH_3-N^+), 31.2 (CH_2-2), 28.94 (CH_2-3,4,5), 28.91 (CH_2-6), 28.84 (CH_2-7), 28.75 (CH_2-8), 28.6 (CH_2-9), 28.5 (CH_2-10), 26.1 (CH_2-11), 23.6 (CH_2-12), 22.0 (CH_2-13), 20.1 (CH_2-2''), 13.8 (CH_3-14).

ESI MS: *m/z* (%) = 891.9 (7%) $[2M + oxalic\ acid + H]^+$, 838.0 (5%) $[2M + HCl + H]^+$, 371.6 (100%) $[M + H]^+$.

N-Octadecyl-*N*-methyltryptamine hydrogen oxalate (Octadecyl-[2-(indol-3-yl)-ethyl]-methylamine hydrogen oxalate) (349)

N-Octadecyl-*N*-methyltryptamine hydrogen oxalate (97.3 mg, $C_{29}H_{50}N_2 \cdot C_2H_2O_4$, 516.76 g/mol, 32%) was obtained as an off-white fine powder from 223.5 mg 1-iodooctadecane (**204**, 380.39 g/mol, 100%, 587.6 µmol) and 85.3 mg *N*-methyltryptamine (**211**, 174.24 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3392, 3207, 2919, 2851, 2684, 1719, 1701, 1636, 1469, 1432, 1341, 1280, 1173, 1105, 942, 754, 720, 703, 492 cm^{-1}.

UV (methanol): λ (%max_A) = 219 (>500%), 268 (87%) sh, 273 (95%), 279 (100%), 283 (96%) sh, 289 nm (87%).

HPLC (gradient B): R_t (%total AUC_{260}) = 12.7 (oxalic acid), 26.1 (2.4%), 29.3 min (97.6%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.98 (s br, 1 H, H-1'''), 7.59 (d, J = 7.5 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.23 (d, J = 2 Hz, 1 H, H-2'''), 7.09 (dd, J = J' = 7.5 Hz, 1 H, H-6'''), 7.00 (dd, J = J' = 7 Hz, 1 H, H-5'''), 3.34 - 3.21 (m, 2 H, H_2-1''), 3.15 - 3.00 (m, 4 H, H_2-1,2''), 2.80 (s, 3 H, N^+-CH_3), 1.71 - 1.56 (m, 2 H, H_2-2), 1.43 - 1.13 (m, 30 H, H_2-3-17), 0.85 (t, J = 6.5 Hz, 3 H, H_3-18).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$ / DMSO-d_6): δ = 164.0 (C_q-oxalate), 136.1 (C_q-7b'''), 126.3 (C_q-3b'''), 122.6 (CH-2'''), 120.9 (CH-5'''), 118.2 (CH-6'''), 117.7 (CH-4'''), 111.2 (CH-7'''), 108.8 (C_q-3'''), 78.3 (t, $CDCl_3$), 55.3 (CH_2-1''), 55.1 (CH_2-1), 39.1 (CH_3-N^+), 31.1 (CH_2-2), 28.9 (CH_2-3,4,5,6,7,8,9), 28.84 (CH_2-10), 28.76 (CH_2-11), 28.7 (CH_2-12), 28.5 (CH_2-13), 28.4 (CH_2-14), 26.0 (CH_2-15), 23.2 (CH_2-16), 21.9 (CH_2-17), 19.8 (CH_2-2''), 13.6 (CH_3-18).

ESI MS: *m/z* (%) = 679.9 (46%) $[M_{quat}]^+$, 427.4 (100%) $[M + H]^+$.

N-Octadecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (Octadecyl-[2-(5-methoxyindol-3-yl)-ethyl]-methylamine hydrogen oxalate) (350)

N-Octadecyl-*N*-methyl-5-methoxytryptamine hydrogen oxalate (61.3 mg, $C_{30}H_{52}N_2O \cdot C_2H_2O_4$, 546.78 g/mol, 19%) was obtained as an off-white fine powder from 223.5 mg 1-iodooctadecane (**204**, 380.39 g/mol, 100%, 587.6 µmol) and 100.0 mg *N*-methyl-5-methoxytryptamine (**208**, 204.27 g/mol, 489.5 µmol) by general procedure E.

IR (KBr, opaque pellet): $\tilde{\nu}$ = 3413, 3261, 3048, 2920, 2852, 1718, 1604, 1488, 1469, 1315, 1216, 1177, 1104, 1071, 1030, 925, 835, 801, 764, 721, 497 cm^{-1}.

UV (methanol): λ (%max_A) = 220 (>300%), 267 (88%) sh, 274 (100%), 296 (78%), 308 nm (60%).

HPLC (gradient B): R_t (%total AUC_{260}) = 13.1 (oxalic acid), 29.2 min (99.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.25 (d, J = 8.5 Hz, 1 H, H-7'''), 7.18 (d, J = 1.5 Hz, 1 H, H-4'''), 7.07 (d, J = 1.5 Hz, 1 H, H-2'''), 6.74 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 3.77 (s, 3 H, -OCH_3-5'''), 3.28 - 3.18 (m, 2 H, H_2-1''), 3.10 - 2.98 (m, 4 H, H_2-1,2''), 2.78 (s, 3 H, N^+-CH_3), 1.70 - 1.55 (m, 2 H, H_2-2), 1.37 - 1.17 (m, 30 H, H_2-3-17), 0.85 (t, J = 6.5 Hz, 3 H, H_3-18).

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.6 (C_q-oxalate), 153.1 (C_q-5'''), 131.3 (C_q-7b'''), 127.0 (C_q-3b'''), 123.7 (CH-2'''), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.2 (C_q-3'''), 100.2 (CH-4'''), 55.4 (OCH_3-5'''), 55.3 (CH_2-1''), 55.0 (CH_2-1), 39.3 (CH_3-N^+), 31.2 (CH_2-2), 28.9 (CH_2-3,4,5,6,7,8,9,10), 28.8 (CH_2-11,12), 28.58 (CH_2-13), 28.5 (CH_2-14), 26.1 (CH_2-15), 23.5 (CH_2-16), 22.0 (CH_2-17), 20.0 (CH_2-2''), 13.8 (CH_3-18).

ESI MS: *m/z* (%) = 709.6 (10%) $[M_{quat}]^+$, 457.4 (100%) $[M + H]^+$, 1003.1 (19%) [2M + oxalic acid + H]$^+$.

_N,N_-diisopropyl-ethylamine hydrogen oxalate (351)

Prepared from diisopropyl-ethylamine as a reference compound ($C_8H_{19}N \cdot C_2H_2O_4$, 219.28 g/mol).

^{1}H NMR (300 MHz, MeOH-d_4): δ = 3.300 (qu, CD_3OD, reference), 3.72 (sept, J = 8 Hz, 2 H, 2 CH), 3.22 (q, J = 7.5 Hz, 2 H, CH_2), 1.36 (d, J = 6.5 Hz, 12 H, 4 CH_3), 1.36 (t, J = 7.5 Hz, 3 H, H_3-Et).

Indol-3-yl-glyoxylic acid chloride
(2-(Indol-3-yl)-2-oxoacetyl chloride) (352)

To a stirred solution of 50.0 g (117.15 g/mol, 426.8 mmol, 1 eq) indole in 500 ml diethyl ether was added 55 ml (126.94 g/mol, d 1.48, 81.4 g, 641 mmol, 1.5 eq) oxalyl chloride dropwise under cooling in an ice bath. The solution was allowed to warm to room temperature and stirring was continued for 1 h. The orange product was filtered off, and washed with cold diethyl ether, and dried under vacuum, yielding 83.1 g of indol-3-yl-glyoxylic acid chloride as a fine orange powder ($C_{10}H_6ClNO_2$, 207.61 g/mol, 400.2 mmol, 94%). This sensitive material was used immediately in the following reactions.

Indol-3-yl-glyoxylic acid propylamide
(2-(Indol-3-yl)-2-oxo-_N_-propylacetamide) (353)

A solution of 20 ml propylamine (59.11 g/mol, d 0.716, 14.32 g, 242.3 mmol, 2.5 eq) in 200 ml diethyl ether was added dropwise to a slurry of 20 g indol-3-yl-glyoxylic acid chloride (**352**) (207.61 g/mol, 96.33 mmol, 1.0 eq) in 500 ml diethyl ether under stirring. The mixture was stirred for another 1 h and filtered. The filter cake was washed with diethyl ether and dried under vacuum. After recrystallization from ethyl acetate 18.81 g indol-3-yl-glyoxylic acid propylamide ($C_{13}H_{14}N_2O_2$, 230.26 g/mol, 81.7 mmol, 85%) was obtained as a white powder.

Indol-3-yl-glyoxylic acid dipropylamide
(2-(Indol-3-yl)-2-oxo-_N,N_-dipropylacetamide) (354)

A solution of 36 ml propylamine (101.19 g/mol, d 0.738, 26.57 g, 262.6 mmol, 2.6 eq) in 200 ml diethyl ether was added dropwise to a slurry of 21.3 g indol-3-yl-glyoxylic acid chloride (**352**) (207.61 g/mol, 102.6 mmol, 1.0 eq) in 500 ml diethyl ether under stirring. The mixture was stirred for another 1 h and filtered. The filter cake was washed with diethyl ether and dried under vacuum. After recrystallization from small amounts of ethanol a combined yield of 16.62 g indol-3-yl-glyoxylic acid dipropylamide ($C_{16}H_{20}N_2O_2$, 272.34 g/mol, 61.02 mmol, 59%) was obtained as a white powder. Additional less pure compound could be isolated from the mother liquor.

_N_-Propyltryptamine

([2-(Indol-3-yl)-ethyl]-propylamine) (355)

17 g indol-3-yl-glyoxylic acid propylamide (**353**) (230.26 g/mol, 73.83 mmol) in 100 ml dried THF was added dropwise to a refluxing suspension of 11.21 g $LiAlH_4$ powder (37.96 g/mol, 295.3 mmol, 4 eq) in 150 ml dried THF. The mixture was refluxed for further 2 h and cooled to room temperature. The reaction was terminated by dropwise addition of saturated $MgSO_4$ solution and then H_2O. Diatomaceous earth was added to the mixture, the slurry filtered through a bed of diatomaceous earth, and the filter cake was washed with THF. The pooled solutions were evaporated on a rotary evaporator and the product was distilled under oil pump vacuum (156 °C), yielding 5.5 g *N*-propyltryptamine ($C_{13}H_{18}N_2$, 202.30 g/mol, 27.18 mmol, 37%) as a white crystalline mass.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.25): δ = 8.19 (s br, 1 H, H-1'''), 7.63 (d, J = 7.5 Hz, 1 H, H-4'''), 7.36 (d, J = 8 Hz, 1 H, H-7'''), 7.19 (dd, J = J' = 8 Hz, 1 H, H-6'''), 7.11 (dd, J = J' = 8 Hz, 1 H, H-5'''), 7.03 (d, J = 2 Hz, 1 H, H-2'''), 2.97 (s, 4 H, H_2-1'',2''), 2.60 (t, J = 7.5 Hz, 2 H, H_2-1), 1.59 - 1.38 (tq, 2 H, H_2-2), 0.88 (t, J = 7.5 Hz, 3 H, H_3-3).

***N,N*-Dipropyltryptamine**
([2-(Indol-3-yl)-ethyl]-dipropylamine) (356)

15 g Indol-3-yl-glyoxylic acid dipropylamide (**354**) (272.34 g/mol, 55.08 mmol) in 100 ml dried THF was added dropwise to a refluxing suspension of 8.36 g $LiAlH_4$ powder (37.96 g/mol, 220.2 mmol, 4 eq) in 150 ml dried THF. The mixture was refluxed for further 2 h and cooled to room temperature. The reaction was terminated by dropwise addition of saturated $MgSO_4$ solution and then H_2O. Diatomaceous earth was added to the mixture, the slurry filtered through a bed of diatomaceous earth, and the filter cake was washed THF. The pooled solutions were evaporated on a rotary evaporator and the product was distilled under oil pump vacuum (166 °C), yielding 10.53 g *N,N*-dipropyltryptamine ($C_{16}H_{24}N_2$, 244.38 g/mol, 43.09 mmol, 78%) as a white crystalline mass.

^{1}H NMR (200 MHz, $CDCl_3$, $\delta_{solvent}$ = 7.24): δ = 8.05 (s br, 1 H, H-1'''), 7.61 (d, J = 7.5 Hz, 1 H, H-4'''), 7.34 (d, J = 7.5 Hz, 1 H, H-7'''), 7.18 (dd, J = J' = 7 Hz, 1 H, H-6'''), 7.11 (dd, J = J' = 7 Hz, 1 H, H-5'''), 7.00 (d, J = 2 Hz, 1 H, H-2'''), 2.98 - 2.86 (m, 2 H, H_2-1''), 2.86 - 2.74 (m, 2 H, H_2-2''), 2.51 (t, J = 7.5 Hz, 4 H, 2 H_2-1), 1.53 (tq, J = 7.5 Hz, 4 H, 2 H_2-2), 0.91 (t, J = 7.5 Hz, 6 H, 2 H_3-3).

Synthesis of *N*-(4-bromobenzyl)-5-methoxytryptamine

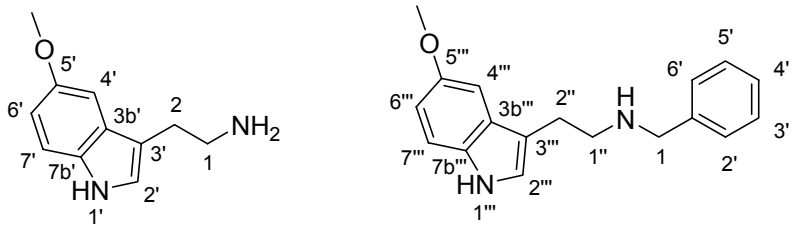


Figure 73: General numbering schemes for 5-methoxytryptamine derivatives.

5-Methoxytryptamine
(2-(5-methoxyindol-3-yl)-ethylamine) (357)

A mixture of 2 g 3-(2-iodoethyl)-5-methoxyindole (**176**, 301.12 g/mol, 6.64 mmol, 1 eq) and 4.28 ml 1-phenyl-ethylamine (4.02 g, d 0.94, 121.18 g/mol, 5eq) in 100 ml acetonitrile were kept at room temperature for 24 h. TLC analysis showed nearly complete consumption of the iodide. The solvent was removed on a rotary evaporator and excess 1-phenyl-ethylamine was removed in a Kugelrohr distillation apparatus under oil pump vacuum. The resulting brown oily residue was adsorbed onto 5 g silica with dichloromethane and purified by a silica column chromatography using ethyl acetate / methanol / triethylamine (97.5 + 5 + 2.5) as eluent and fractions of 15 ml were collected. The product could be separated from minor indolic impurities as shown by TLC analysis using the same solvent system and Ehrlich's reagent and UV_{254} absorption as indicators. The positive fractions were pooled, evaporated using a rotary evaporator, and the resulting brownish oil was further dried under oil pump vacuum for several hours. Yield: 1.38 g (292.37 g/mol, 4.72 mmol, 71%). This product was dissolved in ethanol and hydrogenated at 4 bar H_2 and room temperature for 20 h in a Parr hydrogenation apparatus with 0.25 g Pd/C (10%) as catalyst. The catalyst was filtered off and the solvent was evaporated on a rotary evaporator, yielding 5-methoxytryptamine ($C_{11}H_{14}N_2O \cdot C_2H_2O_4$, 190.25 g/mol).

5-Methoxytryptamine hydrogen oxalate
(2-(5-Methoxyindol-3-yl)-ethylamine hydrogen oxalate) (358)

IR (KBr): $\tilde{\nu}$ = 3432, 2937, 2634, 1720, 1700, 1641, 1573, 1532, 1487, 1456, 1439, 1313, 1287, 1271, 1219, 1179, 1112, 1056, 1029, 970, 924, 891, 839, 813, 802, 761, 734, 709, 457 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (421%), 274 (100%), 293 (82%) sh, 295 (80%) sh, 307 (50%) sh.

HPLC: R_t (%total AUC_{260}) = 6.5 (oxalic acid), 8.1 min (99.5%).

^1H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.75 (s br, 1 H, H-1'), 7.24 (d, J = 8.5 Hz, 1 H, H-7'), 7.15 (d, J = 1 Hz, 1 H, H-4'), 7.02 (d, J = 2 Hz, 1 H, H-2'), 6.73 (dd, J = 8.5 Hz, 1.5 Hz, 1 H, H-6'), 3.77 (s, 3 H, -OCH_3-5'), 3.04 - 2.94 (m, 2 H, H_2-1), 2.94 - 2.93 (m, 2 H, H_2-2).

ESI MS: *m/z* (%) = 381.1 (31%) $[2M + H]^+$, 191.0 (100%) $[M - H]^+$, 174.2 (22%) [vinylindole + $H]^+$.

N-(4-Bromobenzoyl)-5-methoxytryptamine (4-Bromo-*N*-[2-(5-methoxyindol-3-yl)-ethyl]-benzamide) (359)

415 mg 4-bromobenzoylchloride (219.47 g/mol, 1.891 mmol,1.2 eq) 5 ml dry THF was added dropwise to a stirred mixture of 300 mg 5-methoxytryptamine (**358**, 190.25 g/mol, 1.577 mmol, 1 eq) and 383 mg triethylamine (101.19 g/mol, 3.785 mmol, 2.4 eq) in 15 ml dry THF at room temperature. The mixture was kept at room temperature overnight, the precipitate filtered off, and the solvent removed on a rotary evaporator. The oily residue was dissolved in 50 ml $CHCl_3$, successively washed with diluted HCl solution, Na_2CO_3 solution, and H_2O until neutral, dried over $MgSO_4$, and evaporated. The resulting white solid was recrystallized from diethyl ether, yielding *N*-(4-bromobenzoyl)-5-methoxytryptamine ($C_{18}H_{17}BrN_2O_2 \cdot C_2H_2O_4$, 373.24 g/mol).

IR (KBr): $\tilde{\nu}$ = 3414, 2949, 2795, 1721, 1703, 1642, 1584, 1488, 1457, 1441, 1407, 1299, 1281, 1216, 1174, 1107, 1076, 1014, 925, 800, 721, 501 cm^{-1}.

ESI MS: *m/z* (%) = 770.8 (29%) $[2[^{80}Br]M + Na]^+$, 768.8 (71%) $[[^{79}Br]M + [^{81}Br]M + Na]^+$, 766.8 (43%) $[2[^{79}Br]M + Na]^+$, 690.9%) $[[^{80}]M - Br + Na]^+$, 689 (98%) $[[^{79}Br]M - Br + Na]^+$, 611.0 (90%) $[2M - 2Br + Na]^+$, 339.2 (84%).

N-(4-Bromobenzyl)-5-methoxytryptamine ((4-Bromobenzyl)-[2-(5-methoxyindol-3-yl)-ethyl]-amine) (19)

220 mg $LiAlH_4$ (37.95 g/mol, 5.80 mmol, 5.80 eq) was added to 15 ml of dry diethyl ether with stirring and with cooling in an ice bath under a N_2 atmosphere. 0.23 g $AlCl_3$ (133.34 g/mol, 1.72 mmol, 1.72 eq) was added carefully for *in situ* generation of AlH_3. The milky suspension was stirred for 30 min at room temperature and a solution of 370 mg *N*-(4-bromobenzoyl)-5-methoxytryptamine (**359**, 373.24 g/mol, 1.00 mmol, 1 eq) in 10 ml of dry diethyl ether was added dropwise and the mixture was stirred for 5 h at room temperature. The reaction was terminated by the careful addition of water and NaOH solution in an ice bath with stirring. The mixture was mixed with diatomaceous earth and filtered through a layer of diatomaceous

earth. The filter cake was washed with diethyl ether and the combined filtrates washed with H_2O and dried over $MgSO_4$. The product was dissolved in THF and treated with an excess of oxalic acid in THF and kept in the ice bath for several hours. The precipitate was filtered off, washed with cold THF, and was recrystallized from THF. The product was dried under oil pump vacuum at 60 °C overnight, yielding *N*-(4-bromobenzyl)-5-methoxytryptamine hydrogen oxalate ($C_{18}H_{19}BrN_2O \cdot C_2H_2O_4$, 449.30 g/mol) as a fine white powder.

IR (KBr): $\tilde{\nu}$ = 3420, 2935, 2831, 1718, 1700, 1635, 1487, 1456, 1406, 1280, 1215, 1174, 1100, 1075, 1013, 798, 720, 500 cm^{-1}.

UV (H_2O): λ (%max_A) = 220 (575%), 273 (100%), 293 (80%), 305 (58%) sh.

HPLC: R_t (%total AUC_{260}) = 5.7 (oxalic acid), 14.2 (1.8%), 15.6 (4.4%), 18.0 min (93.8%).

^{1}H NMR (300 MHz, DMSO-d_6, $\delta_{solvent}$ = 2.50): δ = 10.80 (s br, 1 H, H-1'''), 7.64 (d, J = 8 Hz, 2 H, H-3',5'), 7.47 (d, J = 8 Hz, 2 H, H-2',6'), 7.25 (d, J = 9 Hz, 1 H, H-7'''), 7.16 (d, J = 2 Hz, 1 H, H-4'''), 7.00 (d, J = 2 Hz, 1 H, H-2'''), 6.73 (dd, J = 9 Hz, 2 Hz, 1 H, H-6'''), 4.18 (s, 2 H, H_2-1), 3.76 (s, 3 H, -OCH_3-5'''), 3.20 - 3.08 (m, 2 H, H_2-1''), 3.08 - 2.97 (m, 2 H, H_2-2'').

^{13}C NMR (50.3 MHz, APT, DMSO-d_6): δ = 164.7 (C_q-oxalate), 153.1 (C_q-5'''), 132.0 (CH-3',5'), 131.8 (C_q-1'), 131.43 (CH-2',6'), 131.35 (C_q-7b'''), 127.0 (C_q-3b'''), 123.8 (CH-2'''), 122.1 (C_q-4'), 112.1 (CH-7'''), 111.2 (CH-6'''), 109.1 (C_q-3'''), 100.0 (CH-4'''), 55.4 (OCH_3-5'''), 49.1 (CH_2-1), 46.8 (CH_2-1''), 21.7 (CH_2-2'').

ESI MS (sample A): *m/z* (%) = 359.1 (100%) [[^{79}Br]M + H]$^+$, 361.1 (96%) [[^{81}Br]M + H]$^+$, 281.2 (29%) [M - Br + 2H]$^+$, 174.2 (25%) [M - CH_3-NH-CH_2-C_6H_4Br + H]$^+$, 718.7 (6%) [[^{79}Br]M + [^{81}Br]M + H]$^+$, 716.8 (3%) [2[^{79}Br]M + H]$^+$, 720.7 (2%) [2[^{80}Br]M + H]$^+$.

ESI MS (sample B): *m/z* (%) = 359.0 (100%) [[^{79}Br]M + H]$^+$, 361.0 (93%) [[^{81}Br]M + H]$^+$, 808.6 (51%) [[^{79}Br]M + [^{81}Br]M + oxalic acid + H]$^+$, 806.7 (22.5%) [2[^{79}Br]M + oxalic acid + H]$^+$, 810.6 (50%) [2[^{80}Br]M + oxalic acid + H]$^+$, 718.6 (38%) [[^{79}Br]M + [^{81}Br]M + H]$^+$, 716.5 (21%) [2[^{79}Br]M + H]$^+$, 720.6 (20%) [2[^{80}Br]M + H]$^+$, 174.2 (13%) [vinylindole + H]$^+$, 281.1 (14%) [M - Br + 2H]$^+$.

Appendix

Aeruginascin spectra

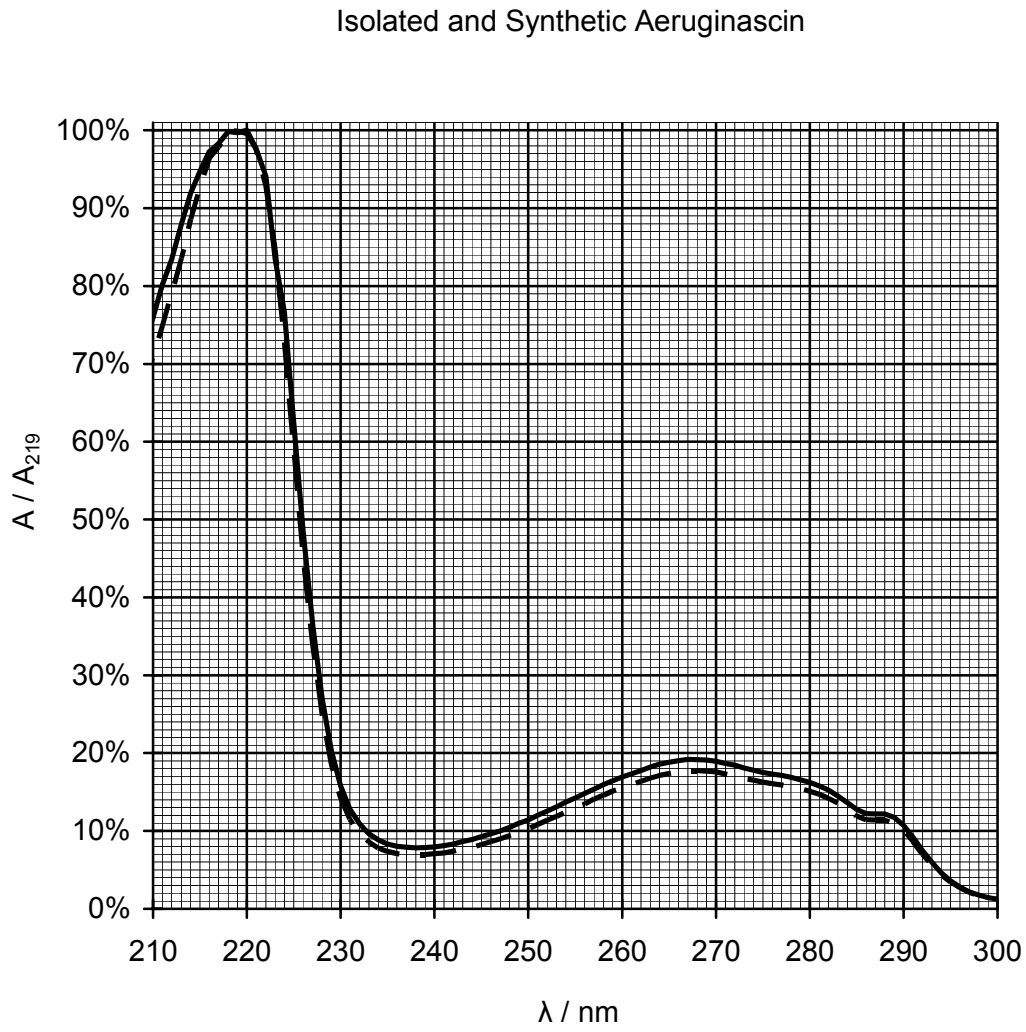


Figure 74: UV spectra of isolated and synthetic aeruginascin.

UV spectra of isolated (continuous line) and synthetic (dashed line) aeruginascin (**4**). The absorption has been normalized to A_{219}.

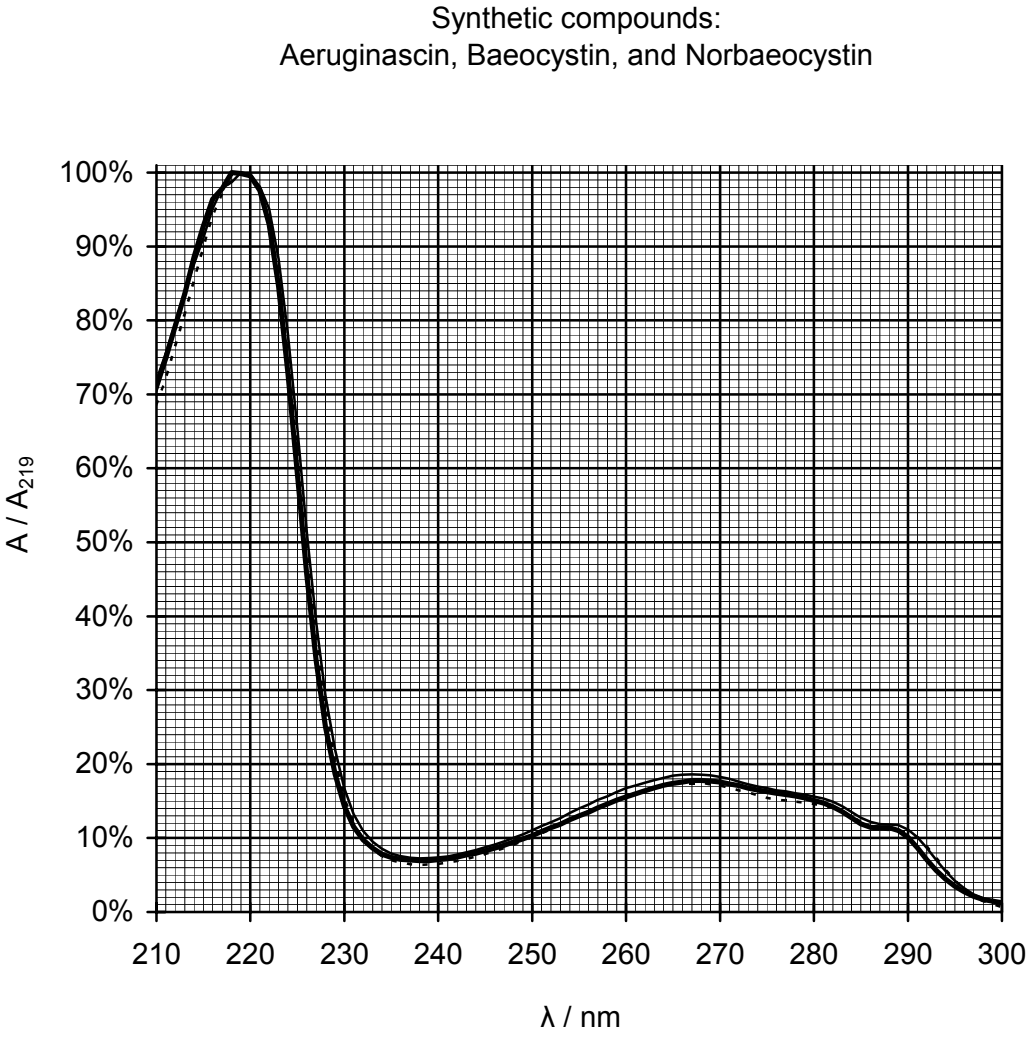


Figure 75: UV spectra of synthetic aeruginascin, baeocystin, and norbaeocystin.

UV spectra of synthetic aeruginascin (**4**) (bold line), baeocystin (**2**) (fine continuous line), and norbaeocystin (**1**) (dashed line). The absorption has been normalized to A_{219}.

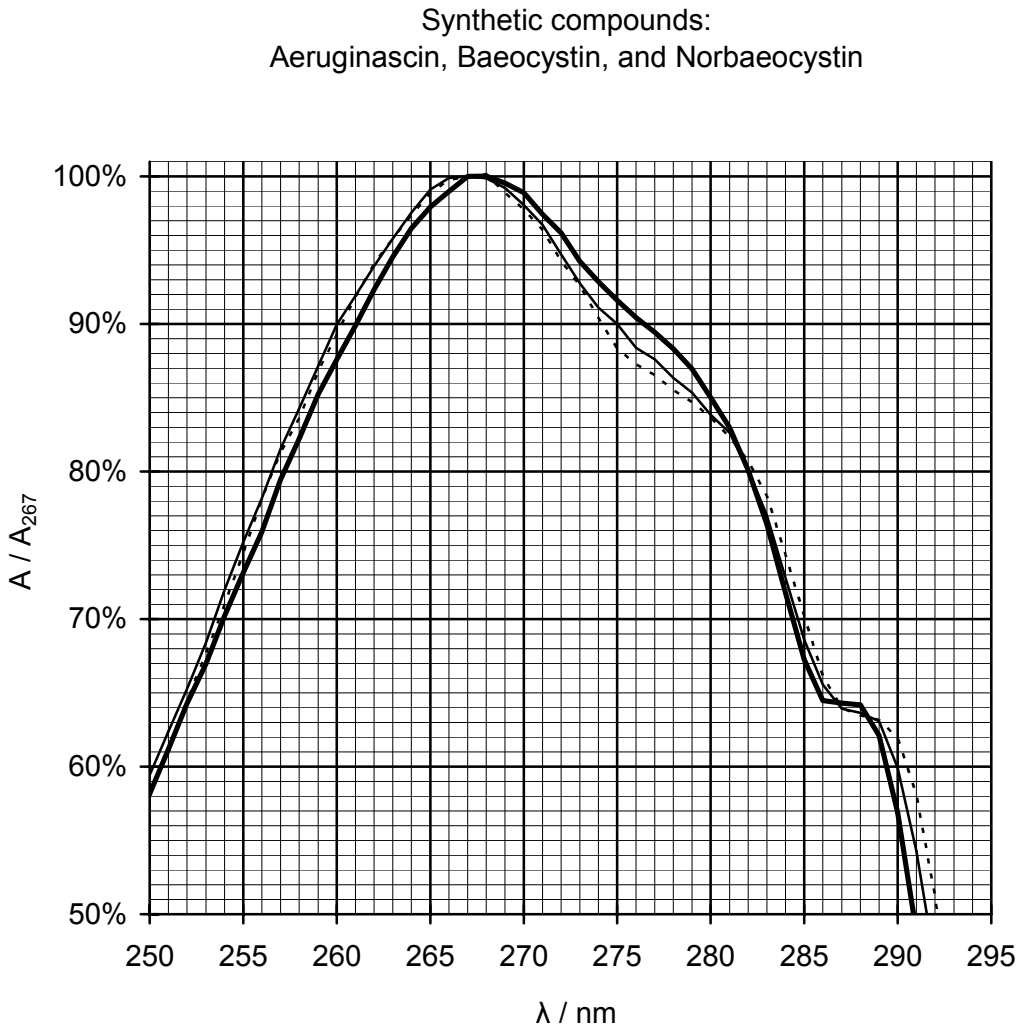


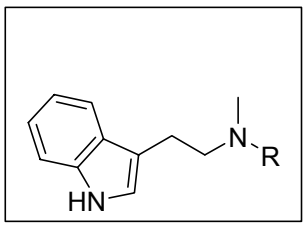
Figure 76: Enlarged UV spectra of the synthetic *Psilocybe* alkaloids.

Enlarged UV spectra of synthetic aeruginascin (**4**) (bold line), baeocystin (**2**) (fine continuous line), and norbaeocystin (**1**) (dashed line). The absorption has been normalized to A_{267}.

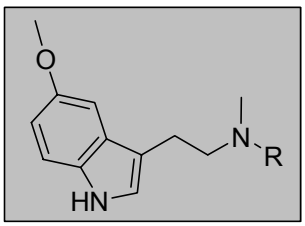
Tested compounds (Table 6)

Table 6: Compounds subjected to the pharmacological assays.

The compounds are grouped by classes of the amino substituent. The substituent, the compound number, and the internal identification code are listed. The order of the compounds is maintained in the following tables with the pharmacological data. Compounds may appear in several different contexts. White columns: 5-unsubstituted tryptamines; gray underlined columns: 5-methoxy substituted tryptamines. ID: internal identification code.



5-unsubstituted tryptamines
(white fields)



5-MeO-tryptamines
(gray fields)

5-Unsubstituted Tryptamines Compound	Number	ID	5-MeO-Tryptamines Compound	Number	ID
Agonist Standards			**Agonist Standards**		
-	**11**	*(R)*-Br-DFLY	-	**11**	(R)-Br-DFLY
-	**46**	2CB-FLEA	-	**46**	2CB-FLEA
-	**47**	2CB-GNAT	-	**47**	2CB-GNAT
5-HT	**6**	5-HT	5-HT	**6**	5-HT
(4-Br-Bn)-5-MeO-T	**19**	33	(4-Br-Bn)-5-MeO-T	**19**	33
Antagonist Standards			**Antagonist Standards**		
Ketanserin	**48**	Ket	Ketanserin	**48**	Ket
AC-90179	**50**	AC-90179	AC-90179	**50**	AC-90179
MDL 100,907	**49**	MDL	MDL 100,907	**49**	MDL
Simple Tryptamines			**Simple Tryptamines**		
Tryptamine	**5**	Tr	5-MeO-Tryptamine	**358**	5-MeO-T
NMT	**212**	NMT	5-MeO-NMT	**208**	5-MeO-NMT
DMT	**45**	DMT	5-MeO-DMT	**15**	5-MeO-DMT
			6-MeO-2-Me-THBC	**226**	NT
			Ethylene-bis(5-MeO-NMT)	**303**	NAZ
Benzyl			**Benzyl**		
Benzyl	**210**	MBT	Benzyl	**207**	5-MeO-MBT
4-Br-benzyl	**221**	Q	4-Br-benzyl	**222**	NQ
			nor-4-Br-benzyl	**19**	33
2-Substituted Phenethyl			**2-Substituted Phenethyl**		
2-H	**233**	AW	2-H	**234**	NAW
2-Me	**235**	AP	2-Me	**236**	NAQ
2-F	**255**	AU	2-F	**256**	NAU
2-Cl	**259**	AH	2-Cl	**260**	NAH
2,5-Me	**196**	AO	2,5-Me	**272**	NAP
2-MeO	**245**	AM	2-MeO	**246**	NAM
2,5-MeO	**275**	AL	2,5-MeO	**276**	NAL
2,6-Cl	**279**	BK	2,6-Cl	**-**	-
3-Substituted Phenethyl			**3-Substituted Phenethyl**		
3-H	**233**	AW	3-H	**234**	NAW
3-Me	**237**	AQ	3-Me	**238**	NAO
3-AcO	**243**	BQ	3-AcO	**-**	-
3-MeO	**247**	AN	3-MeO	**-**	-
3-Cl	**261**	AE	3-Cl	**262**	NAE
3-Br	**267**	AG	3-Br	**268**	NAG
2,5-Me	**196**	AO	2,5-Me	**272**	NAP
3,5-Me	**273**	BP	3,5-Me	**274**	NBP
2,5-MeO	**275**	AL	2,5-MeO	**276**	NAL
3,4-MeO	**277**	E	3,4-MeO	**278**	NE
3,4-Cl	**281**	AF	3,4-Cl	**282**	NAF
4-Substituted Phenethyl			**4-Substituted Phenethyl**		
4-H	**233**	AW	4-H	**234**	NAW
4-Me	**239**	AR	4-Me	**240**	NAR
4-MeO	**249**	V	4-MeO	**250**	NV
4-F	**257**	AI	4-F	**258**	NAI
4-Cl	**263**	AS	4-Cl	**264**	-
4-Br	**269**	Z	4-Br	**270**	NZ
4-NO_2	**253**	H	4-NO_2	**254**	NH

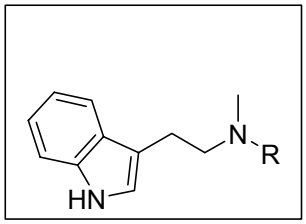
4-Ph	**241**	AX	4-Ph	**242**	NAX
3,4-MeO	**277**	E	3,4-MeO	**278**	NE
3,4-Cl	**281**	AF	3,4-Cl	**282**	NAF
Me-Substituted Phenethyl			**Me-Substituted Phenethyl**		
H	**233**	AW	H	**234**	NAW
2-Me	**235**	AP	2-Me	**236**	NAQ
3-Me	**237**	AQ	3-Me	**238**	NAO
4-Me	**239**	AR	4-Me	**240**	NAR
2,5-Me	**196**	AO	2,5-Me	**272**	NAP
3,5-Me	**273**	BP	3,5-Me	**274**	NBP
MeO-Substituted Phenethyl			**MeO-Substituted Phenethyl**		
H	**233**	AW	H	**234**	NAW
2-MeO	**245**	AM	2-MeO	**246**	NAM
3-MeO	**247**	AN	3-MeO	**-**	-
4-MeO	**249**	V	4-MeO	**250**	NV
2,5-MeO	**275**	AL	2,5-MeO	**276**	NAL
3,4-MeO	**277**	E	3,4-MeO	**278**	NE
F-Substituted Phenethyl			**F-Substituted Phenethyl**		
H	**233**	AW	H	**234**	NAW
2-F	**255**	AU	2-F	**256**	NAU
4-F	**257**	AI	4-F	**258**	NAI
Cl-Substituted Phenethyl			**Cl-Substituted Phenethyl**		
H	**233**	AW	H	**234**	NAW
2-Cl	**259**	AH	2-Cl	**260**	NAH
3-Cl	**261**	AE	3-Cl	**262**	NAE
4-Cl	**263**	AS	4-Cl	**264**	-
3,4-Cl	**281**	AF	3,4-Cl	**282**	NAF
2,6-Cl	**279**	BK	2,6-Cl	**-**	-
Br-Substituted Phenethyl			**Br-Substituted Phenethyl**		
H	**233**	AW	H	**234**	NAW
3-Br	**267**	AG	3-Br	**268**	NAG
4-Br	**269**	Z	4-Br	**270**	NZ
C_2-Spaced Aromatics			**C_2-Spaced Aromatics**		
-CH_2-CH_2-Ph	**233**	AW	-CH_2-CH_2-Ph	**234**	NAW
-CH_2-CH_2-(3-indolyl)	**283**	A	-CH_2-CH_2-(3-indolyl)	**284**	NA, B
-CH_2-CH_2-(5-MeO-3-indolyl)	**284**	NA, B	-CH_2-CH_2-(5-MeO-3-indolyl)	**286**	NB
-CH_2-CH_2-(1-naphthyl)	**287**	D	-CH_2-CH_2-(1-naphthyl)	**288**	ND
-CH_2-CH_2-(2-naphthyl)	**289**	C	-CH_2-CH_2-(2-naphthyl)	**290**	NC
Phenyl-alkyl			**Phenyl-alkyl**		
-CH_2-Ph	**210**	MBT	-CH_2-Ph	**207**	-CH_2-Ph
-CH_2-CH_2-Ph	**233**	AW	-CH_2-CH_2-Ph	**234**	NAW
-CH_2-CH_2-CH_2-Ph	**315**	BI	-CH_2-CH_2-CH_2-Ph	**316**	NBI
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**321**	AK	-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**322**	NAJ
-CH_2-CH_2-CH_2-CH_2-Ph	**335**	BJ	-CH_2-CH_2-CH_2-CH_2-Ph	**336**	NBJ
-CH_2-CH_2-CH_2-S-Ph	**325**	AY	-CH_2-CH_2-CH_2-S-Ph	**326**	NAY
Straight Chain Alkyl			**Straight Chain Alkyl**		
H	**212**	NMT	H	**208**	5-MeO-NMT
n-C1	**45**	DMT	n-C1	**45**	5-MeO-DMT
n-C4	**331**	F	n-C4	**332**	NF
n-C5	**337**	I	n-C5	**338**	NI
n-C6	**339**	J	n-C6	**-**	-
n-C7	**341**	W, NW	n-C7	**-**	-
n-C8	**343**	K	n-C8	**344**	NK

n-C12	**345**	G	n-C12	**346**	NG
n-C14	**347**	BG	n-C14	**348**	NBG
n-C18	**349**	L	n-C18	**350**	NL
C^2-Branched Alkyl			**C^2-Branched Alkyl**		
-CH_2-cPr	**213**	BH	-CH_2-cPr	**-**	-
-CH_2-cPent	**215**	BC	-CH_2-cPent	**216**	NBC
-CH_2-cHex	**217**	BD	-CH_2-cHex	**218**	NBD
-CH_2-(2-Pr)	**309**	BF	-CH_2-(2-Pr)	**310**	NBF
-CH_2-(3-Pent)	**333**	AC	-CH_2-(3-Pent)	**334**	NAC
C_3-Chain			**C_3-Chain**		
-CH_2-CH=CH_2	**305**	R	-CH_2-CH=CH_2	**306**	NR
-CH_2-CH≡CH	**307**	S	-CH_2-CH≡CH	**308**	NS
-CH_2-cPr	**213**	BH	-CH_2-cPr	**-**	-
C_3-Spaced Ring			**C_3-Spaced Ring**		
-CH_2-CH_2-CH_2-cHex	**313**	BE	-CH_2-CH_2-CH_2-cHex	**314**	NBE
-CH_2-CH_2-CH_2-Ph	**315**	BI	-CH_2-CH_2-CH_2-Ph	**316**	NBI
-CH_2-CH=CH-Ph	**317**	X	-CH_2-CH=CH-Ph	**318**	-
Carbonyls			**Carbonyls**		
-CH_2-COOMe	**227**	AD	-CH_2-COOMe	**228**	NAD
-CH_2-COOtBu	**229**	O	-CH_2-COOtBu	**230**	NO
-CH_2-$CONH_2$	**231**	N	-CH_2-$CONH_2$	**232**	NN
-CH_2-CH_2-CN	**293**	Y	-CH_2-CH_2-CN	**294**	NY
-CH_2-CH_2-$CONEt_2$	**-**	-	-CH_2-CH_2-$CONEt_2$	**302**	NAK
-CH_2-CH_2-OAc	**295**	BL	-CH_2-CH_2-OAc	**-**	-

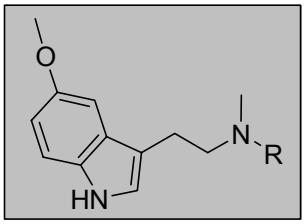
Receptor binding data (Table 7)

Table 7: Receptor binding data.

Binding data at the human 5-HT_{1A}, the rat 5-HT_{2A}, and the rat 5-HT_{2B} receptors. Each experiment was performed in duplicate and has been repeated independently at least three times. Compounds are arranged by classes and may appear in several different contexts. White rows: 5-unsubstituted tryptamines; gray underlined rows: 5-methoxy substituted tryptamines.



5-unsubstituted tryptamines
(white fields)



5-MeO-tryptamines
(gray fields)

5-Unsubstituted Tryptamines		5-HT$_{1A}$			5-HT$_{2A}$			5-HT$_{2C}$		
Compound		K_i	(n,	SEM)	K_i	(n,	SEM)	K_i	(n,	SEM)
Agonist Standards										
-	**11**				0.4 nM	(n = 2,	±0.00 nM)			
-	**46**	601 nM	(n = 3,	±81 nM)	13 nM	(n = 7,	±1.5 nM)	2.2 nM	(n = 3,	±0.14 nM)
-	**47**	132 nM	(n = 3,	±13 nM)	7.3 nM	(n = 5,	±1.2 nM)	2.7 nM	(n = 4,	±0.15 nM)
5-HT	**6**	0.9 nM	(n = 3,	±0.11 nM)	137 nM	(n = 3,	±18 nM)	15 nM	(n = 3,	±2.0 nM)
(4-Br-Bn)-5-MeO-T	**19**	21 nM	(n = 3,	±1.2 nM)	534 nM	(n = 4,	±45 nM)	394 nM	(n = 3,	±19 nM)
Antagonist Standards										
Ketanserin	**48**				1.0 nM	(n = 5,	±0.13 nM)			
AC-90179	**50**				8.4 nM	(n = 1)				
MDL 100,907	**49**									
Simple Tryptamines										
Tryptamine	**5**	48 nM	(n = 3,	±5.2 nM)	1,374 nM	(n = 4,	±154 nM)	60 nM	(n = 3,	±2.6 nM)
NMT	**212**	33 nM	(n = 4,	±4.3 nM)	1,890 nM	(n = 4,	±306 nM)	154 nM	(n = 4,	±12 nM)
DMT	**45**	38 nM	(n = 4,	±6.1 nM)	1,093 nM	(n = 6,	±90 nM)	211 nM	(n = 7,	±30 nM)
Benzyl										
Benzyl	**210**	1,763 nM	(n = 3,	±312 nM)	697 nM	(n = 3,	±86 nM)	469 nM	(n = 3,	±72 nM)
4-Br-benzyl	**221**	144 nM	(n = 3,	±23 nM)	904 nM	(n = 3,	±75 nM)	1,222 nM	(n = 3,	±136 nM)
2-Substituted Phenethyl										
2-H	**233**	40 nM	(n = 4,	±5.9 nM)	73 nM	(n = 5,	±11 nM)	64 nM	(n = 4,	±8.2 nM)
2-Me	**235**	30 nM	(n = 4,	±5.1 nM)	22 nM	(n = 3,	±2.3 nM)	16 nM	(n = 3,	±2.4 nM)
2-F	**255**	42 nM	(n = 4,	±2.9 nM)	18 nM	(n = 6,	±2.9 nM)	17 nM	(n = 4,	±3.2 nM)
2-Cl	**259**	24 nM	(n = 3,	±4.0 nM)	6.1 nM	(n = 3,	±0.96 nM)	4.5 nM	(n = 3,	±0.21 nM)
2,5-Me	**196**	13 nM	(n = 3,	±0.32 nM)	18 nM	(n = 6,	±3.1 nM)	7.7 nM	(n = 3,	±0.33 nM)
2-MeO	**245**	18 nM	(n = 4,	±2.5 nM)	13 nM	(n = 3,	±0.88 nM)	7.4 nM	(n = 3,	±0.68 nM)
2,5-MeO	**275**	9.8 nM	(n = 6,	±1.7 nM)	13 nM	(n = 3,	±1.3 nM)	5.2 nM	(n = 4,	±0.85 nM)
2,6-Cl	**279**	66 nM	(n = 6,	±9.6 nM)	68 nM	(n = 4,	±11 nM)	11 nM	(n = 6,	±2.0 nM)
3-Substituted Phenethyl										
3-H	**233**	40 nM	(n = 4,	±5.9 nM)	73 nM	(n = 5,	±11 nM)	64 nM	(n = 4,	±8.2 nM)
3-Me	**237**	24 nM	(n = 3,	±1.7 nM)	12 nM	(n = 4,	±2.0 nM)	13 nM	(n = 3,	±2.2 nM)
3-AcO	**243**	16 nM	(n = 4,	±1.2 nM)	69 nM	(n = 3,	±4.9 nM)	25 nM	(n = 4,	±2.9 nM)
3-MeO	**247**	12 nM	(n = 3,	±1.2 nM)	32 nM	(n = 4,	±5.6 nM)	11 nM	(n = 4,	±0.61 nM)
3-Cl	**261**	17 nM	(n = 4,	±3.0 nM)	19 nM	(n = 3,	±2.2 nM)	13 nM	(n = 3,	±1.3 nM)
3-Br	**267**	11 nM	(n = 3,	±3.0 nM)	16 nM	(n = 4,	±2.0 nM)	4.7 nM	(n = 3,	±0.51 nM)
2,5-Me	**196**	13 nM	(n = 3,	±0.32 nM)	18 nM	(n = 6,	±3.1 nM)	7.7 nM	(n = 3,	±0.33 nM)
3,5-Me	**273**	27 nM	(n = 5,	±4.4 nM)	8.4 nM	(n = 3,	±0.75 nM)	2.5 nM	(n = 3,	±0.18 nM)
2,5-MeO	**275**	9.8 nM	(n = 6,	±1.7 nM)	13 nM	(n = 3,	±1.3 nM)	5.2 nM	(n = 4,	±0.85 nM)
3,4-MeO	**277**	73 nM	(n = 3,	±7.8 nM)	18 nM	(n = 4,	±2.0 nM)	8.7 nM	(n = 5,	±1.5 nM)
3,4-Cl	**281**	13 nM	(n = 3,	±2.1 nM)	29 nM	(n = 4,	±4.7 nM)	15 nM	(n = 3,	±1.8 nM)
4-Substituted Phenethyl										
4-H	**233**	40 nM	(n = 4,	±5.9 nM)	73 nM	(n = 5,	±11 nM)	64 nM	(n = 4,	±8.2 nM)
4-Me	**239**	42 nM	(n = 4,	±5.9 nM)	22 nM	(n = 5,	±3.4 nM)	53 nM	(n = 3,	±5.9 nM)
4-MeO	**249**	86 nM	(n = 3,	±4.3 nM)	90 nM	(n = 3,	±11 nM)	45 nM	(n = 3,	±4.1 nM)
4-F	**257**	57 nM	(n = 4,	±8.0 nM)	40 nM	(n = 5,	±6.5 nM)	60 nM	(n = 3,	±3.6 nM)
4-Cl	**263**	29 nM	(n = 4,	±4.6 nM)	44 nM	(n = 3,	±6.8 nM)	19 nM	(n = 3,	±3.0 nM)
4-Br	**269**	24 nM	(n = 3,	±3.3 nM)	34 nM	(n = 3,	±5.8 nM)	76 nM	(n = 4,	±11 nM)
4-NO_2	**253**	37 nM	(n = 4,	±6.2 nM)	444 nM	(n = 3,	±34 nM)	283 nM	(n = 3,	±35 nM)

4-Ph	**241**	89 nM (n = 3, ±12 nM)	107 nM (n = 3, ±12 nM)	19 nM (n = 3, ±3.0 nM)
3,4-MeO	**277**	73 nM (n = 3, ±7.8 nM)	18 nM (n = 4, ±2.0 nM)	8.7 nM (n = 5, ±1.5 nM)
3,4-Cl	**281**	13 nM (n = 3, ±2.1 nM)	29 nM (n = 4, ±4.7 nM)	15 nM (n = 3, ±1.8 nM)
Me-Substituted Phenethyl				
H	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
2-Me	**235**	30 nM (n = 4, ±5.1 nM)	22 nM (n = 3, ±2.3 nM)	16 nM (n = 3, ±2.4 nM)
3-Me	**237**	24 nM (n = 3, ±1.7 nM)	12 nM (n = 4, ±2.0 nM)	13 nM (n = 3, ±2.2 nM)
4-Me	**239**	42 nM (n = 4, ±5.9 nM)	22 nM (n = 5, ±3.4 nM)	53 nM (n = 3, ±5.9 nM)
2,5-Me	**196**	13 nM (n = 3, ±0.32 nM)	18 nM (n = 6, ±3.1 nM)	7.7 nM (n = 3, ±0.33 nM)
3,5-Me	**273**	27 nM (n = 5, ±4.4 nM)	8.4 nM (n = 3, ±0.75 nM)	2.5 nM (n = 3, ±0.18 nM)
MeO-Substituted Phenethyl				
H	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
2-MeO	**245**	18 nM (n = 4, ±2.5 nM)	13 nM (n = 3, ±0.88 nM)	7.4 nM (n = 3, ±0.68 nM)
3-MeO	**247**	12 nM (n = 3, ±1.2 nM)	32 nM (n = 4, ±5.6 nM)	11 nM (n = 4, ±0.61 nM)
4-MeO	**249**	86 nM (n = 3, ±4.3 nM)	90 nM (n = 3, ±11 nM)	45 nM (n = 3, ±4.1 nM)
2,5-MeO	**275**	9.8 nM (n = 6, ±1.7 nM)	13 nM (n = 3, ±1.3 nM)	5.2 nM (n = 4, ±0.85 nM)
3,4-MeO	**277**	73 nM (n = 3, ±7.8 nM)	18 nM (n = 4, ±2.0 nM)	8.7 nM (n = 5, ±1.5 nM)
F-Substituted Phenethyl				
H	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
2-F	**255**	42 nM (n = 4, ±2.9 nM)	18 nM (n = 6, ±2.9 nM)	17 nM (n = 4, ±3.2 nM)
4-F	**257**	57 nM (n = 4, ±8.0 nM)	40 nM (n = 5, ±6.5 nM)	60 nM (n = 3, ±3.6 nM)
Cl-Substituted Phenethyl				
H	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
2-Cl	**259**	24 nM (n = 3, ±4.0 nM)	6.1 nM (n = 3, ±0.96 nM)	4.5 nM (n = 3, ±0.21 nM)
3-Cl	**261**	17 nM (n = 4, ±3.0 nM)	19 nM (n = 3, ±2.2 nM)	13 nM (n = 3, ±1.3 nM)
4-Cl	**263**	29 nM (n = 4, ±4.6 nM)	44 nM (n = 3, ±6.8 nM)	19 nM (n = 3, ±3.0 nM)
3,4-Cl	**281**	13 nM (n = 3, ±2.1 nM)	29 nM (n = 4, ±4.7 nM)	15 nM (n = 3, ±1.8 nM)
2,6-Cl	**279**	66 nM (n = 6, ±9.6 nM)	68 nM (n = 4, ±11 nM)	11 nM (n = 6, ±2.0 nM)
Br-Substituted Phenethyl				
H	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
3-Br	**267**	11 nM (n = 3, ±3.0 nM)	16 nM (n = 4, ±2.0 nM)	4.7 nM (n = 3, ±0.51 nM)
4-Br	**269**	24 nM (n = 3, ±3.3 nM)	34 nM (n = 3, ±5.8 nM)	76 nM (n = 4, ±11 nM)
C_2-Spaced Aromatics				
-CH_2-CH_2-Ph	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
-CH_2-CH_2-(3-indolyl)	**283**	22 nM (n = 3, ±2.4 nM)	12 nM (n = 3, ±0.97 nM)	3.1 nM (n = 4, ±0.57 nM)
-CH_2-CH_2-(5-MeO-3-indolyl)	**284**	1.6 nM (n = 6, ±0.25 nM)	9.9 nM (n = 4, ±1.1 nM)	4.2 nM (n = 5, ±0.69 nM)
-CH_2-CH_2-(1-naphthyl)	**287**	17 nM (n = 3, ±2.9 nM)	10 nM (n = 3, ±1.3 nM)	2.5 nM (n = 3, ±0.33 nM)
-CH_2-CH_2-(2-naphthyl)	**289**	13 nM (n = 4, ±0.92 nM)	29 nM (n = 4, ±4.0 nM)	7.7 nM (n = 5, ±1.2 nM)
Phenyl-alkyl				
-CH_2-Ph	**210**	1,763 nM (n = 3, ±312 nM)	697 nM (n = 3, ±86 nM)	469 nM (n = 3, ±72 nM)
-CH_2-CH_2-Ph	**233**	40 nM (n = 4, ±5.9 nM)	73 nM (n = 5, ±11 nM)	64 nM (n = 4, ±8.2 nM)
-CH_2-CH_2-CH_2-Ph	**315**	26 nM (n = 4, ±4.2 nM)	15 nM (n = 4, ±0.98 nM)	17 nM (n = 5, ±2.4 nM)
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**321**	9.2 nM (n = 3, ±1.4 nM)	40 nM (n = 3, ±3.8 nM)	23 nM (n = 3, ±2.5 nM)
-CH_2-CH_2-CH_2-CH_2-Ph	**335**	23 nM (n = 3, ±1.2 nM)	19 nM (n = 4, ±3.2 nM)	35 nM (n = 3, ±5.2 nM)
-CH_2-CH_2-CH_2-S-Ph	**325**	11 nM (n = 4, ±1.2 nM)	1.8 nM (n = 3, ±0.20 nM)	3.3 nM (n = 3, ±0.54 nM)
Straight Chain Alkyl				
H	**212**	33 nM (n = 4, ±4.3 nM)	1,890 nM (n = 4, ±306 nM)	154 nM (n = 4, ±12 nM)
n-C1	**45**	38 nM (n = 4, ±6.1 nM)	1,093 nM (n = 6, ±90 nM)	211 nM (n = 7, ±30 nM)
n-C4	**331**	197 nM (n = 3, ±21 nM)	1,020 nM (n = 3, ±43 nM)	190 nM (n = 3, ±34 nM)
n-C5	**337**	124 nM (n = 3, ±8.5 nM)	655 nM (n = 5, ±111 nM)	657 nM (n = 4, ±113 nM)
n-C6	**339**	50 nM (n = 6, ±7.4 nM)	181 nM (n = 3, ±25 nM)	368 nM (n = 4, ±63 nM)
n-C7	**341**	12 nM (n = 4, ±1.7 nM)	46 nM (n = 3, ±5.7 nM)	84 nM (n = 3, ±7.0 nM)
n-C8	**343**	9.0 nM (n = 3, ±0.95 nM)	17 nM (n = 3, ±1.2 nM)	37 nM (n = 3, ±1.9 nM)

n-C12	**345**	355 nM (n = 4, ±68 nM)	129 nM (n = 3, ±20 nM)	345 nM (n = 6, ±65 nM)
n-C14	**347**	478 nM (n = 3, ±58 nM)	366 nM (n = 3, ±22 nM)	229 nM (n = 3, ±25 nM)
n-C18	**349**	10,376 nM (n = 3, ±1,269 nM)	4,926 nM (n = 4, ±1,754 nM)	7,010 nM (n = 3, ±486 nM)
C^2-Branched Alkyl				
-CH_2-cPr	**213**	191 nM (n = 3, ±21 nM)	1,537 nM (n = 3, ±199 nM)	1,191 nM (n = 3, ±103 nM)
-CH_2-cPent	**215**	332 nM (n = 5, ±57 nM)	585 nM (n = 4, ±107 nM)	743 nM (n = 3, ±59 nM)
-CH_2-cHex	**217**	231 nM (n = 3, ±37 nM)	1,255 nM (n = 3, ±205 nM)	1,287 nM (n = 4, ±219 nM)
-CH_2-(2-Pr)	**309**	417 nM (n = 3, ±51 nM)	538 nM (n = 3, ±62 nM)	904 nM (n = 3, ±57 nM)
-CH_2-(3-Pent)	**333**	288 nM (n = 3, ±42 nM)	1,379 nM (n = 3, ±61 nM)	913 nM (n = 3, ±108 nM)
C_3-Chain				
-CH_2-CH=CH_2	**305**	68 nM (n = 3, ±4.0 nM)	473 nM (n = 3, ±79 nM)	163 nM (n = 3, ±14 nM)
-CH_2-CH≡CH	**307**	150 nM (n = 3, ±3.5 nM)	622 nM (n = 3, ±71 nM)	377 nM (n = 3, ±46 nM)
-CH_2-cPr	**213**	191 nM (n = 3, ±21 nM)	1,537 nM (n = 3, ±199 nM)	1,191 nM (n = 3, ±103 nM)
C_3-Spaced Ring				
-CH_2-CH_2-CH_2-cHex	**313**	20 nM (n = 3, ±2.3 nM)	44 nM (n = 4, ±6.4 nM)	42 nM (n = 3, ±2.8 nM)
-CH_2-CH_2-CH_2-Ph	**315**	26 nM (n = 4, ±4.2 nM)	15 nM (n = 4, ±0.98 nM)	17 nM (n = 5, ±2.4 nM)
-CH_2-CH=CH-Ph	**317**	32 nM (n = 3, ±4.3 nM)	39 nM (n = 4, ±6.5 nM)	90 nM (n = 3, ±15 nM)
Carbonyls				
-CH_2-COOMe	**227**	3,199 nM (n = 3, ±288 nM)	8,252 nM (n = 3, ±1,311 nM)	6,654 nM (n = 3, ±1,596 nM)
-CH_2-COOtBu	**229**	2,319 nM (n = 3, ±301 nM)	994 nM (n = 3, ±149 nM)	3,303 nM (n = 3, ±628 nM)
-CH_2-$CONH_2$	**231**	10,658 nM (n = 3, ±2,016 nM)	44,779 nM (n = 3, ±23,463 nM)	15,431 nM (n = 3, ±4,456 nM)
-CH_2-CH_2-CN	**293**	542 nM (n = 3, ±85 nM)	1,864 nM (n = 3, ±650 nM)	1,093 nM (n = 3, ±94 nM)
-CH_2-CH_2-$CONEt_2$	**-**			
-CH_2-CH_2-OAc	**295**	467 nM (n = 4, ±72 nM)	2,000 nM (n = 4, ±470 nM)	915 nM (n = 3, ±107 nM)

5-MeO-Tryptamines		5-HT$_{1A}$			5-HT$_{2A}$			5-HT$_{2C}$		
Ligand		K_i	(n,	SEM)	K_i	(n,	SEM)	K_i	(n,	SEM)
Agonist Standards										
-	**11**				0.4 nM	(n = 2,	±0.00 nM)			
-	**46**	601 nM	(n = 3,	±81 nM)	13 nM	(n = 7,	±1.5 nM)	2.2 nM	(n = 3,	±0.14 nM)
-	**47**	132 nM	(n = 3,	±13 nM)	7.3 nM	(n = 5,	±1.2 nM)	2.7 nM	(n = 4,	±0.15 nM)
5-HT	**6**	0.9 nM	(n = 3,	±0.11 nM)	137 nM	(n = 3,	±18 nM)	15 nM	(n = 3,	±2.0 nM)
(4-Br-Bn)-5-MeO-T	**19**	21 nM	(n = 3,	±1.2 nM)	534 nM	(n = 4,	±45 nM)	394 nM	(n = 3,	±19 nM)
Antagonist Standards										
Ketanserin	**48**				1.0 nM	(n = 5,	±0.13 nM)			
AC-90179	**50**				8.4 nM	(n = 1)				
MDL 100,907	**49**									
Simple Tryptamines										
5-MeO-Tryptamine	**358**	1.6 nM	(n = 3,	±0.13 nM)	152 nM	(n = 3,	±26 nM)	12 nM	(n = 3,	±1.1 nM)
5-MeO-NMT	**208**	1.9 nM	(n = 5,	±0.34 nM)	525 nM	(n = 7,	±74 nM)	83 nM	(n = 5,	±13 nM)
5-MeO-DMT	**15**	4.2 nM	(n = 5,	±0.67 nM)	558 nM	(n = 6,	±89 nM)	187 nM	(n = 3,	±17 nM)
6-MeO-2-Me-THBC	**226**	88 nM	(n = 3,	±9.1 nM)	1,521 nM	(n = 3,	±255 nM)	201 nM	(n = 3,	±14 nM)
Ethylene-bis-(5-MeO-NMT	**303**	1.9 nM	(n = 3,	±0.29 nM)	1,696 nM	(n = 3,	±175 nM)	612 nM	(n = 4,	±77 nM)
Benzyl										
Benzyl	**207**	239 nM	(n = 3,	±16 nM)	935 nM	(n = 3,	±167 nM)	636 nM	(n = 3,	±88 nM)
4-Br-benzyl	**222**	11 nM	(n = 3,	±1.2 nM)	857 nM	(n = 3,	±94 nM)	575 nM	(n = 3,	±59 nM)
nor-4-Br-benzyl	**19**	21 nM	(n = 3,	±1.2 nM)	534 nM	(n = 4,	±45 nM)	394 nM	(n = 3,	±19 nM)
2-Substituted Phenethyl										
2-H	**234**	1.8 nM	(n = 3,	±0.21 nM)	30 nM	(n = 3,	±4.7 nM)	71 nM	(n = 3,	±4.7 nM)
2-Me	**236**	2.3 nM	(n = 4,	±0.35 nM)	19 nM	(n = 3,	±2.1 nM)	28 nM	(n = 3,	±4.8 nM)
2-F	**256**	1.5 nM	(n = 3,	±0.13 nM)	4.3 nM	(n = 4,	±0.65 nM)	9.1 nM	(n = 3,	±0.84 nM)
2-Cl	**260**	0.5 nM	(n = 3,	±0.07 nM)	5.5 nM	(n = 3,	±0.35 nM)	3.0 nM	(n = 3,	±0.26 nM)
2,5-Me	**272**	0.6 nM	(n = 3,	±0.05 nM)	19 nM	(n = 3,	±1.8 nM)	13 nM	(n = 3,	±0.19 nM)
2-MeO	**246**	2.7 nM	(n = 3,	±0.21 nM)	20 nM	(n = 4,	±3.0 nM)	13 nM	(n = 3,	±0.83 nM)
2,5-MeO	**276**	1.5 nM	(n = 3,	±0.16 nM)	57 nM	(n = 3,	±9.4 nM)	39 nM	(n = 3,	±1.2 nM)
2,6-Cl	**-**									
3-Substituted Phenethyl										
3-H	**234**	1.8 nM	(n = 3,	±0.21 nM)	30 nM	(n = 3,	±4.7 nM)	71 nM	(n = 3,	±4.7 nM)
3-Me	**238**	0.8 nM	(n = 3,	±0.11 nM)	30 nM	(n = 5,	±5.2 nM)	62 nM	(n = 4,	±11 nM)
3-AcO	**-**									
3-MeO	**-**									
3-Cl	**262**	2.0 nM	(n = 5,	±0.32 nM)	12 nM	(n = 3,	±1.4 nM)	10 nM	(n = 3,	±0.74 nM)
3-Br	**268**	0.8 nM	(n = 4,	±0.14 nM)	4.5 nM	(n = 4,	±0.73 nM)	5.2 nM	(n = 4,	±0.69 nM)
2,5-Me	**272**	0.6 nM	(n = 3,	±0.05 nM)	19 nM	(n = 3,	±1.8 nM)	13 nM	(n = 3,	±0.19 nM)
3,5-Me	**274**	2.4 nM	(n = 3,	±0.14 nM)	12 nM	(n = 3,	±1.2 nM)	6.4 nM	(n = 3,	±0.82 nM)
2,5-MeO	**276**	1.5 nM	(n = 3,	±0.16 nM)	57 nM	(n = 3,	±9.4 nM)	39 nM	(n = 3,	±1.2 nM)
3,4-MeO	**278**	7.8 nM	(n = 3,	±0.83 nM)	19 nM	(n = 3,	±1.8 nM)	13 nM	(n = 3,	±0.19 nM)
3,4-Cl	**282**	2.6 nM	(n = 3,	±0.31 nM)	19 nM	(n = 3,	±2.1 nM)	28 nM	(n = 3,	±4.8 nM)
4-Substituted Phenethyl										
4-H	**234**	1.8 nM	(n = 3,	±0.21 nM)	30 nM	(n = 3,	±4.7 nM)	71 nM	(n = 3,	±4.7 nM)
4-Me	**240**	5.6 nM	(n = 3,	±0.61 nM)	16 nM	(n = 4,	±1.3 nM)	30 nM	(n = 3,	±0.66 nM)
4-MeO	**250**	7.5 nM	(n = 4,	±0.54 nM)	53 nM	(n = 3,	±4.8 nM)	65 nM	(n = 3,	±1.2 nM)
4-F	**258**	3.1 nM	(n = 3,	±0.53 nM)	19 nM	(n = 3,	±2.1 nM)	28 nM	(n = 3,	±4.8 nM)
4-Cl	**264**									
4-Br	**270**	5.7 nM	(n = 5,	±0.20 nM)	30 nM	(n = 5,	±5.2 nM)	62 nM	(n = 4,	±11 nM)
4-NO_2	**254**	13 nM	(n = 6,	±1.6 nM)	413 nM	(n = 6,	±37 nM)	311 nM	(n = 5,	±34 nM)

4-Ph	**242**	22 nM (n = 3, ±2.8 nM)	74 nM (n = 3, ±3.5 nM)	27 nM (n = 3, ±4.5 nM)
3,4-MeO	**278**	7.8 nM (n = 3, ±0.83 nM)	19 nM (n = 3, ±1.8 nM)	13 nM (n = 3, ±0.19 nM)
3,4-Cl	**282**	2.6 nM (n = 3, ±0.31 nM)	19 nM (n = 3, ±2.1 nM)	28 nM (n = 3, ±4.8 nM)
Me-Substituted Phenethyl				
H	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
2-Me	**236**	2.3 nM (n = 4, ±0.35 nM)	19 nM (n = 3, ±2.1 nM)	28 nM (n = 3, ±4.8 nM)
3-Me	**238**	0.8 nM (n = 3, ±0.11 nM)	30 nM (n = 5, ±5.2 nM)	62 nM (n = 4, ±11 nM)
4-Me	**240**	5.6 nM (n = 3, ±0.61 nM)	16 nM (n = 4, ±1.3 nM)	30 nM (n = 3, ±0.66 nM)
2,5-Me	**272**	0.6 nM (n = 3, ±0.05 nM)	19 nM (n = 3, ±1.8 nM)	13 nM (n = 3, ±0.19 nM)
3,5-Me	**274**	2.4 nM (n = 3, ±0.14 nM)	12 nM (n = 3, ±1.2 nM)	6.4 nM (n = 3, ±0.82 nM)
MeO-Substituted Phenethyl				
H	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
2-MeO	**246**	2.7 nM (n = 3, ±0.21 nM)	20 nM (n = 4, ±3.0 nM)	13 nM (n = 3, ±0.83 nM)
3-MeO	**-**			
4-MeO	**250**	7.5 nM (n = 4, ±0.54 nM)	53 nM (n = 3, ±4.8 nM)	65 nM (n = 3, ±1.2 nM)
2,5-MeO	**276**	1.5 nM (n = 3, ±0.16 nM)	57 nM (n = 3, ±9.4 nM)	39 nM (n = 3, ±1.2 nM)
3,4-MeO	**278**	7.8 nM (n = 3, ±0.83 nM)	19 nM (n = 3, ±1.8 nM)	13 nM (n = 3, ±0.19 nM)
F-Substituted Phenethyl				
H	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
2-F	**256**	1.5 nM (n = 3, ±0.13 nM)	4.3 nM (n = 4, ±0.65 nM)	9.1 nM (n = 3, ±0.84 nM)
4-F	**258**	3.1 nM (n = 3, ±0.53 nM)	19 nM (n = 3, ±2.1 nM)	28 nM (n = 3, ±4.8 nM)
Cl-Substituted Phenethyl				
H	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
2-Cl	**260**	0.5 nM (n = 3, ±0.07 nM)	5.5 nM (n = 3, ±0.35 nM)	3.0 nM (n = 3, ±0.26 nM)
3-Cl	**262**	2.0 nM (n = 5, ±0.32 nM)	12 nM (n = 3, ±1.4 nM)	10 nM (n = 3, ±0.74 nM)
4-Cl	**264**			
3,4-Cl	**282**	2.6 nM (n = 3, ±0.31 nM)	19 nM (n = 3, ±2.1 nM)	28 nM (n = 3, ±4.8 nM)
2,6-Cl	**-**			
Br-Substituted Phenethyl				
H	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
3-Br	**268**	0.8 nM (n = 4, ±0.14 nM)	4.5 nM (n = 4, ±0.73 nM)	5.2 nM (n = 4, ±0.69 nM)
4-Br	**270**	5.7 nM (n = 5, ±0.20 nM)	30 nM (n = 5, ±5.2 nM)	62 nM (n = 4, ±11 nM)
C_2-Spaced Aromatics				
-CH_2-CH_2-Ph	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
-CH_2-CH_2-(3-indolyl)	**284**	1.6 nM (n = 6, ±0.25 nM)	9.9 nM (n = 4, ±1.1 nM)	4.2 nM (n = 5, ±0.69 nM)
-CH_2-CH_2-(5-MeO-3-indolyl)	**286**	0.3 nM (n = 5, ±0.05 nM)	30 nM (n = 3, ±2.3 nM)	15 nM (n = 3, ±1.4 nM)
-CH_2-CH_2-(1-naphthyl)	**288**	1.5 nM (n = 4, ±0.26 nM)	13 nM (n = 3, ±1.6 nM)	4.9 nM (n = 3, ±0.61 nM)
-CH_2-CH_2-(2-naphthyl)	**290**	2.7 nM (n = 6, ±0.44 nM)	21 nM (n = 3, ±2.3 nM)	14 nM (n = 3, ±1.2 nM)
Phenyl-alkyl				
-CH_2-Ph	**207**	239 nM (n = 3, ±16 nM)	935 nM (n = 3, ±167 nM)	636 nM (n = 3, ±88 nM)
-CH_2-CH_2-Ph	**234**	1.8 nM (n = 3, ±0.21 nM)	30 nM (n = 3, ±4.7 nM)	71 nM (n = 3, ±4.7 nM)
-CH_2-CH_2-CH_2-Ph	**316**	1.6 nM (n = 3, ±0.08 nM)	20 nM (n = 4, ±2.8 nM)	24 nM (n = 3, ±3.4 nM)
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**322**	2.4 nM (n = 3, ±0.32 nM)	156 nM (n = 3, ±22 nM)	23 nM (n = 3, ±3.4 nM)
-CH_2-CH_2-CH_2-CH_2-Ph	**336**	2.2 nM (n = 3, ±0.14 nM)	50 nM (n = 3, ±7.9 nM)	68 nM (n = 4, ±2.0 nM)
-CH_2-CH_2-CH_2-S-Ph	**326**	2.0 nM (n = 4, ±0.35 nM)	9.1 nM (n = 3, ±0.19 nM)	14 nM (n = 4, ±1.9 nM)
Straight Chain Alkyl				
H	**208**	1.9 nM (n = 5, ±0.34 nM)	525 nM (n = 7, ±74 nM)	83 nM (n = 5, ±13 nM)
n-C1	**45**	4.2 nM (n = 5, ±0.67 nM)	558 nM (n = 6, ±89 nM)	187 nM (n = 3, ±17 nM)
n-C4	**332**	10.0 nM (n = 3, ±1.0 nM)	721 nM (n = 3, ±71 nM)	252 nM (n = 3, ±6.9 nM)
n-C5	**338**	9.4 nM (n = 3, ±1.0 nM)	647 nM (n = 3, ±52 nM)	688 nM (n = 3, ±23 nM)
n-C6	**-**			
n-C7	**-**			
n-C8	**344**	0.3 nM (n = 3, ±0.03 nM)	155 nM (n = 5, ±22 nM)	66 nM (n = 3, ±1.4 nM)

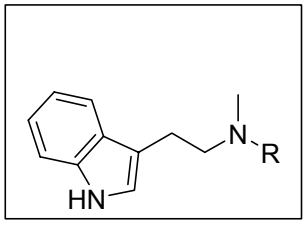
n-C12	**346**	12 nM (n = 3, ±1.4 nM)	253 nM (n = 4, ±33 nM)	132 nM (n = 3, ±7.2 nM)
n-C14	**348**	55 nM (n = 3, ±6.8 nM)	192 nM (n = 6, ±25 nM)	258 nM (n = 5, ±41 nM)
n-C18	**350**	971 nM (n = 3, ±84 nM)	13,907 nM (n = 3, ±970 nM)	10,564 nM (n = 4, ±1,740 nM)
C^2-Branched Alkyl				
$-CH_2$-cPr				
$-CH_2$-cPent	**216**	19 nM (n = 3, ±2.7 nM)	1,194 nM (n = 3, ±177 nM)	691 nM (n = 4, ±70 nM)
$-CH_2$-cHex	**218**	20 nM (n = 3, ±1.2 nM)	1,277 nM (n = 3, ±136 nM)	750 nM (n = 3, ±66 nM)
$-CH_2$-(2-Pr)	**310**	22 nM (n = 3, ±3.4 nM)	2,094 nM (n = 4, ±428 nM)	947 nM (n = 4, ±108 nM)
$-CH_2$-(3-Pent)	**334**	24 nM (n = 3, ±1.7 nM)	761 nM (n = 3, ±121 nM)	992 nM (n = 3, ±43 nM)
C_3-Chain				
$-CH_2-CH=CH_2$	**306**	4.1 nM (n = 5, ±0.76 nM)	443 nM (n = 4, ±34 nM)	178 nM (n = 3, ±21 nM)
$-CH_2-CH\equiv CH$	**308**	11 nM (n = 4, ±1.6 nM)	279 nM (n = 3, ±6.3 nM)	182 nM (n = 5, ±20 nM)
$-CH_2$-cPr	**-**			
C_3-Spaced Ring				
$-CH_2-CH_2-CH_2$-cHex	**314**	0.9 nM (n = 3, ±0.12 nM)	157 nM (n = 3, ±13 nM)	44 nM (n = 3, ±4.6 nM)
$-CH_2-CH_2-CH_2$-Ph	**316**	1.6 nM (n = 3, ±0.08 nM)	20 nM (n = 4, ±2.8 nM)	24 nM (n = 3, ±3.4 nM)
$-CH_2-CH=CH$-Ph	**318**			
Carbonyls				
$-CH_2$-COOMe	**228**	170 nM (n = 3, ±27 nM)	5,535 nM (n = 3, ±687 nM)	5,580 nM (n = 3, ±411 nM)
$-CH_2$-COOtBu	**230**	119 nM (n = 3, ±0.60 nM)	1,925 nM (n = 3, ±102 nM)	4,084 nM (n = 3, ±498 nM)
$-CH_2-CONH_2$	**232**	1,051 nM (n = 3, ±152 nM)	16,519 nM (n = 3, ±4,224 nM)	4,026 nM (n = 3, ±585 nM)
$-CH_2-CH_2$-CN	**294**	43 nM (n = 3, ±0.99 nM)	4,284 nM (n = 5, ±1,195 nM)	1,863 nM (n = 3, ±226 nM)
$-CH_2-CH_2-CONEt_2$	**302**	21 nM (n = 3, ±3.0 nM)	697 nM (n = 5, ±103 nM)	1,184 nM (n = 3, ±169 nM)
$-CH_2-CH_2$-OAc	**-**			

Comparison of binding affinities (Table 8)

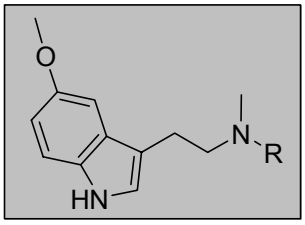
Table 8: Radioreceptor binding data - comparison of affinities.

In this table the binding affinities are compared between the different receptors and between 5-unsubstituted and 5-methoxy compounds.

For the columns "K_i ratio 5-$HT_{1A/2A}$" and "K_i ratio 5-$HT_{2C/2A}$" numbers greater than unity indicate higher affinities for the 5-HT_{1A} or the 5-HT_{2C} receptor over the 5-HT_{2A} receptor, respectively.
For the columns "5-MeO / 5-H" numbers greater than unity indicate a higher affinity of the 5-methoxy substituted tryptamine compared to the 5-unsubstituted tryptamine at the respective receptors.
Compounds are arranged by classes and may appear in several different contexts. White rows: 5-unsubstituted tryptamines; gray underlined rows: 5-methoxy substituted tryptamines.



5-unsubstituted tryptamines
(white fields)



5-MeO-tryptamines
(gray fields)

5-Unsubstituted Tryptamines		K_i ratio	K_i ratio	K_i 5-HT$_{1A}$ ratio	K_i 5-HT$_{2A}$ ratio	K_i 5-HT$_{2C}$ ratio
Compound		5-HT$_{1A\,/\,2A}$	5-HT$_{2C\,/\,2A}$	5-MeO / 5-H	5-MeO / 5-H	5-MeO / 5-H
Agonist Standards						
-	**11**					
-	**46**	0.02 ×	6 ×			
-	**47**	0.06 ×	3 ×			
5-HT	**6**	156 ×	9 ×			
(4-Br-Bn)-5-MeO-T	**19**	26 ×	1 ×			
Antagonist Standards						
Ketanserin	**48**					
AC-90179	**50**					
MDL 100,907	**49**					
Simple Tryptamines						
Tryptamine	**5**	28 ×	23 ×	30 ×	9 ×	5 ×
NMT	**212**	58 ×	12 ×	17 ×	4 ×	2 ×
DMT	**45**	29 ×	5 ×	9 ×	2 ×	1 ×
Benzyl						
Benzyl	**210**	0.4 ×	1 ×	7 ×	0.7 ×	0.7 ×
4-Br-benzyl	**221**	6 ×	0.7 ×	14 ×	1 ×	2 ×
nor-4-Br-benzyl	**359**					
2-Substituted Phenethyl						
2-H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
2-Me	**235**	0.7 ×	1 ×	13 ×	1 ×	0.6 ×
2-F	**255**	0.4 ×	1 ×	27 ×	4 ×	2 ×
2-Cl	**259**	0.3 ×	1 ×	46 ×	1 ×	2 ×
2,5-Me	**196**	1 ×	2 ×	22 ×	0.9 ×	0.6 ×
2-MeO	**245**	0.7 ×	2 ×	7 ×	0.6 ×	0.6 ×
2,5-MeO	**275**	1 ×	2 ×	7 ×	0.2 ×	0.1 ×
2,6-Cl	**279**	1 ×	6 ×			
3-Substituted Phenethyl						
3-H	**233**	2 ×	1 ×	22 ×	2 ×	1 ×
3-Me	**237**	0.5 ×	0.9 ×	28 ×	0.4 ×	0.2 ×
3-AcO	**243**	4 ×	3 ×			
3-MeO	**247**	3 ×	3 ×			
3-Cl	**261**	1 ×	1 ×	9 ×	2 ×	1 ×
3-Br	**267**	1 ×	3 ×	15 ×	4 ×	0.9 ×
2,5-Me	**196**	1 ×	2 ×	22 ×	0.9 ×	0.6 ×
3,5-Me	**273**	0.3 ×	3 ×	11 ×	0.7 ×	0.4 ×
2,5-MeO	**275**	1 ×	2 ×	7 ×	0.2 ×	0.1 ×
3,4-MeO	**277**	0.2 ×	2 ×	9 ×	0.9 ×	0.7 ×
3,4-Cl	**281**	2 ×	2 ×	5 ×	2 ×	0.5 ×
4-Substituted Phenethyl						
4-H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
4-Me	**239**	0.5 ×	0.4 ×	7 ×	1 ×	2 ×
4-MeO	**249**	0.7 ×	2 ×	7 ×	0.6 ×	0.6 ×
4-F	**257**	0.7 ×	0.7 ×	19 ×	2 ×	2 ×
4-Cl	**263**	2 ×	2 ×			
4-Br	**269**	1 ×	0.5 ×	4 ×	1 ×	1 ×
4-NO_2	**253**	12 ×	2 ×	3 ×	1 ×	0.9 ×

4-Ph	**241**	1 ×	6 ×	4 ×	1 ×	0.7 ×
3,4-MeO	**277**	0.2 ×	2 ×	9 ×	0.9 ×	0.7 ×
3,4-Cl	**281**	2 ×	2 ×	5 ×	2 ×	0.5 ×
Me-Substituted Phenethyl						
H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
2-Me	**235**	0.7 ×	1 ×	13 ×	1 ×	0.6 ×
3-Me	**237**	0.5 ×	0.9 ×	28 ×	0.4 ×	0.2 ×
4-Me	**239**	0.5 ×	0.4 ×	7 ×	1 ×	2 ×
2,5-Me	**196**	1 ×	2 ×	22 ×	0.9 ×	0.6 ×
3,5-Me	**273**	0.3 ×	3 ×	11 ×	0.7 ×	0.4 ×
MeO-Substituted Phenethyl						
H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
2-MeO	**245**	0.7 ×	2 ×	7 ×	1 ×	1 ×
3-MeO	**247**	3 ×	3 ×			
4-MeO	**249**	1 ×	2 ×	12 ×	2 ×	0.7 ×
2,5-MeO	**275**	1 ×	2 ×	7 ×	0.2 ×	0.1 ×
3,4-MeO	**277**	0.2 ×	2 ×	9 ×	0.9 ×	0.7 ×
F-Substituted Phenethyl						
H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
2-F	**255**	0.4 ×	1 ×	27 ×	4 ×	2 ×
4-F	**257**	0.7 ×	0.7 ×	19 ×	2 ×	2 ×
Cl-Substituted Phenethyl						
H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
2-Cl	**259**	0.3 ×	1 ×	46 ×	1 ×	2 ×
3-Cl	**261**	1 ×	1 ×	9 ×	2 ×	1 ×
4-Cl	**263**	2 ×	2 ×			
3,4-Cl	**281**	2 ×	2 ×	5 ×	2 ×	0.5 ×
2,6-Cl	**279**	1 ×	6 ×			
Br-Substituted Phenethyl						
H	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
3-Br	**267**	1 ×	3 ×	15 ×	4 ×	0.9 ×
4-Br	**269**	1 ×	0.5 ×	4 ×	1 ×	1 ×
C_2-Spaced Aromatics						
-CH_2-CH_2-Ph	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
-CH_2-CH_2-(3-indolyl)	**283**	0.6 ×	4 ×	14 ×	1 ×	0.8 ×
-CH_2-CH_2-(5-MeO-3-indolyl)	**284**	6 ×	2 ×	6 ×	0.3 ×	0.3 ×
-CH_2-CH_2-(1-naphthyl)	**287**	0.6 ×	4 ×	12 ×	0.8 ×	0.5 ×
-CH_2-CH_2-(2-naphthyl)	**289**	2 ×	4 ×	5 ×	1 ×	0.6 ×
Phenyl-alkyl						
-CH_2-Ph	**210**	0.4 ×	1 ×	7 ×	0.7 ×	0.7 ×
-CH_2-CH_2-Ph	**233**	2 ×	1 ×	22 ×	2 ×	0.9 ×
-CH_2-CH_2-CH_2-Ph	**315**	0.6 ×	0.9 ×	16 ×	0.8 ×	0.7 ×
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**321**	4 ×	2 ×	4 ×	0.3 ×	1.0 ×
-CH_2-CH_2-CH_2-CH_2-Ph	**335**	0.8 ×	0.6 ×	11 ×	0.4 ×	0.5 ×
-CH_2-CH_2-CH_2-S-Ph	**325**	0.2 ×	0.6 ×	5 ×	0.2 ×	0.2 ×
Straight Chain Alkyl						
H	**212**	58 ×	12 ×	17 ×	4 ×	2 ×
n-C1	**45**	29 ×	5 ×	9 ×	2 ×	1 ×
n-C4	**331**	5 ×	5 ×	20 ×	1 ×	0.8 ×
n-C5	**337**	5 ×	1.0 ×	13 ×	1 ×	1.0 ×
n-C6	**339**	4 ×	0.5 ×			
n-C7	**341**	4 ×	0.5 ×			
n-C8	**343**	2 ×	0.4 ×	28 ×	0.1 ×	0.6 ×

n-C12	**345**	0.4 ×	0.4 ×	29 ×	0.5 ×	3 ×
n-C14	**347**	0.8 ×	2 ×	9 ×	2 ×	0.9 ×
n-C18	**349**	0.5 ×	0.7 ×	11 ×	0.4 ×	0.7 ×
C^2-Branched Alkyl						
-CH_2-cPr	**213**	8 ×	1 ×			
-CH_2-cPent	**215**	2 ×	0.8 ×	17 ×	0.5 ×	1 ×
-CH_2-cHex	**217**	5 ×	1.0 ×	12 ×	1.0 ×	2 ×
-CH_2-(2-Pr)	**309**	1 ×	0.6 ×	19 ×	0.3 ×	1.0 ×
-CH_2-(3-Pent)	**333**	5 ×	2 ×	12 ×	2 ×	0.9 ×
C_3-Chain						
-CH_2-CH=CH_2	**305**	7 ×	3 ×	17 ×	1 ×	0.9 ×
-CH_2-CH≡CH	**307**	4 ×	2 ×	13 ×	2 ×	2 ×
-CH_2-cPr	**213**	8 ×	1 ×			
C_3-Spaced Ring						
-CH_2-CH_2-CH_2-cHex	**313**	2 ×	1 ×	22 ×	0.3 ×	0.9 ×
-CH_2-CH_2-CH_2-Ph	**315**	0.6 ×	0.9 ×	16 ×	0.8 ×	0.7 ×
-CH_2-CH=CH-Ph	**317**	1 ×	0.4 ×			
Carbonyls						
-CH_2-COOMe	**227**	3 ×	1 ×	19 ×	1 ×	1 ×
-CH_2-COOtBu	**229**	0.4 ×	0.3 ×	20 ×	0.5 ×	0.8 ×
-CH_2-$CONH_2$	**231**	4 ×	3 ×	10 ×	3 ×	4 ×
-CH_2-CH_2-CN	**293**	3 ×	2 ×	13 ×	0.4 ×	0.6 ×
-CH_2-CH_2-$CONEt_2$	**-**					
-CH_2-CH_2-OAc	**295**	4 ×	2 ×			

5-MeO-Tryptamines		K_i	K_i	K_i 5-HT$_{1A}$	K_i 5-HT$_{2A}$	K_i 5-HT$_{2C}$
Ligand		5-HT$_{1A\ /\ 2A}$	5-HT$_{2C\ /\ 2A}$	5-MeO / 5-H	5-MeO / 5-H	5-MeO / 5-H
Agonist Standards						
-	**11**					
-	**46**	0.02 ×	6 ×			
-	**47**	0.06 ×	3 ×			
5-HT	**6**	156 ×	9 ×			
(4-Br-Bn)-5-MeO-T	**19**	26 ×	1 ×			
Antagonist Standards						
Ketanserin	**48**					
AC-90179	**50**					
MDL 100,907	**49**					
Simple Tryptamines						
5-MeO-Tryptamine	**358**	95 ×	12 ×	30 ×	9 ×	5 ×
5-MeO-NMT	**208**	275 ×	6 ×	17 ×	4 ×	2 ×
5-MeO-DMT	**15**	134 ×	3 ×	9 ×	2 ×	1 ×
6-MeO-2-Me-THBC	**226**	17 ×	8 ×			
Ethylene-bis-(5-MeO-NMT)	**303**	896 ×	3 ×			
Benzyl						
Benzyl	**207**	4 ×	1 ×	7 ×	0.7 ×	0.7 ×
4-Br-benzyl	**222**	81 ×	1 ×	14 ×	1 ×	2 ×
nor-4-Br-benzyl	**19**	26 ×	1 ×			
2-Substituted Phenethyl						
2-H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
2-Me	**236**	8 ×	0.7 ×	13 ×	1 ×	0.6 ×
2-F	**256**	3 ×	0.5 ×	27 ×	4 ×	2 ×
2-Cl	**260**	11 ×	2 ×	46 ×	1 ×	2 ×
2,5-Me	**272**	33 ×	2 ×	22 ×	0.9 ×	0.6 ×
2-MeO	**246**	7 ×	2 ×	7 ×	0.6 ×	0.6 ×
2,5-MeO	**276**	38 ×	1 ×	7 ×	0.2 ×	0.1 ×
2,6-Cl	**-**					
3-Substituted Phenethyl						
3-H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
3-Me	**238**	35 ×	0.5 ×	28 ×	0.4 ×	0.2 ×
3-AcO	**-**					
3-MeO	**-**					
3-Cl	**262**	6 ×	1 ×	9 ×	2 ×	1 ×
3-Br	**268**	6 ×	0.9 ×	15 ×	4 ×	0.9 ×
2,5-Me	**272**	33 ×	2 ×	22 ×	0.9 ×	0.6 ×
3,5-Me	**274**	5 ×	2 ×	11 ×	0.7 ×	0.4 ×
2,5-MeO	**276**	38 ×	1 ×	7 ×	0.2 ×	0.1 ×
3,4-MeO	**278**	2 ×	2 ×	9 ×	0.9 ×	0.7 ×
3,4-Cl	**282**	7 ×	0.7 ×	5 ×	2 ×	0.5 ×
4-Substituted Phenethyl						
4-H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
4-Me	**240**	3 ×	0.5 ×	7 ×	1 ×	2 ×
4-MeO	**250**	7 ×	0.8 ×	12 ×	2 ×	0.7 ×
4-F	**258**	6 ×	0.7 ×	19 ×	2 ×	2 ×
4-Cl	**264**					
4-Br	**270**	5 ×	0.5 ×	4 ×	1 ×	1 ×
4-NO_2	**254**	31 ×	1 ×	3 ×	1 ×	0.9 ×

4-Ph	**242**	3 ×	3 ×	4 ×	1 ×	0.7 ×x
3,4-MeO	**278**	2 ×	2 ×	9 ×	0.9 ×	0.7 ×
3,4-Cl	**282**	7 ×	0.7 ×	5 ×	2 ×	0.5 ×
Me-Substituted Phenethyl						
H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
2-Me	**236**	8 ×	0.7 ×	13 ×	1 ×	0.6 ×
3-Me	**238**	35 ×	0.5 ×	28 ×	0.4 ×	0.2 ×
4-Me	**240**	3 ×	0.5 ×	7 ×	1 ×	2 ×
2,5-Me	**272**	33 ×	2 ×	22 ×	0.9 ×	0.6 ×
3,5-Me	**274**	5 ×	2 ×	11 ×	0.7 ×	0.4 ×
MeO-Substituted Phenethyl						
H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
2-MeO	**246**	7 ×	2 ×	7 ×	0.6 ×	0.6 ×
3-MeO	-					
4-MeO	**250**	7 ×	0.8 ×	12 ×	2 ×	0.7 ×
2,5-MeO	**276**	38 ×	1 ×	7 ×	0.2 ×	0.1 ×
3,4-MeO	**278**	2 ×	2 ×	9 ×	0.9 ×	0.7 ×
F-Substituted Phenethyl						
H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
2-F	**256**	3 ×	0.5 ×	27 ×	4 ×	2 ×
4-F	**258**	6 ×	0.7 ×	19 ×	2 ×	2 ×
Cl-Substituted Phenethyl						
H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
2-Cl	**260**	11 ×	2 ×	46 ×	1 ×	2 ×
3-Cl	**262**	6 ×	1 ×	9 ×	2 ×	1 ×
4-Cl	**264**					
3,4-Cl	**282**	7 ×	0.7 ×	5 ×	2 ×	0.5 ×
2,6-Cl	-					
Br-Substituted Phenethyl						
H	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
3-Br	**268**	6 ×	0.9 ×	15 ×	4 ×	0.9 ×
4-Br	**270**	5 ×	0.5 ×	4 ×	1 ×	1 ×
C_2-Spaced Aromatics						
-CH_2-CH_2-Ph	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
-CH_2-CH_2-(3-indolyl)	**284**	6 ×	2 ×	14 ×	1 ×	0.8 ×
-CH_2-CH_2-(5-MeO-3-indolyl)	**286**	105 ×	2 ×	6 ×	0.3 ×	0.3 ×
-CH_2-CH_2-(1-naphthyl)	**288**	9 ×	3 ×	12 ×	0.8 ×	0.5 ×
-CH_2-CH_2-(2-naphthyl)	**290**	8 ×	1 ×	5 ×	1 ×	0.6 ×
Phenyl-alkyl						
-CH_2-Ph	**207**	4 ×	1 ×	7 ×	0.7 ×	0.7 ×
-CH_2-CH_2-Ph	**234**	17 ×	0.4 ×	22 ×	2 ×	0.9 ×
-CH_2-CH_2-CH_2-Ph	**316**	13 ×	0.8 ×	16 ×	0.8 ×	0.7 ×
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**322**	65 ×	7 ×	4 ×	0.3 ×	1.0 ×
-CH_2-CH_2-CH_2-CH_2-Ph	**336**	23 ×	0.7 ×	11 ×	0.4 ×	0.5 ×
-CH_2-CH_2-CH_2-S-Ph	**326**	5 ×	0.6 ×	5 ×	0.2 ×	0.2 ×
Straight Chain Alkyl						
H	**208**	275 ×	6 ×	17 ×	4 ×	2 ×
n-C1		134 ×	3 ×	9 ×	2 ×	1 ×
n-C4	**332**	72 ×	3 ×	20 ×	1 ×	0.8 ×
n-C5	**338**	69 ×	0.9 ×	13 ×	1 ×	1.0 ×
n-C6	-					
n-C7	-					
n-C8	**344**	479 ×	2 ×	28 ×	0.1 ×	0.6 ×

n-C12	**346**	21 ×	2 ×	29 ×	0.5 ×	3 ×
n-C14	**348**	3 ×	0.7 ×	9 ×	2 ×	0.9 ×
n-C18	**350**	14 ×	1 ×	11 ×	0.4 ×	0.7 ×
C^2-Branched Alkyl						
$-CH_2$-cPr	-					
$-CH_2$-cPent	**216**	62 ×	2 ×	17 ×	0.5 ×	1 ×
$-CH_2$-cHex	**218**	65 ×	2 ×	12 ×	1.0 ×	2 ×
$-CH_2$-(2-Pr)	**310**	96 ×	2 ×	19 ×	0.3 ×	1.0 ×
$-CH_2$-(3-Pent)	**334**	31 ×	0.8 ×	12 ×	2 ×	0.9 ×
C_3-Chain						
$-CH_2-CH=CH_2$	**306**	108 ×	2 ×	17 ×	1 ×	0.9 ×
$-CH_2-CH\equiv CH$	**308**	24 ×	2 ×	13 ×	2 ×	2 ×
$-CH_2$-cPr	-					
C_3-Spaced Ring						
$-CH_2-CH_2-CH_2$-cHex	**314**	177 ×	4 ×	22 ×	0.3 ×	0.9 ×
$-CH_2-CH_2-CH_2$-Ph	**316**	13 ×	0.8 ×	16 ×	0.8 ×	0.7 ×
$-CH_2$-CH=CH-Ph	**318**					
Carbonyls						
$-CH_2$-COOMe	**228**	33 ×	1.0 ×	19 ×	1 ×	1 ×
$-CH_2$-COOtBu	**230**	16 ×	0.5 ×	20 ×	0.5 ×	0.8 ×
$-CH_2-CONH_2$	**232**	16 ×	4 ×	10 ×	3 ×	4 ×
$-CH_2-CH_2$-CN	**294**	100 ×	2 ×	13 ×	0.4 ×	0.6 ×
$-CH_2-CH_2-CONEt_2$	**302**	33 ×	0.6 ×			
$-CH_2-CH_2$-OAc	-					

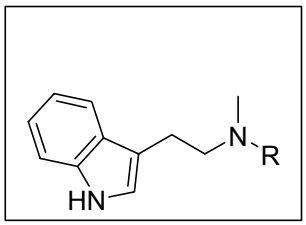
Functional 5-HT_{2A} data (Table 9)

Table 9: Functional data at cells transfected with the 5-HT_{2A} receptor.

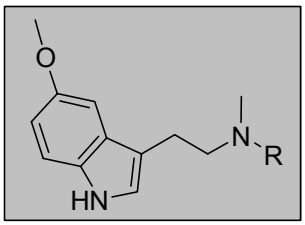
Functional data at cells transfected with the human or the rat 5-HT_{2A} receptor in IP accumulation assays. If not stated otherwise the data for the human receptor is given. Relative efficacies and maximal stimulations are given as the percentage of maximal stimulation by 10 µM 5-HT.

EC_{50} values (bold) and the calculated % max are given for compounds where fitting against a monophasic curve or the low-dose response of a biphasic response was possible.

Compounds are arranged by classes and may appear in several different contexts. White rows: 5-unsubstituted tryptamines; gray underlined rows: 5-methoxy substituted tryptamines. Column Bi: Biphasic response observed.



5-unsubstituted tryptamines
(white fields)



5-MeO-tryptamines
(gray fields)

5-Unsubstituted Tryptamines		Bi	% max 5-HT, Conc. or EC_{50}		% max. 5-HT		% max 5-HT	
Compound			% max	(c, n, SEM) or: (n, SEM), **EC_{50}** (n, SEM)	% max	(c, n, SEM)	% max	(c, n, SEM)
Agonist Standards								
-	**11**							
-	**46**							
-	**47**							
5-HT	**6**	-	108%	(n = 2, ±6%), **123 nM** (n = 2, ±15 nM)				
(4-Br-Bn)-5-MeO-T	**19**		4%	(1 µM, n = 2, ±0%)				
Antagonist Standards								
Ketanserin	**48**							
AC-90179	**50**							
MDL 100,907	**49**							
Simple Tryptamines								
Tryptamine	**5**							
NMT	**212**	-	69%	(n = 1), **2,239 nM** (sic!, n = 1)				
DMT	**45**	-	41%	(n = 1), **2,239 nM** (sic!, n = 1)				
Benzyl								
Benzyl	**210**							
4-Br-benzyl	**221**	+	3%	(1 µM, n = 3, ±3%)	27%	(32 µM, n = 2, ±4%)		
nor-4-Br-benzyl	**359**							
2-Substituted Phenethyl								
2-H	**233**		3%	(1 µM, n = 1)	26%	(32 µM, n = 1, rat)		
2-Me	**235**		1%	(1 µM, n = 1)				
2-F	**255**		1%	(1 µM, n = 1)	14%	(32 µM, n = 1, rat)		
2-Cl	**259**		1%	(1 µM, n = 1)	15%	(32 µM, n = 1, rat)		
2,5-Me	**196**		26%	(n = 3, ±4%), **235 nM** (n = 3, ±24 nM)	112%	(32 µM, n = 5, ±22%)		
2-MeO	**245**		3%	(1 µM, n = 1)	35%	(32 µM, n = 1, rat)		
2,5-MeO	**275**	+	19%	(n = 1), **18 nM** (n = 1)	37%	(10 µM, n = 1)		
2,6-Cl	**279**	+	26%	(n = 1), **1,413 nM** (n = 1)	33%	(10 µM, n = 1)	109%	(32 µM, n = 1)
3-Substituted Phenethyl								
3-H	**233**		3%	(1 µM, n = 1)	26%	(32 µM, n = 1, rat)		
3-Me	**237**		6%	(1 µM, n = 1)	60%	(32 µM, n = 1, rat)		
3-AcO	**243**	+	38%	(n = 2, ±15%), **98 nM** (n = 2, ±0 nM)	57%	(10 µM, n = 2, ±16%)	74%	(32 µM, n = 1)
3-MeO	**247**		28%	(n = 1), **324 nM** (n = 1)	43%	(10 µM, n = 1)	92%	(32 µM, n = 1)
3-Cl	**261**		4%	(1 µM, n = 1)	57%	(32 µM, n = 1, rat)		
3-Br	**267**		4%	(1 µM, n = 1)	40%	(32 µM, n = 1, rat)		
2,5-Me	**196**		26%	(n = 3, ±4%), **235 nM** (n = 3, ±24 nM)	112%	(32 µM, n = 5, ±22%)		
3,5-Me	**273**		41%	(n = 2, ±16%), **281 nM** (n = 2, ±220 nM)	86%	(10 µM, n = 1)	164%	(32 µM, n = 1)
2,5-MeO	**275**		19%	(n = 1), **18 nM** (n = 1)	37%	(10 µM, n = 1)		
3,4-MeO	**277**		34%	(n = 3, ±5%), **44 nM** (n = 3, ±5 nM)	42%	(32 µM, n = 1)		
3,4-Cl	**281**		2%	(1 µM, n = 1)				
4-Substituted Phenethyl								
4-H	**233**		3%	(1 µM, n = 1)	26%	(32 µM, n = 1, rat)		
4-Me	**239**		2%	(1 µM, n = 1)	55%	(32 µM, n = 1, rat)		
4-MeO	**249**							
4-F	**257**		1%	(1 µM, n = 1)	18%	(32 µM, n = 1, rat)		
4-Cl	**263**		2%	(1 µM, n = 1)	50%	(32 µM, n = 1, rat)		
4-Br	**269**		1%	(1 µM, n = 1)	39%	(32 µM, n = 1, rat)		
4-NO_2	**253**		6%	(1 µM, n = 1)	55%	(32 µM, n = 1, rat)		

4-Ph	**241**		6%	(1 μM, n = 1)	49%	(32 μM, n = 1, rat)		
3,4-MeO	**277**		35%	(n = 2, ±8%), **48 nM** (n = 2, ±6 nM)	42%	(32 μM, n = 1)		
3,4-Cl	**281**		2%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)		
Me-Substituted Phenethyl								
H	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
2-Me	**235**		1%	(1 μM, n = 1)				
3-Me	**237**		6%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)		
4-Me	**239**		2%	(1 μM, n = 1)	55%	(32 μM, n = 1, rat)		
2,5-Me	**196**	+	26%	(n = 3, ±4%), **235 nM** (n = 3, ±24 nM)	112%	(32 μM, n = 5, ±22%)		
3,5-Me	**273**	+	41%	(n = 2, ±16%), **281 nM** (n = 2, ±220 nM)	86%	(10 μM, n = 1)	164%	(32 μM, n = 1)
MeO-Substituted Phenethyl								
H	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
2-MeO	**245**		3%	(1 μM, n = 1)	35%	(32 μM, n = 1, rat)		
3-MeO	**247**	+	28%	(n = 1), **324 nM** (n = 1)	43%	(10 μM, n = 1)	92%	(32 μM, n = 1)
4-MeO	**249**							
2,5-MeO	**275**		19%	(n = 1), **18 nM** (n = 1)	37%	(10 μM, n = 1)		
3,4-MeO	**277**	+	35%	(n = 2, ±8%), **48 nM** (n = 2, ±6 nM)	42%	(32 μM, n = 1)		
F-Substituted Phenethyl								
H	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
2-F	**255**		1%	(1 μM, n = 1)	14%	(32 μM, n = 1, rat)		
4-F	**257**		1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)		
Cl-Substituted Phenethyl								
H	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
2-Cl	**259**		1%	(1 μM, n = 1)	15%	(32 μM, n = 1, rat)		
3-Cl	**261**		4%	(1 μM, n = 1)	57%	(32 μM, n = 1, rat)		
4-Cl	**263**		2%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)		
3,4-Cl	**281**		2%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)		
2,6-Cl	**279**	+	26%	(n = 1), **1,413 nM** (n = 1)	33%	(10 μM, n = 1)	109%	(32 μM, n = 1)
Br-Substituted Phenethyl								
H	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
3-Br	**267**		4%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)		
4-Br	**269**		1%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)		
C2-Spaced Aromatics								
$-CH_2-CH_2$-Ph	**233**		3%	(1 μM, n = 1)				
$-CH_2-CH_2$-(3-indolyl)	**283**	+	25%	(n = 1), **132 nM** (n = 1)	30%	(10 μM, n = 2, ±12%)	54%	(32 μM, n = 2, ±25%)
$-CH_2-CH_2$-(5-MeO-3-indolyl)	**284**	+	24%	(n = 3, ±4%), **50 nM** (n = 3, ±15 nM)	30%	(10 μM, n = 4, ±3%)	54%	(32 μM, n = 2, ±2%)
$-CH_2-CH_2$-(1-naphthyl)	**287**	+	26%	(n = 3, ±3%), **290 nM** (n = 3, ±66 nM)	64%	(10 μM, n = 4, ±18%)	94%	(32 μM, n = 8, ±11%)
$-CH_2-CH_2$-(2-naphthyl)	**289**		8%	(1 μM, n = 1)	90%	(32 μM, n = 1, rat)		
Phenyl-alkyl								
$-CH_2$-Ph	**210**							
$-CH_2-CH_2$-Ph	**233**		3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
$-CH_2-CH_2-CH_2$-Ph	**315**		0%	(1 μM, n = 1)	6%	(32 μM, n = 1, rat)		
$-CH_2-CH_2-CH_2$-(3,4,5-MeO-Ph)	**321**		5%	(10 μM, n = 1)	11%	(32 μM, n = 1, rat)		
$-CH_2-CH_2-CH_2-CH_2$-Ph	**335**		0%	(1 μM, n = 1)	7%	(32 μM, n = 1, rat)		
$-CH_2-CH_2-CH_2$-S-Ph	**325**		1%	(10 μM, n = 1)	2%	(32 μM, n = 1, rat)		
Straight Chain Alkyl								
H	**212**							
n-C1	**45**		41%	(n = 1), **2,239 nM** (n = 1)				
n-C4	**331**		4%	(1 μM, n = 1)				
n-C5	**337**		3%	(1 μM, n = 1)	29%	(32 μM, n = 1, rat)		
n-C6	**339**		3%	(1 μM, n = 1)	33%	(32 μM, n = 1, rat)		
n-C7	**341**		0%	(1 μM, n = 1)	21%	(10 μM, n = 1)	61%	(32 μM, n = 1, rat)
n-C8	**343**		0%	(1 μM, n = 1)	34%	(32 μM, n = 1, rat)		

n-C12	**345**		0%	(1 μM, n = 1)	3%	(32 μM, n = 1, rat)	
n-C14	**347**		0%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	
n-C18	**349**		0%	(1 μM, n = 1)	3%	(32 μM, n = 1, rat)	
C2-Branched Alkyl							
$-CH_2$-cPr	**213**		1%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	
$-CH_2$-cPent	**215**		2%	(1 μM, n = 1)	13%	(32 μM, n = 1, rat)	
$-CH_2$-cHex	**217**		2%	(1 μM, n = 1)	15%	(32 μM, n = 1, rat)	
$-CH_2$-(2-Pr)	**309**		2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	
$-CH_2$-(3-Pent)	**333**		2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	
C3-Chain							
$-CH_2-CH=CH_2$	**305**		10%	(1 μM, n = 1)	33%	(32 μM, n = 1, rat)	
$-CH_2-CH\equiv CH$	**307**		0%	(1 μM, n = 1)	43%	(32 μM, n = 1, rat)	
$-CH_2$-cPr	**213**						
C3-Spaced Ring							
$-CH_2-CH_2-CH_2$-cHex	**313**		1%	(1 μM, n = 1)			
$-CH_2-CH_2-CH_2$-Ph	**315**		0%	(1 μM, n = 1)	6%	(32 μM, n = 1, rat)	
$-CH_2$-CH=CH-Ph	**317**		0%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	
Carbonyls							
$-CH_2$-COOMe	**227**		2%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	
$-CH_2$-COOtBu	**229**		1%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	
$-CH_2-CONH_2$	**231**		0%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	
$-CH_2-CH_2$-CN	**293**		2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	
$-CH_2-CH_2-CONEt_2$	**-**						
$-CH_2-CH_2$-OAc	**295**		3%	(1 μM, n = 1)	28%	(32 μM, n = 1, rat)	

5-MeO Tryptamines		Bi	% max 5-HT, Conc. or EC_{50}		% max. 5-HT		% max 5-HT	
Compound			% max	(c, n, SEM) or: (n, SEM), **EC_{50}** (n, SEM)	% max	(c, n, SEM)	% max	(c, n, SEM)
Agonist Standards								
-	**11**							
-	**46**							
-	**47**							
5-HT	**6**	-	108%	(n = 2, ±6%), **123 nM** (n = 2, ±15 nM)				
(4-Br-Bn)-5-MeO-T	**19**		4%	(1 µM, n = 2, ±0%)				
Antagonist Standards								
Ketanserin	**48**							
AC-90179	**50**							
MDL 100,907	**49**							
Simple Tryptamines								
5-MeO-Tryptamine	**358**							
5-MeO-NMT	**208**	-	98%	(n = 1), **575 nM** (n = 1)				
5-MeO-DMT	**19**	-	98%	(n = 1), **741 nM** (n = 1)				
6-MeO-2-Me-THBC	**226**		2%	(1 µM, n = 1)	13%	(32 µM, n = 1, rat)		
Ethylene-bis-(5-MeO-NMT)	**303**		3%	(1 µM, n = 1)	35%	(32 µM, n = 1, rat)		
Benzyl								
Benzyl	**207**							
4-Br-benzyl	**222**		0%	(1 µM, n = 1)	10%	(32 µM, n = 1, rat)		
nor-4-Br-benzyl	**19**		4%	(1 µM, n = 2, ±0%)	83%	(32 µM, n = 1, rat)		
2-Substituted Phenethyl								
2-H	**234**		5%	(10 µM, n = 1)	16%	(32 µM, n = 1, rat)		
2-Me	**236**		1%	(1 µM, n = 1)	18%	(32 µM, n = 1, rat)		
2-F	**256**		0%	(10 µM, n = 1)	2%	(32 µM, n = 1, rat)		
2-Cl	**260**		0%	(1 µM, n = 1)	2%	(32 µM, n = 1, rat)		
2,5-Me	**272**		34%	(n = 2, ±5%), **309 nM** (n = 2, ±127 nM)				
2-MeO	**246**		4%	(1 µM, n = 1)	12%	(32 µM, n = 1, rat)		
2,5-MeO	**276**	+	27%	(n = 2, ±4%), **320 nM** (n = 2, ±69 nM)	31%	(10 µM, n = 2, ±2%)	47%	(32 µM, n = 1)
2,6-Cl								
3-Substituted Phenethyl								
3-H	**234**		5%	(10 µM, n = 1)	16%	(32 µM, n = 1, rat)		
3-Me	**238**		1%	(1 µM, n = 1)	18%	(32 µM, n = 1, rat)		
3-AcO	-							
3-MeO	-							
3-Cl	**262**		2%	(1 µM, n = 1)	40%	(32 µM, n = 1, rat)		
3-Br	**268**		3%	(1 µM, n = 1)	58%	(32 µM, n = 1, rat)		
2,5-Me	**272**		34%	(n = 2, ±5%), **309 nM** (n = 2, ±127 nM)				
3,5-Me	**274**		2%	(1 µM, n = 1)	106%	(32 µM, n = 1, rat)		
2,5-MeO	**276**		27%	(n = 2, ±4%), **320 nM** (n = 2, ±69 nM)	31%	(10 µM, n = 2, ±2%)	47%	(32 µM, n = 1)
3,4-MeO	**278**		62%	(n = 3, ±3%), **84 nM** (n = 3, ±10 nM)	75%	(32 µM, n = 3, ±1%)		
3,4-Cl	**282**		1%	(1 µM, n = 1)				
4-Substituted Phenethyl								
4-H	**234**		5%	(10 µM, n = 1)	16%	(32 µM, n = 1, rat)		
4-Me	**240**		1%	(1 µM, n = 1)	22%	(32 µM, n = 1, rat)		
4-MeO	**250**		40%	(n = 1), **302 nM** (n = 1)				
4-F	**258**		1%	(1 µM, n = 1)	12%	(32 µM, n = 1, rat)		
4-Cl	**264**							
4-Br	**270**		1%	(1 µM, n = 1)	60%	(32 µM, n = 1, rat)		
4-NO_2	**254**		8%	(1 µM, n = 1)	51%	(32 µM, n = 1, rat)		

4-Ph	**242**		26%	(n = 2, ±12%), **1,475 nM** (n = 2,	67%	(10 μM, n = 3, ±3%)	55%	(32 μM, n = 2, ±9%)
3,4-MeO	**278**	+	62%	(n = 3, ±3%), **84 nM** (n = 3, ±10 nM)	75%	(32 μM, n = 3, ±1%)		
3,4-Cl	**282**		1%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)		

Me-Substituted Phenethyl

H	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
2-Me	**236**		1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)		
3-Me	**238**		1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)		
4-Me	**240**		1%	(1 μM, n = 1)	22%	(32 μM, n = 1, rat)		
2,5-Me	**272**	+	34%	(n = 2, ±5%), **309 nM** (n = 2, ±127 nM)	41%	(32 μM, n = 3, ±6%)		
3,5-Me	**274**		2%	(1 μM, n = 1)	106%	(32 μM, n = 1, rat)		

MeO-Substituted Phenethyl

H	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
2-MeO	**246**		4%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)		
3-MeO	-							
4-MeO	**250**	+	40%	(n = 1), **302 nM** (n = 1)	27%	(1 μM, n = 2, ±1%)	42%	(10 μM, n = 1)
2,5-MeO	**276**		27%	(n = 2, ±4%), **320 nM** (n = 2, ±69 nM)	31%	(10 μM, n = 2, ±2%)	47%	(32 μM, n = 1)
3,4-MeO	**278**		62%	(n = 3, ±3%), **84 nM** (n = 3, ±10 nM)	75%	(32 μM, n = 3, ±1%)		

F-Substituted Phenethyl

H	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
2-F	**256**		0%	(10 μM, n = 1)	2%	(32 μM, n = 1, rat)		
4-F	**258**		1%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)		

Cl-Substituted Phenethyl

H	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
2-Cl	**260**		0%	(1 μM, n = 1)	2%	(32 μM, n = 1, rat)		
3-Cl	**262**		2%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)		
4-Cl	**264**							
3,4-Cl	**282**		1%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)		
2,6-Cl	-							

Br-Substituted Phenethyl

H	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
3-Br	**268**		3%	(1 μM, n = 1)	58%	(32 μM, n = 1, rat)		
4-Br	**270**		1%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)		

C_2-Spaced Aromatics

-CH_2-CH_2-Ph	**234**		5%	(10 μM, n = 1)				
-CH_2-CH_2-(3-indolyl)	**284**	+	24%	(n = 3, ±4%), **50 nM** (n = 3, ±15 nM)	30%	(10 μM, n = 4, ±3%)	54%	(32 μM, n = 2, ±2%)
-CH_2-CH_2-(5-MeO-3-indolyl)	**286**		64%	(n = 3, ±11%), **87 nM** (n = 3, ±11 nM)	79%	(32 μM, n = 1)		
-CH_2-CH_2-(1-naphthyl)	**288**	+	14%	(n = 1), **182 nM** (n = 1)	46%	(10 μM, n = 2, ±8%)		
-CH_2-CH_2-(2-naphthyl)	**290**		6%	(1 μM, n = 1)	33%	(10 μM, n = 1)	78%	(32 μM, n = 1, rat)

Phenyl-alkyl

-CH_2-Ph	**207**							
-CH_2-CH_2-Ph	**234**		5%	(10 μM, n = 1)	16%	(32 μM, n = 1, rat)		
-CH_2-CH_2-CH_2-Ph	**316**		1%	(1 μM, n = 2, ±0%)	12%	(32 μM, n = 1, rat)		
-CH_2-CH_2-CH_2-(3,4,5-MeO-	**322**	-	47%	(n = 2, ±9%), **257 nM** (n = 2, ±106 nM)	57%	(32 μM, n = 1)		
-CH_2-CH_2-CH_2-CH_2-Ph	**336**		2%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)		
-CH_2-CH_2-CH_2-S-Ph	**326**		1%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)		

Straight Chain Alkyl

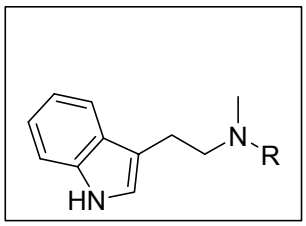
H	**208**		98%	(n = 1), **575 nM** (n = 1)				
n-C1	-	-	98%	(n = 1), **741 nM** (n = 1)				
n-C4	**332**	+	38%	(n = 1), **1,318 nM** (n = 1)	47%	(32 μM, n = 1)		
n-C5	**338**	+	35%	(n = 1), **1,660 nM** (n = 1)				
n-C6	-							
n-C7	-							
n-C8	**344**		6%	(1 μM, n = 1)	118%	(32 μM, n = 1, rat)		

n-C12	**346**		0%	(1 μM, n = 1)	28%	(32 μM, n = 1, rat)		
n-C14	**348**		0%	(1 μM, n = 1)	7%	(32 μM, n = 1, rat)		
n-C18	**350**		0%	(1 μM, n = 1)	8%	(32 μM, n = 1, rat)		
C^2-Branched Alkyl								
$-CH_2$-cPr	**-**							
$-CH_2$-cPent	**216**		5%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)		
$-CH_2$-cHex	**218**		5%	(1 μM, n = 1)	66%	(32 μM, n = 1, rat)		
$-CH_2$-(2-Pr)	**310**		-1%	(1 μM, n = 1)	47%	(10 μM, n = 1)	74%	(32 μM, n = 1, rat)
$-CH_2$-(3-Pent)	**334**		2%	(1 μM, n = 1)	47%	(32 μM, n = 1, rat)		
C_3-Chain								
$-CH_2-CH=CH_2$	**306**	**-**	92%	(n = 1), **575 nM** (n = 1)				
$-CH_2-CH\equiv CH$	**308**		81%	(n = 2, ±2%), **811 nM** (n = 2, ±166 nM)	93%	(32 μM, n = 1)		
$-CH_2$-cPr	**-**							
C_3-Spaced Ring								
$-CH_2-CH_2-CH_2$-cHex	**314**	**+**	8%	(1 μM, n = 3, ±3%)	46%	(10 μM, n = 2, ±10%)	111%	(32 μM, n = 2, ±20%)
$-CH_2-CH_2-CH_2$-Ph	**316**		1%	(1 μM, n = 2, ±0%)	12%	(32 μM, n = 1, rat)		
$-CH_2-CH=CH$-Ph	**318**							
Carbonyls								
$-CH_2$-COOMe	**228**		5%	(1 μM, n = 2, ±4%)	45%	(32 μM, n = 1, rat)		
$-CH_2$-COOtBu	**230**		2%	(1 μM, n = 1)	38%	(32 μM, n = 1, rat)		
$-CH_2-CONH_2$	**232**		0%	(1 μM, n = 1)	24%	(32 μM, n = 1, rat)		
$-CH_2-CH_2$-CN	**294**		1%	(1 μM, n = 1)	28%	(32 μM, n = 1, rat)		
$-CH_2-CH_2-CONEt_2$	**302**	**-**	40%	(n = 2, ±2%), **2,338 nM** (n = 2, ±824 nM)				
$-CH_2-CH_2$-OAc	**-**							

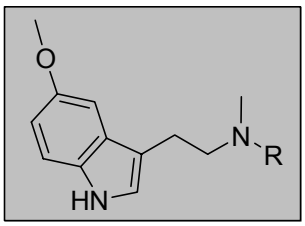
Functional data compared to binding data (Table 10)

Table 10: Functional data in comparison to receptor binding data.

Functional IP accumulation data at cells transfected with the human or the rat 5-HT_{2A} receptor in comparison to human 5-HT_{2A} receptor binding data. Functional antagonism of many of the tested compound is indicated by a negligible activation at concentrations at or above 1 µM in combination with a lower nanomolar binding constant. The binding data are taken from Table 7, the functional data are taken from Table 9. Compounds are arranged by classes and may appear in several different contexts. White rows: 5-unsubstituted tryptamines; gray underlined rows: 5-methoxy substituted tryptamines.



5-unsubstituted tryptamines
(white fields)



5-MeO-tryptamines
(gray fields)

Ligand Category		Percent of Max. 5-HT Stimulation		Percent of Max. 5-HT Stimulation		Binding
Ligand		% max	(c, n, SEM)	% max	(c, n, SEM)	K_i 5-HT_{2A}
Agonist Standards						
-	**11**					0.4 nM
-	**46**					13 nM
-	**47**					7.3 nM
5-HT	**6**	84%	(1 μM, n = 2, ±15%)	100%	(10 μM)	137 nM
(4-Br-Bn)-5-MeO-T	**19**	4%	(1 μM, n = 2, ±0%)	83%	(32 μM, n = 1, rat)	534 nM
Antagonist Standards						
Ketanserin	**48**	0%	(1 μM, n = 1, rat)	0%	(32 μM, n = 1, rat)	1.0 nM
AC-90179	**50**					8.4 nM
MDL 100,907	**49**	-1%	(1 μM, n = 1, rat)	0%	(32 μM, n = 1, rat)	
Simple Tryptamines						
Tryptamine	**5**					1,374 nM
NMT	**212**	20%	(1 μM, n = 1)	62%	(32 μM, n = 1)	1,890 nM
DMT	**45**	16%	(1 μM, n = 2, ±2%)	36%	(32 μM, n = 1)	1,093 nM
Benzyl						
Benzyl	**210**	4%	(1 μM, n = 1, rat)	28%	(32 μM, n = 1, rat)	697 nM
4-Br-benzyl	**221**	3%	(1 μM, n = 3, ±3%)	27%	(32 μM, n = 2, ±4%)	904 nM
nor-4-Br-benzyl	**359**					534 nM
2-Substituted Phenethyl						
2-H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
2-Me	**235**	1%	(1 μM, n = 1)			22 nM
2-F	**255**	1%	(1 μM, n = 1)	14%	(32 μM, n = 1, rat)	18 nM
2-Cl	**259**	1%	(1 μM, n = 1)	15%	(32 μM, n = 1, rat)	6.1 nM
2,5-Me	**196**	21%	(1 μM, n = 5, ±3%)	112%	(32 μM, n = 5, ±22%)	18 nM
2-MeO	**245**	3%	(1 μM, n = 1)	35%	(32 μM, n = 1, rat)	13 nM
2,5-MeO	**275**	23%	(1 μM, n = 2, ±1%)	37%	(10 μM, n = 1)	13 nM
2,6-Cl	**279**	11%	(1 μM, n = 2, ±2%)	109%	(32 μM, n = 1)	68 nM
3-Substituted Phenethyl						
3-H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
3-Me	**237**	6%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)	12 nM
3-AcO	**243**	23%	(1 μM, n = 2, ±0%)	74%	(32 μM, n = 1)	69 nM
3-MeO	**247**	15%	(1 μM, n = 2, ±2%)	92%	(32 μM, n = 1)	32 nM
3-Cl	**261**	4%	(1 μM, n = 1)	57%	(32 μM, n = 1, rat)	19 nM
3-Br	**267**	4%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)	16 nM
2,5-Me	**196**	21%	(1 μM, n = 5, ±3%)	112%	(32 μM, n = 5, ±22%)	18 nM
3,5-Me	**273**	35%	(1 μM, n = 2, ±3%)	164%	(32 μM, n = 1)	8.4 nM
2,5-MeO	**275**	23%	(1 μM, n = 2, ±1%)	37%	(10 μM, n = 1)	13 nM
3,4-MeO	**277**	27%	(1 μM, n = 4, ±5%)	42%	(32 μM, n = 1)	18 nM
3,4-Cl	**281**	2%	(1 μM, n = 1)			29 nM
4-Substituted Phenethyl						
4-H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
4-Me	**239**	2%	(1 μM, n = 1)	55%	(32 μM, n = 1, rat)	22 nM
4-MeO	**249**					90 nM
4-F	**257**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	40 nM
4-Cl	**263**	2%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)	44 nM
4-Br	**269**	1%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)	34 nM
4-NO_2	**253**	6%	(1 μM, n = 1)	55%	(32 μM, n = 1, rat)	444 nM

4-Ph	**241**	6%	(1 μM, n = 1)	49%	(32 μM, n = 1, rat)	107 nM
3,4-MeO	**277**	27%	(1 μM, n = 4, ±5%)	42%	(32 μM, n = 1)	18 nM
3,4-Cl	**281**	2%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)	29 nM
Me-Substituted Phenethyl						
H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
2-Me	**235**	1%	(1 μM, n = 1)			22 nM
3-Me	**237**	6%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)	12 nM
4-Me	**239**	2%	(1 μM, n = 1)	55%	(32 μM, n = 1, rat)	22 nM
2,5-Me	**196**	21%	(1 μM, n = 5, ±3%)	112%	(32 μM, n = 5, ±22%)	18 nM
3,5-Me	**273**	35%	(1 μM, n = 2, ±3%)	164%	(32 μM, n = 1)	8.4 nM
MeO-Substituted Phenethyl						
H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
2-MeO	**245**	3%	(1 μM, n = 1)	35%	(32 μM, n = 1, rat)	13 nM
3-MeO	**247**	15%	(1 μM, n = 2, ±2%)	92%	(32 μM, n = 1)	32 nM
4-MeO	**249**	2%	(1 μM, n = 1)			90 nM
2,5-MeO	**275**	23%	(1 μM, n = 2, ±1%)			13 nM
3,4-MeO	**277**	27%	(1 μM, n = 4, ±5%)	42%	(32 μM, n = 1)	18 nM
F-Substituted Phenethyl						
H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
2-F	**255**	1%	(1 μM, n = 1)	14%	(32 μM, n = 1, rat)	18 nM
4-F	**257**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	40 nM
Cl-Substituted Phenethyl						
H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
2-Cl	**259**	1%	(1 μM, n = 1)	15%	(32 μM, n = 1, rat)	6.1 nM
3-Cl	**261**	4%	(1 μM, n = 1)	57%	(32 μM, n = 1, rat)	19 nM
4-Cl	**263**	2%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)	44 nM
3,4-Cl	**281**	2%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)	29 nM
2,6-Cl	**279**	11%	(1 μM, n = 2, ±2%)	109%	(32 μM, n = 1)	68 nM
Br-Substituted Phenethyl						
H	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
3-Br	**267**	4%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)	16 nM
4-Br	**269**	1%	(1 μM, n = 1)	39%	(32 μM, n = 1, rat)	34 nM
C_2-Spaced Aromatics						
-CH_2-CH_2-Ph	**233**	3%	(1 μM, n = 1)			73 nM
-CH_2-CH_2-(3-indolyl)	**283**	17%	(1 μM, n = 3, ±1%)	54%	(32 μM, n = 2, ±25%)	12 nM
-CH_2-CH_2-(5-MeO-3-indolyl)	**284**	20%	(1 μM, n = 4, ±3%)	54%	(32 μM, n = 2, ±2%)	9.9 nM
-CH_2-CH_2-(1-naphthyl)	**287**	20%	(1 μM, n = 7, ±3%)	94%	(32 μM, n = 8, ±11%)	10 nM
-CH_2-CH_2-(2-naphthyl)	**289**	8%	(1 μM, n = 1)	90%	(32 μM, n = 1, rat)	29 nM
Phenyl-alkyl						
-CH_2-Ph	**210**					697 nM
-CH_2-CH_2-Ph	**233**	3%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	73 nM
-CH_2-CH_2-CH_2-Ph	**315**	0%	(1 μM, n = 1)	6%	(32 μM, n = 1, rat)	15 nM
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**321**	5%	(10 μM, n = 1)	11%	(32 μM, n = 1, rat)	40 nM
-CH_2-CH_2-CH_2-CH_2-Ph	**335**	0%	(1 μM, n = 1)	7%	(32 μM, n = 1, rat)	19 nM
-CH_2-CH_2-CH_2-S-Ph	**325**	1%	(10 μM, n = 1)	2%	(32 μM, n = 1, rat)	1.8 nM
Straight Chain Alkyl						
H	**212**	20%	(1 μM, n = 1)	62%	(32 μM, n = 1)	1,890 nM
n-C1	**45**	16%	(1 μM, n = 2, ±2%)	36%	(32 μM, n = 1)	1,093 nM
n-C4	**331**	4%	(1 μM, n = 1)			1,020 nM
n-C5	**337**	3%	(1 μM, n = 1)	29%	(32 μM, n = 1, rat)	655 nM
n-C6	**339**	3%	(1 μM, n = 1)	33%	(32 μM, n = 1, rat)	181 nM
n-C7	**341**	0%	(1 μM, n = 1)	61%	(32 μM, n = 1)	46 nM
n-C8	**343**	0%	(1 μM, n = 1)	34%	(32 μM, n = 1, rat)	17 nM

n-C12	**345**	0%	(1 μM, n = 1)	3%	(32 μM, n = 1, rat)	129 nM
n-C14	**347**	0%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	366 nM
n-C18	**349**	0%	(1 μM, n = 1)	3%	(32 μM, n = 1, rat)	4,926 nM
C^2-Branched Alkyl						
$-CH_2$-cPr	**213**	1%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	1,537 nM
$-CH_2$-cPent	**215**	2%	(1 μM, n = 1)	13%	(32 μM, n = 1, rat)	585 nM
$-CH_2$-cHex	**217**	2%	(1 μM, n = 1)	15%	(32 μM, n = 1, rat)	1,255 nM
$-CH_2$-(2-Pr)	**309**	2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	538 nM
$-CH_2$-(3-Pent)	**333**	2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	1,379 nM
C_3-Chain						
$-CH_2-CH=CH_2$	**305**	10%	(1 μM, n = 1)	33%	(32 μM, n = 1, rat)	473 nM
$-CH_2-CH\equiv CH$	**307**	0%	(1 μM, n = 1)	43%	(32 μM, n = 1, rat)	622 nM
$-CH_2$-cPr	**213**					1,537 nM
C_3-Spaced Ring						
$-CH_2-CH_2-CH_2$-cHex	**313**	1%	(1 μM, n = 1)			44 nM
$-CH_2-CH_2-CH_2$-Ph	**315**	0%	(1 μM, n = 1)	6%	(32 μM, n = 1, rat)	15 nM
$-CH_2-CH=CH$-Ph	**317**	0%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	39 nM
Carbonyls						
$-CH_2$-COOMe	**227**	2%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	8,252 nM
$-CH_2$-COOtBu	**229**	1%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	994 nM
$-CH_2-CONH_2$	**231**	0%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	44,779 nM
$-CH_2-CH_2$-CN	**293**	2%	(1 μM, n = 1)	21%	(32 μM, n = 1, rat)	1,864 nM
$-CH_2-CH_2-CONEt_2$	**-**					
$-CH_2-CH_2$-OAc	**295**	3%	(1 μM, n = 1)	28%	(32 μM, n = 1, rat)	2,000 nM

Ligand Category		Percent of Max. 5-HT Stimulation		Percent of Max. 5-HT Stimulation		Binding
Ligand		% max	(c, n, SEM)	% max	(c, n, SEM)	K_i 5-HT_{2A}
Agonist Standards						
-	**11**					0.4 nM
-	**46**					13 nM
-	**47**					7.3 nM
5-HT	**6**	84%	(1 μM, n = 2, ±15%)	100%	(10 μM)	137 nM
(4-Br-Bn)-5-MeO-T (33)	**19**	4%	(1 μM, n = 2, ±0%)	83%	(32 μM, n = 1, rat)	534 nM
Antagonist Standards						
Ketanserin	**48**	0%	(1 μM, n = 1, rat)	0%	(32 μM, n = 1, rat)	1.0 nM
AC-90179	**50**					8.4 nM
MDL 100,907	**49**	-1%	(1 μM, n = 1, rat)	0%	(32 μM, n = 1, rat)	
Simple Tryptamines						
5-MeO-Tryptamine	**358**					152 nM
5-MeO-NMT	**208**	52%	(1 μM, n = 1)	91%	(32 μM, n = 1)	525 nM
5-MeO-DMT	**15**	57%	(1 μM, n = 1)	87%	(32 μM, n = 1)	558 nM
6-MeO-2-Me-THBC	**226**	2%	(1 μM, n = 1)	13%	(32 μM, n = 1, rat)	1,521 nM
Ethylene-bis-(5-MeO-NMT)	**303**	3%	(1 μM, n = 1)	35%	(32 μM, n = 1, rat)	1,696 nM
Benzyl						
Benzyl	**207**	8%	(1 μM, n = 1, rat)	37%	(32 μM, n = 1, rat)	935 nM
4-Br-benzyl	**222**	0%	(1 μM, n = 1)	10%	(32 μM, n = 1, rat)	857 nM
nor-4-Br-benzyl	**19**	4%	(1 μM, n = 2, ±0%)	83%	(32 μM, n = 1, rat)	534 nM
2-Substituted Phenethyl						
2-H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
2-Me	**236**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	19 nM
2-F	**256**	0%	(10 μM, n = 1)	2%	(32 μM, n = 1, rat)	4.3 nM
2-Cl	**260**	0%	(1 μM, n = 1)	2%	(32 μM, n = 1, rat)	5.5 nM
2,5-Me	**272**	11%	(1 μM, n = 4, ±7%)	41%	(32 μM, n = 3, ±6%)	19 nM
2-MeO	**246**	4%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)	20 nM
2,5-MeO	**276**	21%	(1 μM, n = 3, ±1%)	47%	(32 μM, n = 1)	57 nM
2,6-Cl	**-**					
3-Substituted Phenethyl						
3-H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
3-Me	**238**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	30 nM
3-AcO	**-**					
3-MeO	**-**					
3-Cl	**262**	2%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)	12 nM
3-Br	**268**	3%	(1 μM, n = 1)	58%	(32 μM, n = 1, rat)	4.5 nM
2,5-Me	**272**	11%	(1 μM, n = 4, ±7%)	41%	(32 μM, n = 3, ±6%)	19 nM
3,5-Me	**274**	2%	(1 μM, n = 1)	106%	(32 μM, n = 1, rat)	12 nM
2,5-MeO	**276**	21%	(1 μM, n = 3, ±1%)	47%	(32 μM, n = 1)	57 nM
3,4-MeO	**278**	52%	(1 μM, n = 4, ±5%)	75%	(32 μM, n = 3, ±1%)	19 nM
3,4-Cl	**282**	1%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)	19 nM
4-Substituted Phenethyl						
4-H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
4-Me	**240**	1%	(1 μM, n = 1)	22%	(32 μM, n = 1, rat)	16 nM
4-MeO	**250**	27%	(1 μM, n = 2, ±1%)	82%	(32 μM, n = 1, rat)	30 nM
4-F	**258**	1%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)	19 nM
4-Cl	**264**					
4-Br	**270**	1%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)	30 nM
4-NO_2	**254**	8%	(1 μM, n = 1)	51%	(32 μM, n = 1, rat)	413 nM

4-Ph	**242**	15%	(1 μM, n = 4, ±4%)	55%	(32 μM, n = 2, ±5%)	4.5 nM
3,4-MeO	**278**	52%	(1 μM, n = 4, ±5%)	75%	(32 μM, n = 3, ±1%)	19 nM
3,4-Cl	**282**	1%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)	19 nM
Me-Substituted Phenethyl						
H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
2-Me	**236**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	19 nM
3-Me	**238**	1%	(1 μM, n = 1)	18%	(32 μM, n = 1, rat)	30 nM
4-Me	**240**	1%	(1 μM, n = 1)	22%	(32 μM, n = 1, rat)	16 nM
2,5-Me	**272**	11%	(1 μM, n = 4, ±7%)	41%	(32 μM, n = 3, ±6%)	19 nM
3,5-Me	**274**	2%	(1 μM, n = 1)	106%	(32 μM, n = 1, rat)	12 nM
MeO-Substituted Phenethyl						
H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
2-MeO	**246**	4%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)	12 nM
3-MeO	-					
4-MeO	**250**	27%	(1 μM, n = 2, ±1%)	82%	(32 μM, n = 1, rat)	9.7 nM
2,5-MeO	**276**	21%	(1 μM, n = 3, ±1%)	47%	(32 μM, n = 1)	57 nM
3,4-MeO	**278**	52%	(1 μM, n = 4, ±5%)	75%	(32 μM, n = 3, ±1%)	19 nM
F-Substituted Phenethyl						
H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
2-F	**256**	0%	(10 μM, n = 1)	2%	(32 μM, n = 1, rat)	4.3 nM
4-F	**258**	1%	(1 μM, n = 1)	12%	(32 μM, n = 1, rat)	19 nM
Cl-Substituted Phenethyl						
H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
2-Cl	**260**	0%	(1 μM, n = 1)	2%	(32 μM, n = 1, rat)	5.5 nM
3-Cl	**262**	2%	(1 μM, n = 1)	40%	(32 μM, n = 1, rat)	12 nM
4-Cl	**264**					
3,4-Cl	**282**	1%	(1 μM, n = 1)	50%	(32 μM, n = 1, rat)	19 nM
2,6-Cl	-					
Br-Substituted Phenethyl						
H	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
3-Br	**268**	3%	(1 μM, n = 1)	58%	(32 μM, n = 1, rat)	4.5 nM
4-Br	**270**	1%	(1 μM, n = 1)	60%	(32 μM, n = 1, rat)	30 nM
C_2-Spaced Aromatics						
-CH_2-CH_2-Ph	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
-CH_2-CH_2-(3-indolyl)	**284**	20%	(1 μM, n = 4, ±3%)	54%	(32 μM, n = 2, ±2%)	9.9 nM
-CH_2-CH_2-(5-MeO-3-indolyl)	**286**	51%	(1 μM, n = 4, ±7%)	79%	(32 μM, n = 1)	30 nM
-CH_2-CH_2-(1-naphthyl)	**288**	14%	(1 μM, n = 2, ±2%)			13 nM
-CH_2-CH_2-(2-naphthyl)	**290**	6%	(1 μM, n = 1)	78%	(32 μM, n = 1, rat)	21 nM
Phenyl-alkyl						
-CH_2-Ph	**207**					935 nM
-CH_2-CH_2-Ph	**234**	6%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	30 nM
-CH_2-CH_2-CH_2-Ph	**316**	1%	(1 μM, n = 2, ±0%)	12%	(32 μM, n = 1, rat)	20 nM
-CH_2-CH_2-CH_2-(3,4,5-MeO-Ph)	**322**	28%	(1 μM, n = 4, ±3%)	57%	(32 μM, n = 1)	156 nM
-CH_2-CH_2-CH_2-CH_2-Ph	**336**	2%	(1 μM, n = 1)	26%	(32 μM, n = 1, rat)	50 nM
-CH_2-CH_2-CH_2-S-Ph	**326**	1%	(1 μM, n = 1)	16%	(32 μM, n = 1, rat)	9.1 nM
Straight Chain Alkyl						
H	**208**	52%	(1 μM, n = 1)	91%	(32 μM, n = 1)	525 nM
n-C1	-	57%	(1 μM, n = 1)	87%	(32 μM, n = 1)	558 nM
n-C4	**332**	13%	(1 μM, n = 2, ±2%)	47%	(32 μM, n = 1)	721 nM
n-C5	**338**	16%	(1 μM, n = 2, ±1%)	72%	(32 μM, n = 1, rat)	647 nM
n-C6	-					
n-C7	-					
n-C8	**344**	6%	(1 μM, n = 1)	118%	(32 μM, n = 1, rat)	155 nM

n-C12	**346**	0%	(1 µM, n = 1)	28%	(32 µM, n = 1, rat)	253 nM
n-C14	**348**	0%	(1 µM, n = 1)	7%	(32 µM, n = 1, rat)	192 nM
n-C18	**350**	0%	(1 µM, n = 1)	8%	(32 µM, n = 1, rat)	13,907 nM
C^2-Branched Alkyl						
$-CH_2$-cPr	-					
$-CH_2$-cPent	**216**	5%	(1 µM, n = 1)	60%	(32 µM, n = 1, rat)	1,194 nM
$-CH_2$-cHex	**218**	5%	(1 µM, n = 1)	66%	(32 µM, n = 1, rat)	1,277 nM
$-CH_2$-(2-Pr)	**310**	-1%	(1 µM, n = 1)	74%	(32 µM, n = 1, rat)	2,094 nM
$-CH_2$-(3-Pent)	**334**	2%	(1 µM, n = 1)	47%	(32 µM, n = 1, rat)	761 nM
C_3-Chain						
$-CH_2-CH=CH_2$	**306**	47%	(1 µM, n = 2, ±7%)	94%	(32 µM, n = 2, ±4%)	443 nM
$-CH_2-CH\equiv CH$	**308**	40%	(1 µM, n = 3, ±3%)	93%	(32 µM, n = 1)	279 nM
$-CH_2$-cPr	-					
C_3-Spaced Ring						
$-CH_2-CH_2-CH_2$-cHex	**314**	8%	(1 µM, n = 3, ±3%)	111%	(32 µM, n = 2, ±20%)	157 nM
$-CH_2-CH_2-CH_2$-Ph	**316**	1%	(1 µM, n = 2, ±0%)	12%	(32 µM, n = 1, rat)	20 nM
$-CH_2$-CH=CH-Ph	**318**					
Carbonyls						
$-CH_2$-COOMe	**228**	5%	(1 µM, n = 2, ±4%)	45%	(32 µM, n = 1, rat)	5,535 nM
$-CH_2$-COOtBu	**230**	2%	(1 µM, n = 1)	38%	(32 µM, n = 1, rat)	1,925 nM
$-CH_2-CONH_2$	**232**	0%	(1 µM, n = 1)	24%	(32 µM, n = 1, rat)	16,519 nM
$-CH_2-CH_2$-CN	**294**	1%	(1 µM, n = 1)	28%	(32 µM, n = 1, rat)	4,284 nM
$-CH_2-CH_2-CONEt_2$	**302**	16%	(1 µM, n = 3, ±0%)	36%	(32 µM, n = 1)	697 nM
$-CH_2-CH_2$-OAc	-					

References

[1] Anon. (**2004**) *Tocris Catalogue 2004.* Tocris Cookson Inc. MO, USA.

[2] Anon. (**2004**) Satellite symposium: Abstracts of the serotonin meeting*. Fund. Clin. Pharmacol.* **18** (S1), 127-134. *DOI: 10.1111/j.1472-8206.2004.00261.x*

[3] Abrams, J. K., Johnson, P. L., Hollis, J. H., Lowry, C. A. (**2004**) Anatomic and functional topography of the dorsal raphe nucleus*. Ann. N. Y. Acad. Sci.* **1018**, 46-57. *PubMed: 15240351 DOI: 10.1196/annals.1296.005*

[4] Adell, A., Celada, P., Abellan, M. T., Artigas, F. (**2002**) Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei*. Brain Res. Brain Res. Rev.* **39** (2-3), 154-180. *PubMed: 12423765 DOI: 10.1016/S0165-0173(02)00182-0*

[5] Adlersberg, M., Arango, V., Hsiung, S., Mann, J. J., Underwood, M. D., Liu, K., Kassir, S. A., Ruggiero, D. A., Tamir, H. (**2000**) In vitro autoradiography of serotonin 5-$HT_{2A/2C}$ receptor-activated G protein: guanosine-5'-(γ-[^{35}S]thio)triphosphate binding in rat brain*. J. Neurosci. Res.* **61** (6), 674-685. *PubMed: 10972964 DOI: 10.1002/1097-4547(20000915)61:6<674::AID-JNR11>3.0.CO;2-F*

[6] Aghajanian, G. K., Marek, G. J. (**2000**) Serotonin model of schizophrenia: emerging role of glutamate mechanisms*. Brain Res. Brain Res. Rev.* **31** (2-3), 302-312. *PubMed: 10719157 DOI: 10.1016/S0165-0173(99)00046-6*

[7] Aghajanian, G. K., Marek, G. J. (**1999**) Serotonin, via 5-HT_{2A} receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release*. Brain Res.* **825** (1-2), 161-171. *PubMed: 10216183*

[8] Agnati, L. F., Lluis, C., Franco, R., Fuxe, K. (**2003**) Molecular mechanisms and therapeutical implications of intramembrane receptor/receptor interactions among heptahelical receptors with examples from the striatopallidal GABA neurons*. Pharmacol. Rev.* **55** (3), 509-550. *PubMed: 12869660 DOI: 10.1124/pr.55.3.2*

[9] Agurell, S., Blomkvist, S., Catalfomo, P. (**1966**) Biosynthesis of psilocybin in submerged culture of *Psilocybe cubensis. Acta Pharm. Suecica* **3**, 37.

[10] Agurell, S., Nilsson, J. G. L. (**1968**) Biosynthesis of psilocybin*. Acta Chem. Scand.* **22**, 1210.

[11] Alberts, G. L., Chio, C. L., Im, W. B. (**2001**) Allosteric modulation of the human 5-HT_{7A} receptor by lipidic amphipathic compounds*. Mol. Pharmacol.* **60** (6), 1349-1355. *PubMed: 11723242*

[12] Almaula, N., Ebersole, B. J., Ballesteros, J. A., Weinstein, H., Sealfon, S. C. (**1996**) Contribution of a helix 5 locus to selectivity of hallucinogenic and nonhallucinogenic ligands for the human 5-hydroxytryptamine$_{2A}$ and 5-hydroxytryptamine$_{2C}$ receptors: direct and indirect effects on ligand affinity mediated by the same locus*. Mol. Pharmacol.* **50** (1), 34-42. *PubMed: 8700116*

[13] Amargos-Bosch, M., Adell, A., Bortolozzi, A., Artigas, F. (**2003**) Stimulation of α_1-adrenoceptors in the rat medial prefrontal cortex increases the local *in vivo* 5-

hydroxytryptamine release: reversal by antipsychotic drugs. *J. Neurochem.* **87** (4), 831-842. *PubMed: 14622114 DOI: 10.1046/j.1471-4159.2003.02044.x*

[14] Amargos-Bosch, M., Bortolozzi, A., Puig, M. V., Serrats, J., Adell, A., Celada, P., Toth, M., Mengod, G., Artigas, F. (**2004**) Co-expression and in vivo interaction of serotonin$_{1A}$ and serotonin$_{2A}$ receptors in pyramidal neurons of prefrontal cortex. *Cereb. Cortex* **14** (3), 281-299. *PubMed: 14754868*

[15] Anguelova, M., Benkelfat, C., Turecki, G. (**2003**) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. *Mol. Psychiatry* **8** (7), 646-653. *PubMed: 12874600 DOI: 10.1038/sj.mp.4001336*

[16] Appleyard, G. D., Stirling, C. J. M. (**1969**) Elimination-addition. Part XVIII. Acylation of amines and alcohols with adducts of carboxylic acids and allenic onium salts. *J. Chem. Soc. (C)*, 1904-1908.

[17] Araneda, R., Andrade, R. (**1991**) 5-Hydroxytryptamine$_2$ and 5-hydroxytryptamine$_{1A}$ receptors mediate opposing responses on membrane excitability in rat association cortex. *Neuroscience* **40** (2), 399-412. *PubMed: 1851255 DOI: 10.1016/0306-4522(91)90128-B*

[18] Arbain, D., Sargent, M. V. (**1987**) *Aust. J. Chem.* **40**, 1527.

[19] Arvanov, V. L., Liang, X., Magro, P., Roberts, R., Wang, R. Y. (**1999**) A pre- and postsynaptic modulatory action of 5-HT and the 5-HT$_{2A, 2C}$ receptor agonist DOB on NMDA-evoked responses in the rat medial prefrontal cortex. *Eur. J. Neurosci.* **11** (8), 2917-2934. *PubMed: 10457188 DOI: 10.1046/j.1460-9568.1999.00708.x*

[20] Arvanov, V. L., Liang, X., Russo, A., Wang, R. Y. (**1999**) LSD and DOB: interaction with 5-HT$_{2A}$ receptors to inhibit NMDA receptor-mediated transmission in the rat prefrontal cortex. *Eur. J. Neurosci.* **11** (9), 3064-3072. *PubMed: 10510170 DOI: 10.1046/j.1460-9568.1999.00726.x*

[21] Ashby, C. R., Jr., Edwards, E., Harkins, K., Wang, R. Y. (**1989**) Effects of (+/-)-DOI on medial prefrontal cortical cells: a microiontophoretic study. *Brain Res.* **498** (2), 393-396. *PubMed: 2790491*

[22] Ashby, C. R., Jr., Edwards, E., Wang, R. Y. (**1994**) Electrophysiological evidence for a functional interaction between 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in the rat medial prefrontal cortex: an iontophoretic study. *Synapse* **17** (3), 173-181. *PubMed: 7974200*

[23] Aznar, S., Qian, Z., Shah, R., Rahbek, B., Knudsen, G. M. (**2003**) The 5-HT$_{1A}$ serotonin receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain. *Brain Res.* **959** (1), 58-67. *PubMed: 12480158 DOI: 10.1016/S0006-8993(02)03727-7*

[24] Babos, M. (**1983**) Beobachtungsangaben bei einer halluzinogenen *Inocybe*-Art. *Mikol. Közlem.* **3**, 143.

[25] Babos, M. (**1968**) Eine neue *Inocybe*-Art in Ungarn: *Inocybe aeruginascens* n.sp. *Fragmenta Botanica* **6**, 19-22.

[26] Baker, J. G., Hall, I. P., Hill, S. J. (**2003**) Agonist actions of "beta-blockers" provide evidence for two agonist activation sites or conformations of the human ß1-adrenoceptor. *Mol. Pharmacol.* **63** (6), 1312-1321. *PubMed: 12761341;, DOI: DOI: 10.1124/mol.63.6.1312*

[27] Barnes, N. M., Sharp, T. (**1999**) A review of central 5-HT receptors and their function. *Neuropharmacology* **38** (8), 1083-1152. *PubMed: 10462127 DOI: 10.1016/S0028-3908(99)00010-6*

[28] Barton, D. H. R., Kirby, G. W., Prager, R. H., Wilson, E. M. (**1965**) On the origin of the C-1 fragment in indole alkaloids. *J. Chem. Soc.*, 3990-3994.

[29] Baxter, G. S., Murphy, O. E., Blackburn, T. P. (**1994**) Further characterization of 5-hydroxytryptamine receptors (putative 5-HT_{2B}) in rat stomach fundus longitudinal muscle. *Br. J. Pharmacol.* **112** (1), 323-331. *PubMed: 8032658*

[30] Becamel, C., Alonso, G., Galeotti, N., Demey, E., Jouin, P., Ullmer, C., Dumuis, A., Bockaert, J., Marin, P. (**2002**) Synaptic multiprotein complexes associated with 5-HT_{2C} receptors: a proteomic approach. *EMBO J.* **21** (10), 2332-2342. *PubMed: 12006486*

[31] Becamel, C., Gavarini, S., Chanrion, B., Alonso, G., Galeotti, N., Dumuis, A., Bockaert, J., Marin, P. (**2004**) The serotonin 5-HT_{2A} and 5-HT_{2C} receptors interact with specific sets of PDZ proteins. *J. Biol. Chem.* **279** (19), 20257-20266. *PubMed: 14988405 DOI: 10.1074/jbc.M312106200*

[32] Benedict, R. G., Brady, L. R., Smith, A. H., Tyler, V. E. (**1972**) Occurrence of psilocybin and psilocin in certain *Conocybe* and *Psilocybe* species. *Lloydia* **25**, 156.

[33] Berg, K. A., Clarke, W. P., Chen, Y., Ebersole, B. J., McKay, R. D., Maayani, S. (**1994**) 5-Hydroxytryptamine type 2A receptors regulate cyclic AMP accumulation in a neuronal cell line by protein kinase C-dependent and calcium/calmodulin-dependent mechanisms. *Mol. Pharmacol.* **45** (5), 826-836. *PubMed: 8190100*

[34] Besl, H., Mack, P. (**1985**) *Galerina steglichii* spec. nov., ein halluzinogener Häubling. *Z. Mykol.* **51**, 183-184.

[35] Bhatnagar, A., Sheffler, D. J., Kroeze, W. K., Compton-Toth, B., Roth, B. L. (**2004**) Caveolin-1 interacts with 5-HT_{2A} serotonin receptors and profoundly modulates the signaling of selected Gá$_q$-coupled GPCRs. *J. Biol. Chem.* **(in print)**. *PubMed: 15190056 DOI: 10.1074/jbc.M404673200*

[36] Bhatnagar, A., Willins, D. L., Gray, J. A., Woods, J., Benovic, J. L., Roth, B. L. (**2001**) The dynamin-dependent, arrestin-independent internalization of 5-hydroxytryptamine 2A (5-HT2A) serotonin receptors reveals differential sorting of arrestins and 5-HT2A receptors during endocytosis. *J. Biol. Chem.* **276** (11), 8269-8277. *PubMed: 11069907 DOI: 10.1074/jbc.M006968200*

[37] Blair, J. B., Kurrasch-Orbaugh, D., Marona-Lewicka, D., Cumbay, M. G., Watts, V. J., Barker, E. L., Nichols, D. E. (**2000**) Effect of ring fluorination on the pharmacology of hallucinogenic tryptamines. *J. Med. Chem.* **43** (24), 4701-4710. *PubMed: 11101361 DOI: 10.1021/jm000339w*

[38] Boger, D. L., Patterson, J. E., Jin, Q. (**1998**) Structural requirements for 5-HT_{2A} and 5-HT_{1A} serotonin receptor potentiation by the biologically active lipid oleamide. *Proc. Natl. Acad. Sci. U S A* **95** (8), 4102-4107. *PubMed: 9539697*

[39] Bohus, G., Babos, M. (**1977**) *Fungorum rariorum icones colorates* (Pars VIII).

[40] Boothman, L. J., Allers, K. A., Rasmussen, K., Sharp, T. (**2003**) Evidence that central 5-HT_{2A} and 5-$HT_{2B/C}$ receptors regulate 5-HT cell firing in the dorsal raphe

nucleus of the anaesthetised rat. *Br. J. Pharmacol.* **139** (5), 998-1004. *PubMed: 12839874 DOI: 10.1038/sj.bjp.0705328*

[41] Bortolozzi, A., margos-Bosch, M., Adell, A., az-Mataix, L., Serrats, J., Pons, S., Artigas, F. (**2003**) *In vivo* modulation of 5-hydroxytryptamine release in mouse prefrontal cortex by local 5-HT_{2A} receptors: effect of antipsychotic drugs. *Eur. J. Neurosci.* **18** (5), 1235-1246. *PubMed: 12956722 DOI: 10.1046/j.1460-9568.2003.02829.x*

[42] Bös, M., Jenck, F., Martin, J. R., Moreau, J. L., Sleight, A. J., Wichmann, J., Widmer, U. (**1997**) Novel agonists of 5HT_{2C} receptors. Synthesis and biological evaluation of substituted 2-(indol-1-yl)-1-methylethylamines and 2-(indeno[1,2-b]pyrrol-1-yl)-1-methylethylamines. Improved therapeutics for obsessive compulsive disorder. *J. Med. Chem.* **40** (17), 2762-2769. *PubMed: 9276022 DOI: 10.1021/jm970030l*

[43] Bouvier, M. (**2001**) Oligomerization of G-protein-coupled transmitter receptors. *Nat. Rev. Neurosci.* **2** (4), 274-286. *PubMed: 11283750 DOI: 10.1038/35067575*

[44] Brack, A., Hofmann, A., Kalberer, F., Kobel, H., Rutschmann, J. (**1961**) Tryptophan als biogenetische Vorstufe des Psilocybins. *Arch. Pharm.* **294**, 230-234.

[45] Brenneisen, R., Borner, S. (**1988**) Synthesis of baeocystin, a natural psilocybin analogue. *Arch. Pharm. (Weinheim)* **321**, 487-489.

[46] Carr, D. B., Cooper, D. C., Ulrich, S. L., Spruston, N., Surmeier, D. J. (**2002**) Serotonin receptor activation inhibits sodium current and dendritic excitability in prefrontal cortex via a protein kinase C-dependent mechanism. *J. Neurosci.* **22** (16), 6846-6855. *PubMed: 12177182*

[47] Carvalho, A. L., Duarte, C. B., Carvalho, A. P. (**2000**) Regulation of AMPA receptors by phosphorylation. *Neurochem. Res.* **25** (9-10), 1245-1255. *PubMed: 11059799*

[48] Catalfomo, P., Tyler, V. E. (**1964**) The production of psilocybin in submerged culture by *Psilocybe cubensis. Lloydia* **27**, 53.

[49] Celada, P., Puig, M. V., Casanovas, J. M., Guillazo, G., Artigas, F. (**2001**) Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: Involvement of serotonin-1A, $GABA_A$, and glutamate receptors. *J. Neurosci.* **21** (24), 9917-9929. *PubMed: 11739599*

[50] Chambers, J. J., Kurrasch-Orbaugh, D. M., Parker, M. A., Nichols, D. E. (**2001**) Enantiospecific synthesis and pharmacological evaluation of a series of super-potent, conformationally restricted 5-$HT_{2A/2C}$ receptor agonists. *J. Med. Chem.* **44** (6), 1003-1010. *PubMed: 11300881*

[51] Chambers, J. J., Nichols, D. E. (**2002**) A homology-based model of the human 5-HT_{2A} receptor derived from an in silico activated G-protein coupled receptor. *J. Comput. Aided Mol. Des* **16** (7), 511-520. *PubMed: 12510883*

[52] Check, E. (**2004**) Psychedelic drugs: the ups and downs of ecstasy. *Nature* **429** (6988), 126-128. *PubMed: 15141183*

[53] Chen, C., Senanayake, C. H., Bill, T. J., Larsen, R. D., Verhoeven, T. R., Reider, P. J. (**1994**) Improved Fischer indole reaction for the preparation of *N,N*-dimethyltryptamines: Synthesis of L-695,894, a potent 5 HT_{1D} receptor agonist. *J. Org. Chem.* **59** (13), 3738-3741.

[54] Chilton, W. C., Bigwood, J., Jensen, R. E. (**1979**) Psilocin, bufotenine and serotonin: historical and biosynthetic observations. *J. Psyched. Drugs* **11**, 61.

[55] Christopoulos, A., Kenakin, T. (**2002**) G protein-coupled receptor allosterism and complexing. *Pharmacol. Rev.* **54** (2), 323-374. *PubMed: 12037145*

[56] Clemett, D. A., Punhani, T., Duxon, M. S., Blackburn, T. P., Fone, K. C. (**2000**) Immunohistochemical localisation of the 5-HT_{2C} receptor protein in the rat CNS. *Neuropharmacology* **39** (1), 123-132. *PubMed: 10665825*

[57] Cohen, Z., Bouchelet, I., Olivier, A., Villemure, J. G., Ball, R., Stanimirovic, D. B., Hamel, E. (**1999**) Multiple microvascular and astroglial 5-hydroxytryptamine receptor subtypes in human brain: molecular and pharmacologic characterization. *J. Cereb. Blood Flow Metab* **19** (8), 908-917. *PubMed: 10458598*

[58] Cornea-Hebert, V., Riad, M., Wu, C., Singh, S. K., Descarries, L. (**1999**) Cellular and subcellular distribution of the serotonin 5-HT2A receptor in the central nervous system of adult rat. *J. Comp Neurol.* **409** (2), 187-209. *PubMed: 10379914*

[59] Cornea-Hebert, V., Watkins, K. C., Roth, B. L., Kroeze, W. K., Gaudreau, P., Leclerc, N., Descarries, L. (**2002**) Similar ultrastructural distribution of the 5-HT(2A) serotonin receptor and microtubule-associated protein MAP1A in cortical dendrites of adult rat. *Neuroscience* **113** (1), 23-35. *PubMed: 12123681*

[60] Correia, S. S., Duarte, C. B., Faro, C. J., Pires, E. V., Carvalho, A. L. (**2003**) Protein kinase Cγ associates directly with the GluR4 α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor subunit. Effect on receptor phosphorylation. *J. Biol. Chem.* **278** (8), 6307-6313. *PubMed: 12471040 DOI: 10.1074/jbc.M205587200*

[61] Cozzi, N. V., Nichols, D. E. (**1996**) 5-HT_{2A} receptor antagonists inhibit potassium-stimulated gamma-aminobutyric acid release in rat frontal cortex. *Eur. J. Pharmacol.* **309** (1), 25-31. *PubMed: 8864689*

[62] Cudennec, A., Duverger, D., Serrano, A., Scatton, B., MacKenzie, E. T. (**1988**) Influence of ascending serotonergic pathways on glucose use in the conscious rat brain. II. Effects of electrical stimulation of the rostral raphe nuclei. *Brain Res.* **444** (2), 227-246. *PubMed: 3359294 DOI: 10.1016/0006-8993(88)90933-X*

[63] Day, M., Olson, P. A., Platzer, J., Striessnig, J., Surmeier, D. J. (**2002**) Stimulation of 5-HT_2 receptors in prefrontal pyramidal neurons inhibits Ca(v)1.2 L type Ca^{2+} currents via a PLCβ/IP_3/calcineurin signaling cascade. *J. Neurophysiol.* **87** (5), 2490-2504. *PubMed: 11976386 DOI: 10.1152/jn.00843.2001*

[64] De Quervain, D. J., Henke, K., Aerni, A., Coluccia, D., Wollmer, M. A., Hock, C., Nitsch, R. M., Papassotiropoulos, A. (**2003**) A functional genetic variation of the 5-HT2a receptor affects human memory. *Nat. Neurosci.* **6** (11), 1141-1142. *PubMed: 14566344 DOI: 10.1038/nn1146*

[65] DeFelipe, J., Arellano, J. I., Gomez, A., Azmitia, E. C., Munoz, A. (**2001**) Pyramidal cell axons show a local specialization for GABA and 5-HT inputs in monkey and human cerebral cortex. *J. Comp Neurol.* **433** (1), 148-155. *PubMed: 11283956*

[66] Dolbeare, K., Pontoriero, G. F., Gupta, S. K., Mishra, R. K., Johnson, R. L. (**2003**) Synthesis and dopamine receptor modulating activity of 3-substituted gamma-

lactam peptidomimetics of L-prolyl-L-leucyl-glycinamide. *J. Med. Chem.* **46** (5), 727-733. *PubMed: 12593653 DOI: 10.1021/jm020441o*

[67] Doly, S., Madeira, A., Fischer, J., Brisorgueil, M. J., Daval, G., Bernard, R., Verge, D., Conrath, M. (**2004**) The 5-HT_{2A} receptor is widely distributed in the rat spinal cord and mainly localized at the plasma membrane of postsynaptic neurons. *J. Comp Neurol.* **472** (4), 496-511. *PubMed: 15065122 DOI: 10.1002/cne.20082*

[68] Dougalis, A., Lees, G., Ganellin, C. R. (**2004**) The sleep inducing brain lipid cis-oleamide (cOA) does not modulate serotonergic transmission in the CA1 pyramidal neurons of the hippocampus in vitro. *Neuropharmacology* **46** (1), 63-73. *PubMed: 14654098 DOI: 10.1016/S0028-3908(03)00297-1*

[69] Dowd, C. S., Herrick-Davis, K., Egan, C., DuPre, A., Smith, C., Teitler, M., Glennon, R. A. (**2000**) 1-[4-(3-Phenylalkyl)phenyl]-2-aminopropanes as 5-HT_{2A} partial agonists. *J. Med. Chem.* **43** (16), 3074-3084. *PubMed: 10956215 DOI: 10.1021/jm9906062*

[70] Drewitz, G. (**1983**) Eine halluzinogene Rißpilzart, der grünlichverfärbende Rißpilz - *Inocybe aeruginascens. Mykol. Mitteilungsblatt (Halle)* **26**, 11-17.

[71] Ebersole, B. J., Visiers, I., Weinstein, H., Sealfon, S. C. (**2003**) Molecular basis of partial agonism: orientation of indoleamine ligands in the binding pocket of the human serotonin 5-HT_{2A} receptor determines relative efficacy. *Mol. Pharmacol.* **63** (1), 36-43. *PubMed: 12488534*

[72] Ellis, B. S., Griffiths, G., Howes, P. D., Stirlibg, C. J. M. (**1977**) Elimination and addition reactions. Part 28. Nucleophilic addition-replacement reactions with allenic sulphonium salts. *J. Chem. Soc. Perk. Trans. 1* **1977**, 286-292.

[73] Fawzi, A. B., Macdonald, D., Benbow, L. L., Smith-Torhan, A., Zhang, H., Weig, B. C., Ho, G., Tulshian, D., Linder, M. E., Graziano, M. P. (**2001**) SCH-202676: An allosteric modulator of both agonist and antagonist binding to G protein-coupled receptors. *Mol. Pharmacol.* **59** (1), 30-37. *PubMed: 11125021*

[74] Figler, H., Olsson, R. A., Linden, J. (**2003**) Allosteric enhancers of A1 adenosine receptors increase receptor-G protein coupling and counteract Guanine nucleotide effects on agonist binding. *Mol. Pharmacol.* **64** (6), 1557-1564. *PubMed: 14645687 DOI: 10.1124/mol.64.6.1557*

[75] Firn, R. D., Jones, C. G. (**2003**) Natural products - a simple model to explain chemical diversity. *Nat. Prod. Rep.* **20** (4), 382-391. *PubMed: 12964834 DOI: 10.1039/b208815k*

[76] Fitzgerald, L. W., Burn, T. C., Brown, B. S., Patterson, J. P., Corjay, M. H., Valentine, P. A., Sun, J. H., Link, J. R., Abbaszade, I., Hollis, J. M., Largent, B. L., Hartig, P. R., Hollis, G. F., Meunier, P. C., Robichaud, A. J., Robertson, D. W. (**2000**) Possible role of valvular serotonin 5-HT_{2B} receptors in the cardiopathy associated with fenfluramine. *Mol. Pharmacol.* **57** (1), 75-81. *PubMed: 10617681*

[77] Fitzgerald, L. W., Conklin, D. S., Krause, C. M., Marshall, A. P., Patterson, J. P., Tran, D. P., Iyer, G., Kostich, W. A., Largent, B. L., Hartig, P. R. (**1999**) High-affinity agonist binding correlates with efficacy (intrinsic activity) at the human serotonin 5-HT_{2A} and 5-HT_{2C} receptors: evidence favoring the ternary complex and two-state models of agonist action. *J. Neurochem.* **72** (5), 2127-2134. *PubMed: 10217294 DOI: 10.1046/j.1471-4159.1999.0722127.x*

[78] Fotiadis, D., Liang, Y., Filipek, S., Saperstein, D. A., Engel, A., Palczewski, K. (**2004**) The G protein-coupled receptor rhodopsin in the native membrane*. FEBS Lett.* **564** (3), 281-288. *PubMed: 15111110 DOI: 10.1016/S0014-5793(04)00194-2*

[79] Franco, L. H., Joffe, E. B., Puricelli, L., Tatian, M., Seldes, A. M., Palerma, J. A. (**1998**) Indole alkaloids from the tunicate *Aplidium meridianum. J. Nat. Prod.* **61**, 1130.

[80] Fukumitsu, H., Nomura, K., Nagamachi, T., Watanabe, K. (**1985**) Production of 4-hydroxyindole*.* (JP 60,146,870 (CA 103: 215169t 1985)).

[81] Gallagher, T. K., Chen, K., Shih, J. C. (**1993**) Higher affinity of psilocin for human than rat 5-HT_2 receptor indicates binding site structure*. Med. Chem. Res.* **3**, 52-66.

[82] Garegg, P. J., Samuelsson, B. (**1980**) Novel reagent system for converting a hydroxy-group into an iodo-group in carbohydrates with inversion of the configuration*. J. Chem. Soc. Perk. Trans. 1*, 2866-2869.

[83] Garegg, P. J., Samuelsson, B. (**1979**) One-step conversion of vicinal diols into olefins, using a novel reagent system*. Synthesis* (6), 469-471.

[84] Garratt, J. C., Kidd, E. J., Wright, I. K., Marsden, C. A. (**1991**) Inhibition of 5-hydroxytryptamine neuronal activity by the 5-HT agonist, DOI*. Eur. J. Pharmacol.* **199** (3), 349-355. *PubMed: 1915582*

[85] Gartz, Jochen (**1998**) *Personal communication.*

[86] Gartz, J. (**1994**) Extraction and analysis of indole derivatives from fungal biomass*. J. Basic Microbiol.* **34**, 17-22.

[87] Gartz, J. (**1987**) Variation der Alkaloidmenge in Fruchtkörpern von *Inocybe aeruginascens. Planta Med.* **53**, 539-541.

[88] Gartz, J. (**1995**) *Inocybe aeruginascens* Babos*. Eleusis, journal of psychoactive plants & compounds* **3**, 31-34.

[89] Gartz, J. (**1986**) Psilocybin in Mycelkulturen von *Inocybe aeruginascens* [Psilocybin in mycelial cultures of *Inocybe aeruginascens*]*. Biochem. Physiol. Pflanzen* **181**, 511-517.

[90] Gartz, J. (**1989**) Analysis of aeruginascin in fruit bodies of the mushroom *Inocybe aeruginascens. Int. J. Crude Drug Res.* **27** (3), 141-144.

[91] Gartz, J. (**1992**) New aspects of the occurrence, chemistry and cultivation of european hallucinogenic mushrooms*. Annali dei Musei Civici di Rovereto* **8** (Suppl.), 107-124.

[92] Gartz, J. (**1985**) Zur Untersuchung von *Psilocybe semilanceata* (Fr.) Kumm*. Pharmazie* **40** (7), 506.

[93] Gartz, J. (**1985**) Dünnschichtchromatographische Analyse der Inhaltsstoffe von Pilzen der Gattung Stropharia*. Pharmazie.* **40** (2), 134-135.

[94] Gartz, J. (**1985**) Vergleichende dünnschichtchromatographische Untersuchung zweier *Psilocybe*- und einer halluzinogenen *Inocybe*art [Comparative thin layer

chromatography studies of two *Psilocybes* and a hallucinogenic *Inocybe*]. *Pharmazie.* **40** (2), 134. *PubMed: 4039823*

[95] Gartz, J. (**1986**) Quantitative Bestimmung der Indolderivate von *Psilocybe semilanceata* (Fr.) Kumm*. Biochem. Physiol. Pflanzen* **181**, 117-124.

[96] Gartz, J. (**1987**) Vorkommen von Psilocybin und Baeocystin in Fruchtkörpern von *Pluteus salicinus. Planta Med.*, 290-291.

[97] Gartz, J. (**1988**) Biotransformation of tryptamine in fruiting body of *Psilocybe cubensis. Planta Med.* **55**, 249.

[98] Gartz, J. (**1989**) Analyse der Indolderivate in Fruchtkörpern und Mycelien von *Paneolus subalteatus* (Berk. & Br.) Sacc. [Annalysis of the indole derivatives in fruit bodies and mycelia of *Paneolus subalteatus* (Berk. & Br.) Sacc.]*. Biochem. Physiol. Pflanzen* **184**, 171-178.

[99] Gartz, J. (**1989**) Bildung und Verteilung der Indolalkaloide in Fruchtkörpern, Mycelien und Sklerotien von *Psilocybe cubensis. Beiträge zur Kenntnis der Pilze Mitteleuropas* **5**, 167-174.

[100] Gartz, J. (**1989**) Biotransformation of tryptamine derivatives in mycelial cultures of *Psilocybe. J. Basic Microbiol.* **29**, 347.

[101] Gartz, Jochen and Allen, John W. (**2001**) *Teonanácatl: A Bibliography of Entheogenic Fungi (CD-ROM).* Kassel, Germany.

[102] Gartz, J., Drewitz, G. (**1986**) Der grünlichverfärbende Rißpilz - eine *Inocybe*art mit halluzinogener Wirkung [The green discolored mushroom Inocybe aeruginascens - an *Inocybe* species with hallucinogenic effects]*. Z. ärztl. Fortbild. (Jena)* **80** (13), 551-553. *PubMed: 3765692*

[103] Gartz, J., Drewitz, G. (**1985**) Der erste Nachweis des Vorkommens von Psilocybin in Rißpilzen [The first evidence of the occurence of psilocybin in the genus *Inocybe*]. *Z. Mykol.* **51** (2), 199-203.

[104] Gartz, J., Müller, G. K. (**1989**) Analysis and cultivation of fruit bodies and mycelia of *Psilocybe bohemica. Biochem. Physiol. Pflanzen.* **184** (3-4), 337-341.

[105] Gelber, E. I., Kroeze, W. K., Willins, D. L., Gray, J. A., Sinar, C. A., Hyde, E. G., Gurevich, V., Benovic, J., Roth, B. L. (**1999**) Structure and function of the third intracellular loop of the 5-hydroxytryptamine$_{2A}$ receptor: the third intracellular loop is α-helical and binds purified arrestins*. J. Neurochem.* **72** (5), 2206-2214. *PubMed: 10217304 DOI: 10.1046/j.1471-4159.1999.0722206.x*

[106] Gerasimov, M., Marona-Lewicka, D., Kurrasch-Orbaugh, D. M., Qandil, A. M., Nichols, D. E. (**1999**) Further studies on oxygenated tryptamines with LSD-like activity incorporating a chiral pyrrolidine moiety into the side chain*. J. Med. Chem.* **42** (20), 4257-4263. *PubMed: 10514296 DOI: 10.1021/jm990325u*

[107] Gewirtz, J. C., Marek, G. J. (**2000**) Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors*. Neuropsychopharmacology* **23** (5), 569-576. *PubMed: 11027922 DOI: 10.1016/S0893-133X(00)00136-6*

[108] Ghavami, A., Hunt, R. A., Olsen, M. A., Zhang, J., Smith, D. L., Kalgaonkar, S., Rahman, Z., Young, K. H. (**2004**) Differential effects of regulator of G protein

signaling (RGS) proteins on serotonin 5-HT_{1A}, 5-HT_{2A}, and dopamine D_2 receptor-mediated signaling and adenylyl cyclase activity. *Cell Signal.* **16** (6), 711-721. *PubMed: 15093612 DOI: 10.1016/j.cellsig.2003.11.006*

[109] Ghosal, S., Mazumder, U. K. (**1971**) Alkaloids of the leaves of *Banistereopsis argentea. Phytochemistry* **10** (11), 2840-2841. *DOI: 10.1016/S0031-9422(00)97304-7*

[110] Ghosal, S., Mazumder, U. K., Bhattacharya, S. K. (**1971**) Chemical and pharmacological evaluation of *Banisteriopsis argentea* Spring ex Juss. *J. Pharm. Sci.* **60** (8), 1209-1212.

[111] Glatt, C. E., Tampilic, M., Christie, C., DeYoung, J., Freimer, N. B. (**2004**) Re-screening serotonin receptors for genetic variants identifies population and molecular genetic complexity. *Am. J. Med. Genet.* **124B** (1), 92-100. *PubMed: 14681923 DOI: 10.1002/ajmg.b.20056*

[112] Glennon, R. A., Dukat, M., El Bermawy, M., Law, H., los Angeles, J., Teitler, M., King, A., Herrick-Davis, K. (**1994**) Influence of amine substituents on 5-HT_{2A} versus 5-HT_{2C} binding of phenylalkyl- and indolylalkylamines. *J. Med. Chem.* **37** (13), 1929-1935. *PubMed: 8027974*

[113] Gompel, M., Leost, M., De Kier Joffe, E. B., Puricelli, L., Franco, L. H., Palermo, J., Meijer, L. (**2004**) Meridianins, a new family of protein kinase inhibitors isolated from the Ascidian *Aplidium meridianum. Bioorg. Med. Chem. Lett.* **14** (7), 1703-1707. *PubMed: 15026054 DOI: 10.1016/j.bmcl.2004.01.050*

[114] González-Maeso, J., Yuen, T., Ebersole, B. J., Wurmbach, E., Lira, A., Zhou, M., Weisstaub, N., Hen, R., Gingrich, J. A., Sealfon, S. C. (**2003**) Transcriptome fingerprints distinguish hallucinogenic and nonhallucinogenic 5-hydroxytryptamine 2A receptor agonist effects in mouse somatosensory cortex. *J. Neurosci.* **23** (26), 8836-8843. *PubMed: 14523084*

[115] Gonzalo-Ruiz, A., Lieberman, A. R., Sanz-Anquela, J. M. (**1995**) Organization of serotoninergic projections from the raphe nuclei to the anterior thalamic nuclei in the rat: a combined retrograde tracing and 5-HT immunohistochemical study. *J. Chem. Neuroanat.* **8** (2), 103-115. *PubMed: 7598811 DOI: 10.1016/0891-0618(94)00039-V*

[116] Gouldson, P. R., Kidley, N. J., Bywater, R. P., Psaroudakis, G., Brooks, H. D., Diaz, C., Shire, D., Reynolds, C. A. (**2004**) Toward the active conformations of rhodopsin and the β_2-adrenergic receptor. *Proteins* **56** (1), 67-84. *PubMed: 15162487 DOI: 10.1002/prot.20108*

[117] Gourevitch, L. (**1999**) *Personal communication.*

[118] Gray, J. A., Compton-Toth, B. A., Roth, B. L. (**2003**) Identification of two serine residues essential for agonist-induced 5-HT_{2A} receptor desensitization. *Biochemistry* **42** (36), 10853-10862. *PubMed: 12962510 DOI: 10.1021/bi035061z*

[119] Gray, J. A., Sheffler, D. J., Bhatnagar, A., Woods, J. A., Hufeisen, S. J., Benovic, J. L., Roth, B. L. (**2001**) Cell-type specific effects of endocytosis inhibitors on 5-hydroxytryptamine$_{2A}$ receptor desensitization and resensitization reveal an arrestin-, GRK2-, and GRK5-independent mode of regulation in human embryonic kidney 293 cells. *Mol. Pharmacol.* **60** (5), 1020-1030.

[120] Grof, Stanislav (**1981**) *LSD Psychotherapy.* Hunter House, Inc., Alameda, CA, ISBN: 0-89-793008-8.

[121] Guillonneau, C., Pierre, A., Charton, Y., Guilbaud, N., Kraus-Berthier, L., Leonce, S., Michel, A., Bisagni, E., Atassi, G. (**1999**) Synthesis of 9-*O*-substituted derivatives of 9-hydroxy-5,6-dimethyl-6*H*- pyrido[4,3-*b*]carbazole-1-carboxylic acid (2-(dimethylamino)ethyl)amide and their 10- and 11-methyl analogues with improved antitumor activity. *J. Med. Chem.* **42** (12), 2191-2203. *PubMed: 10377224 DOI: 10.1021/jm981093m*

[122] Haeselbarth, G., Michaelis, H., Salnikov, J. (**1985**) Nachweis von Psilocybin in *Inocybe aeruginascens* Babos. *Mykol. Mitteilungsblatt (Halle)*.

[123] Hajos, M., Gartside, S. E., Varga, V., Sharp, T. (**2003**) In vivo inhibition of neuronal activity in the rat ventromedial prefrontal cortex by midbrain-raphe nuclei: role of 5-HT_{1A} receptors. *Neuropharmacology* **45** (1), 72-81. *PubMed: 12814660 DOI: 10.1016/S0028-3908(03)00139-4*

[124] Hasler, F., Grimberg, U., Benz, M. A., Huber, T., Vollenweider, F. X. (**2004**) Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. *Psychopharmacology* **172** (2), 145-156. *PubMed: 14615876 DOI: 10.1007/s00213-003-1640-6*

[125] Hatfield, G. M., Valdes, L. J., Smith, A. H. (**1978**) The occurence of psilocybin in *Gymnopilus* species. *Lloydia* **41**, 140.

[126] Hayashi, A., Sonoda, R., Kimura, Y., Takasu, T., Suzuki, M., Sasamata, M., Miyata, K. (**2004**) Antiobesity effect of YM348, a novel 5-HT_{2C} receptor agonist, in Zucker rats. *Brain Res.* **1011** (2), 221-227. *PubMed: 15157808 DOI: 10.1016/j.brainres.2004.03.032*

[127] Hedlund, P. B., Carson, M. J., Sutcliffe, J. G., Thomas, E. A. (**1999**) Allosteric regulation by oleamide of the binding properties of 5-hydroxytryptamine$_7$ receptors. *Biochem. Pharmacol.* **58** (11), 1807-1813. *PubMed: 10571256*

[128] Heim, R., Hofmann, A., Brack, A., Kobel, H., Cailleux, R. (**1959**) Verfahren zur Herstellung und Gewinnung von Psilocybin und Psilocin. (DBP 1087321).

[129] Hepler, J. R. (**2003**) RGS protein and G protein interactions: a little help from their friends. *Mol. Pharmacol.* **64** (3), 547-549. *PubMed: 12920189 DOI: 10.1124/mol.64.3.547*

[130] Hermle, L., Gouzoulis-Mayfrank, E., Spitzer, M. (**1998**) Blood flow and cerebral laterality in the mescaline model of psychosis. *Pharmacopsychiatry* **31 Suppl 2**, 85-91. *PubMed: 9754839*

[131] Hirschhorn, I. D., Hayes, R. L., Rosecrans, J. A. (**1975**) Discriminative control of behavior by electrical stimulation of the dorsal raphe nucleus: generalization to lysergic acid diethylamide (LSD). *Brain Res.* **86** (1), 134-138. *PubMed: 1115989*

[132] Hoffman, A. J., Nichols, D. E. (**1985**) Synthesis and LSD-like discriminative stimulus properties in a series of *N*(6)-alkyl norlysergic acid *N,N*-diethylamide derivatives. *J. Med. Chem.* **28** (9), 1252-1255. *PubMed: 4032428*

[133] Hofmann, A. (**1980**) *LSD, my problem child.* McGraw-Hill, New York, ISBN: 0-07-029325-2.

[134] Hofmann, A., Heim, R., Brack, A., Kobel, H., Frey, A., Ott, H. (**1959**) Psilocybin and Psilocin, zwei psychotrope Wirkstoffe aus mexikanischen Rauschpilzen. *Helv. Chim. Acta* **52**, 1557.

[135] Horner, J. K., Skinner, W. A. (**1966**) A general method for selective N-methylation of substituted tryptamines. *Can. J. Chem.* **44**, 315-319.

[136] Hornung, J. P. (**2003**) The human raphe nuclei and the serotonergic system. *J. Chem. Neuroanat.* **26** (4), 331-343. *PubMed: 14729135 DOI: 10.1016/S0165-0173(02)00182-0*

[137] Hoyer, D., Hannon, J. P., Martin, G. R. (**2002**) Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol. Biochem. Behav.* **71** (4), 533-554. *PubMed: 11888546 DOI: 10.1016/S0091-3057(01)00746-8*

[138] Huidobro-Toro, J. P., Harris, R. A. (**1996**) Brain lipids that induce sleep are novel modulators of 5-hydroxytrypamine receptors. *Proc. Natl. Acad. Sci. U S A* **93** (15), 8078-8082. *PubMed: 8755606*

[139] Im, W. B., Chio, C. L., Alberts, G. L., Dinh, D. M. (**2003**) Positive allosteric modulator of the human 5-HT_{2C} receptor. *Mol. Pharmacol.* **64** (1), 78-84. *PubMed: 12815163 DOI: 10.1124/mol.64.1.78*

[140] Jakab, R. L., Goldman-Rakic, P. S. (**1998**) 5-Hydroxytryptamine$_{2A}$ serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proc. Natl. Acad. Sci. U. S. A* **95** (2), 735-740. *PubMed: 9435262*

[141] Jakab, R. L., Goldman-Rakic, P. S. (**2000**) Segregation of serotonin 5-HT_{2A} and 5-HT_3 receptors in inhibitory circuits of the primate cerebral cortex. *J. Comp Neurol.* **417** (3), 337-348. *PubMed: 10683608 DOI: 10.1002/(SICI)1096-9861(20000214)417:3<337::AID-CNE7>3.0.CO;2-O*

[142] Jansson, A., Tinner, B., Bancila, M., Verge, D., Steinbusch, H. W., Agnati, L. F., Fuxe, K. (**2001**) Relationships of 5-hydroxytryptamine immunoreactive terminal-like varicosities to 5-hydroxytryptamine-2A receptor-immunoreactive neuronal processes in the rat forebrain. *J. Chem. Neuroanat.* **22** (3), 185-203. *PubMed: 11522440 DOI: 10.1016/S0891-0618(01)00133-8*

[143] Jin, Z. (**2003**) Muscarine, imidazole, oxazole, and thiazole alkaloids. *Nat. Prod. Rep.* **20** (6), 584-605. *PubMed: 14700201 DOI: 10.1039/b304142p*

[144] Johnson, M. P., Baez, M., Kursar, J. D., Nelson, D. L. (**1995**) Species differences in 5-HT_{2A} receptors: cloned pig and rhesus monkey 5-HT_{2A} receptors reveal conserved transmembrane homology to the human rather than rat sequence. *Biochim. Biophys. Acta* **1236** (1), 201-206. *PubMed: 7794950*

[145] Johnson, M. P., Loncharich, R. J., Baez, M., Nelson, D. L. (**1994**) Species variations in transmembrane region V of the 5-hydroxytryptamine type 2A receptor alter the structure-activity relationship of certain ergolines and tryptamines. *Mol. Pharmacol.* **45** (2), 277-286. *PubMed: 8114677*

[146] Jones, B. J., Blackburn, T. P. (**2002**) The medical benefit of 5-HT research. *Pharmacol. Biochem. Behav.* **71** (4), 555-568. *PubMed: 11888547*

[147] Julia, M. (**1971**) Preparation of oxygen containing indole derivatives. (US3625973).

[148] Kalir, A., Szara, S. (**1966**) Synthesis and pharmacological activity of alkylated tryptamines. *J. Med. Chem.* **9** (3), 341-344. *PubMed: 5960901*

[149] Kantor, S., Jakus, R., Balogh, B., Benko, A., Bagdy, G. (**2004**) Increased wakefulness, motor activity and decreased theta activity after blockade of the 5-HT_{2B} receptor by the subtype-selective antagonist SB-215505. *Br. J. Pharmacol. PubMed: 15265808 DOI: 10.1038/sj.bjp.0705887*

[150] Kehne, J. H., Baron, B. M., Carr, A. A., Chaney, S. F., Elands, J., Feldman, D. J., Frank, R. A., van Giersbergen, P. L., McCloskey, T. C., Johnson, M. P., McCarty, D. R., Poirot, M., Senyah, Y., Siegel, B. W., Widmaier, C. (**1996**) Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT_{2A} antagonist with a favorable CNS safety profile. *J. Pharmacol. Exp. Ther.* **277** (2), 968-981. *PubMed: 8627580*

[151] Kennett, G., Lightowler, S., Trail, B., Bright, F., Bromidge, S. (**2000**) Effects of RO 60 0175, a 5-HT_{2C} receptor agonist, in three animal models of anxiety. *Eur. J. Pharmacol.* **387** (2), 197-204. *PubMed: 10650160 DOI: 10.1016/S0014-2999(99)00706-2*

[152] Kennett, G. A., Ainsworth, K., Trail, B., Blackburn, T. P. (**1997**) BW 723C86, a 5-HT_{2B} receptor agonist, causes hyperphagia and reduced grooming in rats. *Neuropharmacology* **36** (2), 233-239. *PubMed: 9144661*

[153] Kennett, G. A., Trail, B., Bright, F. (**1998**) Anxiolytic-like actions of BW 723C86 in the rat Vogel conflict test are 5-HT_{2B} receptor mediated. *Neuropharmacology* **37** (12), 1603-1610. *PubMed: 9886683*

[154] Klaver, W. J., Hiemstra, H., Speckamp, W. N. (**1989**) Synthesis and absolute configuration of the *Aristotelia* alkaloid peduncularine. *J. Am. Chem. Soc* **111** (7), 2588-2595.

[155] Knöfel, D., Unverricht, A., Orban, U., Schütte, H. R. (**1966**) Hydroxyindole; Substituierte 4-Hydroxyindole durch Dehydrierung von 4-keto-4,5,6,7-tetrahydro-indolen. *Z. Chem.* **6** (5), 183-185.

[156] Knoflach, F., Mutel, V., Jolidon, S., Kew, J. N., Malherbe, P., Vieira, E., Wichmann, J., Kemp, J. A. (**2001**) Positive allosteric modulators of metabotropic glutamate 1 receptor: characterization, mechanism of action, and binding site. *Proc. Natl. Acad. Sci. U S A* **98** (23), 13402-13407. *PubMed: 11606768 DOI: 10.1073/pnas.231358298*

[157] Koike, Y., Wada, K., Kusano, G., Nozoe, S. (**1981**) Isolation of psilocybin from *Psilocybe argentipes* and its determination in specimens of some mushrooms. *J. Nat. Prod.* **44**, 362.

[158] Kopach, M. E., Fray, A. H., Meyers, A. I. (**1996**) An asymmetric route to the conanine BCDE ring system. A formal total synthesis of (+) conessine. *J. Am. Chem. Soc.* **118** (41), 9876-9883. *DOI: 10.1021/ja961903o*

[159] Koshcheenko, K. A., Baklashova, T. G., Kozlovskii, A. G., Arinbasarov, M. U., Skriabin, G. K. (**1977**) Hydroxylation of indolyl-3-acetic acid by the fungus *Aspergillus niger* IBFM-F-12 (translation from russian). *Prikl. Biokhim. Mikrobiol.* **13** (2), 248-254. *PubMed: 866301*

[160] Krebs, A., Edwards, P. C., Villa, C., Li, J., Schertler, G. F. (**2003**) The three-dimensional structure of bovine rhodopsin determined by electron

cryomicroscopy. *J. Biol. Chem.* **278** (50), 50217-50225. *PubMed: 14514682 DOI: 10.1074/jbc.M307995200*

[161] Kreisel, H., Lindequist, U. (**1988**) *Gymnopilus purpuratus*, ein psilocybinhaltiger Pilz adventiv im Bezirk Rostock. *Z. Mykol.* **54**, 73.

[162] Krout, K. E., Belzer, R. E., Loewy, A. D. (**2002**) Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *J. Comp Neurol.* **448** (1), 53-101. *PubMed: 12012375 DOI: 10.1002/cne.10236*

[163] Kurrasch-Orbaugh, D. M., Parrish, J. C., Watts, V. J., Nichols, D. E. (**2003**) A complex signaling cascade links the serotonin2A receptor to phospholipase A2 activation: the involvement of MAP kinases. *J. Neurochem.* **86** (4), 980-991. *PubMed: 12887695 DOI: 10.1046/j.1471-4159.2003.01921.x*

[164] Kurrasch-Orbaugh, D. M., Watts, V. J., Barker, E. L., Nichols, D. E. (**2003**) Serotonin 5-hydroxytryptamine$_{2A}$ receptor-coupled phospholipase C and phospholipase A_2 signaling pathways have different receptor reserves. *J. Pharmacol. Exp. Ther.* **304** (1), 229-237. *PubMed: 12490596 DOI: 10.1124/jpet.102.042184*

[165] Lambe, E. K., Aghajanian, G. K. (**2001**) The role of Kv1.2-containing potassium channels in serotonin-induced glutamate release from thalamocortical terminals in rat frontal cortex. *J. Neurosci.* **21** (24), 9955-9963. *PubMed: 11739602*

[166] Larsson, M., Nguyen, B.-V., Hoegberg, H.-E., Hedenstroem, E. (**2001**) Syntheses of the sixteen stereoisomers of 3,7,11-trimethyl-2-tridecanol, including the *(2S,3S,7S,11R)* and *(2S,3S,7S,11S)* stereoisomers identified as pheromone precursors in females of the pine sawfly *Microdiprion pallipes* (Hymenoptera: Diprionidae). *Eur. J. Org. Chem* **2001** (2), 353-364. *DOI: 10.1002/1099-0690(200101)2001:2<353::AID-EJOC353>3.0.CO;2-Z*

[167] LeBoulluec, K. L., Mattson, R. J., Mahle, C. D., McGovern, R. T., Nowak, H. P., Gentile, A. J. (**1995**) Bivalent indoles exhibiting serotonergic binding affinity. *Bioorg. Med. Chem. Lett.* **5** (2), 123-126.

[168] Lemonde, S., Turecki, G., Bakish, D., Du, L., Hrdina, P. D., Bown, C. D., Sequeira, A., Kushwaha, N., Morris, S. J., Basak, A., Ou, X. M., Albert, P. R. (**2003**) Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J. Neurosci.* **23** (25), 8788-8799. *PubMed: 14507979*

[169] Leung, A. L., Paul, A. G. (**1968**) Baeocystin and norbaeocystin, new analogs of psilocybin from *Psilocybe baeocystis. J. Pharm. Sci.* **57**, 1667.

[170] Leung, A. Y., Paul, A. G. (**1967**) Baeocystin, a mono-methyl analog of psilocybin from *Psilocybe baeocystis* saprophytic culture. *J. Pharm. Sci.* **56**, 146.

[171] Leung, A. Y., Paul, A. G. (**1969**) The relationship of carbon and nitrogen nutrition of *Psilocybe baeocystis* to the production of psilocybin and ist analogs. *Lloydia* **32**, 66.

[172] Mackowiak, M., Chocyk, A., Fijal, K., Czyrak, A., Wedzony, K. (**1999**) c-Fos proteins, induced by the serotonin receptor agonist DOI, are not expressed in 5-HT$_{2A}$ positive cortical neurons. *Brain Res. Mol. Brain Res.* **71** (2), 358-363. *PubMed: 10521592 DOI: 10.1016/S0169-328X(99)00195-3*

[173] Mackowiak, M., Chocyk, A., Sanak, M., Czyrak, A., Fijal, K., Wedzony, K. (**2002**) DOI, an agonist of 5-$HT_{2A/2C}$ serotonin receptor, alters the expression of cyclooxygenase-2 in the rat parietal cortex. *J. Physiol Pharmacol.* **53** (3), 395-407. *PubMed: 12369737*

[174] Mackowiak, M., Czyrak, A., Wedzony, K. (**2002**) Inhibition of arachidonic acid cascade attenuates the induction of c-Fos proteins by DOI, 5-$HT_{2A/2C}$ receptor agonist, in the rat cortex. *Pol. J. Pharmacol.* **54** (1), 73-76. *PubMed: 12020047*

[175] Macor, J. E., Fox, C. B., Johnson, C., Koe, B. K., Lebel, L. A., Zorn, S. H. (**1992**) 1-(2-Aminoethyl)-3-methyl-8,9-dihydropyrano[3,2-*e*]indole: a rotationally restricted phenolic analog of the neurotransmitter serotonin and agonist selective for serotonin (5-HT_2-type) receptors. *J. Med. Chem.* **35** (20), 3625-3632. *PubMed: 1433172*

[176] Mantz, J., Godbout, R., Tassin, J. P., Glowinski, J., Thierry, A. M. (**1990**) Inhibition of spontaneous and evoked unit activity in the rat medial prefrontal cortex by mesencephalic raphe nuclei. *Brain Res.* **524** (1), 22-30. *PubMed: 2119244*

[177] Marek, G. J. (**2003**) Behavioral evidence for mu-opioid and 5-HT_{2A} receptor interactions. *Eur. J. Pharmacol.* **474** (1), 77-83. *PubMed: 12909198*

[178] Marek, G. J., Aghajanian, G. K. (**1998**) The electrophysiology of prefrontal serotonin systems: therapeutic implications for mood and psychosis. *Biol. Psychiatry* **44** (11), 1118-1127. *PubMed: 9836015 DOI: 10.1016/S0006-3223(98)00036-5*

[179] Marek, G. J., Aghajanian, G. K. (**1999**) 5-HT_{2A} receptor or alpha1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. *Eur. J. Pharmacol.* **367** (2-3), 197-206. *PubMed: 10078993*

[180] Marek, G. J., Aghajanian, G. K. (**1998**) 5-Hydroxytryptamine-induced excitatory postsynaptic currents in neocortical layer V pyramidal cells: suppression by μ-opiate receptor activation. *Neuroscience* **86** (2), 485-497. *PubMed: 9881863*

[181] Marek, G. J., Carpenter, L. L., McDougle, C. J., Price, L. H. (**2003**) Synergistic action of 5-HT_{2A} antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. *Neuropsychopharmacology* **28** (2), 402-412. *PubMed: 12589395 DOI: 10.1038/sj.npp.1300057*

[182] Marek, G. J., Wright, R. A., Gewirtz, J. C., Schoepp, D. D. (**2001**) A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in the rat neocortex. *Neuroscience* **105** (2), 379-392. *PubMed: 11672605*

[183] Marek, G. J., Wright, R. A., Schoepp, D. D., Monn, J. A., Aghajanian, G. K. (**2000**) Physiological antagonism between 5-hydroxytryptamine$_{2A}$ and group II metabotropic glutamate receptors in prefrontal cortex. *J. Pharmacol. Exp. Ther.* **292** (1), 76-87. *PubMed: 10604933*

[184] Marinelli, S., Schnell, S. A., Hack, S. P., Christie, M. J., Wessendorf, M. W., Vaughan, C. W. (**2004**) Serotonergic and non-serotonergic dorsal raphe neurons are pharmacologically and electrophysiologically heterogeneous. *J. Neurophysiol. PubMed: 15254076 DOI: 10.1152/jn.00437.2004*

[185] Martin, J. R., Bös, M., Jenck, F., Moreau, J., Mutel, V., Sleight, A. J., Wichmann, J., Andrews, J. S., Berendsen, H. H., Broekkamp, C. L., Ruigt, G. S., Kohler, C., Delft, A. M. (**1998**) 5-HT_{2C} receptor agonists: pharmacological characteristics and

therapeutic potential. *J. Pharmacol. Exp. Ther.* **286** (2), 913-924. *PubMed: 9694950*

[186] Martín-Ruiz, R., Puig, M. V., Celada, P., Shapiro, D. A., Roth, B. L., Mengod, G., Artigas, F. (**2001**) Control of serotonergic function in medial prefrontal cortex by serotonin-2A receptors through a glutamate-dependent mechanism. *J. Neurosci.* **21** (24), 9856-9866. *PubMed: 11739593*

[187] Matsuno, S., Goto, K. (**1986**) Production of 4-hydroxyindole compounds. (JP 61,180,768 (CA 106: 67111n 1987)).

[188] May, J. A., Chen, H. H., Rusinko, A., Lynch, V. M., Sharif, N. A., McLaughlin, M. A. (**2003**) A novel and selective 5-HT_2 receptor agonist with ocular hypotensive activity: (*S*)-(+)-1-(2-aminopropyl)-8,9-dihydropyrano[3,2-*e*]indole. *J. Med. Chem.* **46** (19), 4188-4195. *PubMed: 12954071 DOI: 10.1021/jm030205t*

[189] May, J. A., McLaughlin, M. A., Sharif, N. A., Hellberg, M. R., Dean, T. R. (**2003**) Evaluation of the ocular hypotensive response of serotonin 5-HT_{1A} and 5-HT_2 receptor ligands in conscious ocular hypertensive cynomolgus monkeys. *J. Pharmacol. Exp. Ther.* **306** (1), 301-309. *PubMed: 12676887 DOI: 10.1124/jpet.103.049528*

[190] McKenna, D. J., Repke, D. B., Lo, L., Peroutka, S. J. (**1990**) Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. *Neuropharmacology* **29** (3), 193-198. *PubMed: 2139186*

[191] Mehler, E. L., Periole, X., Hassan, S. A., Weinstein, H. (**2002**) Key issues in the computational simulation of GPCR function: representation of loop domains. *J. Comput. Aided Mol. Des* **16** (11), 841-853. *PubMed: 12825797*

[192] Meltzer, H. Y., Li, Z., Kaneda, Y., Ichikawa, J. (**2003**) Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **27** (7), 1159-1172. *PubMed: 14642974 DOI: 10.1016/j.pnpbp.2003.09.010*

[193] Michaelis, H. (**1977**) *Psilocybe semilanceata* (Fr.) Quel. (Spitzkegeliger Kahlkopf). *Z. Pilzkunde* **43**, 305.

[194] Mielke, T., Villa, C., Edwards, P. C., Schertler, G. F., Heyn, M. P. (**2002**) X-ray diffraction of heavy-atom labelled two-dimensional crystals of rhodopsin identifies the position of cysteine 140 in helix 3 and cysteine 316 in helix 8. *J. Mol. Biol.* **316** (3), 693-709. *PubMed: 11866527 DOI: 10.1006/jmbi.2001.5352*

[195] Miner, L. A., Backstrom, J. R., Sanders-Bush, E., Sesack, S. R. (**2003**) Ultrastructural localization of serotonin$_{2A}$ receptors in the middle layers of the rat prelimbic prefrontal cortex. *Neuroscience* **116** (1), 107-117. *PubMed: 12535944 DOI: 10.1016/S0306-4522(02)00580-8*

[196] Mishra, R. K., Srivastava, L. K., Johnson, R. (**1990**) Modulation of high-affinity CNS dopamine D_2 receptor by L-Pro-L-Leu-glycinamide (PLG) analogue 3(R)-(*N*-L-prolylamino)-2-oxo-1-pyrrolidineacetamide. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* **14** (5), 821-827. *PubMed: 1981396 DOI: 10.1016/0278-5846(90)90054-K*

[197] Mitchell, R., McCulloch, D., Lutz, E., Johnson, M., MacKenzie, C., Fennell, M., Fink, G., Zhou, W., Sealfon, S. C. (**1998**) Rhodopsin-family receptors associate with small G proteins to activate phospholipase D. *Nature* **392** (6674), 411-414. *PubMed: 9537328 DOI: 10.1038/32937*

[198] Mokler, D. J., Dixon, M., Stambaugh, L. (**1994**) Electrical stimulation of the dorsal raphe nucleus as a discriminative stimulus: generalization to (+/-)-DOI. *Pharmacol. Biochem. Behav.* **48** (4), 1041-1045. *PubMed: 7972283*

[199] Motulsky, Harvey (**1995**) *The GraphPad Guide to Analyzing Radioligand Binding Data.* GraphPad Software, San Diego, CA, USA.

[200] Muñoz, M. A., Guardado, P., Hidalgo, J., Carmona, C., Balón, M. (**1992**) An experimental and theoretical study of the acid-base properties of substituted indoles. *Tetrahedron* **48** (28), 5901-5914. *DOI: 10.1016/S0040-4020(01)90181-4*

[201] Muschamp, J. W., Regina, M. J., Hulla, E. M., Winter, J. C., Rabin, R. A. (**2004**) Lysergic acid diethylamide and *[-]*-2,5-dimethoxy-4-methylamphetamine increase extracellular glutamate in rat prefrontal cortex. *Brain Res.* (in press). *DOI: doi:10.1016/j.brainres.2004.07.044*

[202] Nagao, K., Suzui, A., Nakagawa, M. (**1985**) Preparation of 4-hydroxyindole derivatives as intermediates for antiarrhythmics. ((CA 107: 236506y 1987)).

[203] Nelson, D. L., Lucaites, V. L., Wainscott, D. B., Glennon, R. A. (**1999**) Comparisons of hallucinogenic phenylisopropylamine binding affinities at cloned human 5-HT_{2A}, -HT_{2B} and 5-HT_{2C} receptors. *Naunyn Schmiedeberg's Arch. Pharmacol.* **359** (1), 1-6. *PubMed: 9933142*

[204] Nichols, C. D., Garcia, E. E., Sanders-Bush, E. (**2003**) Dynamic changes in prefrontal cortex gene expression following lysergic acid diethylamide administration. *Brain Res. Mol. Brain Res.* **111** (1-2), 182-188. *PubMed: 12654518 DOI: 10.1016/S0169-328X(03)00029-9*

[205] Nichols, C. D., Sanders-Bush, E. (**2002**) A single dose of lysergic acid diethylamide influences gene expression patterns within the mammalian brain. *Neuropsychopharmacology* **26** (5), 634-642. *PubMed: 11927188 DOI: 10.1016/S0893-133X(01)00405-5*

[206] Nichols, C. D., Sanders-Bush, E. (**2004**) Molecular genetic responses to lysergic acid diethylamide include transcriptional activation of MAP kinase phosphatase-1, C/EBP-beta and ILAD-1, a novel gene with homology to arrestins. *J. Neurochem.* **90** (3), 576-584. *PubMed: 15255935 DOI: 10.1111/j.1471-4159.2004.02515.x*

[207] Nichols, D. E. (**2004**) Hallucinogens. *Pharmacol. Ther.* **101** (2), 131-181. *PubMed: 14761703 DOI: 10.1016/j.pharmthera.2003.11.002*

[208] Nichols, D. E., Frescas, S. (**1999**) Improvements to the synthesis of psilocybin and a facile method for preparing the *O*-acetyl prodrug of psilocin. *Synthesis* **6**, 935-938.

[209] Nichols, D. E., Frescas, S., Marona-Lewicka, D., Kurrasch-Orbaugh, D. M. (**2002**) Lysergamides of isomeric 2,4-dimethylazetidines map the binding orientation of the diethylamide moiety in the potent hallucinogenic agent *N,N*-diethyllysergamide (LSD). *J. Med. Chem.* **45** (19), 4344-4349. *PubMed: 12213075*

[210] Nishizaki, T., Matsuoka, T., Nomura, T., Enikolopov, G., Sumikawa, K. (**1999**) Arachidonic acid potentiates currents through Ca2+-permeable AMPA receptors by interacting with a CaMKII pathway. *Brain Res. Mol. Brain Res.* **67** (1), 184-189. *PubMed: 10101246 DOI: 10.1016/S0169-328X(99)00042-X*

[211] Nitta, K., Stadelmann, R. J., Eugster, C. H. (**1977**) Studies on the biosynthesis of muscarine in mycelial cultures of *Clitocybe rivulosa. Helv. Chim. Acta* **60** (5), 1747-1753. *PubMed: 893124*

[212] Nuccio, M. L., Ziemak, M. J., Henry, S. A., Weretilnyk, E. A., Hanson, A. D. (**2000**) cDNA cloning of phosphoethanolamine *N*-methyltransferase from spinach by complementation in *Schizosaccharomyces pombe* and characterization of the recombinant enzyme*. J. Biol. Chem.* **275** (19), 14095-14101. *PubMed: 10799484*

[213] O'Brien, J. A., Lemaire, W., Wittmann, M., Jacobson, M. A., Ha, S. N., Wisnoski, D. D., Lindsley, C. W., Schaffhauser, H. J., Rowe, B., Sur, C., Duggan, M. E., Pettibone, D. J., Conn, P. J., Williams, D. L., Jr. (**2004**) A novel selective allosteric modulator potentiates the activity of native metabotropic glutamate receptor subtype 5 in rat forebrain*. J. Pharmacol. Exp. Ther.* **309** (2), 568-577. *PubMed: 14747613 DOI: 10.1124/jpet.103.061747*

[214] Ojida, A., Abe, A., Kanematsu, K. (**1994**) Synthesis of annulated furans with various 3-substituents via a sequential furannulation/ene route*. Heterocycles* **38** (12), 2585-2588.

[215] Okada, T., Fujiyoshi, Y., Silow, M., Navarro, J., Landau, E. M., Shichida, Y. (**2002**) Functional role of internal water molecules in rhodopsin revealed by X-ray crystallography*. Proc. Natl. Acad. Sci. U. S. A* **99** (9), 5982-5987. *PubMed: 11972040 DOI: 10.1073/pnas.082666399*

[216] Ornstein, P. L., Bleisch, T. J., Arnold, M. B., Wright, R. A., Johnson, B. G., Schoepp, D. D. (**1998**) 2-Substituted (2*SR*)-2-amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)glycines as potent and selective antagonists of group II metabotropic glutamate receptors. 1. Effects of alkyl, arylalkyl, and diarylalkyl substitution*. J. Med. Chem.* **41** (3), 346-357. *PubMed: 9464366 DOI: 10.1021/jm970497w*

[217] Ott, J. (**1994**) *Ayahuasca Analogues.* Natural Products Co., Kennewick, WA, 1st Ed., ISBN: 0-96-14234-4-7.

[218] Ott, J. (**1993**) *Pharmacotheon.* Natural Products Co., Kennewick, WA, 1st Ed., ISBN: 0-96-14234-3-9.

[219] Ozaki, N., Manji, H., Lubierman, V., Lu, S. J., Lappalainen, J., Rosenthal, N. E., Goldman, D. (**1997**) A naturally occurring amino acid substitution of the human serotonin 5-HT_{2A} receptor influences amplitude and timing of intracellular calcium mobilization*. J. Neurochem.* **68** (5), 2186-2193. *PubMed: 9109547 DOI: 10.1046/j.1471-4159.1997.68052186.x*

[220] Palczewski, K., Kumasaka, T., Hori, T., Behnke, C. A., Motoshima, H., Fox, B. A., Le, T., I, Teller, D. C., Okada, T., Stenkamp, R. E., Yamamoto, M., Miyano, M. (**2000**) Crystal structure of rhodopsin: A G protein-coupled receptor*. Science* **289** (5480), 739-745. *PubMed: 10926528 DOI: 10.1126/science.289.5480.739*

[221] Parker, M. A., Marona-Lewicka, D., Lucaites, V. L., Nelson, D. L., Nichols, D. E. (**1998**) A novel (benzodifuranyl)aminoalkane with extremely potent activity at the 5-HT_{2A} receptor*. J. Med. Chem.* **41** (26), 5148-5149. *PubMed: 9857084 DOI: 10.1021/jm9803525*

[222] Pei, Q., Tordera, R., Sprakes, M., Sharp, T. (**2004**) Glutamate receptor activation is involved in 5-HT_2 agonist-induced Arc gene expression in the rat cortex*.*

Neuropharmacology **46** (3), 331-339. *PubMed: 14975688 DOI: 10.1016/j.neuropharm.2003.09.017*

[223] Perez, M., Jorand-Lebrun, C., Pauwels, P. J., Pallard, I., Halazy, S. (**1998**) Dimers of $5HT_1$ ligands preferentially bind to $5HT_{1B/1D}$ receptor subtypes. *Bioorg. Med. Chem. Lett.* **8** (11), 1407-1412. *PubMed: 9871775 DOI: 10.1016/S0960-894X(98)00222-4*

[224] Perez, M., Pauwels, P. J., Fourrier, C., Chopin, P., Valentin, J. P., John, G. W., Marien, M., Halazy, S. (**1998**) Dimerization of sumatriptan as an efficient way to design a potent, centrally and orally active 5-HT_{1B} agonist. *Bioorg. Med. Chem. Lett.* **8** (6), 675-680. *PubMed: 9871581 DOI: 10.1016/S0960-894X(98)00090-0*

[225] Picker, J., Rickards, R. W. (**1970**) The occurrence of the psychomimetic agent psilocybin in an Australian agaric, *Psilocybe subaeruginosa. Aust. J. Chem.* **23** (4), 853-855.

[226] Plieninger, H., Klinga, K. (**1968**) Notiz zur Darstellung des 4-Hydroxy- und 4-Cyan-indols. *Chem. Ber.* **101**, 2605-2607.

[227] Pollock, S. H. (**1976**) Psilocybian mycetismus with special reference to Paneolus. *J. Psyched. Drugs* **8**, 43.

[228] Pooley, E. C., Fairburn, C. G., Cooper, Z., Sodhi, M. S., Cowen, P. J., Harrison, P. J. (**2004**) A 5-HT_{2C} receptor promoter polymorphism (HTR_{2C} - 759C/T) is associated with obesity in women, and with resistance to weight loss in heterozygotes. *Am. J. Med. Genet.* **126B** (1), 124-127. *PubMed: 15048662 DOI: 10.1002/ajmg.b.20143*

[229] Prioleau, C., Visiers, I., Ebersole, B. J., Weinstein, H., Sealfon, S. C. (**2002**) Conserved helix 7 tyrosine acts as a multistate conformational switch in the 5HT2C receptor. Identification of a novel "locked-on" phenotype and double revertant mutations. *J. Biol. Chem.* **277** (39), 36577-36584. *PubMed: 12145300 DOI: 10.1074/jbc.M206223200*

[230] Prossnitz, E. R. (**2004**) Novel roles for arrestins in the post-endocytic trafficking of G protein-coupled receptors. *Life Sci.* **75** (8), 893-899. *PubMed: 15193949 DOI: 10.1016/j.lfs.2004.04.003*

[231] Puig, M. V., Artigas, F., Celada, P. (**2004**) Modulation of the activity of pyramidal neurons in rat prefrontal cortex by raphe stimulation *in vivo*: Involvement of serotonin and GABA. *Cereb. Cortex*. *PubMed: 15238448 DOI: 10.1093/cercor/bhh104*

[232] Puig, M. V., Celada, P., Diaz-Mataix, L., Artigas, F. (**2003**) *In vivo* modulation of the activity of pyramidal neurons in the rat medial prefrontal cortex by 5-HT_{2A} receptors: relationship to thalamocortical afferents. *Cereb. Cortex* **13** (8), 870-882. *PubMed: 12853374*

[233] Puig, M. V., Santana, N., Celada, P., Mengod, G., Artigas, F. (**2004**) In Vivo Excitation of GABA Interneurons in the Medial Prefrontal Cortex through 5-HT_3 Receptors. *Cereb. Cortex*. *PubMed: 15166106 DOI: 10.1093/cercor/bhh097*

[234] Quintard, J.-P., Elissondo, B., Jousseaume, B. (**1984**) A convenient synthesis of *N,N*-disubstituted aminomethyltri-*n*-butylstannanes, precursors of the corresponding lithium reagents. *Synthesis* **1984**, 459-498.

[235] Rabin, R. A., Regina, M., Doat, M., Winter, J. C. (**2002**) 5-HT_{2A} receptor-stimulated phosphoinositide hydrolysis in the stimulus effects of hallucinogens. *Pharmacol. Biochem. Behav.* **72** (1-2), 29-37. *PubMed: 11900766 DOI: 10.1016/S0091-3057(01)00720-1*

[236] Rees, S., Morrow, D., Kenakin, T. (**2002**) GPCR drug discovery through the exploitation of allosteric drug binding sites. *Receptors and Channels* **8** (5-6), 261-268. *PubMed: 12690954*

[237] Regina, M. J., Bucelli, R. C., Winter, J. C., Rabin, R. A. (**2004**) Cellular mechanisms of serotonin 5-HT_{2A} receptor-mediated cGMP formation: the essential role of glutamate. *Brain Res.* **1003** (1-2), 168-175. *PubMed: 15019576 DOI: 10.1016/j.brainres.2004.01.014*

[238] Regina, M. J., Winter, J. C., Rabin, R. A. (**2003**) Characterization of a novel effect of serotonin 5-HT_{1A} and 5-HT_{2A} receptors: increasing cGMP levels in rat frontal cortex. *Neuropharmacology* **45** (8), 1041-1049. *PubMed: 14614947 DOI: 10.1016/S0028-3908(03)00287-9*

[239] Remers, W. A., Roth, R. H., Gibs, G. J., Weiss, M. J. (**1971**) Synthesis of indoles from 4-oxo-4,5,6,7-tetrahydroindoles. III. Introduction of substituents by electrophilic substitution. *J. Org. Chem.* **36** (9), 1232-1240.

[240] Repke, D. B. (**1977**) Baeocystin in *Psilocybe semilanceata. J. Pharm. Sci.* **66**, 113.

[241] Repke, D. B. (**1977**) Baeocystin in *Psilocybe*, *Conocybe* and *Paneolus. Lloydia* **40**, 566.

[242] Repke, D. B., Ferguson, W. J. (**1982**) Psilocin analogs. III. Synthesis of 5-methoxy- and 5-hydroxy-1,2,3,4-tetrahydro-*9H*-pyrido[3,4-*b*]indoles. *J. Het. Chem.* **19**, 845.

[243] Repke, D. B., Ferguson, W. J., Bates, D. K. (**1977**) Psilocin analogs. 1. Synthesis of 3-[2-(dialkylamino)ethyl]- and 3-[2-(cycloalkylamino)ethyl]indol-4ols. *J. Het. Chem.* **14**, 71-74.

[244] Rieder, Böhmer (**1960**) *Helv. Chim. Acta* **43**, 683.

[245] Robertson, D. N., Johnson, M. S., Moggach, L. O., Holland, P. J., Lutz, E. M., Mitchell, R. (**2003**) Selective interaction of ARF1 with the carboxy-terminal tail domain of the 5-HT_{2A} receptor. *Mol. Pharmacol.* **64** (5), 1239-1250. *PubMed: 14573774 DOI: 10.1124/mol.64.5.1239*

[246] Rochin, C., Babot, O., Dunoguès, J., Duboudin, F. (**1986**) A new convenient synthesis of dialkyl(methylene)ammonium chloride. *Synthesis* (3), 228-229. *DOI: 10.1055/s-1986-31627*

[247] Rogines-Velo, M. P., Pelorosso, F. G., Zold, C. L., Nowak, W., Pesce, G. O., Sardi, S. P., Brodsky, P. T., Rothlin, R. P. (**2002**) Characterization of 5-HT receptor subtypes mediating contraction in human umbilical vein. 1. Evidence of involvement of 5-HT_{2A} receptors using functional and radioligand binding assays. *Naunyn Schmiedebergs Arch. Pharmacol.* **366** (6), 587-595. *PubMed: 12444501 DOI: 10.1007/s00210-002-0636-9*

[248] Roth, B. L., Willins, D. L., Kristiansen, K., Kroeze, W. K. (**1998**) 5-Hydroxytryptamine$_2$-family receptors (5-hydroxytryptamine$_{2A}$, 5-hydroxytryptamine$_{2B}$, 5-hydroxytryptamine$_{2C}$): where structure meets function. *Pharmacol. Ther.* **79** (3), 231-257. *PubMed: 9776378 DOI: 10.1016/S0163-7258(98)00019-9*

[249] Rousselle, J. C., Plantefol, M., Fillion, M. P., Massot, O., Pauwels, P. J., Fillion, G. (**1998**) Specific interaction of 5-HT-moduline with human 5-HT_{1b} as well as 5-HT_{1d} receptors expressed in transfected cultured cells. *Naunyn Schmiedeberg's Arch. Pharmacol.* **358** (3), 279-286. *PubMed: 9774213*

[250] Sandrini, M., Vitale, G., Pini, L. A. (**2002**) Central antinociceptive activity of acetylsalicylic acid is modulated by brain serotonin receptor subtypes. *Pharmacology* **65** (4), 193-197. *PubMed: 12119448 DOI: 10.1159/000064343*

[251] Santana, N., Bortolozzi, A., Serrats, J., Mengod, G., Artigas, F. (**2004**) Expression of Serotonin$_{1A}$ and Serotonin$_{2A}$ Receptors in Pyramidal and GABAergic Neurons of the Rat Prefrontal Cortex. *Cereb. Cortex*. *PubMed: 15115744 DOI: 10.1093/cercor/bhh070*

[252] Scruggs, J. L., Patel, S., Bubser, M., Deutch, A. Y. (**2000**) DOI-Induced activation of the cortex: dependence on 5-HT_{2A} heteroceptors on thalamocortical glutamatergic neurons. *J. Neurosci.* **20** (23), 8846-8852. *PubMed: 11102493*

[253] Scruggs, J. L., Schmidt, D., Deutch, A. Y. (**2003**) The hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) increases cortical extracellular glutamate levels in rats. *Neurosci. Lett.* **346** (3), 137-140. *PubMed: 12853103 DOI: 10.1016/S0304-3940(03)00547-0*

[254] Seggel, M. R., Yousif, M. Y., Lyon, R. A., Titeler, M., Roth, B. L., Suba, E. A., Glennon, R. A. (**1990**) A structure-affinity study of the binding of 4-substituted analogues of 1-(2,5-dimethoxyphenyl)-2-aminopropane at 5-HT_2 serotonin receptors. *J. Med. Chem.* **33** (3), 1032-1036. *PubMed: 2308135*

[255] Semerdžieva, M., Wurst, M., Koza, T., Gartz, J. (**1986**) Psilocybin in Fruchtkörpern von *Inocybe aeruginascens. Planta Med.* **47**, 83-85.

[256] Shapiro, D. A., Kristiansen, K., Weiner, D. M., Kroeze, W. K., Roth, B. L. (**2002**) Evidence for a model of agonist-induced activation of 5-hydroxytryptamine 2A serotonin receptors that involves the disruption of a strong ionic interaction between helices 3 and 6. *J. Biol. Chem.* **277** (13), 11441-11449. *PubMed: 11801601 DOI: 10.1074/jbc.M111675200*

[257] Shirota, O., Hakamata, W., Goda, Y. (**2003**) Concise large-scale synthesis of psilocin and psilocybin, principal hallucinogenic constituents of "magic mushroom". *J. Nat. Prod.* **66** (6), 885-887. *PubMed: 12828485 DOI: 10.1021/np030059u*

[258] Shulgin, Alexander and Shulgin, Ann (**1991**) *PIHKAL.* Transform Press, Berkeley, CA, 1st Ed., ISBN: 0-96-300960-5.

[259] Shulgin, Alexander and Shulgin, Ann (**1997**) *TIHKAL.* Transform Press, Berkeley, CA, 1st Ed., ISBN: 0-96-300969-9.

[260] Shulgin, A. T. (**1963**) Psychotomimetic agents related to mescaline. *Experientia* **19**, 127-128.

[261] Singh, U. P., Sarma, B. K., Mishra, P. K., Ray, A. B. (**2000**) Antifungal activity of venenatine, an indole alkaloid isolated from *Alstonia venenata. Folia Microbiol. (Praha)* **45** (2), 173-176. *PubMed: 11271828*

[262] Sleight, A. J., Stam, N. J., Mutel, V., Vanderheyden, P. M. (**1996**) Radiolabelling of the human 5-HT_{2A} receptor with an agonist, a partial agonist and an antagonist:

effects on apparent agonist affinities. *Biochem. Pharmacol.* **51** (1), 71-76. *PubMed: 8534270*

[263] Snyder, H. R., Hansch, C. H., Katz, L., Parmerter, S. M., Spaeth, E. C. (**1948**) The synthesis of derivatives of β-carboline. II. Synthesis from *dl*-tryptophan and aldehydes. *J. Am. Chem. Soc* **70**, 219-221.

[264] Spaeth, M., Plischka, P., Bohnen, F.-M., Herbst-Irmer, R. (**1997**) Konformation und Rotationsbarrieren substituierter Glyoxylsäureamide. *J. Prakt. Chem.* **339**, 243-249.

[265] Speeter, M. E., Anthony, W. C. (**1954**) The action of oxalyl chloride on indoles: a new approach to tryptamines. *J. Am. Chem. Soc.* **76** (23), 6208-6210.

[266] Spratling, M. W. (**2002**) Cortical region interactions and the functional role of apical dendrites. *Behav. Cogn. Neurosci. Rev.* **1** (2), 219-228.

[267] Srikiatkhachorn, A., Tarasub, N., Govitrapong, P. (**1999**) Acetaminophen-induced antinociception via central 5-HT(2A) receptors. *Neurochem. Int.* **34** (6), 491-498. *PubMed: 10402224 DOI: 10.1016/S0197-0186(99)00023-6*

[268] Srivastava, L. K., Bajwa, S. B., Johnson, R. L., Mishra, R. K. (**1988**) Interaction of L-prolyl-L-leucyl glycinamide with dopamine D_2 receptor: evidence for modulation of agonist affinity states in bovine striatal membranes. *J. Neurochem.* **50** (3), 960-968. *PubMed: 2892892*

[269] St-Gelais, F., Menard, C., Congar, P., Trudeau, L. E., Massicotte, G. (**2004**) Postsynaptic injection of calcium-independent phospholipase A2 inhibitors selectively increases AMPA receptor-mediated synaptic transmission. *Hippocampus* **14** (3), 319-325. *PubMed: 15132431*

[270] Stijve, T. (**1992**) Psilocin, psilocybin, serotonin and urea in *Paneolus cyanescens* from various origin. *Persoonia* **15**, 117.

[271] Stijve, T., Klan, T., Kuyper.T.W. (**1985**) Occurrence of psilocybin and baeocystin in the genus *Inocybe* Fr (Fr.). *Persoonia* **12**, 469-473.

[272] Stijve, T., Kuyper, T. W. (**1985**) Occurrence of psilocybin in various higher fungi from several European countries. *Planta Med.* **46**, 385-387.

[273] Stutzmann, G. E., Marek, G. J., Aghajanian, G. K. (**2001**) Adenosine preferentially suppresses serotonin$_{2A}$ receptor-enhanced excitatory postsynaptic currents in layer V neurons of the rat medial prefrontal cortex. *Neuroscience* **105** (1), 55-69. *PubMed: 11483300 DOI: 10.1016/S0306-4522(01)00170-1*

[274] Sukalovic, V., Roglic, G., Husinec, S., Kostic-Rajacic, S., Andric, D., Sosakic, V. (**2003**) D_2 dopaminergic and 5-HT$_{1A}$ serotonergic activity of 2-(1-naphthyl)ethyl- and 2-(2-naphthyl)ethyl amines. *Arch. Pharm. (Weinheim)* **336** (11), 514-522. *PubMed: 14639744 DOI: 10.1002/ardp.200300776*

[275] Takayama, H. (**2004**) Chemistry and pharmacology of analgesic indole alkaloids from the Rubiaceous plant, *Mitragyna speciosa. Chem. Pharm. Bull. (Tokyo)* **52** (8), 916-928. *PubMed: 15304982 DOI: 10.1248/cpb.52.916*

[276] Thomas, E. A., Carson, M. J., Neal, M. J., Sutcliffe, J. G. (**1997**) Unique allosteric regulation of 5-hydroxytryptamine receptor-mediated signal transduction by oleamide. *Proc. Natl. Acad. Sci. U S A* **94** (25), 14115-14119. *PubMed: 9391162*

[277] Troxler, F., Seeman, F., Hofmann, A. (**1959**) Abwandlungsprodukte von Psilocybin und Psilocin. *Helv. Chim. Acta* (42), 2073-2103.

[278] Tyson, P. J., Roberts, K. H., Mortimer, A. M. (**2004**) Are the cognitive effects of atypical antipsychotics influenced by their affinity to 5HT-2A receptors? *Int. J. Neurosci.* **114** (6), 593-611. *PubMed: 15204055 DOI: 10.1080/00207450490430552*

[279] van den Berg, E. M. M., Jansen, F. J. H. M., de Goede, A. T. J. W., Baldew, A. U., Lugtenburg, J. (**1990**) Chemo-enzymatic synthesis and characterization of L-tryptophans selectively ^{13}C-enriched or hydroxylated in the six-membered ring using transformed *Escherichia coli* cells. *Recl. Trav. Chim. Pays-Bas* **109** (4), 287-297.

[280] Van, O. D., Luyten, W. H., Leysen, J. E. (**2003**) 5-HT_{2A} and 5-HT_{2C} receptors and their atypical regulation properties. *Life Sci.* **72** (22), 2429-2449. *PubMed: 12650852*

[281] Vangveravong, S., Kanthasamy, A., Lucaites, V. L., Nelson, D. L., Nichols, D. E. (**1998**) Synthesis and serotonin receptor affinities of a series of *trans*-2-(indol-3-yl)cyclopropylamine derivatives. *J. Med. Chem.* **41** (25), 4995-5001. *PubMed: 9836617 DOI: 10.1021/jm980318q*

[282] Vanover, K. E., Harvey, S. C., Son, T., Risso, B. S., Kold, H., Makhay, M., Veinbergs, I., Spalding, T. A., Weiner, D. M., Andersson, C. M., Tolf, B. R., Brann, M. R., Hacksell, U., Davis, R. E. (**2004**) Pharmacological Characterization of AC-90179: a Selective 5-HT_{2A} Receptor Inverse Agonist. *J. Pharmacol. Exp. Ther. PubMed: 15102927 DOI: 10.1124/jpet.104.066688*

[283] Visiers, I., Ebersole, B. J., Dracheva, S., Ballesteros, J., Sealfon, S. C., Weinstein, H. (**2002**) Structural motifs as functional microdomains in G-protein-coupled receptors: Energetic considerations in the mechanism of activation of the serotonin 5-HT_{2A} receptor by disruption of the ionic lock of the arginine cage. *Int. J. Quant. Chem.* **88** (1), 65-75. *DOI: 10.1002/qua.10078*

[284] Vollenweider, F. X., Geyer, M. A. (**2001**) A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res. Bull.* **56** (5), 495-507. *PubMed: 11750795 DOI: 10.1016/S0361-9230(01)00646-3*

[285] Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Antonini, A., Maguire, P., Missimer, J., Angst, J. (**1997**) Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG). *Eur. Neuropsychopharmacol.* **7** (1), 9-24. *PubMed: 9088881 DOI: 10.1016/S0924-977X(96)00039-9*

[286] Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Maguire, P., Stadelmann, O., Angst, J. (**1997**) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology* **16** (5), 357-372. *PubMed: 9109107 DOI: 10.1016/S0893-133X(96)00246-1*

[287] Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F., Babler, A., Vogel, H., Hell, D. (**1998**) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* **9** (17), 3897-3902. *PubMed: 15190056 DOI: 10.1074/jbc.M404673200*

[288] Wang, Q., Zhao, J., Brady, A. E., Feng, J., Allen, P. B., Lefkowitz, R. J., Greengard, P., Limbird, L. E. (**2004**) Spinophilin blocks arrestin actions in vitro and in vivo at G protein-coupled receptors. *Science* **304** (5679), 1940-1944. *PubMed: 15218143 DOI: 10.1126/science.1098274*

[289] Wasson, V. P. and Wasson, R. G. (**1957**) *Mushrooms, Russia, and history. Volumes 1 and 2.* Pantheon Books, New York.

[290] Weeks, R. A. (**1979**) A new psilocybian species of *Copelandia. J. Nat. Prod.* **42**, 469.

[291] Weinstein, Harel (**2003**) *Personal communication.*

[292] Weniger, B., Rafik, W., Bastida, J., Quirion, J.-C., Anton, R. (**1995**) Indole alkaloids from *Antirhea lucida. Planta Med.* **61**, 569-570.

[293] Winter, J. C., Eckler, J. R., Rabin, R. A. (**2004**) Serotonergic/glutamatergic interactions: the effects of $mGlu_{2/3}$ receptor ligands in rats trained with LSD and PCP as discriminative stimuli. *Psychopharmacology (Berl)* **172** (2), 233-240. *PubMed: 14598016 DOI: 10.1007/s00213-003-1636-2*

[294] Wood, M. D., Reavill, C., Trail, B., Wilson, A., Stean, T., Kennett, G. A., Lightowler, S., Blackburn, T. P., Thomas, D., Gager, T. L., Riley, G., Holland, V., Bromidge, S. M., Forbes, I. T., Middlemiss, D. N. (**2001**) SB-243213; a selective 5-HT_{2C} receptor inverse agonist with improved anxiolytic profile: lack of tolerance and withdrawal anxiety. *Neuropharmacology* **41** (2), 186-199. *PubMed: 11489455 DOI: 10.1016/S0028-3908(01)00054-5*

[295] Wright, I. K., Garratt, J. C., Marsden, C. A. (**1990**) Effects of a selective 5-HT_2 agonist, DOI, on 5-HT neuronal firing in the dorsal raphe nucleus and 5-HT release and metabolism in the frontal cortex. *Br. J. Pharmacol.* **99** (2), 221-222. *PubMed: 1691671*

[296] Xia, Z., Gray, J. A., Compton-Toth, B. A., Roth, B. L. (**2003**) A direct interaction of PSD-95 with 5-HT_{2A} serotonin receptors regulates receptor trafficking and signal transduction. *J. Biol. Chem.* **278** (24), 21901-21908. *PubMed: 12682061 DOI: 10.1074/jbc.M301905200*

[297] Xia, Z., Hufeisen, S. J., Gray, J. A., Roth, B. L. (**2003**) The PDZ-binding domain is essential for the dendritic targeting of 5-HT_{2A} serotonin receptors in cortical pyramidal neurons in vitro. *Neuroscience* **122** (4), 907-920. *PubMed: 14643760 DOI: 10.1016/S0306-4522(03)00589-X*

[298] Xu, T., Pandey, S. C. (**2000**) Cellular localization of serotonin$_{2A}$ ($5HT_{2A}$) receptors in the rat brain. *Brain Res. Bull.* **51** (6), 499-505. *PubMed: 10758340 DOI: 10.1016/S0361-9230(99)00278-6*

[299] Zhai, Y., George, C. A., Zhai, J., Nisenbaum, E. S., Johnson, M. P., Nisenbaum, L. K. (**2003**) Group II metabotropic glutamate receptor modulation of DOI-induced *c-fos* mRNA and excitatory responses in the cerebral cortex. *Neuropsychopharmacology* **28** (1), 45-52. *PubMed: 12496939 DOI: 10.1038/sj.npp.1300013*

Acknowledgements

I would like to acknowledge the contributions of the many people who helped make this thesis possible. First and foremost, Prof. Dr. Hartmut Laatsch and Prof. David E. Nichols for providing the opportunity to work at this project. The NMR department, especially Reinhard Machinek, for measuring the NMR spectra of my compounds. The analytical department, especially Dr. Holm Frauendorf and Gabriele Krökel, for measuring the MS spectra of the ligands. Deborah Kurrasch-Orbough for introducing me to the pharmacological techniques used (and to the American lifestyle). Stewart Frescas for his help with housing and all those formalities, and for his chemical advice. The state of Niedersachsen and the DAAD (Deutscher Akademischer Austauschdienst) for financial support. Prof. Dr. Wolfgang Poser for being a referee for my scholarship application. The members of the Laatsch group and of the Nichols group. Last but not least, I would like to thank Ulrike for several great vacations and my former and present flat mates, especially Christina, Corina, and Martin.

Lebenslauf

Am 16. Juli 1968 wurde ich in Hamburg geboren und besitze seitdem die deutsche Staatsbürgerschaft. Nach Bestehen meines Abiturs 1987 am Gymnasium Osterbek in Hamburg begann ich das Studium der Informatik an der Universität Hamburg. 1989 unterbrach ich das Studium um meinen Zivildienst in einer gemeindepsychiatrischen Rehabilitationseinrichtung in Hamburg abzuleisten. Danach begann ich 1992 eine landwirtschaftliche Lehre auf dem Gut Adolphshof in Hämelerwald. Anschliessend begann ich 1993 das Studium der Biologie an der Universität Regensburg. Nach meinem Vordiplom 1995 wechselte ich für einen einjährigen Forschungsaufenthalt nach Göttingen an das Max-Planck-Institut für Experimentelle Medizin in die Arbeitsgruppe von Prof. H. Ehrenreich. Dort charakterisierte ich astrocytäre Cannabinoid- und Endothelin-Rezeptoren mithilfe von Radiorezeptor-Bindungsstudien. Diese Arbeit resultierte in zwei Publikationen im *Journal of Neurochemistry* und *Brain Research*. Danach setzte ich mein Studium in Regensburg mit den Schwerpunkten Biochemie, organische Chemie, Neuroanatomie und Neurophysiologie fort. Für meine Diplomarbeit wechselte ich an das Institut für Pharmazeutische Biologie der Universität München in die Arbeitsgruppe von Prof. T. Kutchan um an der molekularen Klonierung von Enzymen der Psilocybin-Biosynthese zu arbeiten. 1999 beendete ich mein Biologiestudium mit dem Diplom und begann meine Doktorarbeit am Institut für Organische und Biomolekulare Chemie der Universität Göttingen in der Arbeitsgruppe von Prof. H. Laatsch. Dort arbeitete ich an der Strukturaufklärung des Naturstoffs Aeruginascin und an der Synthese und pharmakologischen Charakterisierung von Serotonin-Rezeptor-Liganden. Für den pharmakologischen Teil dieses Projektes wechselte ich von 2001 bis 2002 für einen Forschungsaufenthalt an das Department of Medicinal Chemistry and Molecular Pharmacology der Purdue University in Indiana, USA, in die Arbeitsgruppe von Prof. D. E. Nichols. Meine Doktorarbeit wurde durch ein Promotions-Stipendium des Landes Niedersachsen und durch ein Auslands-Stipendium des Deutschen Akademischen Austauschdienstes (DAAD) gefördert.

Göttingen, den 21. September 2004

Niels Jensen