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Synthesis and Structure–Affinity Relationship Investigations of 5-Aminomethyl and 5-Carbamoyl Analogues of the Antipsychotic Sertindole. A New Class of Selective α_1 Adrenoceptor Antagonists

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Abstract—A new class of selective α_1 adrenoceptor antagonists derived from the antipsychotic drug sertindole is described. The most potent and selective compound 1-(2-{4-[5-aminomethyl-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (**11**) binds with 0.50 nM affinity for α_1 adrenergic receptors and with more than 44 times lower affinity for dopamine D_2,D_3, D_4 and serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors. The molecular features providing high affinity for adrenergic α_1 receptors and high selectivity towards dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors are discussed.

Introduction

The adrenergic α_1 receptors belong to the superfamily of G-protein coupled receptors. m-RNA coding for three native receptor subtypes nominated α_{1A}, α_{1B} and α_{1D}[1] have been identified in the human brain, and the presence of the α_{1A}[2] and α_{1D}[3] adrenoceptor subtypes have been confirmed by radioligand-binding experiments.

A common feature of 'atypical' antipsychotics such as clozapine, sertindole (**1**, Chart 1), olanzapine and seroquel is nanomolar affinity for α_1-adrenoceptors in addition to their affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors.[4] The contribution of the α_1-component to the therapeutic effect of these antipsychotic agents has been thoroughly investigated. Studies seem to indicate a central role of the α_1-component for the atypical profile of clozapine[5,6] and that a combination of dopamine D_2 and α_1 adrenoceptor blockade could be effective as antipsychotic treatment without producing extrapyramidal side effects.[7,8]

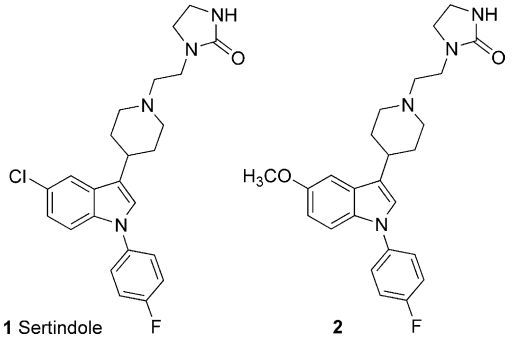

Chart 1. Sertindole (**1**) and the methoxy analogue of sertindole (**2**).

Efficacy of the α_1 antagonist prazosin in animal models predictive of antipsychotic activity[9,10] and electrophysiological investigations[11,12] suggest that blockade of noradrenergic neurotransmission alone could be beneficial in the treatment of schizophrenia. In contrast to these observations, prazosin has been tested in a small, placebo controlled, clinical trial on schizophrenic patients without promising results.[13] Furthermore, centrally acting α_1 adrenoceptor antagonists may have a potential as therapeutics for the treatment of diseases characterised by noradrenergic over-activity such as

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mania[14] and posttraumatic stress disorder.[15] The role of central α_1 adrenergic receptors in neurological function has recently been reviewed.[16]

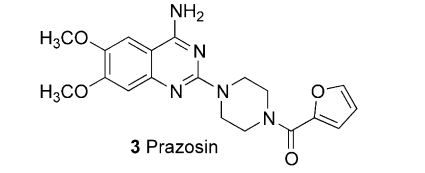
α_1 Adrenoceptor antagonists belonging to a variety of chemical classes, such as 2,4-diaminoquinazolines, aryl piperazines, imidazolines, dihydropyridines and phenethylamines[17–19] have primarily been developed for the treatment of cardiovascular diseases and benign prostatic hyperplasia.[17,18,20–22] Examples of selective compounds belonging to selected structural classes are shown in Chart 2. Whereas prazosin is subtype unselective,[20] (−)-SNAP-5089 [(−)-**4**],[23] (+)-cyclazosin [(+)-**5**][24] and SNAP-8719 (**6**)[25] represent compounds selective for α_{1a}, α_{1b} and α_{1d} receptors, respectively.

The 'atypical' antipsychotic Sertindole (**1**) has nanomolar affinity for adrenergic (α_1), dopamine (D_1, D_2, D_3, D_4) and serotonin (5-HT_{2A}, 5-HT_{2C}) receptors.[4] In addition, it has been reported that sertindole is a specific inhibitor of α_{1A} adrenoceptors in rat small arteries and binds with nanomolar affinity for the adrenergic α_{1a}-receptor.[26]

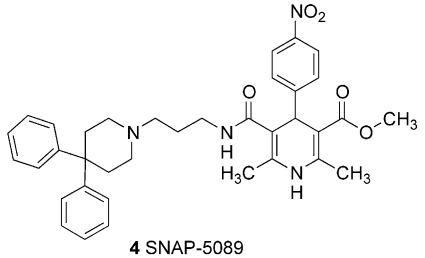
The phenyl-indole skeleton of sertindole has previously been used as a template for the development of selective ligands for serotonin 5-HT_2[27–29] and dopamine D_2[29] receptors.[30] The high affinity of sertindole and of a series of close analogues for adrenergic α_1 adrenoceptors[27,28] indicate that the sertindole skeleton may also be used as a template for the development of selective α_1 adrenoceptor antagonists.

Evaluation of a series of previously reported analogues of sertindole[31] revealed that small polar substituents in place of the chlorine atom in sertindole resulted in compounds with retained or improved α_1 adrenoceptor affinity.[32] Interestingly, the 5-methoxy derivative (**2**, Chart 1)[31] of sertindole has an affinity for adrenergic α_1 receptors of 1.3 nM,[32] comparable to the affinity of sertindole (Table 2) and 6-fold decreased affinity for dopamine D_2 receptors.[31] These observations indicate a potential for discrimination between the two types of receptors by substitution in the area corresponding to the indole 5-position of sertindole with polar substituents containing some additional steric bulk.

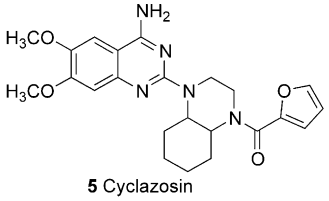
We here report the preparation and in vitro pharmacological characterisation of a series of sertindole analogues with enhanced affinity and selectivity for α_1 adrenoceptors. In addition, the selectivity with regard to dopamine D_2 and D_4 as well as setotonin 5-HT_2 receptors are discussed in relation to previously published receptor interaction models for antagonists at these receptors.[33–36] The present results may be interesting in connection to the development of new selective CNS active α_1 adrenoceptor antagonists and the development of new antipsychotic compounds possessing balanced antagonism of dopamine D_2 and adrenergic α_1 receptors.



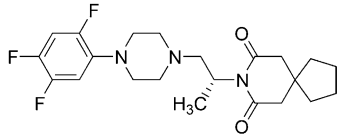
3 Prazosin



4 SNAP-5089



5 Cyclazosin



6 SNAP-8719

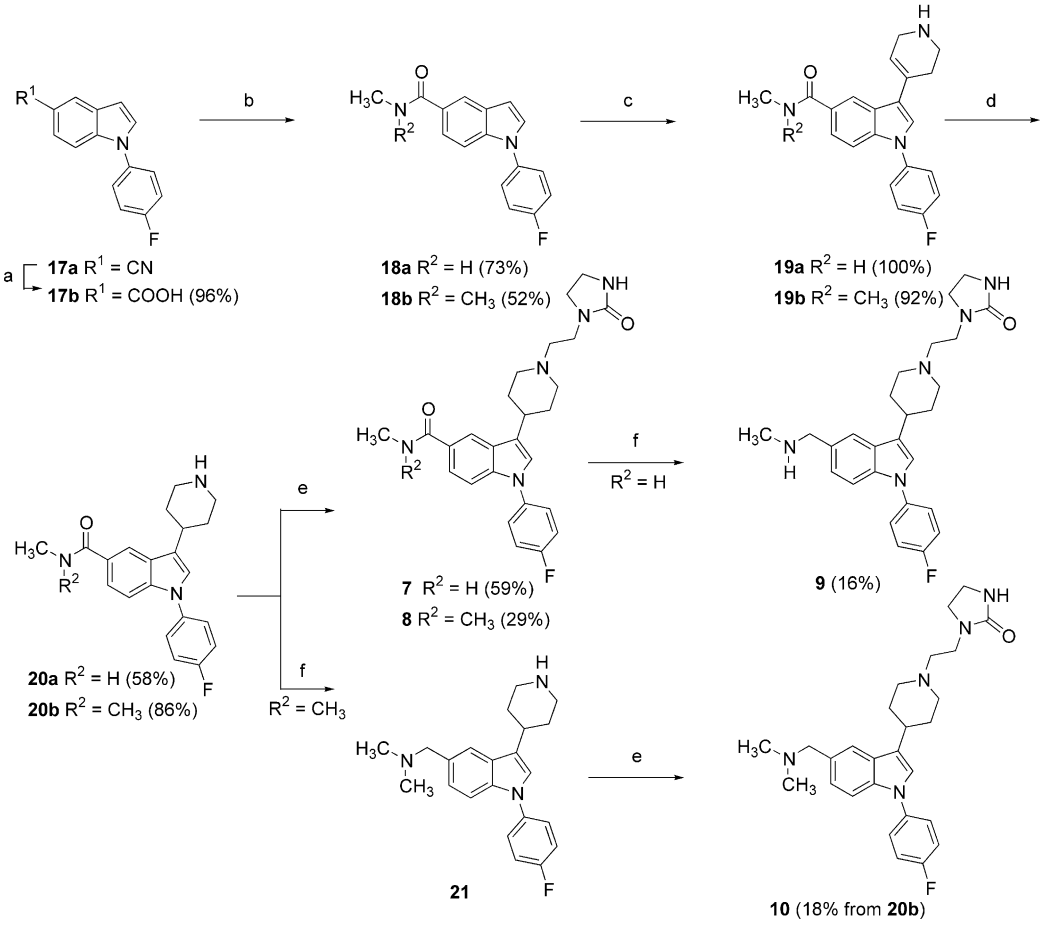
Chart 2. Selected selective α_1 adrenoceptor antagonists.

Chemistry

The preparation of 3-(4-piperidinyl)-1-(4-fluorophenyl)-1*H*-indoles substituted in the 5- and 6-positions of the indole nucleus has previously been described by Perregaard et al.[27,31]

Preparation of the carboxamides **7** and **8** as well as the aminomethyl derivatives **9** and **10** are described in Scheme 1. 1-(4-Fluorophenyl)-1*H*-indole-5-carboxylic acid, **17b** was obtained by alkaline hydrolysis of the corresponding cyano derivative **17a** prepared according to published procedures.[31] Activation of the carboxylic acid **17b** with 1,1-carbonyldiimidazole[37] or ethyl chloroformate[38] and subsequent reaction with methyl amine or dimethyl amine afforded the carboxamides **18a** and **18b**. Reaction of the carboxamides **18a** and **18b** with 4-piperidone hydrochloride, hydrate using acidic conditions gave the 5-substituted 1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indoles **19a** and **19b**. Subsequent catalytic hydrogenation using platinum as catalyst gave the corresponding piperidines **20a** and **20b**. The final carboxamides **7** and **8** were obtained by alkylation with 1-(2-chloroethyl)imidazolidin-2-one.

The corresponding aminomethyl derivatives **9** and **10** were obtained from the carboxamides **7** and **20b** by reduction with lithium aluminium hydride. Reduction of the *N*-methyl-carbamoyl derivative **7** with lithium aluminium hydride afforded the final *N*-methyl-aminiomethyl derivative **9** directly. The *N,N*-dimethyl-aminomethyl

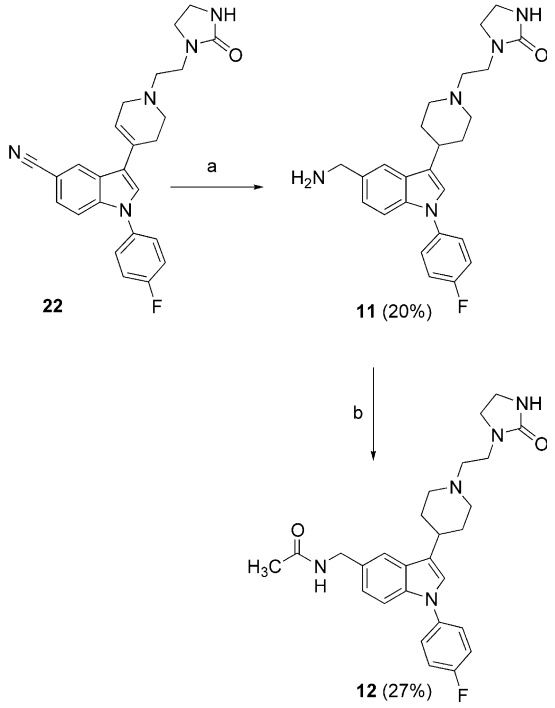


Scheme 1. Reagents: (a) KOH, EtOH, reflux, 24 h; (b) For $R^2=H$: (i) 1,1-carbonyldiimidazole, THF, 20 °C, 45 min; (ii) CH_3NH_2, 0–20 °C, 65 min; for $R^2=CH_3$: (i) ClCOOEt, NEt_3, CH_2Cl_2, −30 to −10 °C, 2 h; (ii) $(CH_3)_2NH$, −10 to 20 °C, 2 h; (c) 4-piperidone hydrochloride hydrate, TFA/AcOH, reflux, 1 h; (d) H_2, PtO_2, AcOH, 5 h; (e) 1-(2-chloroethyl)-imidazolidin-2-one, K_2CO_3, KI, 4-methyl-2-pentanone, reflux, 8 h; (f) $LiAlH_4$, THF, reflux, 3 h.

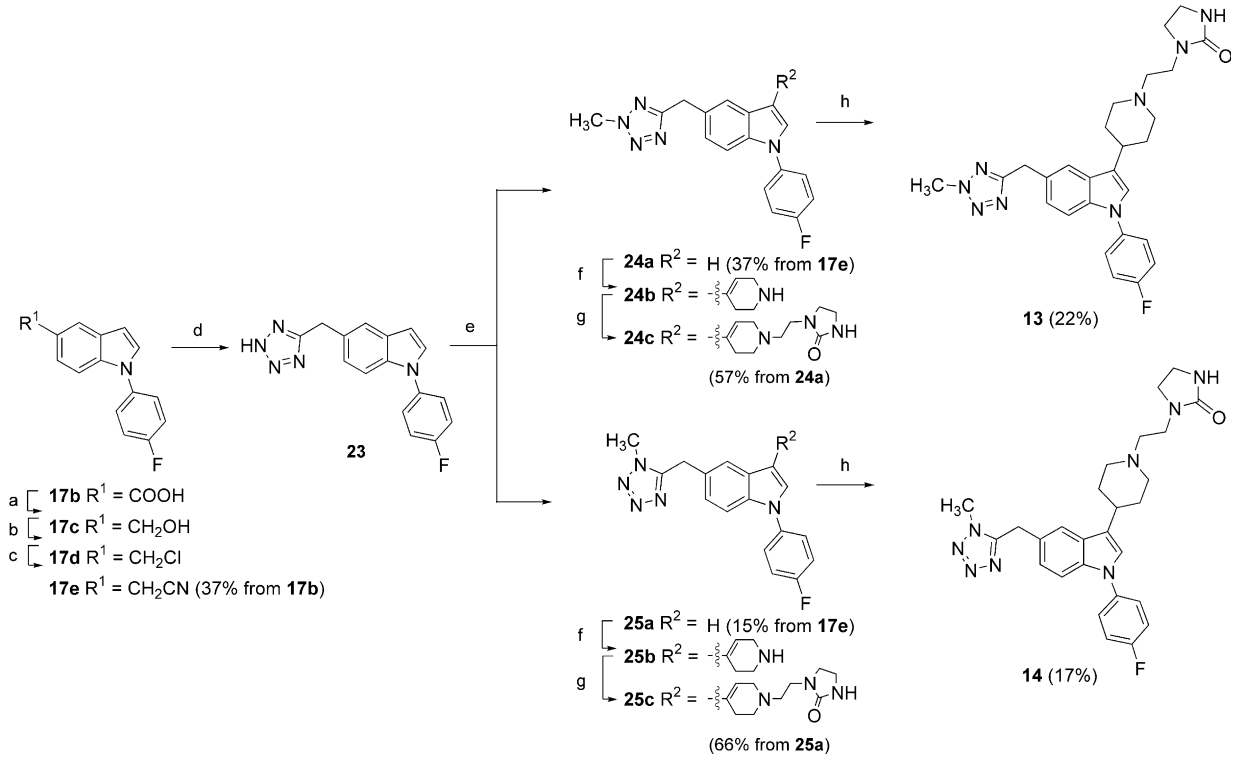
derivative **10** was obtained by reduction of the intermediate **20b** with lithium aluminium hydride followed by alkylation with 1-(2-chloroethyl)imidazolidin-2-one as described above.

The 5-aminomethyl and 5-acetylaminomethyl derivatives **11** and **12** were obtained from the nitrile **22**[31] as outlined in Scheme 2. Catalytic hydrogenation using platinum resulted in simultaneous reduction of the double bond in the tetrahydropyridine ring and the nitrile group giving the 5-aminomethyl derivative **11** directly. Subsequent reaction of the 5-aminomethyl derivative **11** with acetyl chloride gave the 5-acetylaminomethyl derivative **12**.

The tetrazolylmethyl-indole derivatives **13** and **14** were prepared as outlined in Scheme 3. Reduction of the carboxylic acid **17b** with lithium aluminium hydride and subsequent reaction with methanesulfonyl chloride gave the chloromethyl derivative **17d** as expected for benzylic alcohols. Reaction with sodium cyanide followed by 1,3-dipolar cycloaddition with sodium azide afforded the unsubstituted tetrazole **23**. Methylation of the N-unsubstituted tetrazole **23** and subsequent separation of the formed isomers by column chromatography gave the *N*-methyl-tetrazolylmethyl derivatives **24a** and **25a**.



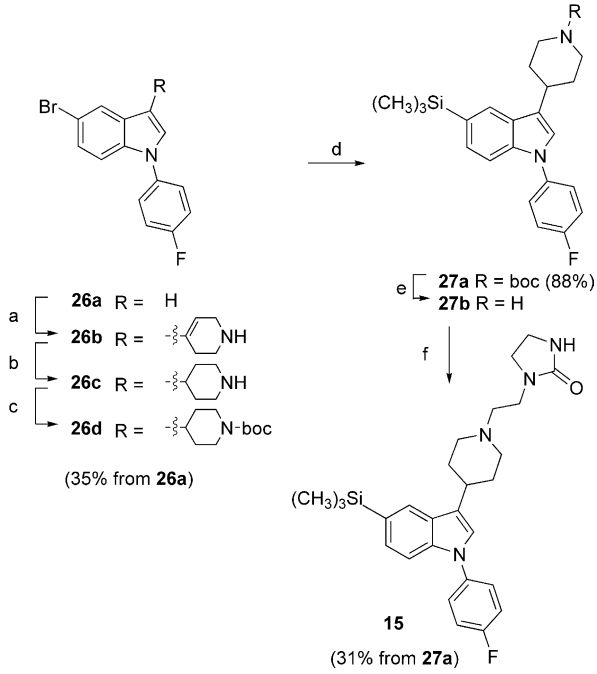
Scheme 2. Reagents: (a) H_2, PtO_2, AcOH, 5 h; (b) $ClCOCH_3$, NEt_3, CH_2Cl_2, 20 °C, 1 h.



Scheme 3. Reagents: (a) $LiAlH_4$, THF, reflux, 2 h; (b) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0–5 °C, 2 h; (c) NaCN, DMSO, 140 C, 40 min; (d) NaN_3, NEt_3 hydrochloride, 1,2-dimethoxyethan, reflux, 48 h; (e) $(CH_3)_3COK$, CH_3I, column chromatography; (f) 4-piperidone hydrochloride hydrate, TFA/AcOH, reflux, 1 h; (g) 1-(2-chloroethyl)-imidazolidin-2-one, K_2CO_3, KI, 4-methyl-2-pentanone, reflux, 8 h; (h) H_2, PtO_2, AcOH, 5 h.

These were converted into the final 1-(piperidin-4yl) ethyl-imidazolidin-2-ones **13** and **14** as described above for the preparation of the carboxamides in Scheme 1, with the exception, that the order of alkylation and reduction to the piperidines was reversed without significant effects on the yields of the reactions. The position of the methyl groups in the 1- and 2-methyl-tetrazole isomers were confirmed by 2D-NOESY experiments[39] on the tetrahydropyridine-substituted analogues **24c** and **25c** as described in the Experimental section.

The trimethylsilyl-substituted indole **15** was prepared from the *N*-boc-protected 5-bromo-piperidinyl-1*H*-indole **26d** as described in Scheme 4. The intermediate **26d** was prepared in three steps from 5-bromo-1-(4-fluorophenyl)-1*H*-indole (**17**) as described for the preparation of the caboxamides **7** and **8** above followed by boc protection. Halogen metal exchange of the bromine in the indole 5-position in analogy to procedures reported by us recently[40] and subsequent reaction with trimethylsilyl chloride gave the intermediate **27a**. The *N*-boc-group was removed by stirring of neat **27a** at 230 °C resulting in the deprotected piperidinyl derivative **27b**. Acidic conditions were unsuccessful due to partial removal of the trimethylsilyl group. Trimethylsilyl groups at electron-rich aromatic carbons are known to be labile under acidic conditions.[41] The final product **15** was achieved by alkylation of the deprotected piperidinyl derivative **27b** with 1-(2-chloroethyl)imidazolidin-2-one as described above.



Scheme 4. Reagents: (a) 4-piperidone hydrochloride hydrate, TFA/AcOH, reflux, 90 min; (b) H_2, PtO_2, AcOH, 5 h; (c) $(boc)_2O$, THF/water, 60 °C, 8 h; (d) (i) *n*-BuLi, reverse addition, −78 °C, 3 min; (ii) $(CH_3)_3SiCl$, −78 to 20 °C, 30 min; (e) neat, 230 °C, 3 h; (f) 1-(2-chloroethyl)-imidazolidin-2-one, K_2CO_3, KI, 2-methyl-pentanone, reflux, 8 h.

Table 1.[a]

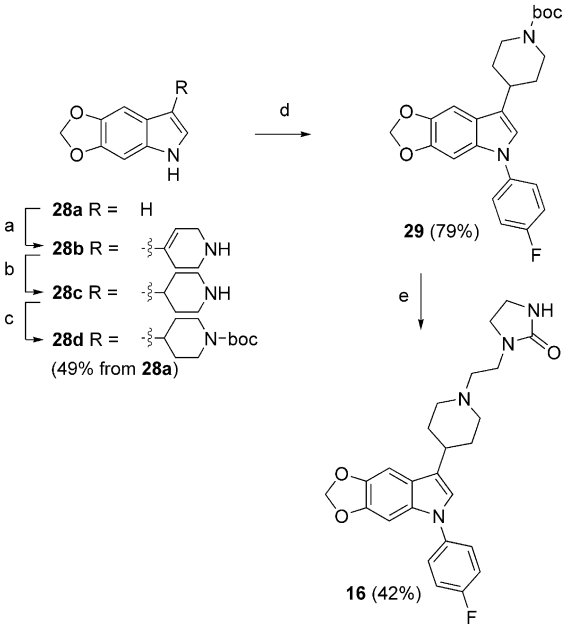
Receptor	Species	Membrane source	Radioligand (mM)	Ref. Compd.	K_i (nM)
α_1	Rat	Whole brain	[^{3}H]prazosin (0.25)	Prazosin	0.29
α_{1a}	Bovine[b]	BHK cells	[^{3}H]prazosin (0.3)	Prazosin	0.93
α_{1b}	Hamster[b]	Rat-1 cells	[^{3}H]prazosin (0.5)	(±)-Cyclazosin	0.46
α_{1d}	Rat[b]	CHO cells	[^{3}H]prazosin (0.3)	SNAP-8719	1.4
D_2	Rat	Corpus striatum	[^{3}H]spiperone (0.5)	Haloperidol	1.9
D_3	Human[b]	CHO cells	[^{3}H]spiperone (0.3)	Haloperidol	2.7
D_4	Human[b]	CHO cells	[^{3}H]YM-09151–2 (0.06)	Clozapine	30
5-HT$_{1A}$	Human[b]	HeLa cells	[^{3}H]5-CT (2.0)	Metitepine	2.2
5-HT$_{1B}$	Human[b]	HeLa cells	[^{3}H]5-CT (1.5)	Serotonin	4.8
5-HT$_{2A}$	Rat	Cerebral cortex	[^{3}H]ketanserin (0.5)	Mianserine	2.5
5-HT$_{2C}$	Rat[b]	SR-3T3 cells	[^{3}H]mesulergine (0.5)	Mesulergine	0.37

[a]For detailed description of assays, see Experimental.
[b]Cloned receptors.

Preparation of the 5,6-methylenedioxy-1*H*-indole derivative **16** is described in Scheme 5. Base-catalysed reaction of 4-piperidone with 5,6-methylenedioxy-1*H*-indole (**28a**) followed by catalytic hydrogenation in the presence of platinum according to previously published procedures[27] gave the piperidine **28c** which was subsequently boc-protected. 1-Arylation with 4-fluoro-iodobenzene using Ullmann conditions[27,42] resulted in the 1-(4-fluorophenyl)-5,6-methylenedioxy-1*H*-indole **29**. Removal of the boc group by means of hydrochloric acid in methanol and alkylation according to the procedure employed in the preparation of the *N,N*-dimethyl-amminomethyl derivative **10** afforded the final product **16**.

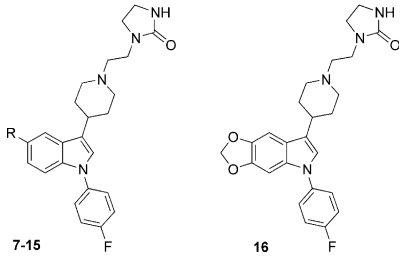
Results and Discussion

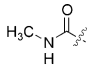
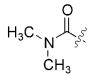
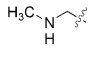
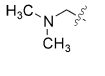
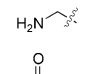
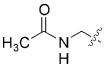
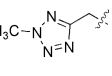
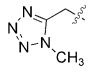
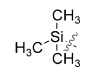
The receptor-binding assays are described in Table 1 and in detail in the Experimental section. Receptor-binding affinities (adrenergic α_1, dopamine D_2 and serotonin 5-HT$_{1A}$, 5HT$_{1B}$, 5HT$_{2A}$ and 5-HT$_{2C}$ receptors) for sertindole and compounds prepared in the present study are reported in Table 2. In addition, receptor-binding affinities for the α_1 adrenergic receptor subtypes α_{1a}, α_{1b} and α_{1d} and the dopamine D_1, D_3 and D_4 receptors are reported in Table 3 for selected compounds and reference compounds. Good correlation based on receptor-binding affinities between the human clones and



Scheme 5. Reagents: (a) 4-piperidone hydrochloride hydrate, KOH, EtOH, reflux, 24 h; (b) H_2, PtO_2, AcOH/EtOH, 20 h; (c) $(boc)_2O$, K_2CO_3, THF/H_2O, 60 °C, 22 h; (d) 4-fluoro-iodobenzene, K_2CO_3, KI, ZnO, NMP, 100 °C, 48 h; (e) (i) HCl/MeOH, rt, 4 h; (ii) 1-(2-chloroethyl)-imidazolidin-2-one, K_2CO_3, KI, 2-methyl-pentanone, reflux, 8 h.

Table 2. Receptor-binding affinities for 5-substituted 1-(4-fluorophenyl)-1*H*-indoles and 5,6-methylenedioxy derivative **16**



Compd	R	K_i (nM)[a] α_1	D_2	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{2A}$	5-HT$_{2C}$
Sertindole **(1)**		1.4[b]	0.45[b]	33	56	0.20[b]	0.51[b]
7		2.5	170	91	85	21	450
8		3.9	40	100	40	17	68
9		0.45	6.6	62	570	4.1	12
10		0.58	16	58	180	15	27
11		0.50	37	290	640	22	64
12		0.46	3.1	62	67	11	82
13		0.58	2.7	22	NT	NT	NT
14		0.28	1.9	24	32	10	130
15		23	100	NT	NT	7.5	NT
16		0.52	7.7	NT	NT	0.65	NT

[a]For details on assays, see Table 1.
[b]Ref 4.

Table 3. Receptor-binding affinities for selected 5-substituted 1-(4-fluorophenyl)-1*H*-indoles and reference compounds[a]

		Ki (nM)[a]										
Compd	R[b]	α_1	α_{1a}	α_{1b}	α_{1d}	D_2	D_3	D_4	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2C}
1	Sertindole	1.4[c]	0.37	0.33	0.66	0.45[c]	2.6[c]	11[c]	33	56	0.20[c]	0.51[c]
3	Prazosin	0.29	0.93	0.83	0.26	NT	NT	NT	NT	NT	NT	NT
6	SNAP-8719	840	5900	170	1.4	NT	NT	NT	NT	NT	NT	NT
7		2.5	3.7	4.4	14	170	2100	6000	91	85	21	450
9		0.45	0.80	0.60	0.48	6.6	NT	NT	62	570	4.1	12
10		0.58	0.60	0.18	0.59	16	170	280	58	180	15	27
11		0.50	0.18	1.1	0.69	37	560	740	290	640	22	64

[a]For details on assays, see Table 1.
[b]See Table 2.
[c]Ref 4.

the corresponding cloned α_{1a} (bovine), α_{1b} (hamster), and α_{1d} (rat) receptors has been documented.[4]

Replacement of the chlorine atom in the 5-position of the indole moiety in sertindole (**1**) with aminomethyl (**9**–**11**), acetylaminomethyl (**12**) and tetrazolylmethyl groups (**13**–**14**) resulted in compounds with enhanced, subnanomolar, affinity for adrenergic α_1 receptors as apparent from Table 2. Replacement with carbamoyl groups (**7**–**8**) resulted in slightly reduced affinities.

Compared to sertindole, all compounds have reduced affinity for dopamine D_2 receptors. The most pronounced reduction is noted for the carboxamides **7** and **8,** the aminomethyl derivative **11.** These compounds have 377-, 88- and 82-fold reduced affinity compared to sertindole. These compounds are also among the least potent at serotonin 5-HT_{2A} and 5-HT_{2C} receptors.

The effects of the 5-substituents studied on the receptor-binding affinities for dopamine D_2 receptors and serotonin 5-HT_{2A} and 5-HT_{2C} receptors seem to be essentially parallel, and the 5-HT_{2C} receptor seems to be more sensitive to the replacements of the chlorine atom in sertindole with the substituents listed in Table 2. Exceptions are the acetylaminomethyl derivative **12** and the 1-methyl-tetrazolylmethyl derivative **14**. These compounds have 50- to 55-fold and 160- to 254-fold reduced affinity for serotonin 5-HT_{2A} and 5-HT_{2C} receptors, respectively, compared to sertindole, whereas the affinity for dopamine D_2 receptors is in the nanomolar range.

Sertindole has moderate affinity for serotonin 5-HT_{1A} ($K_i = 33$ nM) and 5-HT_{1B} ($K_i = 56$ nM) receptors as apparent from Table 2. These data are in contrast with the previously published receptor-binding affinity for 5-HT_{1A} receptors of 2200[6] and 1050 nM.[43] However, the data presented in this paper is obtained from an assay of human recombinant 5-HT_{1A} receptors expressed in HeLa-cells using [^{3}H]5-CT as radioligand, whereas the previously published value was obtained in an assay of rat or human brain membranes using the [^{3}H]8-OH-DPAT radioligand. Thus, We can not exclude that species differences may affect the apparent affinity for certain compounds.

Replacement of the chlorine atom in sertindole with acetylaminomethyl (**12**) and tetrazolylmethyl (**13**–**14**) substituents had no effect on the binding affinity for serotonin 5-HT_{1A} and 5-HT_{1B} receptors. In contrast, replacement with an aminomethyl substituent (**11**) resulted in 8- to 11-fold reduced affinity. Apparently, the affinity for both 5-HT_{1A} and 5-HT_{1B} receptors increases gradually with increasing methyl substitution on the amine as apparent by comparing the affinity of the aminomethyl derivatives **9**–**11**. The same trend is indicated for the carboxamides **7** and **8** for 5-HT_{1B} receptors.

The most selective of the compounds listed in Table 2 is the aminomethyl derivative **11** having more than 40-fold reduced affinity for the receptors listed in Table 2 compared to the adrenergic α_1 receptors. The receptor-binding affinities for the adrenergic α_{1a}, α_{1b}, α_{1d} and dopamine D_3 and D_4 receptor subtypes for this compound and for reference compounds are listed in Table 3. In addition, the receptor-binding affinities for the carboxamide **7** and the *N,N*-dimethyl-aminomethyl derivative **10**, showing α_1/D_2 selectivities higher than 25, are reported.

The affinities of the compounds **7**, **10** and **11** for dopamine D_3 and D_4 receptors are reduced with a factor of 85–1050 and 16–350 compared to sertindole, respectively. Thus, affinity for these receptors does not pose problems with regard to selectivity.

In our hands, sertindole (**1**) binds with sub-nanomolar affinity for the three α_1 adrenoceptor adrenergic subtypes (α_{1a}, α_{1b}, α_{1d}) as shown in Table 3. These data are in contrast with previously published values by Ipsen et al. who found that sertindole was selective for the α_{1a} adrenoceptor compared to α_{1b} and α_{1d}.[26] However, the use of different radioligands and/or different assay conditions may account for this discrepancy.

The aminomethyl derivative **11** binds with an affinity of 0.18 nM for the α_{1a} receptor and have 6 and 4 times lower affinity for α_{1b} and α_{1d} receptors. In contrast, the *N,N*-dimethyl-aminomethyl derivative **10** has higher affinity for the α_{1b} receptors compared to α_{1a} and α_{1d} as apparent from Table 3. The carboxamide **7** has similar affinities for α_{1a} and α_{1b} receptors and three times lower affinity for α_{1d} receptors. Thus, none of the compounds show any significant difference in affinity for the adrenergic α_1 receptor subtypes.

It has previously been shown that steric bulk in the area corresponding to the indole 5-position increased affinity for dopamine D_2 receptors.[36] In contrast, bulk in the area corresponding to the indole 6-position resulted in decreased affinity.[27,36] Similar, substitution effects were found for the dopamine D_4 receptor.[35] These observations are based on a number of small lipophilic substituents such as methyl and trifluoromethyl groups as well as halogen atoms. To further extend these studies, we synthesised the trimethylsilyl-substituted derivative **15**. Reduced affinity of this compound for α_1, D_2 and 5-HT_{2A} receptors compared to sertindole indicates a limit for the size of lipophilic indole 5-substituents. The effect is most pronounced for dopamine D_2 receptors where the affinity is reduced more than 200-fold.

As previously mentioned, the carboxamides **7** and **8** have low affinity for dopamine D_2 receptors, whereas the acetylaminomethyl and tetrazolylmethyl derivatives **12**–**14** (Table 2) have nanomolar affinity for these receptors.

Superimposition of the carboxamides **7** and **8** (Fig. 1) shows that the carbamoyl substituents superimpose in their minimum energy conformations inducing bulk in the plane of the indole. In contrast, superimposition of the minimum energy conformation of the tetrazolylmethyl derivative **13** with a low energy conformation of the acetylaminomethyl-substituted derivative **12** (0.36 kcal/mol above minimum energy conformation) (Fig. 2) shows that these substituents may adopt conformations where the steric bulk of the substituents is situated out off the plane of the indole.

According to these molecular modelling results, the dopamine D_2 receptor apparently accommodates large substituents out of the plane of the indole. In contrast, large substituents in the plane seem to be disfavoured for both dopamine D_2 and D_4 receptors. Low affinity for serotonin 5-HT_{2A} and 5-HT_{2C} receptors is observed both with 'in plane' and 'out of plane' substituents.

A number of previously reported data[27] indicate that substituents inducing steric bulk in the area corresponding to the indole 6-position in phenylindoles result in decreased affinity for α_1 adrenoceptors for substituents larger than fluorine. Interestingly, the affinity for adrenergic α_1 receptors of the 5,6-methylenedioxy derivative **16** is enhanced compared to sertindole. Electrostatic interactions compensating for the substitution in the sterically unfavourable area of the indole 6-position may account for the high affinity of this compound. This is evident by comparing the affinity of the methylenedioxy derivative **16** with the affinity of the corresponding 5,6-propano derivative[44] (not shown), where the oxygen atoms in the 5,6-methylenedioxy moiety are replaced with methylene groups. The latter derivative binds with 21 nM affinity for adrenergic α_1 receptors[32] corresponding to a 40-fold reduction in affinity.

Apparently, the set of molecular features describing the affinity and selectivities for α_1 adrenoceptors for the present set of molecules is a delicate balance between favourable electrostatic and unfavourable steric interactions. All of the present molecules, except the trimethylsilyl derivative **15**, may benefit from favourable electrostatic interactions with the adrenergic α_1 receptor which may explain the high affinity of these compounds despite unfavourable steric interactions as described above. The combination of these features is difficult to address by qualitative means. We are therefore currently investigating this topic by means of a 3-D-QSAR analysis.

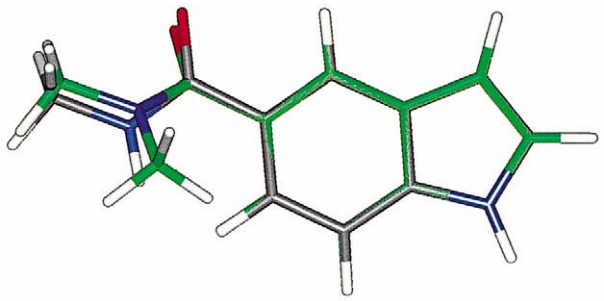


Figure 1. Superimposition of carboxamides **7** (grey) and **8** (green). Indole C3 and N1 substituents are replaced with hydrogens for clarity. Colour code: Nitrogens: Blue; Oxygen: Red.

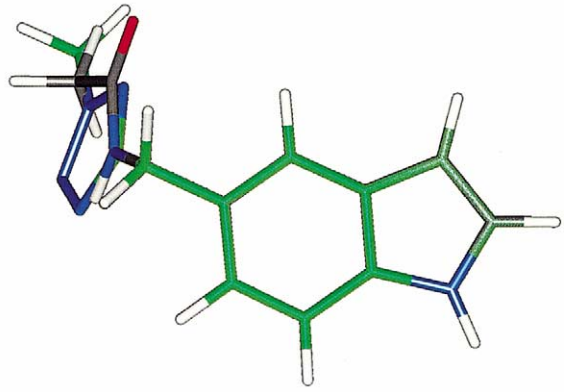


Figure 2. Superimposition of **12** (grey) and **13** (green). Indole C3 and N1 substituents are replaced with hydrogens for clarity. Colour code: Nitrogens: Blue; Oxygen: Red.

The combination of a hydrogen bond acceptor to maintain high affinity for adrenergic α_1 receptors and some additional steric bulk in the plane of the indole to reduce affinity for dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors may explain the high affinity and selectivity for adrenergic α_1 receptors of the compounds presented in the present paper. We are currently exploring a series of phenylindoles where the substituent in the indole 5-position has electron-donating properties combined with some additional steric bulk.

Conclusion

The present study has shown that selective α_1 adrenoceptor antagonists can be developed by the replacement of the chlorine atom in sertindole with polar substituents. Replacement of chlorine with an aminomethyl substituent resulted in a selective α_1 adrenoceptor antagonist, 1-(2-{4-[5-aminomethyl-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (**11**) with subnanomolar affinity for α_1 adrenoceptors and more than 44-fold lower affinity for dopamine D_2, D_3, D_4 and serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors. Electrostatic interactions with the receptor seem to be responsible for the high affinity for adrenergic α_1 receptors. In addition, new information has been added to previously developed serotonin 5-HT_{2A} and dopamine D_2 and D_4 receptor interaction models. There seems to be limits to the size of substituents allowed in the plane of the aromatic pharmacophore corresponding to the indole 5-position. In contrast, large substituents out of plane result in compounds with high affinity for both dopamine D_2 and adrenergic α_1 receptors. This information may be exploited in the development of new selective α_1 antagonists.

Experimental

General

All reactions were carried out under a positive pressure of nitrogen or argon. Glassware for water-sensitive reactions was dried in an oven at 150 °C overnight. For flash chromatography, either silica gel of type Kiesel gel 60, 230–400 mesh ASTM or Biotage Flash40 (50 or 100 g columns) were used. ^{1}H NMR spectra were recorded of all novel compounds at 250 MHz on a Bruker AC 250 or at 500 MHz on a Bruker Avance DRX500 instrument. Deuterated chloroform (99.8%D) or DMSO-d_6 (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qd = quartet of doublets, dd = double doublet, dt = double triplet, tt = triplet of triplets, m = multiplet. NMR signals corresponding to acidic protons are generally omitted. Melting points are reported uncorrected. Solvent residuals in elemental analysis samples were measured by Karl Fisher titration (H_2O) or by Thermo Gravimetric Analysis (TGA) on a TA-instruments TGA 2950 with heating rate 10 °C per min. Results are reported in% (w/w). The nature of the solvent was identified by ^{1}H NMR. Solvent residuals are not reported in the NMR data. LC–MS data (Liquid Chromatography Mass Spectroscopy) were obtained on a PE Sciex API150EX equipped with a Heated Nebulizer source operating at 425 °C. The LC–MS pumps were Shimadzu 8A series running with a Waters C-18 4.6×50 mm, 3.5 μm column. Solvent A: 100% H_2O + 0.05% trifluoroacetic acid, solvent B: 95% CH_3CN, 5% H_2O + 0.035% TFA. Gradient (2 mL/min): 10% B-100% B in 4 min, 10% B for 1 min. Total time including equilibration 5 min. Injection volume 10 μL from a Gilson 215 Liquid Handler. The reported purities are based on the integration of the peaks in the UV and ELSD spectrum.

1-(4-Fluorophenyl)-1*H*-indole-5-carboxylic acid (17b). 5-Cyano-1-(4-fluorophenyl)-1*H*-indole[31] (**17a**) (60.0 g, 0.25 mol) and KOH (60.0 g, 1.1 mol) was boiled under reflux for 24 h in 90% EtOH (500 mL). H_2O (1.5 L) was added and the aqueous phase extracted with diisopropyl ether (2×500 mL). After acidifying with HCl (4 M), 60.0 g of the title compound **17b** (0.24 mol, 96%) was filtered off and dried: mp 224–227 °C; ^{1}H NMR (DMSO-d_6) δ: 6.90 (d, 1H), 7.45 (t, 2H), 7.55 (d, 1H), 7.60–7.72 (m, 3H), 7.85 (d, 1H), 8.40 (s, 1H), 12.70 (s, broad, 1H).

5-Cyanomethyl-1-(4-fluorophenyl)-1*H*-indole (17e). A solution of 1-(4-fluorophenyl)-1*H*-indole-5-carboxylic acid (**17b**) (33.5 g, 0.13 mol) in THF (700 mL) was added cautiously to a mixture of $LiAlH_4$ (9.8 g, 0.26 mol) in THF (400 mL) at 0 °C. The resulting mixture was boiled under reflux for 2 h. After cooling to 0 °C, H_2O (10 mL) and 14% aqueous NaOH (10 mL) was carefully added. Filtration using Celite and evaporation of the solvents afforded 27 g (87%) of crude 1-(4-fluorophenyl)-5-hydoxymethyl-1*H*-indole (**17c**): mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ: 1.85–1.95 (broad s, 1H), 4.75 (s, 2H), 6.65 (d, 1H), 7.15–7.25 (m, 3H), 7.25 (d, 1H), 7.35–7.45 (m, 3H), 7.65 (broad s, 1H). To a solution of crude **17c** (21.5 g, 89 mmol) and NEt_3 (21.5 mL) in CH_2Cl_2 (400 mL), a solution of methanesulfonyl chloride (15.3 g, 0.13 mol) in CH_2Cl_2 (200 mL) was added at 0–5 °C. After stirring at 0–5 °C for 2 h, H_2O (600 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (500 mL). The combined organic phases were dried ($MgSO_4$), and the solvents evaporated in vacuo affording 27.0 g crude 5-chloromethyl-1-(4-fluorophenyl)-1*H*-indole (**17d**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 4.65 (s, 2H), 6.60 (d, 1H), 7.00–7.20 (m, 4H), 7.25–7.40 (m, 2H), 7.45 (d, 1H), 7.65 (s, 1H). A solution of the crude **17d** (27.0 g) in DMSO (300 mL) was added to a solution of NaCN (10.5 g, 0.21 mol) in DMSO (600 mL) at 80 °C. After heating of the reaction mixture at 80 °C for further 40 min, the reaction mixture was cooled to room temperature and H_2O (900 mL) was added. The resulting mixture was extracted with Et_2O (2×1.5 L), and the combined organic phases were washed with brine (2×1.5 L). Drying of the combined organic phases (Na_2SO_4), evaporation of the solvents in vacuo and purification by column

chromatography on silica gel (EtOAc/heptane 1:3) afforded 8.2 g of 5-cyanomethyl-1-(4-fluorophenyl)-1*H*-indole (**17e**) as an oil (37% from **17b**): ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 2H), 6.60 (d, 1H), 7.05–7.25 (m, 3H), 7.25 (d, 1H), 7.35–7.45 (m, 3H), 7.60 (broad s, 1H).

1-(4-Fluorophenyl)-*N*-methyl-1*H*-indole-5-carboxamide (18a). 1-(4-Fluorophenyl)-1*H*-indole-5-carboxylic acid (**17b**) (16.0 g, 63 mmol) was dissolved in THF (120 mL). 1,1-Carbonyldiimidazole (15.0 g, 93 mmol) was added, and the solution was stirred at room temperature for 50 min. After cooling to 0 °C, CH_3NH_2 (125 mL, 2 M in THF, 0.25 mol) was added keeping the solution below 10 °C. After the addition, the solution was stirred for 20 min at 0 °C and 45 min at room temperature. After removal of the solvent in vacuo, the mixture was dissolved in EtOAc (250 mL), washed with H_2O (100 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL) and dried over $MgSO_4$. The product was recrystallised from EtOAc/heptane 1:3 to yield 12.3 g (73%) of the title compound **18a**: mp 126–128 °C (EtOAc/heptane); ^{1}H NMR (DMSO-d_6) δ: 2.80 (d, 3H), 6.80 (d, 1H), 7.45 (t, 2H), 7.50 (d, 1H), 7.65 (m, 2H), 7.70 (m, 2H), 8.20 (s, 1H), 8.40 (d, broad, 1H). Anal. ($C_{16}H_{13}FN_2O$): C, H, N.

***N,N*-Dimethyl-1-(4-fluorophenyl)-1*H*-indole-5-carboxamide (18b).** 1-(4-Fluorophenyl)-1*H*-indole-5-carboxylic acid (**17b**) (20.0 g, 81 mmol) and NEt_3 (8.0 g, 81 mmol) in CH_2Cl_2 (325 mL) was cooled to −30 °C. Ethyl chloroformate (8.7 g, 81 mmol) was added, and the temperature kept below −10 °C for 2 h. A 33% solution of $(CH_3)_2NH$ in ethanol (16.0 g, 117 mmol) was added at −10 °C. After the addition, the cooling bath was removed, and the solution was stirred at room temperature for 45 min. A solution of 0.5 M NaOH (125 mL) was added, and the mixture was extracted with CH_2Cl_2 (2×150 mL). After evaporation of the solvent, the crude product was filtered through silica gel (EtOAc/heptane/NEt_3 20/80/1), and the solvent removed in vacuo to yield 12.0 g (52%) of the title compound **18b** as an oil: ^{1}H NMR ($CDCl_3$) δ: 3.10 (s, 6H), 6.70 (s, 1H), 7.20 (t, 2H), 7.20–7.35 (m, 2H), 7.35–7.50 (m, 3H), 7.80 (s, 1H).

1-(4-Fluorophenyl)-*N*-methyl-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole-5-carboxamide (19a). A solution of 1-(4-fluorophenyl)-*N*-methyl-1*H*-indole-5-carboxamide (**18a**) (12.3 g, 45.8 mmol) in a mixture of AcOH (60 mL) and TFA (15 mL) was added during 0.5 h to a refluxing solution of 4-piperidone, HCl, H_2O (34.6 g, 0.23 mol) in a mixture of AcOH (50 mL) and TFA (100 mL). The reaction mixture was boiled under reflux for 1 h, cooled to room temperature, and the solvents were removed in vacuo. H_2O (200 mL) was added and pH was adjusted to 10 by the addition of 14% aqueous NaOH. The aqueous phase was extracted with EtOAc (3×150 mL). The combined organic phases were washed with H_2O (100 mL) and brine (50 mL) and dried over $MgSO_4$. Evaporation of the solvents in vacuo afforded 16.0 g (100%) of the title compound **19a** as a foam: ^{1}H NMR (DMSO-d_6) δ: 2.48 (s, broad, 2H), 2.80 (d. 3H), 2.98 (t, 2H), 3.50 (d, 2H), 6.40(s, 1H), 7.45 (t, 2H), 7.50 (d, 1H), 7.65 (dd, 2H), 7.70–7.80 (m, 2H), 8.40 (s, 1H), 8.45 (q, broad, 1H).

Compound **19b** was obtained accordingly from **18b.**

***N,N*-Dimethyl-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole-5-carboxamide (19b).** Yield 14.0 g (92%); oil: ^{1}H NMR ($CDCl_3$) δ: 2.65 (m, 2H), 3.05 (s, 6H), 3.25 (t, 2H), 3.70 (d. 2H), 5.00 (s, broad, 1H), 6.30 (s, broad, 1H), 7.10–7.40 (m, 4H), 7.40–7.50 (m, 3H), 8.02 (s, 1H).

1-(4-Fluorophenyl)-*N*-methyl-3-(piperidin-4-yl)-1*H*-indole-5-carboxamide (20a). 1-(4-Fluorophenyl)-*N*-methyl-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole-5-carboxamide (**19a**) (6.8 g, 19.5 mmol) was dissolved in a mixture of AcOH (150 mL) and TFA (25 mL). After the addition of PtO_2 (300 mg), the mixture was reacted with H_2 in a Parr apparatus at 3 ato for 5 h at room temperature. Solids were filtered off, and the solvent removed in vacuo. H_2O (100 mL) was added, pH adjusted to 10 by addition of 28% aqueous NaOH, and the aqueous phase was extracted with EtOAc (3×150 mL). After removal of the solvent in vacou, the product was filtered through silica gel (EtOAc/EtOH/NEt_3 50/50/5). Evaporation of the solvents in vacuo afforded 4.0 g (58%) of the title compound **20a** as a foam: ^{1}H NMR (DMSO-d_6) δ: 1.65 (qd, 2H), 1.95 (d, 2H), 2.70 (t, 2H), 2.80 (d, 3H), 2.95 (t, 1H), 3.10 (d, 2H), 7.40 (t, 2H), 7.45–7,52 (m, 2H), 7.65 (m, 2H), 7.75 (d, 1H), 8.25 (s, 1H), 8.45 (q, 1H).

Compound **20b** was obtained accordingly from **19b.**

***N,N*-Dimethyl-1-(4-fluorophenyl)-3-(piperidin-4-yl)-1*H*-indole-5-carboxamide (20b).** Yield 6.0 g (86%); Foam: ^{1}H NMR: ($CDCl_3$) δ: 1.75 (qd, 2H), 2.1 (d, 2H), 2.85 (dt, 2H), 3.00 (tt, 1H), 3.15 (s, 6H), 3.25 (t, 2H), 7.10 (s, 1H), 7.15–7.35 (m, 3H), 7.35–7.50 (m, 3H), 7.80 (s, 1H).

5-Dimethylaminomethyl-1-(4-fluorophenyl)-3-(piperidin-4-yl)-1*H*-indole (21). *N,N*-Dimethyl-1-(4-fluorophenyl)-3-(piperidin-4-yl)-1*H*-indole-5-carboxamide (**20b**) (4.3 g, 12 mmol) in dry THF (25 mL) was added slowly to a solution of $LiAlH_4$ (1.5 g, 40 mmol) in THF (50 mL) keeping the temperature below 40 °C. The solution was stirred for 2 h at 40 °C. After cooling to room temperature the excess of $LiAlH_4$ was destroyed by cautious drop-wise addition of water. Subsequently, water (100 mL) and 1 M aqueous NaOH (5 mL) were added and the aqueous phase extracted with Et_2O (2×200 mL) to yield 3.5 g (86%) of crude **21** as an oil: ^{1}H NMR ($CDCl_3$) δ: 1.70 (2H), 2.05 (d, 2H), 2.25 (s, 6H), 2.85 (td, 2H), 3.00 (tt, 1H), 3.20 (d, 2H), 3.50 (s, 2H), 7.00 (s, 1H), 7.10–7.30 (m, 3H), 7.30–7.50 (m, 3H), 7.60 (s, 1H).

1-(4-Fluorophenyl)-5-[(tetrazol-5-yl)methyl]-1*H*-indole (23). A solution of 5-cyanomethyl-1-(4-fluorophenyl)-1*H*-indole (**17e**) (8.2 g, 32.8 mmol), NaN_3 (7.7 g, 0.29 mol), NEt_3,HCl (13.5 g, 98 mmol) in 1,2-dimethoxyethane (100 mL) was boiled under reflux for 2 days. After cooling to room temperature, solids were filtered off and the volatile solvents were evaporated in vacuo.

H_2O (100 mL) and glacial AcOH (15 mL) were added, and the resulting mixture was extracted with EtOAc (2×150 mL). The combined organic phases were washed with H_2O (200 mL) and brine (200 mL) and subsequently dried (Na_2SO_4). Evaporation of the solvents in vacuo gave 14.0 g of crude 1-(4-fluorophenyl)-5-(tetrazol-5-ylmethyl)-1*H*-indole **23** as an oil containing some residual acetic acid. ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, 4H, acetic acid) 4.25 (s, 2H), 6.49 (s, 1H), 7.00 (d, 1H), 7.03–7–40 (m, 6H), 7.45 (s, 1H). The crude product was used directly in the next step without further purification.

1-(4-Fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indole (24a) and 1-(4-fluorophenyl)-5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indole (25a). A solution of crude 1-(4-fluorophenyl)-5-[(tetrazol-5-yl)methyl]-1*H*-indole (**23**) (14.0 g) in NMP (200 mL) was cooled on an ice bath and potassium *tert*-butoxide (6.4 g, 57 mmol) was added cautiously over 20 min keeping the temperature below 20 °C. When the addition was complete, the reaction mixture was cooled to 0 °C, and CH_3I (15.6 g, 0.11 mol) was added. After stirring at room temperature for 2 h, H_2O (200 mL) was added and the resulting mixture was extracted with EtOAc (2×200 mL). The combined organic phases were washed with H_2O (2×200 mL) and brine (2×250 mL), dried (Na_2SO_4), and the volatile solvents evaporated in vacuo. The resulting mixture of 1- and 2-methyl-substituted tetrazoles was separated by column chromatography on silica gel (EtOAc/heptane 1:2). Evaporation of the fastest eluting fractions in vacuo afforded 3.7 g (37% from **17e**) of 1-(4-fluorophenyl)-5-(2-methyltetrazol-5-ylmethyl)-1*H*-indole (**24a**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 4.25 (s, 3H), 4.30 (s, 2H), 6.60 (d, 1H), 7.10–7.20 (m, 3H), 7.20 (d, 1H), 7.30–7.45 (m, 3H), 7.60 (broad s, 1H).

Evaporation in vacuo of the slowest eluting fractions afforded 1.5 g (15% from **17e**) 1-(4-fluorophenyl)-5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indole (**25a**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 4.35 (s, 2H), 6.50 (d, 1H), 7.00 (broad d, 1H), 7.15 (t, 2H), 7.25 (d, 1H), 7.30–7.40 (m, 3H), 7.45 (broad s, 1H).

1-(2-{4-[1-(4-Fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl)-2-imidazolidinone (24c). Reaction of 1-(4-Fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indole (**24a**) (3.7 g, 12 mmol) with 4-piperidone, HCl, H_2O (11.1 g, 72 mmol) in analogy to the procedure described in the preparation of **19a** gave 4.7 g (100%) of crude 1-(4-fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**24b**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 2.05–2.20 (broad s, 1H), 2.45–2.55 (m, 2H), 3.15 (t, 2H), 3.55–3.65 (m, 2H), 4.25 (s, 3H), 4.35 (s, 2H), 6.25–6.30 (m, 1H), 7.10–7.25 (m, 4H), 7.30–7.45 (m, 3H), 7.90 (broad s, 1H). Crude **24b** (4.7 g, 12 mmol), 1-(2-chloroethyl)imidazolidin-2-one[31,45] (2.0 g, 13 mmol), K_2CO_3 (2.5 g, 18 mmol) and KI (0.60 g, 3.6 mmol) were boiled under reflux for 8 h in 4-methyl-2-pentanone (150 mL). After cooling to room temperature H_2O (100 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×200 mL). After evaporation of the solvents in vacuo the crude product was purified by column chromatography (EtOAc/EtOH/NEt_3 80/20/4) to yield 3.5 g (57%) of the title compound **24c**: mp 129–131 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 2.55–2.75 (m, 4H), 2.80 (t, 2H), 3.25–3.35 (m, 2H), 3.35–3.50 (m, 4H), 3.50–3.65 (m, 2H), 4.30 (s, 3H), 4.35 (s, 2H), 4.50 (broad s, 1H), 6.20–6.25 (m, 1H), 7.10–7.25 (m, 4H), 7.30–7.45 (m, 3H), 7.90 (broad s, 1H); 2D-NOE cross peak between δ = 4.30 (tetrazole *N*-CH_3) and δ = 4.35 (CH_2) absent; MS *m*/*z*: 501 (MH^+, 22), 142 (100), 113 (91). Anal. ($C_{28}H_{31}FN_8O$·0.40% H_2O): C, H; N calcd 22.30, found 21.63.

Compound **25c** was obtained accordingly from **25a.**

1-(2-{4-[1-(4-Fluorophenyl)-5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl)-2-imidazolidinone (25c). Yield 1.6 g (66% from **25a**): mp 174–176 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.55–2.65 (m, 4H), 2.80 (t, 2H), 3.20–3.35 (m, 2H), 3.35–3.50 (m, 4H), 3.50–3.65 (m, 2H), 3.80 (s, 3H), 4.35 (broad s, 1H), 4.40 (s, 2H), 6.10–6.20 (m, 1H), 7.05 (broad d, 1H), 7.15–7.30 (m, 3H), 7.30–7.45 (m, 3H), 7.75 (broad s, 1H); 2D-NOE cross peak between δ = 3.80 (tetrazole *N*-CH_3) and δ = 4.40 (CH_2) present; MS *m*/*z*: 501 (MH^+, 6), 142 (100), 113 (97). Anal. ($C_{28}H_{31}FN_8O$·0.53% H_2O): C, H, N.

4-[5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (26d). Reaction of 5-bromo-1-(4-fluorophenyl)-1*H*-indole[31] (**26a**) (172 g, 0.59 mol) with 4-piperidone, HCl, H_2O (550 g, 3.6 mol) in analogy to the procedure described in the preparation of compound **19a** gave 220 g (100%) of crude 5-bromo-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (**26b**) as a white solid: ^{1}H NMR ($CDCl_3$) δ: 2.40–2.55 (m, 2H), 3.15 (t, 2H), 3.55–3.65 (m, 2H), 6.25 (s, broad, 1H), 7.12–7.30 (m, 5H), 7.35–7.45 (m, 2H), 8.03 (s, 1H). Crude **26b** (220 g) and PtO_2 (5.0 g) in glacial acetic acid (1.5 L) was treated with H_2 in a Parr apparatus at 2–3 ato for 24 h. Additional PtO_2 (4.0 g) was added, and reaction was continued for 24 h. Solids were filtered off and the solvent was removed in vacuo. 10% aqueous NH_4OH (1 L) was added and the aqueous phase was extracted with EtOAc (3×1 L). The combined organic phases were dried over $MgSO_4$ and the solvent removed in vacuo to yield 125 g (57%) of crude 5-bromo-1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indole (**26c**) as an oil: ^{1}H NMR (DMSO-d_6) δ: 1.78 (qd, 2H), 2.05 (d, 2H), 2.90 (td, 2H), 3.05 (m, 1H), 3.25 (d, 2H), 7.30 (d, 1H), 7.35–7.45 (m, 3H), 7.49 (s, 1H), 7.56–7.63 (m, 2H), 7.93 (d, 1H). A solution of crude **26c** (125 g, 0.33 mol) and di-*tert*-butyl dicarbonate (260 g, 1.2 mol) in 1:1 THF/H_2O mixture (1 L) was stirred overnight with K_2CO_3 (300 g, 2.2 mol) at 60 °C. EtOAc (1 L) was added. After separation of the two phases, the aqueous phase was extracted with EtOAc (3×500 mL). The combined organic phases were washed with brine (200 mL) and dried over $MgSO_4$. The crude product (115 g) was washed with cold MeOH (2 L) to yield 97.0 g of the title compound **26d** (35% from **26a**) as a white solid: mp 160–162 °C (heptane); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.65 (q, 2H), 2.04 (d, 2H), 2.85–3.00 (m, 3H), 4.25 (d,

2H), 7.03 (s, 1H), 7.15–7.35 (m, 4H), 7.39–7.43 (m, 2H), 7.78 (s, 1H); MS *m/z* (relative intensity): 473 + 475 (MH^+, 1%), 417 + 419 (40%), 373 + 375 (100%). Anal. ($C_{24}H_{26}BrFN_2O_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(trimethylsilyl)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (27a). 4-[5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (**26d**) (3.0 g, 6.3 mmol) in THF (20 mL) was added during 2 min to a solution of *n*-butyllithium (7.9 mL, 12.7 mmol) in THF (50 mL) at −78 °C. After stirring for 3 min, $(CH_3)_3SiCl$ (2.8 g, 25 mmol) was added. The solution was heated to room temperature during 30 min, and H_2O (50 mL) was added. After extraction of the aqueous phase with EtOAc (3×30 mL) and evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (EtOAc/heptane 10/90→30/70) to give 2.8 g of the title compound. Recrystallisation (EtOAc/heptane 1/4) gave 2.6 g (88%) of the title compound **27a**: mp 81–82 °C (EtOAc/heptane); ^1H NMR ($CDCl_3$) δ: 0.33 (s, 9H), 1.49 (s, 9H), 1.70 (q, 2H), 2.09 (d, 2H), 2.96 (t, 2H), 3.06 (tt, 1H), 4.27 (s, broad, 2H), 7.02 (s, 1H), 7.1–7.22 (m, 2H), 7.37 (d, 1H), 7.46 (d, 1H), 7.4–7.44 (m, 2H), 7.81 (s, 1H). Anal. ($C_{27}H_{35}FN_2O_2Si$): C, H, N.

4-[(5,6-Methylenedioxy)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (28d). 5,6-Methylenedioxy-1*H*-indole (**28a**) (6.5 g, 40 mmol) and 4-piperidone, HCl, H_2O (17.9 g, 0.12 mol) were added to a solution of KOH (10.1 g, 0.18 mol) in EtOH (200 mL) at 5 °C. The solution was boiled under reflux for 14 h. After cooling to room temperature, solids were filtered off, and the solvents removed in vacuo. The remaining material was purified by column chromatography (EtOAc/EtOH/TEA 70/30/5) to yield 7.5 g of crude 5,6-methylenedioxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (**28b**) as a yellow solid. ^1H NMR (DMSO-d_6) δ: 2.36 (s, broad, 2H), 2.95 (t, 2H), 3.44 (s, broad, 2H), 5.94 (s, 2H), 6.03 (s, 1H), 6.89 (s, 1H), 7.19 (s, 1H),7.23 (s, 1H). Reaction of crude **28b** (7.5 g) with H_2 in analogy to the procedure described in the preparation of **20a** gave 5.7 g of crude 5,6-methylenedioxy-3-(piperidin-4-yl)-1*H*-indole (**28c**) as an oil: ^1H NMR (DMSO-d_6) δ: 1.50 (qd, 2H), 1.82 (d, 2H), 2.61 (t, 2H), 2.72 (tt, 1H), 2.98 (d, 2H), 5.89 (s, 2H), 6.81 (s, 1H), 6.87 (s, 1H), 6.99 (s, 1H). A solution of crude **28c** (5.7 g), $(Boc)_2O$ (6.4 g, 29 mmol) and K_2CO_3 (10.0 g, 73 mmol) in THF (400 mL) and H_2O (200 mL) was stirred for 14 h at 60 °C. Additional $(Boc)_2O$ (5.0 g, 23 mmol) and K_2CO_3 (3.3 g, 24 mmol) were added, and the solution was stirred for further 5 h. After cooling to room temperature, the phases were separated, and the aqueous phase extracted with EtOAc (3×250 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and the solvents evaporated in vacuo. The resulting 6.9 g was purified by flash chromatography (EtOAc/heptane 40/60) to give 6.8 g (49% from **28a**) of the title compound **28d** as pink crystals: mp 191–192 °C (EtOAc/heptane); ^1H NMR ($CDCl_3$) δ: 1.48 (s, 9H), 1.98 (q, 2H), 2.00 (d, 2H), 2.8–2.95 (m, 3H), 4.20 (s, broad, 2H), 5.92 (s, 2H), 6.81 (s, 1H), 6.82 (s, 1H), 6.98 (s, 1H). Anal. ($C_{19}H_{24}N_2O_4$): C, H, N.

4-[1-(4-Fluorophenyl)-5,6-methylenedioxy-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (29). A suspension of 4-[(5,6-methylenedioxy)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (**28d**) (5.0 g, 14.5 mmol), 4-fluoro-iodobenzene (5.8 g, 26.1 mmol), K_2CO_3 (6.0 g, 44 mmol), CuI (1.0 g, 5.4 mmol), and ZnO (0.34 g, 4.2 mmol) in NMP (60 mL) was stirred at 100 °C for 48 h. After cooling to room temperature solids were filtered off, and the solid washed with EtOAc (200 mL). The organic phase was washed with H_2O (100 mL) and brine (3×100 mL), and the solvents were removed in vacuo. Purification by flash chromatography (EtOAc/heptane 0/100→20/80) afforded 5.0 g (79%) of the title compound **29**: mp 108–110 °C (EtOAc/heptane); ^1H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1,66 (qd, 2H), 2.03 (d, 2H), 2.80–2.95 (m, 4H), 4.25 (s, broad, 2H), 5.94 (s, 2H), 6.89 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.15–7.20 (m, 2H), 7.35–7.41 (m, 2H). Anal. ($C_{25}H_{27}FN_2O_4$): C, H, N.

1-(4-Fluorophenyl)-3-{1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidinyl]-*N*-methyl-1*H*-indole-5-carboxamide (7). 1-(4-Fluorophenyl)-*N*-methyl-3-(piperidin-4-yl)-1*H*-indole-5-carboxamide (**20a**) (4.4 g, 12.5 mmol), K_2CO_3 (5.2 g, 38 mmol), KI (1.0 g, 6 mmol) and 1-(2-chloroethyl)imidazolidin-2-one (2.2 g, 13.6 mmol) were boiled under reflux for 8 h in 4-methyl-2-pentanone (250 mL). After cooling to room temperature, solids were filtered off and the residue washed with 4-methyl-2-pentanone (50 mL). After evaporation of the solvent, the remaining compound was dissolved in CH_2Cl_2 and washed twice with H_2O. The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/15/5) to yield 3.5 g (59%) of the title compound **7**: mp 150–155 °C (EtOH/Et_2O 1/1); ^1H NMR (DMSO-d_6) δ: 1.75 (qd, 2H), 2.0 (d, 2H), 2.15 (t, 2H), 2.45 (t, 2H), 2.82 (d, 3H), 2.85 (t, 1H), 3.02 (d, 2H), 3.2 (q, 4H), 3.4 (q, 2H), 6.25 (s, 1H), 7.40 (t, 2H), 7.49 (m, 2H), 7.60 (m, 2H), 7.70 (d, 1H), 8.20 (s, 1H), 8.4 (q, 1H). Anal. ($C_{27}H_{32}FN_5O_2 \cdot 2.71\%$ EtOH):N, H; C calcd 66.96, found 65.69.

Compound **8** was prepared accordingly from **20b**.

***N,N*-Dimethyl-1-(4-fluorophenyl)-3-{1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidinyl}-1*H*-indole-5-carboxamide (8).** Yield 0.60 g (29%): mp 172–176 (acetone); ^1H NMR ($CDCl_3$) δ: 1.80 (dq, 2H), 2.05 (d, 2H), 2.15 (t, 2H), 2.55 (t, 2H), 2.90 (tt, 1H), 3.10 (m, 8H), 3.40 (m, 4H), 3.50 (m, 2H), 4.80 (s, broad, 1H), 7.10 (s, 1H), 7.15–7.40 (m, 3H), 7.35–7.50 (m, 3H), 7.80 (s, 1H). Anal. ($C_{28}H_{34}FN_5O_2 \cdot 1/3$ mol acetone): C, H, N.

1-{4-[1-(4-Fluorophenyl)-5-methylaminomethyl-1*H*-indol-3-yl]-1-piperidinyl}ethyl-2-imidazolidinone (9). Compound **7** (2.0 g, 4.2 mmol) and $LiAlH_4$ (0.33 g, 9 mmol) were boiled under reflux in dry THF (150 mL) for 3 h. After cooling to room temperature the excess of $LiAlH_4$ was destroyed by cautious drop-wise addition of water. Subsequently water (100 mL) and 1 M aqueous NaOH (5 mL) were added and the aqueous phase extracted with EtOAc (3×100 mL). After removal of the solvent in vacuo, the crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/15/5) to yield

0.30 g of the title compound **9** as an oil, ^{1}H NMR (DMSO-d_6) δ: 1.72 (q, 2H), 1.97 (d, 2H), 2.12 (t, 2H), 2.28 (s, 3H), 2.45 (t, 2H), 2.77 (tt, 1H), 3.00 (d. 2H), 3.10–3.60 (m, 6H),3.72 (s, 2H), 6.25 (s, 2H), 7.14 (d. 1H), 7.35–7.45 (m, 4H), 7.55–7.65 (m, 3H). LC–MS *m*/*z*: 438 (MH^+, 100%). Purity UV: >98%; purity ELSD >99%.

1-(2-{4-[5-Dimethylaminomethyl-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (10). 5-Dimethylaminomethyl-1-(4-fluorophenyl)-3-(piperidin-4-yl)-1*H*-indole (**21**) (3.5 g, 10 mmol) was reacted with 1-(2-chloroethyl)imidazolidin-2-one[31,45] in analogy to the procedure described in the preparation of **7**: Yield 1.0 g (21%): mp 155–165 °C (acetone); ^{1}H NMR ($CDCl_3$) δ: 1.80 (q, 2H), 2.05 (d, 2H), 2.18 (t, 2H), 2.25 (s, 6H), 2.57 (t, 2H), 2.85 (tt, 1H), 3.08 (d, 2H), 3.40 (q, 4H), 3.45–3.55 (m, 4H), 4.40 (s, 1H), 7.00 (s, 1H), 7.15 (m, 3H), 7.30–7.50 (m, 3H), 7.60 (s, 1H). Anal. ($C_{27}H_{34}FN_5O$): C, H, N.

1-(2- {4-[5-Aminomethyl-1-(4-fluorophenyl)- 1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (11). 1-(2-{4-[5-Cyano-1-(4-fluorophenyl)- 1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl)-2-imidazolidinone[31] (**22**) (4.6 g, 11 mmol) was reacted with H_2 as described in the preparation of **20a**, except, no TFA was used. The crude product was purified by preparative HPLC (Merck Hibar 250–25, LiChrosorb RP-8, 7 μM) (EtOH/25% aqueous NH_3 solution 100/4). Yield 0.92 g (20%); mp 171–175 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ: 1.85 (d, 2H), 2.10 (d, 2H), 2.25 (td, 2H), 2.60 (t, 2H), 2.90 (tt, 1H), 3.10 (d, 2H), 3.4 (q, 4H), 3.6 (q, 2H), 3.95 (s, 2H), 4.70 (s, broad, 1H), 7.00 (s, 1H), 7.10–7.25 (m, 3H), 7.30–7.50 (m, 3H), 7.60 (s, 1H). Anal. ($C_{26}H_{32}FN_5O$·1.0% H_2O): H, N; C: calcd 68.22, found 67.51.

***N*-(1-(4-Fluorophenyl)-3-{1-[2-(2-imidazolidin-2-one-1-yl)-ethyl]-piperidin-4-yl}-1*H*-indol-5-ylmethyl)-acetamide (12).** Acetyl chloride (0.33 g, 4.2 mmol) was added slowly to a solution of 1-(2-{4-[5-aminomethyl-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (**11**) (1.7 g, 3.9 mmol) and NEt_3 (1.1 mL) in CH_2Cl_2 (25 mL) at 0 °C. The solution was stirred for 1 h at room temperature before evaporation of the solvent in vacuo. The crude product was purified by column chromatography (EtOAc/EtOH/NEt_3 80/20/4) to give 0.93 g of crude product, which was crystallised from EtOAc to give 0.55 g (27%) of the title compound **12**: mp 167 °C; ^{1}H NMR ($CDCl_3$) δ: 1.82 (qd, 2H), 2.03 (s, 3H), 2.04 (d, 2H), 2.23 (t, 2H), 2.58 (t, 2H), 2.83 (tt, 1H), 3.10 (d, 2H), 3.30–3.45 (m, 4H), 3.55 (t, 2H), 4.55 (d, 2H), 4.67 (s, broad, 1H), 5.95 (s, broad, 1H), 7.06 (s, 1H), 7.10–7.25 (m, 3H), 7.33–7.43 (m, 3H), 7.60 (s, 1H). Anal. ($C_{27}H_{32}FN_5O_2$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imazolidinone, 2.25 fumarate (13). Reaction of 1-(2-{4-[1-(4-fluorophenyl)-5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl)-2-imidazolidinone (**24c**) (1.5 g, 3.0 mmol) with H_2 in analogy to the procedure described in the preparation of **20a** gave the title compound **13** after precipitatation with fumaric acid from MeOH: Yield: 0.25 g (22%); mp 171–173 °C (MeOH). ^{1}H NMR (DMSO-d_6) δ: 1.75–1.95 (m, 2H), 1.95–2.15 (m, 2H), 2.45–2.60 (m, 2H), 2.70–2.85 (m, 2H), 2.95 (tt, 1H), 3.15–3.35 (m, 6H), 3.35–3.50 (m, 2H), 4.30 (broad s, 5H), 6.35 (broad s, 1H), 6.60 (s, 4.5H), 7.10 (broad d, 1H), 7.35–7.45 (m, 4H), 7.60 (dd, 2H), 7.70 (broad s, 1H); MS *m*/*z*: 503 (MH^+, 11), 419 (10), 194 (82), 168 (69), 113 (100). Anal. ($C_{28}H_{33}FN_8O$·2.25 $C_4H_4O_4$): C, H, N.

Compound **14** was obtained accordingly from **25c**.

1-(2-{4-[1-(4-Fluorophenyl)-5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone, 2.5 fumarate (14). The title compound **14** was obtained after precipitation with fumaric acid from EtOH: Yield: 0.25 g (17%); mp 169–171 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ: 1.75–2.00 (m, 2H), 2.00–2.15 (m, 2H), 2.55–2.75 (m, 2H), 2.85 (t, 2H), 2.95 (tt, 1H), 3.20–3.50 (m, 8H), 4.00 (s, 3H), 4.40 (s, 2H), 6.40 (broad s, 1H), 6.60 (s, 5H), 7.05 (broad d, 1H), 7.30–7.50 (m, 4H), 7.50 (dd, 2H), 7.65 (broad s, 1H); MS *m*/*z*: 503 (MH^+, 100), 446 (7), 419 (10), 194 (36), 168 (32), 113 (65). Anal. ($C_{28}H_{33}FN_8O$·2.50 $C_4H_4O_4$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(trimethylsilyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (15). Neat 4-[1-(4-fluorophenyl)-5-(trimethylsilyl)-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (**27a**) (2.5 g, 5.3 mmol) was heated to 230 °C during 3 h. After cooling to room temperature, EtOAc (75 mL) and H_2O (50 mL) were added, and the aqueous phase was extracted with EtOAc (3×75 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated in vacuo to give 2.0 g of crude 1-(4-fluoro-phenyl)-3-(piperidin-4-yl)-5-trimethylsislyl-1*H*-indole (**27b**). Crude **27b** (1g, 2.7 mmol) was reacted with 1-(2-chloroethyl)imidazolidin-2-one[31,45] in analogy to the procedure described in the preparation of **24c**. The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 50/40/10) and recrystallised from EtOAc/heptane to give 0.40 g (31%) of the title compound **15**: mp 182–184 °C (EtOAc/heptane); ^{1}H NMR (DMSO-d_6) δ: 0.28 (s, 9H), 1.73 (q, 2H), 1.97 (d, 2H), 2.15 (t, 2H), 2.44 (t, 2H), 2.85 (tt, 1H), 3.01 (d, 2H), 3.17–3.22 (m, 4H), 3.40 (t, 2H), 6.19 (s, broad), 7.30 (d, 1H), 7.36–7.40 (m, 3H), 7.48 (d, 1H), 7.50–7.60 (m, 2H), 7.79 (s, 1H); ($C_{27}H_{35}FN_4OSi$): C, H, N.

1-{4-[1-(4-Fluorophenyl)-5,6-methylenedioxy-1*H*-indol-3-yl]-1-piperidinyl}ethyl-2-imidazolidinone (16). A solution of 4-[1-(4-Fluorophenyl)-5,6-methylenedioxy-1*H*-indol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (**29**) (1.5 g, 3.4 mmol) in THF (30 mL) was reacted with a saturated solution of HCl in MeOH (20 mL) for 4 h at room temperature. Evaporation of the solvent and reaction with 1-(2-chloroethyl)imidazolidin-2-one[31,45] in analogy to the procedure described in the preparation of **7**, except an excess of K_2CO_3 (10 equivalents) was used, afforded 0.62 g (42%) of the title compound **16**: mp 216–217 °C (EtOAc/heptane); ^{1}H NMR (DMSO-d_6) δ: 1.64 (qd, 2H), 1.95 (d, 2H), 2.10 (t, 2H), 2.41 (t, 2H),

2.70 (tt, 1H), 2.99 (d, 2H), 3.13–3.23 (m, 4H), 3.39 (t, 2H), 5.96 (s, 2H), 6.23 (s, broad, 1H), 6.98 (s, 1H), 7.13 (s, 1H), 7.21 (s, 1H), 7.32–7.40 (m, 2H), 7.53–7.59 (m, 2H). Anal. ($C_{25}H_{27}FN_4O_3$): C, H, N.

Pharmacology

Cell lines and animals. CHO cell lines expressing the rat $\alpha_{1d,}$ human D_3, and human D_4 receptors and BHK cell lines expressing bovine α_{1a} receptors were generated in-house at H. Lundbeck A/S using standard stable transfection techniques. The Rat-1 cell line expressing the hamster α_{1b} receptor was obtained from the University of Utah, Utah, USA. The HeLa cells expressing the 5-HT_{1A} receptor were obtained from Dr. Hamblin (Duke University, NC, USA) and those expressing the 5-HT_{1B} receptor from Medical Center University, Washington, USA. The SR-3T3 cells expressing the rat 5-HT_{2C} receptors were purchased from the American Type Culture Collection.

Brain preparations were generated from male Sprague–Dawley rats weighing approximately 220 g. The animals were decapitated prior to brain extraction.

In vitro binding assays. α_1 and serotonin receptors: The tissues were homogenised in ice-cold 50 mM Tris, pH 7.7, using an Ultra-Turrax and the homogenates either kept on ice or stored at −80 °C until used. The assay buffer subsequently used contained 50 mM Tris, pH 7.7. Non-specific binding for the α_1 assays was defined as the binding in the presence of prazosin (1 μM) for the α_1 (rat brain) and of WB-4101 (1 μM) for the cloned α_{1a}, $\alpha_{1b,}$ and α_{1d} assays, respectively. For the serotonin assays, non-specific binding was defined using metergoline (1 μM) for the 5-HT_{1A} assay, 5-HT (10 μM) for the 5-HT_{1B} assay and mianserine (1 μM) for both the 5-HT_{2A} and 5-HT_{2C} assays. In All the α_1 assays samples were incubated at 25 °C for 20 min. The 5-HT_{1A} and 5-HT_{1B} assays were incubated for 15 min at 37 °C whereas the 5-HT_{2A} and 5-HT_{2C} assays were incubated for 30 min at 37 °C. In All assays bound and free radioactivity were separated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux).

Dopamine receptors: D_2 tissue was homogenised in ice-cold 50 mM phosphate buffer, pH 7.4 using an Ultra-Turrax and the homogenates were kept on ice or stored at −80 °C until used. The homogenisation buffer was also used as assay buffer. For the D_3 receptor, 25 mM Tris containing 6.0 mM $MgCl_2$ and 1.0 mM EDTA, pH 7.4, was used as homogenisation and assay buffer. The D_4 receptor tissue was homogenised and tested in 50 mM Tris containing 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, pH 7.4. To define non-specific binding, ADTN was used (10 μM) for the D_2 assay, haloperidol (10 μM) for the D_3 assay, and clozapine (10 μM) for the D_4 assay. Incubation times and temperatures were 15 min at 37 °C for the D_2 assay, and 60 min at 25 °C for both the D_3 and D_4 assays. All assays were terminated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux).

For details regarding the source of the membranes, radioligand, and radioligand concentration, refer to Table 1. Data shown in tables are means from a minimum of two full concentration–response curves using 10 concentrations of drugs (covering 3 decades). The results are given as K_i values (nM) derived from computer-fitted IC_{50} values converted to K_i values using the Cheng–Prusoff equation. Standard errors for pK_i-values were within 0.3 for all reported compounds.

Molecular modelling

Conformational analysis was performed in Macromodel version 7[46] using the MMFFs forcefield[47] on the entire molecules protonated at the piperidine nitrogens. Calculations were performed using the default aqueous solvation model implemented in Macomodel. Molecules were built in their proposed receptor-active conformations[33] with the imidazolidinone-ethyl side chains in an extended conformation. Energy minimisations were performed without constraints. Conformational analysis of the substituents in the indole 5-positions were performed by systematic drives around flexible bonds. The templates for superimpositions (**7** and **13**) were in the lowest possible energy minimum with the imidazolidinone-ethyl side chains in an extended conformation. The superimposed molecules were in the lowest energy minimum (**8**) or in a local minimum 0.36 kcal/mol above the the lowest energy minimum (**12**), both with the the imidazolidinone-ethyl side chain in an extended conformation. Indole C3 and N1 substituents are removed in Figures 1 and 2 for clarity.

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