4 Indole-based ligands as potential 5-HT$_7$ receptor agonists

4.1 Introduction

Previous studies on the characterization of the pharmacophore for 5-HT$_7$ receptor agonism, as described in Chapter 3, suggested a limited steric freedom with respect to the basic skeleton of potential new agonists. Unlike the indication obtained from the initial molecular modeling studies that THIQ-based ligands might be interesting candidates as novel 5-HT$_7$ receptor agonists, binding data demonstrated that this class of compounds has no affinity for this receptor subtype. As a result, it was hypothesized that ligands might experience considerable steric repulsions of amino acid residues at the binding site of the receptor if they have to adopt a non-equiplanar orientation as compared to the ligands used to derive the initial pharmacophore model. Similarly, ligands that possess atoms and/or substituents which are oriented out of this plane might also show substantial lower affinity for the binding site of the receptor.

Among the 5-HT$_7$ receptor agonists that were used to determine the pharmacophore model for this receptor subtype was a considerable number of tryptamine-based ligands. The presumed active conformation of these highly flexible tryptamines could be deduced from the rigid ergoline structure of (+)-LSD (1), a high affinity 5-HT$_7$ receptor agonist$^{11}$.

![Chemical structure of (+)-LSD. Tryptamine group emphasized with thick lines.](image)

Because of the perfectly flat character of the aromatic heterocyclic ring structure of the indole nucleus, along with the greater synthetic accessibility of tryptamines compared to ergolines, it seemed likely that tryptamines could provide us with valuable information for the present pharmacophore model and future computational models (e.g. Comparative Molecular Field Analysis, CoMFA), and help to extend the knowledge of the SAR of this class of compounds. In addition, the effect of introducing (small) substituents to the core of the indole-based ligands on the binding affinity could disclose the capacity of the binding site of the receptor to host these (small)
substituents, while the rest of the molecule complies with the prerequisites of the pharmacophore model (i.e. the flat aromatic ring structure).

4.1.1 5-Methoxy-tryptamines

From the initial pharmacophore-identifying procedure described in Chapter 2, it was concluded that the substituent at the 5-position of indole-based ligands should be hydrogen bond accepting. Apart from 6-methoxy-tryptamine and tryptamine – two fairly binding ligands lacking a hydrogen bond accepting group at the 5-position – all indole ligands possess a substituent at this position capable of forming a hydrogen bond. Moreover, there is no significant loss of receptor affinity when the 5-hydroxyl group is disposed of its hydrogen bond donating capacity by alkylation of this substituent (compare affinities of 5-HT and 5-MeOT). Hence, a series of 5-methoxy-tryptamines was synthesized with a variety of substituents at the ethylamine nitrogen and the indole nucleus to verify this rationale and study the SAR of this class of ligands.

4.1.2 6-Methoxy-\(N\)-ethylamino-indoles

In line with the rationale to design and synthesize a series of 5-methoxy-tryptamines, it should be interesting to investigate the binding affinity of 6-methoxy-indoles and analogues as well. As was known from the formulation of the initial pharmacophore model, 6-methoxy-tryptamine showed moderate affinity for the 5-HT\(_7\) receptor\(^{15}\). However, the importance of the hydrogen bond donating \(NH\)-group of the indole nucleus was unclear. The high affinity of 1-methyl-5-HT\(^{15}\) suggested that substitution of this group by a methyl group had no considerable effect on the binding affinity. Also, the affinities for the 5-HT\(_7\) receptor of \((R)\)-8-OH-DPAT and 1-naphthylpiperazine, despite the absence of a similar functional group, supported this hypothesis. For that reason, the synthesis of 6-substituted indoles with the ethylamine side chain attached to the nitrogen of the 5-membered heterocyclic ring of the indole nucleus was considered. As a regioisomer (Figure 4.2) of the typical tryptamines, these compounds could offer a valuable contribution to the refinement of the initial pharmacophore model and could be used to examine the importance of the hydrogen bond donating \(NH\)-group of indoles. Additionally, verification of the binding properties of the precursors of these target compounds, the indolines, being intermediates in this synthesis pathway (see Scheme 4.4), could possibly validate the hypothesis that the aromatic core of 5-HT\(_7\) receptor agonists is flat.
4.1.3 3-Tetrahydro-pyridinyl-indoles

3-(1,2,5,6-Tetrahydropyridin-4-yl)-indoles (4-THPI) represent a group of semi-rigid analogues of tryptamines, possessing the inherent properties of acting on serotonin receptors. As a consequence of the amino group being part of the tetrahydropyridine (THP) ring, it offered an interesting opportunity to study the difference in binding affinity of this class of compounds with respect to the rigid structure of 1 and the flexible tryptamine-based ligands.

![Figure 4.2: Indole regio-isomers.](image)

Despite the presence of a rotatable bond between the pyridine group and the 3-carbon atom of the indole nucleus, this bond is constrained to near-planar conformations as a result of conjugation between the indole ring and the double bond of the THP ring. The distance between the basic nitrogen of the THP ring and the centroid of the six-membered aromatic ring of the indole nucleus is only slightly larger compared to the freely moving ethylamine side chains of tryptamines, as can be derived from molecular modeling calculations (Table 4.1). Nevertheless, a series of ligands based on 4-THPI had shown to bind to the closely related 5-HT$_{1A}$ receptor and 5-HT$_2$ receptor with moderate to high affinity. Encouraged by these data, the applicability of 4-THPI as 5-HT$_7$ receptor ligands was investigated.
4.2 Chemistry

4.2.1 Synthesis of 5-methoxytryptamines

The synthesis of a series of possible 5-HT\textsubscript{7} receptor ligands with a hydrogen bond accepting group at the 5-position started with either 5-methoxy-indole or 5-methoxy-2-methyl-indole, as illustrated in Scheme 4.1. By varying the substituents at the ethylamine nitrogen, and by introduction of small alkyl substituents at different positions of the indole nucleus, we aimed to retrieve supplementary information about the SAR of these indoles.

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node (5a) at (0,0) [draw,shape=circle] {5a-b};
\node (6a) at (2,0) [draw,shape=circle] {6a-b};
\node (7a) at (4,0) [draw,shape=circle] {7a-j};
\node (7a) at (6,0) [draw,shape=circle] {8a-j};
\node (9a) at (8,0) [draw,shape=circle] {9a-j};
\node (5b) at (0,-2) [draw,shape=circle] {5b-6b};
\node (7b) at (2,-2) [draw,shape=circle] {7b-9b};
\node (7c) at (4,-2) [draw,shape=circle] {7c-9c};
\node (7d) at (6,-2) [draw,shape=circle] {7d-9d};
\node (7e) at (8,-2) [draw,shape=circle] {7e-9e};
\node (7f) at (0,-4) [draw,shape=circle] {7f-9f};
\node (7g) at (2,-4) [draw,shape=circle] {7g-9g};
\node (7h) at (4,-4) [draw,shape=circle] {7h-9h};
\node (7i) at (6,-4) [draw,shape=circle] {7i-9i};
\node (7j) at (8,-4) [draw,shape=circle] {7j-9j};
\node (5a) at (0,-6) {5a-6a: R1 = H};
\node (5b) at (0,-8) {5b-6b: R1 = CH\textsubscript{3}};
\node (7a) at (2,-6) {7-9a: R1, R2, R3 = H};
\node (7b) at (2,-8) {7-9b: R1 = H, R2, R3 = CH\textsubscript{3}};
\node (7c) at (2,-10) {7-9c: R1 = H, R2, R3 = n-Pr};
\node (7d) at (4,-6) {7-9d: R1 = H, R2, R3 = -(CH\textsubscript{2})\textsubscript{4}O(CH\textsubscript{2})\textsubscript{2}-};
\node (7e) at (4,-8) {7-9e: R1 = H, R2, R3 = -(CH\textsubscript{2})\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}-};
\node (7f) at (6,-6) {7-9f: R1 = H, R2 = CH\textsubscript{3}, R3 = Bn};
\node (7g) at (6,-8) {7-9g: R1 = CH\textsubscript{3}, R2, R3 = H};
\node (7h) at (6,-10) {7-9h: R1, R2, R3 = CH\textsubscript{3}};
\node (7i) at (8,-6) {7-9i: R1 = CH\textsubscript{3}, R2, R3 = n-Pr};
\node (7j) at (8,-8) {7-9j: R1 = CH\textsubscript{3}, R2, R3 = -(CH\textsubscript{2})\textsubscript{4}O(CH\textsubscript{2})\textsubscript{2}-};
\end{tikzpicture}
\end{center}
\textbf{Scheme 4.1: Synthesis of 5-methoxytryptamines.} Reagents and conditions: (a) Oxalyl chloride, diethyl ether. (b) Amine, H\textsubscript{2}O / CHCl\textsubscript{3}. (c) LiAlH\textsubscript{4}, THF. (d) KO-t-Bu, dimethyl-oxalate, DMF, reflux.

All ligands within this class of compounds were accessible by introduction of the ethylamine side chain through coupling of the indole nucleus with oxalyl chloride\textsuperscript{13}. The oxo-acetyl chloride intermediate, which precipitates readily from ether, can subsequently be derivatized with the primary or secondary amine of choice to form the oxo-amid. Reduction of the side chain was effectuated using an excess of LiAlH\textsubscript{4} in refluxing THF. There was no difference observed in reactivity when 2-methyl-indole was used as a starting material in this procedure.
On the other hand, attempts to synthesize N-methyl derivatives of these compounds, starting directly by methylation of 5-methoxy-1H-indole, followed by coupling with oxalyl chloride and the appropriate amine, failed at the stage of reduction of the 2-oxo-acetamide group using LiAlH₄ (Scheme 4.2 and Scheme 4.3). Under these circumstances, intermediates with an 2-oxo-acetamide group (like 12) could not be converted to the desired products with ethylamine side chains. The use of a large excess of reducing agent, elevated temperature, and extended reaction times was not helpful, and the reaction stopped at the stage of 2-hydroxy-ethylamine 13 as depicted in Scheme 4.3. It is hypothesized that, in case of the unsubstituted NH-indole derivatives, the final step in this reduction is facilitated by the formation of an indolyl anion upon dissociation of the aluminum oxide complex. In case of the N-methylated indoles, deprotonation of the indole-NH is impossible. Therefore, isomerization of an indolyl anion does not occur, and LiAlH₄ reduction of this carbonyl group stops at the stage of a secondary alcohol. As a consequence, N-methylated analogs of 8a-f were obtained through alkylation of the tryptamines in the final step after reduction of the 2-oxo-acetamides, according to the synthesis route described in Scheme 4.1.
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**Indole based ligands as potential 5-HT\textsubscript{7} receptor agonists**

![Chemical structures and reactions](image)

**Scheme 4.3** Differences in reactivity between unsubstituted (top) and N-substituted indole substrates (bottom).

*Reagents and conditions: (a) LiAlH\textsubscript{4}, THF, reflux. (b) H\textsubscript{2}O.*

### 4.2.2 Synthesis of 6-methoxy-\(N\)-ethylamine-indole ligands

Due to the considerable reactivity of the 2- and 3-position of the indole nucleus, it seemed wise to synthesize the series of 6-methoxy-\(N\)-ethylamine-indole ligands via the reduced indole core – the indoline or 2,3-dihydro-indole – as illustrated in Scheme 4.4. As stated before, with this precursor of the desired 6-methoxy-indole-\(N\)-ethylamine, it was possible to study the relevance of the flat architecture of the heterocyclic ring system in more detail, as well as the importance of its aromatic character.

6-Methoxy-indole (16) was prepared from 4-methyl-3-nitroanisole (14) via the Batcho-Leimgruber pathway with dimethylformamide dimethyl acetal in pyrrolidine followed by ring closure, which occurs after hydrogenation of the nitro group\textsuperscript{4,5}. To prevent substitution of the 2- and 3-positions of the indole nucleus during the succeeding steps, the indole was reduced with NaCNBH\textsubscript{3} in glacial acetic acid to indoline 17. Subsequent substitution of the nitrogen atom with an ethylamine side chain proceeded via the 2-chloroacetylated intermediate 18. Reduction of the
amide group at this stage appeared to be problematic, typically resulting in cleavage of the amide bond. Instead of LiAlH₄ which resulted in complete cleavage of amide, other reducing agents like BH₃-dimethylsulphide complex, and AlH₃ (prepared from LiAlH₄ and H₂SO₄ or AlCl₃) were used. The latter giving the best results, although yields remain low in some cases. During the final step, oxidation of the indoline to the indole was achieved by the use of MnO₂ in refluxing acetonitrile.

4.2.3 Synthesis of 3-tetrahydropyridinylindoles

A limited number of ligands based on the indole core, again with the hydrogen bond accepting group at the 5-position, but with restricted rotational freedom of the ethylamine side chain by ‘locking’ it into a THP ring, was prepared in a simple one step synthesis according to Scheme 4.5. Using N-benzyl protected piperidone, this approach offers the possibility to introduce different substituents at the tetrahydropyridinyl nitrogen after removal of the protecting group.
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Scheme 4.5: Synthesis of 3-tetrahydro-pyridinyl-indole ligands. Reagents and conditions: (a) Piperidone, NaOCH_3, CH_3OH, reflux. (b) Pd/C, H_2, EtOH.

4.3 Pharmacology

Compounds 8b, 8d, 8g-j, 9b-f, 20a-d, 21a, and 22a-c were evaluated at Pfizer and former SmithKline-Beecham laboratories for their ability to compete for [3H]5-CT binding to cloned rat 5-HT_7 receptors expressed in HEK-293 cells. Additionally, the effect on adenylate cyclase activity relative to the effects of 5-CT (agonist, 100%) and methiothepin (inverse agonist, 100%) was determined at Pfizer laboratories for a selection of these compounds. These results are summarized in Table 4.1.

4.4 Results and discussion

By extending the series of indole-based ligands that were known from literature to interact with the 5-HT_7 receptor, we aimed to get a more detailed image of the agonist pharmacophore. Additionally, association of the pharmacological data obtained with the chemical structures of the tested compounds, could help to reveal the characteristics of the binding site of the receptor in future molecular modeling computations (3D-QSAR, CoMFA).

When the pharmacological data were collected, it appeared that the higher binding affinities were limited to those tryptamines that lack (small) substituents attached to the indole ring structure. For comparison, structural and pharmacological data of the earlier tested ligands serotonin, 5-methoxytryptamine (5-MeOT), and bufotenin (N,N-dimethyl-5-hydroxytryptamine) are also listed in Table 4.1. Substitution of the ethylamine nitrogen with alkyl groups of increasing size results in a decrease of 5-HT_7 receptor affinity: roughly 25-fold per carbon atom, while calculated logP values show a less pronounced increase. Nevertheless, despite its decreased receptor affinity, 8b can be classified as a full agonist, while 8d is capable of increasing basal adenylate cyclase activity with only 39% compared to 5-CT.
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Table 4.1: Calculated physical properties<sup>1</sup>, geometries, experimental 5-HT<sub>7</sub> receptor binding affinities and relative potencies of basal adenylate cyclase stimulation of compounds 8b-8j, 9b-9f, 20a-20d, 21a, and 22a-22c.<sup>2</sup> Effect on basal adenylate cyclase activity relative to potencies of 5-CT (+100% at 1.0 x 10<sup>-5</sup> M, full agonist) and methiothepin (-100% at 1.0 x 10<sup>-5</sup> M, full inverse agonist). Ligand concentration 1.0 x 10<sup>-4</sup> M. <sup>2</sup> Data derived from literature<sup>11,15</sup>. <sup>6</sup> 5-HT<sub>7</sub> receptor affinity reported in literature: 145 nM<sup>6</sup>. <sup>d</sup> pK<sub>a</sub>piperazine-NCH<sub>3</sub> = 9.61. Not determined abbreviated as n.d.

Introduction of a methyl group at the 2-position of the indole ring of 8g-8j provokes a dramatic drop of affinity (ca. 150 fold when 5-MeOT and 8g are compared) and of efficacy (compare 8b and 8h). With regard to the findings described in Chapter 3, the current results are in agreement with the hypothesis that amino acid residues at the agonist binding site of the 5-HT<sub>7</sub> receptor cause steric hindrance, resulting in low(-er) binding affinities for those compounds that have bulky substituents pointing in that particular direction. By comparison of Figure 2.4, Figure 3.3, and Figure 3.4 it becomes evident that the methyl group at the 2-position of the indole ring of 8g-8j, and the ethylamine side chain of the THIQs described in Chapter 3, both share this characteristic, but to a different extent. In case of 8g-8j, the smaller 2-methyl group experiences slight steric hindrance of the interior of the agonist binding site causing decreased affinities. In case of THIQs, the larger ethylamine side chain is too big to fit the cavity of the binding site, resulting in...
no affinity for the 5-HT\(_7\) receptor at all. Yet, – presuming that the ligands within this group of indoles with a methyl group at the 2-position show comparable efficacy data (efficacy of 8g, 8i-j not tested) – these compounds, like 8h, still act as (partial) agonists.

A shift of the methyl group around the heterocyclic ring of the indole nucleus results in a significant decrease of 5-HT\(_7\) receptor affinity, similar to that observed for compounds 8g-8j. With the methyl group positioned at the indole-NH, there is also a remarkable change in efficacy. Within this series, 9b turned out to be an inverse agonist with moderate potency. This result was surprising, while the chemical structure and physical properties are very similar to other tryptamines that act as (partial) 5-HT\(_7\) receptor agonists. In addition, the structure does not comply with the prerequisites formulated by the pharmacophore model for 5-HT\(_7\) receptor antagonism\(^6\) discussed in Chapter 1, which is in fact primarily based on ligands that show inverse agonism as well\(^7,9,14\). As a consequence, this finding brings about undiscovered aspects of the pharmacophore model. It not only requires further examination of this model, but also raises questions about the differences in molecular interactions between agonists and inverse agonists. Unfortunately, 9b was the only ligand tested for its effect on adenylate cyclase stimulation within this series. However, compounds with larger substituents at the ethylamine side chain lack affinity for the receptor, which disqualify them for further screening.

Within the series of regio isomers of the common tryptamines 20a-20d and 21a, none of the ligands showed substantial affinity for the 5-HT\(_7\) receptor. In view of the preceding findings and the relative similarities of the chemical structures of the THIQs and ligands 20a-20d, these results were consistent with the hypothesis that the (bicyclic) core ring structure should be completely flat. The 5-membered heterocyclic ring of the indoline-based ligands does not comply with this condition and thus no high affinity ligands were to be expected within this series of compounds. Additionally, the somewhat smaller distance between the nitrogen of the ethylamine side chain and the (hydrogen bond accepting group of the) six-membered aromatic ring compared to the geometries of the normal tryptamines may contribute to this lack of affinity as well. However, the unmistakable lack of affinity for the 5-HT\(_7\) receptor of the flat 21a was astonishing, and may suggest a crucial role for a hydrogen bond donating NH-group. Considering the set of ligands that was used to develop the initial pharmacophore model for 5-HT\(_7\) receptor agonists, this effect was estimated to be considerably smaller, where (R)-8-OH-DPAT and 1-naphthylpiperazine showed substantial affinity for this receptor subtype. In addition, the slightly shorter distance between this nitrogen atom and the (hydrogen bond accepting group of the) six-membered aromatic ring may contribute to this lack of affinity. On the other hand, this distance was calculated for 1 to be even smaller (5.18 Å) and therefore appears to be less important. However, in this case, it may be counterbalanced by the highly restricted conformation of the embedded tryptamine structure, as well as by other characteristics of this particular ergoline (e.g. presence of diethyl-amide group).
Regarding 22a-22c, we assume that the different orientation of the THP ring of these ligands, compared to the rigid structure of the ergoline skeleton of 1, is primarily responsible for the low affinity of these compounds for the 5-HT$_7$ receptor. A similar phenomenon could also be seen within the series of 6- and 7-substituted 1,2,3,4-tetrahydroisoquinolines with an ethylamine side chain at the 2-position, discussed in Chapter 3. Additionally, the inherently larger distance between the positively charged nitrogen atom of the THP ring and the (hydrogen bond accepting group of the) six-membered aromatic ring may contribute to this observation as well. The moderate affinity of 22b with the large benzyl substituent attached to the THP ring appears not to be in line with the previous observations as seen within the other series of tryptamines. However, the intrinsic activity of this ligand is less surprising, considering the fact that molecular modeling computations indicated that 22b fits the hypothesized pharmacophore model for 5-HT$_7$ receptor antagonism. Given the fact that THPI-based ligands generally show higher affinity for the 5-HT$_{1A}$ receptor than for the receptor subtype of current interest, these findings may contribute to the further exploration of differences between the closely related receptor subtypes, and the development of subtype selective ligands.

4.5 Conclusions

Summarizing, it can be stated that the number of tryptamines that bind to the 5-HT$_7$ receptor has been extended, resulting in a more detailed view of the pharmacophore model for 5-HT$_7$ receptor agonism, and several interesting candidates for computational studies on 3D structure-activity relationships, as will be discussed in Chapter 6. Based on the series of 5-methoxytryptamines, it has become clear that the binding site of the 5-HT$_7$ receptor offers limited space for substituents attached to the positively charged nitrogen atom of the ethylamine side chain. A methyl group at the 2-position of the indole ring is acceptable without affecting the nature of intrinsic activity, but is accompanied by generally lower affinity values. These results are in agreement with the conclusions of Chapter 3, stating that the interior of the agonist binding site of the 5-HT$_7$ receptor does not allow larger substituents at the 2-position of the indole nucleus nor at the nitrogen atom of the ethylamine side chain of THIQ-based ligands. Substitution of the indole-NH with a methyl group not only causes a significant drop of affinity, but changes the nature of these ligands from agonists to inverse agonists as well. This observation, combined with the observed lack of affinity of the regio-isomer 21a, suggests an important role for the indole-NH group with respect to conformational changes (at the binding site) of the receptor that subsequently results in activation of the G-protein.
4.6 Experimental Section

4.6.1 Chemistry

General remarks

For general remarks on molecular computations, origin and use of solvents and reactants, as well as characterization methods of compounds and determination of their ability to compete for [3H]5-CT binding to cloned rat 5-HT7 receptors expressed in HEK-293 cells, the reader is referred to Sections 3.7.1 – 3.7.3.

5-Methoxy-1-methyl-1H-indole (10)

5-Methoxyindole (5a, 5.00 g, 34.0 mmol) and KO-t-Bu (4.16 g, 37.4 mmol) were suspended in DMF (50 mL) in a 3-necked flask with reflux condenser under nitrogen. After addition of dimethyl oxalate (4.41 g, 37.4 mmol), the mixture was heated to reflux for 4 hr. The suspension was then poured into water (200 mL), and extracted with EtOAc (5 x 50 mL). The combined organic layers were washed (brine), dried (Na2SO4), and filtered. The volatiles were removed in vacuo to yield an off white solid (5.44 g) that was crystallized from diisopropyl ether.

1H-NMR (300 MHz, CDCl3) (ppm): 3.83 (d, J = 0.5 Hz, 3H), 3.93 (d, J = 0.7 Hz, 3H), 6.48 (d, J = 3.2 Hz, 1H), 6.95 (d, J = 2.4 Hz, 0.5H), 6.99 (dd, J = 0.5 Hz, Jb = 2.0 Hz, 0.5H), 7.09 (d, J = 2.9 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 2.9 Hz, 1H).

13C-NMR (75 MHz, CDCl3) (ppm): 31.4, 54.4, 98.9, 101.1, 108.3, 126.5, 127.8, 138.0, 152.5. IR (KBr, cm−1): 2949, 2904, 2831, 1619, 1574, 1495, 1418, 1245, 1149, 1099, 1023, 851, 753, 724. MS (EI): 161 (100%), 146 (100%), 130, 118(100%), 103, 91, 77, 65, 51.

(5-Methoxy-1-methyl-1H-indol-3-yl)-oxo-acetyl chloride (11)

Oxalylchloride (2.35 g, 18.6 mmol) was dissolved in ether (75 mL) at 0 °C. 5-Methoxy-1-methyl-1H-indole (10, 2.50 g, 15.5 mmol) was added portionwise. The red precipitate (3.73g) was collected by filtration, dried in vacuo, and used without further purification. IR (KBr, cm−1): 3140, 3015, 2955, 2829, 1779, 1716, 1602, 1577, 1485, 1456, 1350, 1271, 1145, 1066, 1027, 963, 848, 805, 694, 629.

2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (7a)

(5-Methoxy-1H-indol-3-yl)-oxo-acetyl chloride (6a, 0.25 g, 1.05 mmol) was added portionwise to a solution of dimethylamine (5 mL, 40% in water) at 0 °C. After 30 min, CH2Cl2 (50 mL) was added. The layers were separated and the inorganic phase was washed with CH2Cl2. The combined organic layers were dried (Na2SO4), filtered, and concentrated in vacuo. The residue was crystallized from EtOAc/hexanes to yield 0.23 g of a white solid. 1H-NMR (200 MHz, CD3OD /
CDCl$_3$ δ (ppm): 2.80 (d, J = 8.8 Hz, 6H), 3.64 (d, 8.8 Hz, 3H), 6.66 (s, 1H), 7.08 (d, J = 8.1 Hz), 7.50 (s, 1H), 7.58 (s, 1H). IR (KBr, cm$^{-1}$): 3090, 3038, 2984, 1605, 1518, 1490, 1437, 1265, 1210, 1149, 1030, 808.

**[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-dimethyl-amine (8a)**

In a 3-necked flask with cooler, LiAlH$_4$ (0.11 g, 2.89 mmol) was suspended in THF (10 mL) under nitrogen. 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (7a, 0.20 g, 0.81 mmol), dissolved in THF (10 mL) was added dropwise at rt. The suspension was heated to a gentle reflux for 2 hr. After cooling to rt, the excess of LiAlH$_4$ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts were filtered over Celite, washed extensively (diethyl ether), and the residue was concentrated in vacuo to yield a colorless oil, which was pure 8a according to NMR and GC. The free base was converted in the DTTA-salt by addition of 1 equivalent of (+)-DTTA to a solution of the free base in i-PrOAc.

**[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-dimethyl-amine (8a)**

In a 3-necked flask with cooler, LiAlH$_4$ (0.18 g, 0.83 mmol) was dissolved in DMF under nitrogen. After addition of KO-t-Bu (0.10 g, 0.89 mmol) and dimethyl oxalate (0.10 g, 0.85 mmol), the mixture was heated to reflux for 4 hr. The mixture was then allowed to cool to rt, and ammonia (30 mL, 10% in water) was added. Extraction with diethyl ether (3 x 15 mL), drying (Na$_2$SO$_4$) of the combined organic layers and subsequent evaporation of the volatiles yielded a brown oil (0.17 g), which was purified by chromatography (Silica, gradient CH$_2$Cl$_2$/CH$_3$OH). 1H-NMR (300 MHz, CDCl$_3$) δ (ppm): 2.30 (s, 6H), 2.57 (dd, $J_a = 7.3$ Hz, $J_b = 8.4$ Hz, 2H), 2.82-2.89 (m, 2H), 3.63 (s, 3H), 3.82 (s, 3H), 6.80 (s, 1H), 6.84 (dd, $J_a = 2.2$ Hz, $J_b = 6.6$ Hz, 1H), 7.00 (d, $J = 1.8$ Hz, 1H), 7.12 (d, $J = 8.8$ Hz). 13C-NMR (75 MHz, CDCl$_3$) δ (ppm): 21.2, 30.2, 43.0, 53.5, 57.7, 98.2, 107.5, 109.1, 109.7, 125.6, 129.9, 151.1. MS (EI$^+$): 232, 174, 131, 58 (100%). Analysis calc. for: C$_{14}$H$_{20}$N$_2$O-C$_2$H$_4$O$_4$: C 59.62%, H 6.88%, N 8.69%, O 24.82%; obsd: C 59.43%, H 6.933%, N 8.83%.

**2-(5-Methoxy-1H-indol-3-yl)-2-oxo,N,N-dipropyl-acetamide (7c)**

(5-Methoxy-1H-indol-3-yl)-oxo-acetyl chloride (6a, 0.25 g, 1.05 mmol) was added portionwise to a solution of dipropylamine (5 mL, 50% in water). After 30 min CH$_2$Cl$_2$ (50 mL) was added. The layers were separated. The inorganic phase was diluted with water (25 mL), and washed with CH$_2$Cl$_2$. The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to yield a semi solid (0.40 g). Crystallization from EtOAc / hexane yielded pure 7c as a colorless solid. 1H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.72 (t, $J = 7.3$ Hz, 3H), 0.92 (t, $J = 7.3$ Hz, 3H), 1.49-1.65 (m, 4H), 3.18 (t, $J = 7.7$ Hz, 2H), 3.35 (t, $J = 7.7$ Hz, 2H), 3.81 (s, 3H), 6.80 (dd, $J_a = 2.6$ Hz, $J_b = 6.2$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 1H), 7.47 (d, $J = 3.3$ Hz, 1H), 7.71 (d, $J = 1.8$ Hz, 1H), 10.36 (br, 1H). 13C-NMR (75 MHz, CDCl$_3$) δ (ppm): 8.6, 8.9, 18.1, 19.4, 43.7, 47.2, 53.2, 100.6, 110.5, 111.6, 112.0, 123.6, 129.0, 133.0, 148.5, 154.1, 165.9, 183.6. IR (KBr, cm$^{-1}$): 3147, 2962, 1632, 1609, 1442, 1271, 1213, 1125, 1086, 1026, 811, 682.

**[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-dipropyl-amine (8c)**

In a 3-necked flask with cooler, LiAlH$_4$ (0.18 g, 4.74 mmol) was suspended in THF (20 mL) under nitrogen. 2-(5-methoxy-1H-indol-3-yl)-2-oxo,N,N-dipropylacetamide (7c, 0.40 g, 1.32 mmol), dissolved in THF (5 mL) was added dropwise. The suspension was heated to a gentle reflux for 2 hr. After cooling to rt, the excess of LiAlH$_4$ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts were filtered over Celite, washed extensively (diethyl ether), and the residue was concentrated in vacuo to yield a colorless oil, which was pure 8c according to NMR and GC.
In a 3-necked flask with cooler, \( \text{LiAlH}_4 \) (0.32 g, 8.42 mmol), dissolved in THF (20 mL) was added dropwise. The suspension was heated to a gentle reflux for 2 hr. After cooling to rt, the excess of \( \text{LiAlH}_4 \) was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts were filtered over Celite, washed extensively (Ether), and the residue was concentrated in vacuo to yield a white solid (0.57 g). Crystallization from EtOAc / hexane yielded pure \( 7d \) as a colorless solid. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 1.85-1.89 (m, 4H), 3.54 (q, \( J = 6.2 \) Hz, 2H), 3.84 (s, 3H), 6.81 (s, 1H), 6.85 (dd, \( J_a = 6.3 \) Hz, \( J_b = 1.9 \) Hz, 1H), 7.03 (d, \( J = 2.6 \) Hz, 1H), 7.13 (d, \( J = 8.8 \) Hz). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm): 22.4, 24.6, 44.3, 45.9, 54.3, 101.8, 111.3, 112.4, 113.0, 129.7, 134.8, 155.2, 182.4. IR (KBr, cm\(^{-1}\))): 3096, 3038, 2943, 2894, 1602, 1518, 1483, 1438, 1265, 1212, 1148, 1032, 807, 696.

5-Methoxy-3-(2-pyrrolidin-1-yl-ethyl)-1H-indole (8d)

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH\(_4\) (0.32 g, 8.42 mmol) was suspended in THF (20 mL) under nitrogen. \( 7d \) (0.57 g, 2.10 mmol), dissolved in THF (20 mL) was added dropwise. The suspension was heated to a gentle reflux for 2 hr. After cooling to rt, the excess of LiAlH\(_4\) was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts were filtered over Celite, washed extensively (Ether), and the residue was concentrated in vacuo to yield a slightly yellow oil (0.53 g), which was the pure \( 8d \) according to NMR and GC. The free base was converted in the (+)-DTTA salt by addition of 1 equivalent of (+)-DTTA to a solution of the indole in isopropyl acetate. \(^1\)H-NMR (free base, 200 MHz, CDCl\(_3\)) \( \delta \) (ppm): 1.80-1.87(m, 4H), 2.62-2.69 (m, 4H), 2.77-2.81 (m, 2H), 2.90-3.00 (m, 2H), 3.85 (s, 3H), 6.84 (dd, \( J_a = 2.4 \) Hz, \( J_b = 6.4 \) Hz, 1H), 6.93 (d, \( J = 2.2 \) Hz, 1H), 7.06 (d, \( J = 2.2 \) Hz, 1H), 7.18 (dd, \( J_a = 0.5 \) Hz, \( J_b = 8.3 \) Hz, 1H), 8.60 (br, 1H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \( \delta \) (ppm): 22.0, 23.6, 52.7, 54.4, 55.7, 99.1, 110.4, 112.4, 121.0, 126.3, 130.0, 152.2. IR (free base, neat, cm\(^{-1}\))): 3412, 3140, 2934, 2800, 1624, 1584, 1485, 1438, 1265, 1212, 1148, 1032, 795. MS (free base, EI\(^*\)): 244, 160, 84 (100%).

5-Methoxy-1-methyl-3-(2-pyrrolidin-1-yl-ethyl)-1H-indole (9d)

In a 3-necked flask with cooler, \( 8d \) (0.40 g, 1.64 mmol), KO-t-Bu (0.28 g, 2.46 mmol), and dimethyl oxalate (0.29 g, 2.46 mmol) were suspended in DMF (15 mL) under nitrogen. The mixture was heated to a gentle reflux for 2 hr. The reaction mixture was allowed to cool to rt, and ammonia (50mL, 10% in water) was added. The water layer was extracted with

\[^1\]H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 0.89 (t, \( J = 7.3 \) Hz, 6H), 1.47-1.57 (m, 4H), 2.52 (t, \( J = 7.7 \) Hz, 4H), 2.76-2.81 (m, 2H), 2.85-2.90 (m, 2H), 3.83 (s, 3H), 6.82 (dd, \( J_a = 1.8 \) Hz, \( J_b = 7.0 \) Hz, 1H), 6.91 (s, 1H), 7.02 (d, \( J = 1.8 \) Hz, 1H), 7.17 (d, \( J = 8.8 \) Hz, 1H), 8.41 (br, 1H). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm): 9.6, 17.7, 20.3, 52.1, 53.4, 53.7, 98.2, 109.4, 111.6, 120.0, 125.4, 129.0, 151.2. MS (EI\(^*\)): 274, 174, 160, 114 (100%).
EtOAc (4 x 20 mL), and the combined organic layers were washed (brine), dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure. This yielded a brown oil (0.37 g) that was purified by chromatography (Silica, CH₂Cl₂/CH₃OH, ratio 20:1). ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 1.83-1.90 (m, 4H), 2.67-2.74 (m, 4H), 2.78-2.89 (m, 2H), 2.95-3.05 (m, 2H), 3.69 (s, 3H), 3.86 (s, 3H), 6.87 (dd, J₂ = 2.4 Hz, J₁ = 6.4 Hz, 1H), 6.86 (s, 1H), 7.06 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 21.9, 23.1, 31.2, 52.7, 54.5, 55.7, 99.3, 108.5, 110.2, 110.4, 125.6, 125.3, 130.9, 152.2. MS (EI⁺): 258, 174, 131, 84 (100%), 70.

1-(5-Methoxy-1H-indol-3-yl)-2-morpholin-4-yl-ethane-1,2-dione (7e)

(5-Methoxy-1H-indol-3-yl)-oxo-acetyl chloride (6a, 0.40 g, 1.68 mmol) was added portionwise to a two-phase system of morpholine (1.46 g, 16.8 mmol) in water (10 mL) and CHCl₃ (10 mL). The mixture was stirred vigorously overnight at rt, then portioned, and the water layer was washed with CHCl₃ (3 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to yield 0.58 g of a white solid. Pure 7e was obtained by crystallization from ethanol. ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 3.51-3.56 (m, 2H), 3.64-3.69 (m, 2H), 3.76 (s, 4H), 3.88 (s, 3H), 6.90 (dd, J₂ = 2.4 Hz, J₁ = 6.4 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.75-7.80 (m, 2H), 9.65 (br, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 40.4, 45.1, 54.3, 65.2, 65.5, 101.7, 111.3, 113.4, 124.6, 129.7, 134.1, 155.8, 164.8, 183.7. IR (KBr, cm⁻¹): 3159, 2906, 2857, 1614, 1517, 1482, 1439, 1270, 1211, 1113, 1032, 966, 918, 808.

5-Methoxy-3-(2-morpholin-4-yl-ethyl)-1H-indole (8e)

In a 3-necked flask with cooler, LiAlH₄ (0.18 g, 4.74 mmol) was suspended in THF (20 mL) under nitrogen. 7e (0.40 g, 1.39 mmol), suspended in THF (5 mL) was added dropwise. The suspension was heated to a gentle reflux for 3 hr. After cooling to rt, the excess of LiAlH₄ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts were filtered over Celite, washed extensively (Ether), and the residue was concentrated in vacuo to yield a slightly yellow oil, which was the pure 8e according to NMR and GC. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.52-2.55 (m, 4H), 2.63-2.68 (m, 2H), 2.87-2.93 (m, 2H), 3.73-3.76 (m, 4H), 3.81 (s, 3H), 6.81 (dd, J₂ = 2.6 Hz, J₁ = 6.2 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 8.43 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 20.1, 51.2, 53.5, 57.1, 64.4, 98.2, 109.5, 111.0, 120.1, 125.3, 129.0, 151.3. MS (EI⁺): 260, 100 (100%).

5-Methoxy-1-methyl-3-(2-morpholin-4-yl-ethyl)-1H-indole (9e)

In a 3-necked flask with cooler, 5-methoxy-3-(2-morpholin-4-yl-ethyl)-1H-indole (8e, 0.36 g, 1.39 mmol), KO-t-Bu (0.23 g, 2.08 mmol), and dimethyl oxalate (0.25 g, 2.08 mmol) were suspended in DMF (15 mL) under nitrogen. The mixture was heated to a gentle reflux for 3 hr, then allowed to cool to rt, and quenched with ammonia (50mL, 10% in water). The water layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed (brine), dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure, yielding a brown oil (0.33 g) that crystallized upon standing. Recrystallization from EtOAc/hexane yielded the pure 9e as a white solid. ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 2.53 (d, J = 4.4 Hz, 4H), 2.61-2.66 (m, 2H), 2.86-2.91 (m, 2H), 3.64 (s, 3H), 3.74 (t, J = 4.8 Hz, 4H), 3.82 (3H), 6.81 (s, 1H), 6.84 (dd, J₂ = 2.2 Hz, J₁ = 6.6 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 20.1, 30.2, 51.3, 53.5, 57.3, 64.5, 98.3, 107.5, 109.2, 109.5, 124.5, 125.6, 129.9, 151.2. MS (EI⁺): 274, 174, 131, 100 (100%).

N-Benzyl-2-(5-methoxy-1H-indol-3-yl)-N-methyl-2-oxo-acetamide (7f)

(5-Methoxy-1H-indol-3-yl)-oxo-acetyl chloride (6a, 0.40 g, 1.68 mmol) was added portionwise to a two-phase system of benzylmethylamine (0.61g, 5.45 mmol) in water (10 mL) and CHCl₃ (10 mL). The mixture was stirred vigorously for 2 hr at rt. The organic phase was separated, and the water layer was diluted with water (30 mL) and successively washed with CHCl₃ (3 x 10 mL). The combined organic layers were washed with HCl (0.25 N, 15 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to yield 0.51 g of a white solid. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.96-2.96 (m, 3H), 3.86...
was purified by chromatography (Silica, CHCl₃) were filtered over Celite and washed thoroughly (ether). Evaporation of solvents yielded a slightly yellow oil (0.21 g), that excess of LiAlH₄ in THF (5 mL), was added dropwise at rt. The mixture was heated to reflux overnight, and successively cooled to rt. The inorganic phase was washed with CHCl₃/CH₃OH gradient). ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.34 (d, J = 6.9 Hz, 1H), 6.87-6.92 (m, 1H), 7.17 (dd, J₂ = 0.5 Hz, J₁ = 8.3 Hz, 1H), 7.74 (s, 1H), 7.76 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 32.4, 32.8, 36.0, 54.3, 102.4, 109.4, 111.2, 112.7, 125.5, 131.0, 137.8, 155.4, 166.2, 184.0.

**Benzyl-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-methylamine (8f)**

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH₄ (0.21 g, 5.53 mmol) was suspended in THF (10 mL) under nitrogen. N-Benzyl-2-(5-methoxy-1H-indol-3-yl)-N-methyl-2-oxo-acetamide (7f, 0.45 g, 1.40 mmol), dissolved in THF (10 mL), was added dropwise at rt. The mixture was heated to reflux overnight, and successively cooled to rt. The excess of LiAlH₄ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts formed were filtered over Celite and washed well (ether). Evaporation of solvents yielded pure 8f as a colorless oil (0.42 g), according to TLC and NMR. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.41 (s, 3H), 7.29-7.84 (m, 2H), 3.00-3.06 (m, 2H), 3.67 (s, 2H), 3.85 (s, 3H), 6.88-6.92 (m, 2H), 7.03 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.30-7.42 (m, 5H), 8.37 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 20.9, 39.9, 53.5, 55.3, 98.2, 109.6, 111.4, 120.2, 124.7, 125.5, 125.9, 126.8, 129.1, 136.4, 151.3. IR (neat, cm⁻¹): 3134, 2942, 1622, 1584, 1486, 1455, 1352, 1213, 1065, 1029, 923, 829, 795, 739, 699. MS (EI⁺): 294, 160, 134, 117, 91 (100%).

**Benzyl-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-methylamine (9f)**

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH₄ (0.38 g, 1.00 mmol) was added portionwise to a solution of dimethyl oxalate (0.25 g, 2.08 mmol) in DMF (15 mL) under nitrogen. The mixture was heated to a gentle reflux for 2 hr, then allowed to cool to rt, and quenched with ammonia (50 mL) was added. The layers were separated and the water layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed (brine), dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure, yielding a brown oil (0.43 g) that crystallized upon standing. Recrystallization from EtOAc/hexane yielded the pure 9f as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.39 (s, 3H), 2.74-2.79 (m, 2H), 2.96-3.02 (m, 2H), 3.67 (s, 3H), 6.83 (s, 1H), 6.91 (dd, J₂ = 2.2 Hz, J₁ = 6.6 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.21-7.40 (m, 5H). IR (neat, cm⁻¹): 2941, 2832, 2787, 1620, 1578, 1492, 1455, 1322, 1267, 1258, 1225, 1062, 1036, 791, 738, 698. MS (EI⁺): 308, 174, 159, 134, 117, 91 (100%).

**2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (12)**

(5-Methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (11, 0.25 g, 1.00 mmol) was added portionwise to a solution of dimethylamine (5 mL, 40% in water) at 0 °C. After 30 min CH₂Cl₂ (50 mL) was added. The layers were separated and the inorganic phase was washed with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was recrystallized from diisopropyl ether to yield 12 as a white solid (0.21 g). ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.98-3.03 (m, 6H), 3.73 (s, 3H), 3.83 (d, J = 1 Hz, 3H), 6.87-6.92 (m, 1H), 7.17 (dd, J₂ = 0.5 Hz, J₁ = 8.3 Hz, 1H), 7.74 (s, 1H), 7.76 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 32.4, 32.8, 36.0, 54.3, 102.4, 109.4, 111.2, 112.7, 125.5, 131.0, 137.8, 155.4, 166.2, 184.0.

**2-Dimethylamino-1-(5-methoxy-1H-indol-3-yl)-ethanol (13)**

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH₄ (0.38 g, 10.0 mmol) was suspended in THF (10 mL) under nitrogen. 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (12, 0.20 g, 0.77 mmol), dissolved in THF (5 mL), was added dropwise at rt. The mixture was heated to reflux overnight, and successively cooled to rt. The excess of LiAlH₄ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts formed were filtered over Celite and washed thoroughly (ether). Evaporation of solvents yielded a slightly yellow oil (0.21g), that was purified by chromatography (Silica, CH₂Cl₂/CH₃OH gradient). ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 2.34 (s, 6H), 2.44 (d, J = 2.9 Hz, 0.5H), 2.48 (d, J = 3.3 Hz, 0.5H), 2.75-2.83 (m, 1H), 3.64 (s, 3H), 3.81 (s, 3H), 4.04 (br, 1H), 4.98 (dd, J₂ = 1.8 Hz, J₁ = 6.9 Hz, 1H), 6.87-6.92 (m, 2H), 7.03 (d, J = 1.8 Hz, 1H), 7.21-7.40 (m, 5H). IR (neat, cm⁻¹): 2941, 2832, 2787, 1620, 1584, 1486, 1455, 1322, 1267, 1258, 1225, 1062, 1036, 791, 738, 698. MS (EI⁺): 308, 174, 159, 134, 117, 91 (100%).
2.9 Hz, \( \mathcal{J}_b = 7.7 \text{ Hz, 1H} \), 6.82 (d, \( J = 2.2 \text{ Hz, 0.5H} \)), 6.85 (d, \( J = 2.6 \text{ Hz, 0.5H} \)), 6.96 (s, 1H), 7.11-7.14 (m, 2H). \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\)) \( \delta \) (ppm): 30.4, 42.9, 53.5, 61.4, 63.5, 95.5, 99.2, 107.6, 109.3, 112.4, 124.3, 130.2, 151.3

2-(5-Methoxy-2-methyl-1H-indol-3-yl)-2-oxo-acetamide (7g)

To a two-phase system of ammonia (4.00 mL, conc. solution in water) and CHCl\(_3\) (5 mL) was added portionwise (5-methoxy-2-methyl-1H-indol-3-yl)-oxo-acetyl chloride (6b, 0.25 g, 1.00 mmol). The mixture was stirred vigorously at rt for 4 hr. The layers were separated, and the inorganic phase was diluted with water (25 mL), and extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The organic layers all combined, were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. This yielded a semi-solid (0.18 g), which was purified by chromatography (Silica, CH\(_2\)Cl\(_2\)/CH\(_3\)OH). \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 2.98 (s, 3H), 3.73 (s, 3H), 6.63 (dd, \( J_a = 2.2 \text{ Hz, } J_b = 6.6 \text{ Hz, 1H} \)), 7.04 (d, \( J = 6.9 \text{ Hz, 1H} \)), 7.40 (br, 1H), 9.80 (br, 1H). \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\)) \( \delta \) (ppm): 18.2, 54.0, 100.2, 109.5, 109.9, 125.0, 127.7, 153.8, 167.1, 183.7. IR (KBr, cm\(^{-1}\)): 3340, 2925, 1613, 1480, 1437, 1302, 1212, 1134, 1030, 637. MS (EI\(^{+}\)): 232, 188 (100%), 173, 145, 117.

2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethylamine (8g)

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH\(_4\) (0.16 g, 4.21 mmol) was suspended in THF (10 mL) under nitrogen. Dissolved in THF (10 mL), 2-(5-methoxy-2-methyl-1H-indol-3-yl)-2-oxo-acetamide (7g, 0.14 g, 0.60 mmol) was added at rt. The mixture was heated to reflux for 2.5 hr. Excess of LiAlH\(_4\) was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts thus formed, were filtered over Celite and washed thoroughly (ether). Evaporation of solvents yielded a yellow oil (0.12 g), which was purified by chromatography (Silica, CH\(_2\)Cl\(_2\)/CH\(_3\)OH gradient). \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 2.31 (s, 3H), 2.55-2.65 (m, 2H), 2.85-2.94 (m, 2H), 3.25 (br, 2H), 3.76 (s, 3H), 6.74 (dd, \( J_a = 2.6 \text{ Hz, } J_b = 6.2 \text{ Hz, 1H} \)), 6.94 (d, \( J = 2.2 \text{ Hz, 1H} \)), 7.06 (d, \( J = 8.6 \text{ Hz} \)), 8.16 (br, 1H). \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\)) \( \delta \) (ppm): 8.9, 24.3, 41.8, 54.5, 100.0, 106.8, 107.6, 108.5, 126.0, 128.2, 130.8, 154.2. MS (EI\(^{+}\)): 204, 174 (100%), 131.

2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (7h)

To a two-phase system of dimethylamine (5.00 mL, 40% in water) and CHCl\(_3\) (5 mL) was added portionwise (5-methoxy-2-methyl-1H-indol-3-yl)-oxo-acetyl chloride (6b, 0.25 g, 1.00 mmol). The mixture was stirred vigorously at rt for 1 hr. The layers were separated, the inorganic phase was diluted with water (25 mL), and extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The organic layers all combined, were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. This yielded a semi-solid (0.21 g), which was purified by chromatography (Silica, CH\(_2\)Cl\(_2\)/CH\(_3\)OH gradient). \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 2.26 (s, 3H), 2.90 (s, 3H), 3.02 (s, 3H), 3.72 (s, 3H), 5.30 (br, 2H), 6.62 (dd, \( J_a = 2.2 \text{ Hz, } J_b = 6.6 \text{ Hz, 1H} \)), 7.02 (d, \( J = 7.0 \text{ Hz, 1H} \)), 7.39 (br, 1H), 9.78 (br, 1H). \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\)) \( \delta \) (ppm): 19.3, 31.5, 34.6, 53.2, 100.2, 109.9, 125.0, 127.6, 153.8, 167.1, 183.7. IR (KBr, cm\(^{-1}\)): 3215, 2937, 1479, 1439, 1302, 1212, 1134, 1030, 637. MS (EI\(^{+}\)): 260, 188 (100%), 173, 145, 117.

2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-dimethyl-amine (8h)

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH\(_4\) (0.16 g, 4.21 mmol) was suspended in THF (10 mL) under nitrogen. Dissolved in THF (10 mL), 2-(5-methoxy-2-methyl-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (7h, 0.21 g, 0.81 mmol) was added at rt. The mixture was heated to reflux for 2 hr. The excess of LiAlH\(_4\) was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts thus formed, were filtered over Celite and washed thoroughly (ether). Evaporation of solvents yielded an yellow oil (0.21 g), which was purified by acid-base separation. \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 2.25 (s, 3H), 2.33 (s, 6H), 2.44-2.50 (m, 2H), 2.78-2.84 (m, 2H), 3.79 (s, 3H), 6.71 (dd, \( J_a = 2.6 \text{ Hz, } J_b = 6.2 \text{ Hz, 1H} \)), 6.92 (d, \( J = 2.2 \text{ Hz, 1H} \)), 7.05 (d, \( J = 8.8 \text{ Hz} \)), 8.17 (br, 1H). \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\)) \( \delta \) (ppm): 8.9, 20.3, 42.9, 53.5, 57.7, 98.0, 106.7, 107.7, 108.5, 126.5, 128.0, 129.8, 151.2. MS (EI\(^{+}\)): 232, 174, 131, 58 (100%).
1-(5-Methoxy-2-methyl-1H-indol-3-yl)-2-pyrrolidin-1-yl-ethene-1,2-dione (7)

To a 2-phase system of pyrrolidine (10 mL, 15% in water) and CHCl₃ (10 mL) was added portionwise (5-methoxy-2-methyl-1H-indol-3-yl)-oxo-acetyl chloride (6b, 0.25 g, 1.00 mmol). The mixture was stirred vigorously at rt for 0.5 hr. The layers were separated, the inorganic phase was diluted with water (30 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The organic layers all combined, were washed with water (10 mL), dried (Na₂SO₄), filtered, and concentrated. This yielded a semi-solid (0.33 g), which was crystallized from EtOAc / hexane. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 1.78-1.87 (m, 4H), 2.39 (s, 3H), 3.33 (t, J = 6.2 Hz, 2H), 3.53 (t, J = 6.2 Hz, 2H), 3.72 (s, 3H), 6.64 (dd, J₆ = 2.2 Hz, J₀ = 6.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 7.41 (br, 1H), 9.95 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 11.4, 20.9, 21.6, 42.6, 50.2, 53.1, 100.1, 109.6, 109.8, 125.4, 127.9, 153.6, 165.3, 184.0. IR (KBr, cm⁻¹): 3178, 2948, 1613, 1484, 1441, 1274, 1213, 1156, 1107, 1029, 857, 802, 704, 654. MS (El⁺): 286, 188 (100%), 173, 145, 117, 55.

5-Methoxy-2-methyl-3-(2-pyrrolidin-1-yl-ethyl)-1H-indole (8)

In a 3-necked flask equipped with cooler and dropping funnel, LiAlH₄ (0.20 g, 5.26 mmol) was suspended in THF (15 mL) under nitrogen. 1-(5-Methoxy-2-methyl-1H-indol-3-yl)-2-pyrrolidin-1-yl-ethene-1,2-dione (7, 0.30 g, 1.05 mmol) dissolved in THF (10 mL) was added at rt. The mixture was then heated to reflux for 2 hr. Excess of LiAlH₄ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts thus formed, were filtered over Celite and washed extensively (ether). Evaporation of solvents yielded a yellow oil (0.31 g), which was purified by acid-base separation. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 1.79 (s, 4H), 2.22 (s, 3H), 2.60-2.66 (m, 6H), 2.83-2.89 (m, 2H), 3.77 (s, 3H), 6.69 (dd, J₆ = 2.2 Hz, J₀ = 6.2 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 8.29 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 9.1, 21.0, 21.6, 51.7, 53.5, 54.6, 97.9, 106.7, 107.7, 108.5, 126.5, 128.0, 129.8, 151.2. MS (El⁺): 258, 174, 131, 84 (100%), 55.

[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-dipropyl-amine (8i)

To a two-phase system of dipropylamine (10 mL, 15% in water) and CHCl₃ (10 mL) was added portionwise (5-Methoxy-2-methyl-1H-indol-3-yl)-oxo-acetyl chloride (6b, 0.19 g, 5.00 mmol) in THF (10 mL) under a nitrogen. The mixture was heated to a gentle reflux for 2 hr. After cooling to rt, the excess of LiAlH₄ was destroyed by careful addition of adequate amounts of water and NaOH (4N). The salts thus formed, were filtered over Celite and washed extensively (ether). The amine was then extracted from the organic phase with HCl (1N, 3 x 15 mL). The inorganic phase was made alkaline (NaOH, 4N). The salts were filtered over Celite, washed thoroughly (ether). The amine was then extracted from the organic phase with HCl (1N, 3 x 10 mL). The inorganic phase was made alkaline (NaOH, 1N) and extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were washed (water), dried (Na₂SO₄), filtered, and concentrated in vacuo to yield a colorless oil (0.19 g), which appeared to be pure 8i according to NMR and TLC. ¹H-NMR (300 MHz, CDCl₃) δ (ppm): 0.89 (t, J = 7.3 Hz, 6H), 1.45-1.55 (m, 4H), 2.28 (s, 3H), 2.48-2.53 (m, 4H), 2.59-2.64 (m, 2H), 2.75-2.81 (m, 2H), 3.82 (s, 3H), 6.73 (dd, J₆ = 1.5 Hz, J₀ = 7.3 Hz, 1H), 6.94 (s, 1H), 7.07 (d, J = 8.2 Hz, 1H), 7.73 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 9.2, 9.6, 17.8, 19.5, 52.0, 53.4, 53.8, 98.0, 107.4, 107.8, 108.4, 108.7, 126.7, 127.9, 129.6, 151.3. IR (neat, cm⁻¹): 3414, 3141, 2934, 2810, 1622, 1580, 1485, 1215, 1172, 1059, 798. MS (free base, El⁺): 288, 188, 174, 114 (100%), 86.

6-Methoxy-1H-indole (16)

4-Methoxy-1-methyl-2-nitro-benzene (14, 1.00 mL, 7.25 mmol), pyrrolidine (0.7 mL, 8.70 mmol), and dimethylformamide dimethyl acetal (1.25 mL, 8.80 mmol) were dissolved in DMF (10 mL). The mixture was heated to 100-110 °C overnight. The dark purple solution was then quenched with water (100 mL), and extracted with EIOAc (8 x 25 mL). The combined
organic layers were washed with brine (2 x 20 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the crude [2-(4-Methoxy-2-nitro-phenyl)-vinyl]-dimethylamine (15) as a purple oil (1.80 g). Without further purification, the oil was dissolved in EtOH (250 mL) and treated with Pd on carbon (75 mg, 10%). The mixture was hydrogenated in a Parr apparatus for 4 hr (1 bar H₂). The mixture was then filtered over Celite and the solvent was removed. The residue was purified by chromatography (silica, CH₂Cl₂) to yield pure 16 (0.68 g, 4.62 mmol) as colorless crystals (mp 93 °C). ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 3.85 (s, 3H), 6.49 (m, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.88 (s, 1H), 7.09 (m, 1H), 7.52 (d, J = 8.6 Hz, 1H), 8.02 (s, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 54.2, 93.0, 101.0, 108.4, 119.7, 121.5. IR (KBr, cm⁻¹): 3394, 2959, 1628, 1508, 1299, 1161, 1026, 813. MS (El⁺): 149, 107 (100%).

6-Methoxy-2,3-dihydro-1H-indole (17)

6-Methoxy-1H-indole (16, 1.50 g, 10.2 mmol) was dissolved in glacial acetic acid (30 mL). NaCNBH₃ (1.9 g, 30.6 mmol) was added portionwise, while the temperature did not exceed 20 °C. After stirring at rt for 3 hr, the solvent was removed under reduced pressure and the residue was treated with NaHCO₃ (150 mL, sat.). The water layer was extracted with ether (3 x 75 mL), and the combined organic phase was washed with brine (30 mL), dried (Na₂SO₄) and filtered. Evaporation of solvent yielded a colorless oil (1.48 g) that was purified by chromatography (silica, CH₂Cl₂) to obtain pure 17. ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 2.95 (t, J = 16.6 Hz, 2H), 3.55 (t, J = 16.6 Hz, 2H), 3.75 (s, 3H), 3.88 (br, 1H), 6.26 (s, 1H), 6.30 (d, J = 2.4 Hz, 1H), 7.00 (d, J = 10.7 Hz, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 27.5, 53.9, 95.1, 102.2, 120.2, 123.3, 151.1, 158.3. IR (neat, cm⁻¹): 3375, 2947, 2847, 1614, 1500, 1286, 1196, 1150, 1030, 830. MS (El⁺): 149 (100 %), 133, 117, 104, 91, 77, 63, 51.

2-Chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18)

A solution of 6-ethoxy-2,3-dihydro-1H-indole (17, 2.20 g, 14.8 mmol) in CH₂Cl₂ (35 mL) was added dropwise to a mixture of 2-chloroacetyl chloride (3.35 g, 29.5 mmol), and K₂CO₃ (4.50 g, 32.6 mmol) in CH₂Cl₂ (75 mL). After addition, the suspension was stirred at rt for 6 hr. Water (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and filtered. Evaporation of the solvent yielded an off-white solid (2.95 g). Pure 18 was obtained by crystallization from diisopropyl ether (mp 126 °C). ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 3.17 (t, J = 16.4 Hz, 2H), 3.80 (s, 3H), 4.16 (s, 2H), 4.17 (t, J = 16.6 Hz, 2H), 6.62 (d, J = 10.5 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.90 (s, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 25.9, 41.7, 47.2, 54.1, 101.6, 109.5, 123.2. IR (KBr, cm⁻¹): 2964, 1680, 1497, 1404, 1231, 1028, 842.

2-Dimethylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19a)

Dimethylamine hydrochloride (0.18 g, 2.20 mmol) was added to a suspension of 2-chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.20 mmol), and K₂CO₃ (0.61 g, 4.42 mmol) in acetonitril (25 mL, cat. amount DMF) under a nitrogen. The mixture was stirred overnight at 50 °C. After filtration, the volatiles were removed in vacuo to yield the crude 19a as a semi solid (2.20 g), which was used for reduction without further purification. ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 2.35 (s, 3H), 3.05 (t, J = 16.6 Hz, 2H), 3.16 (s, 2H), 3.76 (s, 3H), 4.11 (t, J = 16.8 Hz, 2H), 6.53 (d, J = 10.5 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.89 (s, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): 25.9, 44.1, 46.7, 54.0, 62.0, 101.4, 108.5, 123.1. IR (KBr, cm⁻¹): 2933, 2827, 2772, 1654, 1492, 1283, 1157, 1029, 859. MS (El⁺): 234, 58 (100%).

[2-(6-Methoxy-2,3-dihydro-indol-1-yl)-ethyl]-dimethylamine (20a)

LiAlH₄ (0.26 g, 6.84 mmol) was suspended in THF (25 mL) under nitrogen and cooled to 0 °C. AlCl₃ (1.07 g, 8.04 mmol) was carefully added and stirred for 15 min. Then, a solution of 2-dimethylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19a, 0.52 g, 2.20 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at rt for 4 hr. Careful workup of the reaction by addition of water and NaOH (1N) resulted in the formation of salts, which were removed by filtration over Celite. The mother liquor was concentrated in vacuo, and the remainder was partitioned between NaHCO₃...
methoxy-2,3-dihydro-indol-1-yl)-ethanone (19c).

A solution of morpholine (0.40 g, 4.60 mmol) in acetonitril (10 mL) was added dropwise to a suspension of 2-chloro-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.22 mmol), and K₂CO₃ (0.61 g, 4.42 mol) in acetonitril (25 mL, cat amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 2-dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19a), which was used for reduction without further purification.

A solution of dipropylamine (0.65 g, 6.43 mmol) in acetonitril (10 mL) was added dropwise to a suspension of 2-chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.22 mmol), and K₂CO₃ (0.61 g, 4.42 mol) in acetonitril (25 mL, cat amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 2-dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19b) as a yellow oil (0.51 g), which was used for reduction without further purification.

[2-(6-Methoxy-indol-1-yl)-ethyl]-dimethylamine (20a)

[2-(6-Methoxy-2,3-dihydro-indol-1-yl)-ethyl]-dimethylamine (20a, 0.15 g, 0.68 mmol) and MnO₂ (0.30 g, 3.45 mmol) were dissolved in acetonitril, and heated to reflux for 4 hr. The reaction by addition of water and NaOH (1N) resulted in formation of salts, which were removed by filtration. The mother liquor was concentrated in vacuo, and the remainder was partioned between NaHCO₃ (30 mL, sat.) and CH₂Cl₂ (50 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by chromatography (silica, gradient CH₂Cl₂ / CH₂OH) yielded pure 20a as a colorless oil (0.21 g, 0.95 mmol).

The free base was converted to its oxalate salt by treatment with oxalic acid dihydrate (15 mg, 0.12 mmol). The free base was converted in the oxalate by treatment of the free base dissolved in ethanol with oxalic acid dihydrate (15 mg, 0.12 mmol). The reaction was stirred at rt overnight. Careful workup of the reaction by addition of water and NaOH (1N) resulted in formation of salts, which were removed by filtration. The mother liquor was concentrated in vacuo, and the remainder was partioned between NaHCO₃ (30 mL, sat.) and CH₂Cl₂ (50 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by chromatography (silica, gradient CH₂Cl₂ / CH₂OH) yielded pure 20a as a colorless oil (0.01 g, 0.40 mmol).

[2-(6-Methoxy-2,3-dihydro-indol-1-yl)-ethyl]-dimethylamine (20b)

LiAlH₄ (0.20 g, 5.26 mmol) was suspended in THF (20 mL) under nitrogen and cooled to 0 °C. H₂SO₄ (145 μL, 96 %) was added and stirred for 15 min. Then, a solution of 2-dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19b, 0.50 g, 1.72 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at rt overnight. Careful workup of the reaction by addition of water and NaOH (1N) resulted in formation of salts, which were removed by filtration. The mother liquor was concentrated in vacuo, and the remainder was partioned between NaHCO₃ (30 mL, sat.) and CH₂Cl₂ (50 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by chromatography (silica, gradient CH₂Cl₂ / CH₂OH) yielded pure 20b as a colorless oil (0.11 g, 0.40 mmol).

1-(6-Methoxy-2,3-dihydro-indol-1-yl)-2-morpholin-4-yl-ethanone (19c)

A solution of morpholine (0.40 g, 4.60 mmol) in acetonitril (10 mL) was added dropwise to a suspension of 2-chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.22 mmol), and K₂CO₃ (0.61 g, 4.42 mol) in acetonitril (25 mL, cat amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 2-dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19a), which was used for reduction without further purification.

2-Dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19b)

A solution of dipropylamine (0.65 g, 6.43 mmol) in acetonitril (10 mL) was added dropwise to a suspension of 2-chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.22 mmol), and K₂CO₃ (0.61 g, 4.42 mol) in acetonitril (25 mL, cat amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 2-dipropylamino-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (19b) as a yellow oil (0.51 g), which was used for reduction without further purification.

[2-(6-Methoxy-2,3-dihydro-indol-1-yl)-ethyl]-dimethylamine (21a)

[2-(6-Methoxy-2,3-dihydro-indol-1-yl)-ethyl]-dimethylamine (20a, 0.15 g, 0.68 mmol) and MnO₂ (0.30 g, 3.45 mmol) were dissolved in acetonitril, and heated to reflux for 4 hr. The dark mixture was then cooled to rt, filtered over Celite and concentrated in vacuo to yield a brown oil (0.11 g). The oil was purified by chromatography, to yield 21a as a light brown oil (26 mg, 0.12 mmol). The free base was converted in the oxalate by treatment of the free base dissolved in ethanol with oxalic acid dihydrate (15 mg, 0.12 mmol).
amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 1-(6-methoxy-2,3-dihydro-indol-1-yl)-2-morpholin-4-yl-ethanone (19c) as a slightly yellow solid (0.58 g). Crystallization from EtOAc/hexane yielded the pure compound (mp 103 °C). 1H-NMR (200 MHz, CDCl3) δ (ppm): 2.67 (d, J = 2.7 Hz, 4H), 3.06 (t, J = 16.6 Hz, 2H), 3.30 (s, 2H), 3.71 (s, 3H), 3.72 (d, J = 9.3 Hz, 4H), 6.52 (d, J = 10.5 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H). 13C-NMR (50 MHz, CDCl3) δ (ppm): 25.8, 46.6, 52.0, 53.9, 60.1, 64.9, 101.5, 108.9, 123.2. IR (KBr, cm−1): 3519, 2947, 2867, 1655, 1456, 1306, 1109, 857. MS (EI+): 276, 100 (100%).

### 6-Methoxy-1-(2-morpholin-4-yl-ethyl)-2,3-dihydro-1H-indole (20c)

LiAlH4 (0.07 g, 1.84 mmol) was suspended in THF (10 mL) under nitrogen and cooled on ice to 0 °C. H2SO4 (50 μL, 96%) was added and stirred for 15 min. Then, a solution of 1-(6-methoxy-2,3-dihydro-indol-1-yl)-2-morpholin-4-yl-ethanone (19c, 0.25 g, 0.91 mmol) in THF (5 mL) was added dropwise. The reaction was stirred at rt overnight. Careful workup of the reaction by addition of water and NaOH (1N) resulted in formation of salts, which were removed by filtration over Celite. The mother liquor was concentrated in vacuo, and the remainder was partitioned between NaHCO3 (30 mL, sat.) and CH2Cl2 (50 mL). The organic phase was dried (Na2SO4), filtered, and concentrated in vacuo. Purification by chromatography (silica, gradient CH2Cl2 / CH3OH) yielded pure 20c as a colorless oil (0.10 g, 0.38 mmol). 1H-NMR (200 MHz, CDCl3) δ (ppm): 2.51 (t, J = 8.4 Hz, 4H), 2.57 (t, J = 14.3 Hz, 2H), 2.84 (t, J = 16.1 Hz, 2H), 3.19 (t, J = 14.3 Hz, 2H), 3.37 (t, J = 16.5 Hz, 2H), 3.69 (t, J = 10.6 Hz, 4H), 3.71 (s, 3H), 6.02 (s, 1H), 6.11 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H). 13C-NMR (50 MHz, CDCl3) δ (ppm): 25.3, 44.1, 51.5, 51.7, 52.9, 53.7, 64.3, 91.9, 98.8, 121.9. IR (neat, cm−1): 3372, 2948, 2847, 1617, 1498, 1286, 1106, 820. MS (EI+): 262, 162 (100%).

### 1-(6-Methoxy-2,3-dihydro-indol-1-yl)-2-(4-methyl-piperazin-1-yl)-ethanone (19d)

A solution of N-methylpiperazine (0.28 g, 2.80 mmol) in acetonitril (10 mL) was added dropwise to a suspension of 2-chloro-1-(6-methoxy-2,3-dihydro-indol-1-yl)-ethanone (18, 0.50 g, 2.22 mmol), and K2CO3 (0.61 g, 4.42 mol) in acetonitril (25 mL, cat amount DMF) under nitrogen. The reaction was stirred at 50 °C overnight. After filtration, the volatiles were removed in vacuo to yield the crude 1-(6-methoxy-2,3-dihydro-indol-1-yl)-2-(4-methyl-piperazin-1-yl)-ethanone (19d) as a slightly yellow semi solid (0.64 g), that contained only minor contaminants according to NMR and GC. The sample was used for further synthesis without purification. 1H-NMR (200 MHz, CDCl3) δ (ppm): 2.26 (s, 3H), 2.54 (d, J = 35.9 Hz, 8H), 3.05 (t, J = 16.5 Hz, 2H), 3.18 (s, 2H), 3.73 (s, 3H), 4.10 (t, J = 16.8 Hz, 2H), 6.51 (d, J = 10.3 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H). 13C-NMR (50 MHz, CDCl3) δ (ppm): 25.0, 43.4, 45.8, 50.8, 52.4, 53.0, 59.9, 100.3, 107.9, 120.3, 122.1, 156.9, 165.2. IR (neat, cm−1): 2932, 2800, 1664, 1454, 1302, 1162, 1010, 827. MS (EI+): 289, 113 (100%).

### 6-Methoxy-1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2,3-dihydro-1H-indole (20d)

LiAlH4 (0.25 g, 6.58 mmol) was suspended in THF (25 mL) under nitrogen and cooled on ice to 0 °C. H2SO4 (170 μL, 96%) was added and stirred for 15 min. Then, a solution of 1-(6-methoxy-2,3-dihydro-indol-1-yl)-2-(4-methyl-piperazin-1-yl)-ethanone (19d, 0.64 g, 2.21 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at rt for 6 hr. Careful workup of the reaction by addition of water and NaOH (1N) resulted in formation of salts, which were removed by filtration over Celite. The mother liquor was concentrated in vacuo, and the remainder was partitioned between NaHCO3 (30 mL, sat.) and CH2Cl2 (50 mL). The organic phase was dried (Na2SO4), filtered, and concentrated in vacuo. Purification by chromatography (silica, gradient CH2Cl2/CH3OH/CH3OH) yielded pure 20d as a colorless oil (0.05 g, 0.18 mmol). The product was converted in the (+)-DTTA salt by treatment of the free base with 1 equivalent of (+)-DTTA. 1H-NMR (free base, 200 MHz, CDCl3) δ (ppm): 2.35 (s, 3H), 2.62 (m, 10 H), 2.88 (t, J = 16.4 Hz, 2H), 3.21 (t, J = 14.2 Hz, 2H), 3.40 (t, J = 16.6 Hz, 2H), 3.75 (s, 3H), 6.07 (s, 1H), 6.16 (d, J = 10.3 Hz, 1H), 6.13 (d, J = 8.1 Hz, 1H). 13C-NMR (free base, 50 MHz, CDCl3) δ (ppm): 26.3, 44.1, 45.4, 51.5, 52.6, 53.3, 53.9, 54.0, 93.0, 99.8, 122.7. IR ((+)-DTTA salt, KBr, cm−1): 2954, 2841, 1719, 1615, 1497, 1349, 1266, 1107, 752. MS (free base, EI+): 275, 113 (100%).
Chapter 4  Indole based ligands as potential 5-HT<sub>7</sub> receptor agonists

5-Methoxy-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole (22a)

In a 3-necked flask with cooler, 5-methoxyindole (5a, 0.50 g, 3.40 mmol) was dissolved in CH<sub>3</sub>OH (5 mL) under nitrogen. N-methyl-4-piperidone (1.15 g, 10.2 mmol) and NaOCH<sub>3</sub> (5 mL, 50% solution in CH<sub>3</sub>OH) were added, and the mixture was heated to reflux for 3 hr. The reaction was allowed to cool to rt. The volatiles were removed under reduced pressure, and the residue was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. Extraction of the water layer with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL) and drying of the combined organic layers (Na<sub>2</sub>SO<sub>4</sub>) was followed by filtration and evaporation of the solvent. This yielded an orange semi-solid (0.80 g) that was recrystallized from EtOAc.

1H-NMR (300 MHz, CDCl<sub>3</sub>) (ppm): 2.24 (s, 3H), 2.46-2.48 (m, 2H), 2.54-2.58 (m, 2H), 3.03 (d, J<sub>1</sub> = 2.9 Hz, 2H), 3.69 (s, 3H), 5.94 (s, 1H), 6.67 (dd, J<sub>a</sub> = 2.2 Hz, J<sub>b</sub> = 6.6 Hz, 1H), 7.01 (s, 1H), 7.10 (d, J<sub>1</sub> = 9.2 Hz, 1H), 7.14 (d, J<sub>2</sub> = 2.2 Hz, 1H).

13C-NMR (75 MHz, CDCl<sub>3</sub>) (ppm): 25.9, 42.7, 49.5, 52.0, 53.4, 77.7, 100.2, 109.0, 109.5, 114.4, 120.1, 122.6, 127.5, 130.0, 136.0, 151.8. IR (KBr, cm<sup>-1</sup>): 3032, 2854, 2794, 1650, 1615, 1477, 1448, 1379, 1260, 1210, 1125, 1034, 982, 807, 736. MS (EI<sup>+</sup>): 242, 227, 198, 84.

3-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-methoxy-1H-indole (22b)

In a 3-necked flask with cooler, 5-methoxyindole (5a, 0.50 g, 3.40 mmol) was dissolved in CH<sub>3</sub>OH (5 mL) under nitrogen. N-benzyl-4-piperidone (0.96 g, 5.08 mmol) and NaOCH<sub>3</sub> (5 mL, 30% solution in CH<sub>3</sub>OH) were added, and the mixture was heated to reflux for 4 hr. The reaction was allowed to cool to rt. The precipitate that was formed, was collected by filtration (0.90 g), and dried in vacuo. Crystallization from EtOAc yielded pure 22b as a white solid.

1H-NMR (300 MHz, CDCl<sub>3</sub>) (ppm): 2.53 (d, J<sub>1</sub> = 1.5 Hz, 2H), 2.68-2.72 (m, 2H), 3.20 (dd, J<sub>a</sub> = 2.6 Hz, J<sub>b</sub> = 2.9 Hz, 2H), 3.62 (s, 2H), 3.80 (s, 3H), 6.07-6.09 (m, 1H), 6.79-6.83 (m, 1H), 7.07 (d, J<sub>1</sub> = 2.6 Hz, 1H), 7.17-7.38 (m, 7H), 8.00 (br, 1H).

13C-NMR (75 MHz, CDCl<sub>3</sub>) (ppm): 26.7, 47.6, 50.8, 53.5, 60.5, 100.5, 109.3, 109.7, 116.4, 119.5, 123.1, 124.6, 125.8, 126.8, 127.4, 151.9.

IR (KBr, cm<sup>-1</sup>): 3032, 2925, 2854, 2794, 1650, 1614, 1601, 1479, 1447, 1380, 1260, 1211, 1125, 1034, 962, 880, 807, 736. MS (EI<sup>+</sup>): 318, 227, 198, 160, 128, 91 (100%). Analysis calc. for: C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O: C 79.21%, H 6.96%, N 8.80%, O 5.02%; obsd: C 79.11%, H 7.05%, N 9.01%.

4-(6-Methoxy-3H-inden-1-yl)-1,2,3,6-tetrahydro-pyridine (22c)

3-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-methoxy-1H-indole (22b, 0.40 g, 1.26 mmol), dissolved in ethanol (25 mL), was reacted with Pd/C (0.10 g, 10%) under a hydrogen atmosphere (1 atm) in a Parr shaker apparatus for 2 hr at rt. The reaction mixture was filtered over Celite and concentrated in vacuo to yield 22c as a slightly yellow oil (0.27 g, 1.25 mmol).

1H-NMR (300 MHz, CDCl<sub>3</sub>) (ppm): 2.38-2.46 (m, 2H), 2.52-2.56 (m, 2H), 3.20 (dd, J<sub>a</sub> = 2.6 Hz, J<sub>b</sub> = 2.9 Hz, 2H), 3.62 (s, 2H), 3.80 (s, 3H), 6.07-6.09 (m, 1H), 6.79-6.83 (m, 1H), 7.07 (d, J<sub>1</sub> = 2.6 Hz, 1H), 17.7-17.38 (m, 7H), 8.00 (br, 1H).

13C-NMR (75 MHz, CDCl<sub>3</sub>) (ppm): 26.7, 47.6, 50.8, 53.5, 60.5, 100.5, 109.3, 109.7, 116.4, 119.5, 123.1, 124.6, 125.8, 126.8, 127.4, 151.9.

IR (KBr, cm<sup>-1</sup>): 3254, 3028, 2824, 2794, 1650, 1614, 1601, 1479, 1447, 1380, 1260, 1211, 1125, 1034, 962, 880, 807, 736. MS (EI<sup>+</sup>): 318, 227, 198, 160, 128, 91 (100%). Analysis calc. for: C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O: C 79.21%, H 6.96%, N 8.80%, O 5.02%; obsd: C 79.11%, H 7.05%, N 9.01%.

4.6.2 Pharmacology

5-HT<sub>7</sub> Adenylate Cyclase Assay

Effects on adenylate cyclase activity were measured according to previously published methods<sup>12</sup>. HEK-293 cells expressing the rat 5-HT<sub>7</sub> were grown in Dulbecco's modified Eagle's media (DMEM) containing fetal bovine serum (10%), G418 (Geneticin, 400 μg), and glutamine (2 mM) until flasks were confluent. Cells from confluent flasks were harvested by replacing the media with phosphate buffered saline (PBS) containing EDTA (5 mM, pH = 7.4). Cells were homogenized in HEPES buffer (5 mM) containing EGTA (1 mM, pH = 7.4) using a hand-held glass-teflon homogenizer. The homogenate was centrifuged in 35,000 g for ten minutes. The cell pellet was resuspended in HEPES buffer (100 mM) containing EGTA (1 mM, pH = 7.4). Membranes (30-40 μg protein) were incubated at 37 °C in a reaction medium
containing Hepes (100 mM, pH = 7.4), MgCl₂ (5.0 mM), ATP (0.5 mM), cAMP (1.0 mM), IBMX (0.5 mM), phosphocreatine (10 mM), creatine phosphokinase (0.31 mg/mL), GTP (100 µM), µ-[³³P]ATP (1 µCi) per tube and test drugs (final volume of 100 µl). Incubations were terminated after 15 minutes by adding sodium dodecyl sulfate (2%). After separation of [³³P]cAMP from [³³P]ATP as described by Salomon¹², [³³P]cAMP levels were determined by liquid scintillation counting, with the results expressed as picomoles per minute per milligram of protein. EC₅₀ and IC₅₀ values were calculated by linear regression analysis of the concentration-response curves. Efficacy values were calculated as the maximal effect of an agonist in terms of the maximal effect produced by a known agonist such as 5-HT. Apparent Kᵢ values for antagonists were calculated as follows: Kᵢ = IC₅₀/(1 + (C/EC₅₀)), where C is the concentration of the agonist used in the experiment and EC₅₀ is the EC₅₀ for the agonist.
List of References


