Indolebutylamines as Selective 5-HT$_{1A}$ Agonists

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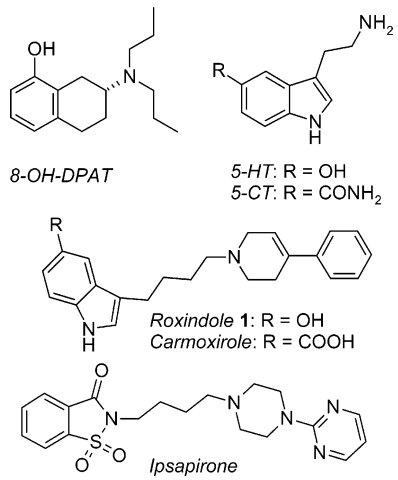
A series of new 1-[4-(indol-3-yl)butyl]-4-arylpiperazines was prepared to identify highly selective and potent 5-HT$_{1A}$ agonists as potential pharmacological tools in studies of mood disorders. The combination of structural elements (indole−alkyl−amine and aryl−piperazine) known to introduce 5-HT$_{1A}$ receptor affinity and the proper selection of substituents (R on the indole moiety and R′ on the aryl moiety) led to compounds with high receptor specificity and affinity. In particular, the introduction of the methyl ether or the unsubstituted carboxamide as substituents in position 5 of the indole (R) guaranteed serotonergic 5-HT$_{1A}$ affinity compared to the unsubstituted analogue. Para-substituted arylpiperazines (R′) decreased dopaminergic D$_2$ binding and increased selectivity for the 5-HT$_{1A}$ receptor. Agonistic 5-HT$_{1A}$ receptor activity was confirmed in vivo in the ultrasonic vocalization test, and the results suggest that the introduction of the carboxamide residue leads to better bioavailability than the corresponding methyl ether. 3-{4-[4-(4-Carbamoylphenyl)piperazin-1-yl]butyl}-1*H*-indole-5-carboxamide **54** was identified as a highly selective 5-HT$_{1A}$ receptor agonist [GTPγS, ED$_{50}$ = 4.7 nM] with nanomolar 5-HT$_{1A}$ affinity [IC$_{50}$ = 0.9 nM] and selectivity [D$_2$, IC$_{50}$ > 850 nM]. 3-{4-[4-(4-Methoxyphenyl)piperazin-1-yl]butyl}-1*H*-indole-5-carboxamide **45** is one of the most potent and selective 5-HT$_{1A}$ agonists known [5-HT$_{1A}$, IC$_{50}$ = 0.09 nM; D$_2$, IC$_{50}$ = 140 nM].

Introduction

Diseases of the central nervous system are often correlated with a malfunction of the dopaminergic (e.g., schizophrenia, Parkinsonism) and/or serotonergic (e.g., anxiety, depression) system. Although in some cases treatment is available with drugs targeting the mentioned neurotransmitter systems without a specific selectivity, therapy is far from being satisfactory. The search for discriminating ligands is a thoroughly considered approach in medicinal chemistry for a better understanding of serotonin (5-HT) and dopamine (D) receptor subtypes in mood disorders. Among the 5-HT receptors, the 5-HT$_{1A}$ receptor subtype is the best studied and several classes of agents are known to interact with high affinity. Aminotetralines[1] with 8-OH-DPAT as the most prominent member and arylpiperazines[2] with the spirone class of compounds (e.g., ipsapirone[3]) have been extensively evaluated (Chart 1).[4] Besides these, additional different chemical classes such as indolylalkylamines,[5] ergolines, aporphines and aryloxyalkylamines have been investigated.[4] We entered into the field with the discovery that the indolealkylamine roxindole **1** is not only a dopamine but also a potent 5-HT$_{1A}$ receptor agonist. Classic indolealkylamines such as 5-CT show no selectivity for a distinct 5-HT receptor subtype like the endogenous neurotransmitter 5-HT itself. Published efforts to improve selectivity and affinity of derivatives of 5-HT and 5-CT were not successful so far.[2,4,6] To elucidate whether it is possible to find compounds in the structural class of roxindole,

Chart 1



with selectivity for the 5-HT$_{1A}$ receptor and devoid of dopamine receptor affinity, we first recall the structural elements responsible for the dopamine receptor interaction.

As published previously[7] within the indolealkylamine class of roxindole, a set of four structural elements was found to be essential for high-affinity agonism at the D$_2$ autoreceptor: (1) the aryl unsubstituted 4-phenyl-1,2,3,6-tetrahydropyridine, (2) the double bond and the basic center of the tetrahydropyridine, (3) the saturated four-carbon chain linking the basic nitrogen with the 3-indole position, and (4) the indole heterocycle unsubstituted in positons 1, 2, and 7.[8]

Besides dopamine receptor affinity (D$_2$, IC$_{50}$ = 5.6 nM) roxindole **1** shows nanomolar 5-HT$_{1A}$ binding (5-HT$_{1A}$, IC$_{50}$ = 0.8 nM) as full agonist (GTPγS, ED$_{50}$ = 5 nM)

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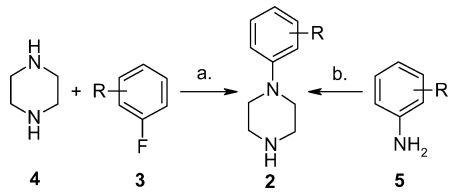
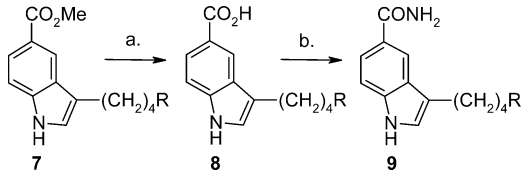
Scheme 1[a]



[a] (a) AcCN; (b) NMP, TEA **6**.

Scheme 2[a]



[a] (a) NaOH, dioxane; (b) 1-methyl-2-chloropyridinium iodide, NH_3. R = phenylpiperidine or phenylpiperazine.

and nanomolar 5-HT reuptake inhibition (RUI, IC_{50} = 1.4 nM).[7d] In addition to these predominant affinities, roxindole binds fairly well to a couple of other targets too and shares a multireceptor activity profile like most successful antipsychotics of the past and the present.[9] To further exploit the potential of these indolebutylamines, it was decided to elucidate the possibility of preparing more selective compounds in this class. Furthermore, to receive bioavailable drug candidates, we wanted to avoid structural elements that could be target of phase II metabolism at the 5-hydroxyindole group of roxindole.[7,10]

It soon turned out to be difficult to suppress serotonergic activities in order to obtain more selective dopamine agonists. In contrast, suppression of dopaminergic activity to yield selectivity for the 5-HT receptor subtype 1A seemed to be feasible and became the focus of our interest as presented subsequently.

Chemistry

The synthetic pathway to the 4-phenyl-1,2,3,6-tetrahydropyridines (THP) from Table 1 has already been published.[8] The piperidines listed in Table 2 were obtained by hydrogenation of the appropriate tetrahydropyridines following a known literature synthesis methodology.[11] The piperazines **2** used to build the compounds shown in Tables 3−5 were synthesized by either one of the two pathways from Scheme 1, if not commercially available.

Piperazine **4** was arylated with fluorobenzene **3** in acetonitrile at elevated temperature[12] or an aniline **5** was reacted with bis(2-chloroethyl)ammonium chloride **6** in 1-methylpyrrolidin-2-one (NMP) and a tertiary amine.[13] The compounds from Tables 2−5 were prepared according to the procedure from Scheme 2 or as previously described.[14]

The esters **7** were saponified under basic conditions, and the resulting acids **8** reacted with gaseous ammonia to the carboxamides **9** after activation with Mukaiyama's reagent.[15] Direct aminolysis of the ester did not work with our 5-indolyl esters. The synthesis of the 5-indolyl ethers (**10**−**13**, **22**−**42**),[7,14] 5-indolylphenols (**14**, **15**),[8,16] and 5-indolyl methyl esters (**16**, **17**)[11] is known from the literature.[17]

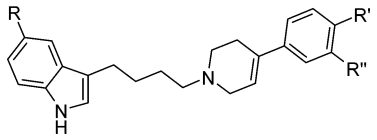
Biology

The affinity of the compounds toward the dopamine D_2 receptor subtype was evaluated by their ability to displace [^{3}H]spiperone (dopamine antagonist)[18] in rat striatal membranes or cloned human receptors. Serotonergic 5-HT_{1A} activity of the compounds was measured in rat hippocampal membranes with [^{3}H]-8-OH-DPAT as ligand.[17] The intrinsic activity of the compounds as 5-HT_{1A} agonist or antagonist was tested in the GTPγS assay with recombinant human 5-HT_{1A} receptors stably expressed in membranes of Chinese hamster ovary (CHO) cells.[19] The 5-HT_{1A} agonistic activity in vivo was determined by the ability of the compounds to inhibit ultrasonic vocalization in rats.[20]

Results and Discussion

First, to avoid phase II metabolism of roxindole **1**,[10] we examined closely related indolebutylamines with the alkylated 5-hydroxy function on the indole (Table 1). The methyl ether **10** shows decreased 5-HT_{1A} binding affinity in comparison to **1**, but the introduction of oxygen functionality on the aromatic substituent on THP (**11**−**13**) reinstalls 5-HT_{1A} binding and further diminishes D_2 affinity (vide infra). This structural relationship points to a possible cooperative effect of substituents on the indole and the second aryl group with regard to the 5-HT_{1A} receptor affinity.[21]

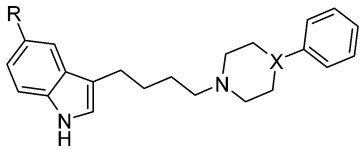
Table 1. Roxindole and Close Analogues (IC_{50} ± SEM (nM))[a]



compd	R	R′	R″	5-HT_{1A}	D_2
1	OH	H	H	0.8 ± 0.1	5.6 ± 0.4
10	OCH_3	H	H	20 ± 9	20 ± 5.4
11	OCH_3	OH	H	0.4 ± 0.2	∼100
12	OCH_3	OCH_3	H	0.6 ± 0.1	>100
13	OCH_3	OCH_2CH_2O		0.4 ± 0.3	>100

[a] IC_{50} values were obtained from 5 to 10 concentrations of the compound, each in triplicate, and are defined as the concentration (nM) resulting in 50% inhibition of binding.

Table 2. Comparison of Piperidines and Piperazines (IC_{50} ± SEM (nM))[a]



compd	R	X	5-HT_{1A}	D_2
14	OH	C	1 ± 0.5	80 ± 23
15		N	0.8 ± 0.1	4.2 ± 4
16	CO_2CH_3	C	20 ± 2	113 ± 65
17		N	40 ± 23	31 ± 14
18	CO_2H	C	100 ± 55	1000
19		N	40 ± 17	>100
20	$CONH_2$	C	0.1 ± 0.1	17 ± 1.7
21		N	0.1 ± 0.2	7 ± 0.2

[a] IC_{50} values were obtained from 5 to 10 concentrations of the compound, each in triplicate, and are defined as the concentration (nM) resulting in 50% inhibition of binding.

Because the styrene-like moiety in the aryl-THP of roxindole was found to be solely essential for the dopaminergic D_2 binding,[8] we compared structurally similar piperidines and piperazines for further improvement of the serotonergic activity (Table 2). Though there are differences in binding affinity and selectivity be-

tween piperidines and piperazines with the same substitution pattern (e.g., D_2 of **14** vs **15**), there is no obvious preference in one or the other heterocycle. The carboxylic acids **18** and **19** show no dopaminergic activity, in contrast to the previously described THP derivative carmoxirole[22] (pointing to the importance of the unsubstituted 4-aryl-THP as the D_2 pharmacophore). The corresponding esters **16** and **17** are only weakly active on both targets without any selectivity. The most striking observation is that the hydroxy (**14**, **15**) and the carboxamide derivatives (**20**, **21**) show the highest 5-HT_{1A} receptor affinity in this series and the values are comparable to those of the methoxy derivatives (**11**−**13**) in Table 1. To scrutinize the 5-methoxyindoles, a larger series with modified phenyl substituents on the piperazine moiety was prepared (Table 3).

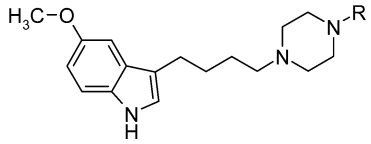
As can be seen from Table 3, the core structure 5-methoxyindole with a 1-butyl-4-phenylpiperazine leads to robust 5-HT_{1A} binding tolerating a variety of phenyl substituents. In contrast, the dopaminergic D_2 binding affinity is low with this scaffold as soon as the phenyl group is substituted and this is not influenced distinctively by different phenyl residues. Benzyl ether **26** and methoxy ethoxy ether **27** are tolerated as well as the acetyl ester **28** and acetamide **29**. The same is valid even for the more bulky *tert*-butyl ester **30** or the lipophilic silyl ether **31**. Further information about steric limitations was available by comparison of the methoxy derivatives **24**, **32**, **35**, and **38**. The 4-methoxyphenyl derivative **24** shows nanomolar binding (4 nM), the 3,4-bis(methoxyphenyl) compound **35** is weakly active (10 nM), but obviously the second methoxy group can be rotated so that repulsive interactions are negligible. The 3,5-bis(methyl-4-methoxy) derivative **32** seems to have no possibility of circumventing steric obstructions by rotation, but it is still tolerated (60 nM), whereas the even more spaciously demanding 3,4,5-trimethoxy-substituted phenyl in compound **38** decreases 5-HT_{1A} binding to 300 nM.

While aryl substituents were optimized, more 5-indolyl ethers and carboxylates were under closer examination. As a resumption of the work with the THP derivatives from Table 1 (4-methoxyphenyl residue reduces dopamine affinity) and integration of the gained piperazine expertise, the compounds from Table 4 were made to elucidate the influence of different indole 5-substituents on the receptor binding profile.

The larger alkyl and alkaryl ethers as indole residues (**39**−**42**) show only moderate binding affinity to both 5-HT_{1A} and D_2 receptors. Nevertheless, it is interesting to see that the derivatives with two small alkyl ether substituents (**24**, **25**, and **39**) show nanomolar or even subnanomolar 5-HT_{1A} receptor binding and selectivity of a factor of 100. The observed high affinity of the indolyl-5-carboxamides **20**, **21**, and **45** motivated us to evaluate the 5-HT_{1A} receptor binding potential of this scaffold by preparing and examining a series of indolyl-5-carboxamides with various aryl substituents on the piperazine moiety (Table 5).

As can be seen from Table 5, the indolyl-5-carboxamide is an optimal structural element to enhance 5-HT_{1A} receptor binding. Independent from the phenyl substitution, nanomolar or even subnanomolar binding affinities could be reached. Obviously the steric and electronic requirements of the phenyl at the piperazine ring for this receptor are negligible. Electron-rich (**45**, **46**, **48**−**53**) as well as electron-poor (**54**−**58**), lean (**21**), and bulky (**59**) aromatic systems are accepted. Because of their excellent 5-HT_{1A} receptor potency and D_2 receptor selectivity, the bis-carboxamide **54** and the acetanilide **56** were tested for their affinity to other G-protein-coupled receptors (GPCRs). Compound **54** shows good 5-HT_{1A} receptor selectivity versus further

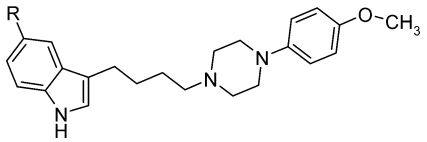
Table 3. Influence of Aryl Substitution in 5-Methoxyindolyl-3-butylpiperazines on 5-HT_{1A} and D_2 Binding (IC_{50} ± SEM (nM))[a]



compd	R	5-HT_{1A}	D_2
22	C_6H_5	20 ± 3	32 ± 4.6
23	4-OHC_6H_4	2 ± 0.3	53 ± 13
24	4-$OCH_3C_6H_4$	4 ± 0.4	420 ± 127
25	4-$OCH_2CH_3C_6H_4$	0.8 ± 0.05	>100
26	4-$OCH_2C_6H_5C_6H_4$	30 ± 12	220 ± 69
27	4-$O(CH_2)_2OCH_3C_6H_4$	2 ± 0.7	n.d.
28	4-$OC(O)CH_3C_6H_4$	1 ± 0.5	>100
29	4-$NHC(O)CH_3C_6H_4$	3 ± 0.5	>100
32	4-$OC(O)C(CH_3)_3C_6H_4$	24 ± 15	n.d.
31	4-$OTBDMSC_6H_4$	70 ± 25	n.d.
32	3,5-$(CH_3)_2$-4-$OCH_3C_6H_2$	60 ± 19	>100
33		0.4 ± 0.1	>100
34		2 ± 0.4	>100
35	3,4-$(OCH_3)_2C_6H_3$	10 ± 4	100 ± 52
36		4 ± 1.7	100 ± 29
37		0.5 ± 0.2	120 ± 49
38	3,4,5-$(OCH_3)_3C_6H_2$	333 ± 117	>100

[a] IC_{50} values were obtained from 5 to 10 concentrations of the compound, each in triplicate, and are defined as the concentration (nM) resulting in 50% inhibition of binding. TBDMS = *tert*-butyldimethylsilyl.

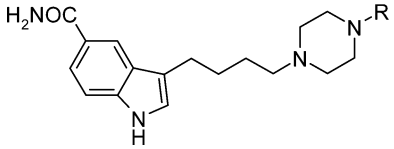
Table 4. Influence of Different Indole Residues on Binding in Indolealkylamines (IC_{50} ± SEM (nM))[a]

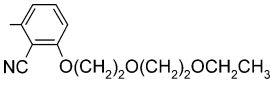


compd	R	5-HT_{1A}	D_2
39	OCH_2CH_3	2 ± 0.6	300 ± 170
40	$O(CH_2)_4CH_3$	200 ± 175	>100
41	$OCH(CH_2)_4$	90 ± 5	>100
42	$OCH_2C_6H_5$	34 ± 23	>100
43	$OC(O)CH_3$	0.5 ± 0.3	>100
44	CO_2CH_3	8 ± 1	>100
45	$CONH_2$	0.09 ± 0.09	140 ± 23

[a] IC_{50} values were obtained from 5 to 10 concentrations of the compound, each in triplicate, and are defined as the concentration (nM) resulting in 50% inhibition of binding.

Table 5. Receptor Binding Profile of Indolyl-5-carboxamide Derivatives (IC_{50} ± SEM (nM))



compd	R	5-HT_{1A}	D_2
46	4-OHC_6H_4	0.2 ± 0.2	156 ± 95
47	4-OCH_3-3,5-$Cl_2C_6H_2$	0.7 ± 0.2	>100
48	2-$OCH_3C_6H_4$	0.1 ± 0.07	1.2 ± 0.3
49		0.5 ± 0.2	>100
50		0.5[a] ± 0.3	100 ± 52
51	2,4-$(OCH_3)_2C_6H_3$	0.07 ± 0.02	100 ± 29
52		0.4 ± 0.2	22 ± 1.9
53		0.2 ± 0.2	40 ± 17
54	4-$CONH_2C_6H_4$	0.9[b] ± 0.5	>850
55	2-$CONH_2C_6H_4$	0.3 ± 0.2	97 ± 56
56	4-$NHC(O)CH_3C_6H_4$	0.1 ± 0.1	>100
57	2-CNC_6H_4	0.2 ± 0.08	6.2 ± 1.6
58	2-CN-3-FC_6H_3	0.01 ± 0.01	5 ± 2.9
59		0.9 ± 0.6	28 ± 16

[a] GTPγS, ED_{50} = 0.07 nM. [b] GTPγS, ED_{50} = 4.7 nM.

serotonin and dopamine receptor subtypes [IC_{50} (nM)]: 5-HT_{1D} = 200; 5-HT_{2A} = 1400; 5-HT_{2C} > 1000; D_3 = 950; D_4 > 1000. Derivative **56** was also tested against α-adrenergic receptors and showed no relevant affinity [IC_{50} (nM)]: 5-HT_{1D} = 200; 5-HT_{2C} = 1000; α_1 = 3000; α_2 = 1000. These results emphasize the selectivity potential within the discussed scaffold.

To compare the role of the 5-indolyl residue for potent 5-HT_{1A} receptor binding, eight couples of compounds have to be mentioned explicitly. Within each pair the phenylpiperazine part is kept constant and the substituent on the indole is changed (5-methoxy or 5-carboxamide respectively). The unsubstituted phenylpiperazines **21** and **22** show comparable two-digit-nanomolar D_2 binding, but the carboxamide **21** binds 200 times better to the 5-HT_{1A} receptor than **22**. The phenol **23** is 10-fold less active in 5-HT_{1A} binding as methoxyindole than as the corresponding carboxamide **46**. The introduction of a methyl group improves 5-HT_{1A} binding affinity of both derivatives equally (**24** vs **45**), but the D_2 selectivity is better for the carboxamide **45**. The compound pairs **33**/**49** and **34**/**50** are selective 5-HT_{1A} ligands with only weak D_2 affinity. In compound pairs **36**/**52** and **37**/**53**, there are differences between 5-methoxyindole and indolyl-5-carboxamide: The benzodioxolecarboxamide **52** binds 20 times better to the 5-HT_{1A} receptor than the corresponding ether **36** and is 1 order of magnitude more active at the D_2 receptor. The benzodioxanecarboxamide **53** has comparable 5-HT_{1A} potential but one power of 10 more D_2 affinity than the ether **37**. The acetanilide **56** shows better 5-HT_{1A} binding as carboxamide than the corresponding methyl ether **29**. Taking these results together, it can be concluded that in general the 5-indolylcarboxamides show higher 5-HT_{1A} affinity than the corresponding 5-methoxyindoles.

The results from Table 1 (**1**, **10** vs **11**−**13**) suggest that the introduction of substituents on the phenyl ring decreases D_2 binding, but obviously the position of the substituents is very important. In most cases (e.g., **22** vs **23**−**38** or **21** vs **46**, **47**, **54**, **56**), para substitution leads to a decrease in D_2 binding affinity, but ortho or meta substitution have no detectable influence (**48**, **55**, **57**, and **58**).

By application of the GTPγS test, it is confirmed that the compounds **50** and **54** act as full agonists at the 5-HT_{1A} receptor, though the difference in activity by a factor of 70 between the ED_{50} values of these two derivatives cannot be explained (Table 5). The intrinsic activity was ascertained in vitro only for these two compounds in this publication, but we have much evidence for agonism in the whole structural class as can be shown by the results in the in vivo inhibition of ultrasonic vocalization (Table 6).

The fact that the 5-hydroxyindole **1** (roxindole) is subject to phase II metabolism explains the remarkable discrepancy in activity after sc and po administration in Table 6. The oral activity of the ethers **24** and **37** is still by a factor of 50 and 160 weaker than after sc application. For the carboxamides **45** and **50**, the factor between sc and po doses is smaller (17 and 21), indicating that this indole substitution is able to improve oral bioavailability.

Table 6. In Vivo Inhibition of Ultrasonic Vocalization by Selected Compounds in Rats (ID_{50} (mg/kg))

	1	**24**	**37**	**39**	**45**	**50**
sc	0.07	0.2	0.1	3	0.1	0.07
po	16	10	16	n.d.[a]	1.7	1.5

[a] n.d. = not determined.

In conclusion, it was found that the 3-(piperazinobutyl)indole-5-carboxamide is a very potent 5-HT_{1A} binding scaffold. When the appropriate arylpiperazine substituent is chosen, very selective 5-HT_{1A} agonists can be obtained. The following overview shows the selectivity profile of a selection of compounds to a series of other 5-HT receptor subtypes and related GPCRs (Table 7).[23]

Table 7. Comparison of Selected Compounds in Binding Affinity to Certain GPCRs (IC_{50} (nM))

target	**24**	**45**	**52**	ipsapirone
5-HT_{1A}	4	0.09	0.4	8.2
5-HT_{1D}	>10000	700	400	3000
5-HT_{2A}	750	220	240	2600
5-HT_{2C}	4000	n.d.	800	>1000
H_1	41	1000	19	24
α_1	1000	700	100	500
α_2	7000	2000	900	1000
D_2	420	140	24	2900[a]

[a] D_3 = 1200. D_4 = 1800. n.d. = not determined.

Compounds **24** and **52** have some histamine H_1 receptor binding affinity that could lead to sedative side effects in vivo and the affinity of **45** and **52** to the D_2 receptor subtype is 140 and 24 nM, respectively.

The combination of typical structural elements of 5-HT agonists (indolealkylamine and phenylpiperazine)

not only improves 5-HT_{1A} binding affinity but also has impact on the selectivity to other GPCRs. The described class of compounds compares well with the structural elements described previously for arylpiperazines. The 1,1-dioxobenzoisothiazolone of ipsapirone,[3] for example, is replaced by an indole that is preferably substituted in the 5-position. By suitable substitution of the phenyl moiety (replacing the pyrimidine moiety in ipsapirone), selectivity to other GPCRs can be reached. The best compound in this series is clearly the indolylcarboxamide **45**. The affinity of compound **45** to the dopaminergic receptor subtype 2 is by a factor of more than 1000 weaker than to the serotonergic receptor subtype 1A. For comparison, this ratio (D_2/5-HT_{1A}) for ipsapirone is 300. Furthermore, compound **45** has less histaminergic potential than ipsapirone (by a factor of 40). With this finding, we were able to provide a new interesting tool with selectivity and potency for serotonin receptor research.

Experimental Section

Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. IR, ^{1}H NMR, and mass spectra are in agreement with the structures and were recorded on a Bruker IFS 48 IR spectrophotometer, a Bruker AMX 300 MHz or DRX 500 MHz NMR spectrometer (TMS as an internal standard), and Vaccum Generators VG 70-70 or 70-250 at 70 eV. Elemental analyses (obtained with a Perkin-Elmer 240 BCHN analyzer) for the final products were within 0.4% of calculated values if not otherwise stated. All reactions were followed by TLC carried out on Merck KGaA F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure. Phenylpiperazines were available from EMKA.

The synthesis of compounds **1** and **10**−**13** is known from the literature.[14]

General Method for Hydrogenation: 3-[4-(Phenylpiperidin-1-yl)butyl]-1*H*-indol-5-ol (14). A solution of 4.1 g (10.7 mmol) of 3-[4-(4-phenyl-3,6-dihydro-2*H*-pyridin-1-yl)-butyl-1*H*-indol-5-ol hydrochloride in 30 mL of methanol was reacted with 0.56 L of hydrogen (normal pressure) with a 5% Pd/charcoal contact (1.4 g) for 120 min at 40 °C and filtered hot after complete conversion. The precipitate was recrystallized from methanol, yielding 2.6 g (63%) of **14**: mp 228−230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 10.41 (br s, 1H), 8.58 (s, 1H), 7.33 (t, 2H, J = 7.1 Hz), 7.23 (d, 3H, J = 7.1 Hz), 7.12 (d, 1H, J = 8.6 Hz), 7.04 (s, 1H), 6.82 (s, 1H), 6.60 (dd, 1H, J = 2.2 Hz and J = 8.6 Hz), 3.51 (d, 2H, J = 11.8 Hz), 3.07 (m, 2H), 2.98 (m, 2H), 2.80 (m, 1H), 2.64 (t, 2H, J = 7.1 Hz), 2.06 (m, 2H), 1.93 (m, 2H), 1.79 (m, 2H), 1.66 (m, 2H). Anal. ($C_{23}H_{28}N_2O$·HCl) C, H, N, Cl.

General Method for Coupling of an Indolebutyl Moiety with Phenylpiperidine or Phenylpiperazine: Methyl 3-[4-(4-Phenylpiperidin-1-yl)butyl]-1*H*-indole-5-carboxylate (16). A solution of 65 g (0.2 mol) of methyl 3-(4-methanesulfonyloxybutyl)-1*H*-indole-5-carboxylate,[14] 19.7 g (0.1 mol) of 4-phenylpiperidine hydrochloride, and 55.4 mL of triethylamine in 500 mL of methanol was refluxed for 7 h. After complete conversion of the piperidine ingredient, the solvent was removed and the crude product was dissolved in acetone. After the addition of HCl-saturated ethanol to pH 4 the precipitate was filtered and washed with acetone and diethyl ether, yielding 6.1 g (14%) of **16** as colorless crystals: mp 204−206 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.50 (br s, 1H), 8.23 (s, 1H), 7.72 (dd, 1H, J = 1.5 Hz and J = 8.5 Hz), 7.43 (d, 1H, J = 8.5 Hz), 7.33 (m, 3H), 7.23 (m, 3H), 3.85 (s, 3H), 3.52 (d, 2H, J = 11.0 Hz), 3.10 (m, 2H), 2.99 (q, 2H, J = 11.0 Hz), 2.79 (t, 3H, J = 7.7 Hz), 2.09 (m, 2H), 1.94 (m, 2H), 1.83 (m, 2H), 1.71 (m, 2H). Anal. ($C_{25}H_{30}N_2O_2$·HCl) C, H, N.

3-[4-(4-Phenylpiperidin-1-yl)butyl]-1*H*-indole-5-carboxylic Acid (18). A solution of 2.4 g (5.6 mmol) of the previously prepared ester **16** in 80 mL of 1 N NaOH and 80 mL of dioxane was heated to 80 °C for 2 h. After the mixture was cooled to room temperature, concentrated HCl was added to give pH 4 and the precipitate was filtered, washed with water, acetone, and diethyl ether, and dried to yield 2.0 g (86%) of **18** as colorless crystals: mp 196−198 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (br s, 1H), 11.26 (s, 1H), 10.65 (br s, 1H), 8.23 (s, 1H), 7.71 (dd, 1H, J = 1.2 Hz and J = 8.5 Hz), 7.41 (d, 1H, J = 8.5 Hz), 7.33 (m, 2H), 7.29 (s, 1H), 7.24 (m, 3H), 3.51 (m, 2H), 3.34 (m, 3H), 3.01 (m, 2H), 2.99 (m, 2H), 2.79 (m, 3H), 2.10 (m, 2H), 1.93 (m, 2H), 1.83 (m, 2H), 1.71 (m, 2H). Anal. ($C_{24}H_{28}N_2O_2$·HCl·H_2O) H, N. C: calcd, 66.9; found 65.8.

Compounds **15**, **17**, and **19**−**59** were synthesized according to the following procedures.

3-{4-[4-(2,3-Dihydrobenzofuran-5-yl)piperazin-1-yl]butyl}-5-methoxy-1*H*-indole (33). A solution of 52.5 g (0.39 mol) of commercially available 2,3-dihydro-1-benzofuran-5-amine in 300 mL of hot 1-butanol was reacted with 69.6 g (0.34 mol) of bis-(2-chloroethyl)ammonium chloride at 145 °C for 12 h. After addition of 30.4 g (0.22 mol) of potassium carbonate, the suspension was heated to the given temperature for a further 12 h. After it was cooled to 80 °C, the precipitating starting material was filtered, and finally the product was crystallized at room temperature. The crude material was recrystallized from ethanol, and an amount of 25.2 g (31%) of 1-(2,3-dihydrobenzfuran-5-yl)piperazine was collected: mp 213−215 °C. Anal. ($C_{12}H_{16}N_2O$·HCl) C, H, N. Cl: calcd, 14.7; found, 15.2. To a solution of 4.6 g (20 mmol) of 4-(5-methoxy-1*H*-indol-3-yl)butyric acid in 80 mL of THF was added 2.4 mL (20 mmol) of 2,2-dimethylpropionyl chloride, and the resulting suspension was stirred for 30 min. Then a solution of 4.8 g (20 mmol) of the previously prepared 1-(2,3-dihydrobenzfuran-5-yl)piperazine was added and the solution was stirred for 48 h. For workup, the reaction mixture was concentrated in a vacuum and the residue was dissolved in 1 N NaOH and ethyl acetate. After phase separation, the organic precipitate was filtered and washed with ethyl acetate, yielding 6.1 g (72%) of 1-[4-(2,3-dihydrobenzofuran-5-yl)piperazin-1-yl]-4-(5-methoxy-1*H*-indol-3-yl)butan-1-one: mp 149 °C. A suspension of 6.1 g (15 mmol) of the previously prepared amide in 100 mL of THF was treated with 10.5 mL (38 mmol) of Vitride (70% in toluene) and stirred for 2 h at room temperature. After complete conversion of the starting material, an amount of 8 mL of water was added at 0 °C, the resulting precipitate was filtered, and the remaining solution was concentrated in vacuum. The crude product was recrystallized from ethyl acetate, yielding 2.7 g (45%) of **33** as colorless crystals: mp 110−112 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.21 (d, 1H, J = 8.7 Hz), 7.05 (d, 1H, J = 2.2 Hz), 6.96 (d, 1H, J = 2.4 Hz), 6.86 (d, 1H, J = 1.3 Hz), 6.69 (dd, 1H, J = 2.4 Hz and J = 8.7 Hz), 6.62 (m, 2H), 4.43 (t, 2H, J = 8.6 Hz), 3.75 (s, 3H), 3.10 (t, 2H, J = 8.6 Hz), 2.95 (m, 4H), 2.67 (t, 2H, J = 7.3 Hz), 2.46 (m, 4H), 2.36 (t, 2H, J = 7.2 Hz), 1.66 (m, 2H), 1.52 (m, 2H). Anal. ($C_{25}H_{31}N_3O_2$) H. C: calcd, 74.0; found, 73.3. N: calcd, 10.3; found, 9.3.

3-[4-(4-Chroman-6-ylpiperazin-1-yl)butyl]-1*H*-indole-5-carboxamide (50). A suspension of 9.3 g (35 mmol) of methyl 3-(4-chlorobutyl)-1*H*-indole-5-carboxylate,[14] 10.2 g (35 mmol) of 1-chroman-6-ylpiperazine,[24] 14.5 g (0.11 mol) of potassium carbonate, and 14.6 mL (0.11 mol) of triethylamine in 300 mL of acetonitrile was heated to reflux for 20 h. After the reaction mixture had cooled to room temperature, the suspension was filtered and the filtrate was evaporated to dryness. The resulting crude material was stirred in ethyl acetate and water, after phase separation the organic phase was dried and evaporated, and the resulting oil was purified via chromatography. The combined and evaporated product fractions were crystallized from ether/cyclohexane, yielding 5.9 g (37%) of yellow crystals of methyl 3-[4-(4-chroman-6-ylpiperazin-1-yl)-butyl]-1*H*-indole-5-carboxylate: mp 118−121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.22 (d, 1H, J = 1.1 Hz), 7.70 (dd, 1H, J = 1.6 Hz and J = 8.6 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.24 (d, 1H, J = 2.0 Hz), 6.65 (dd, 1H, J = 2.7 Hz and J = 8.9 Hz), 6.59 (m, 2H), 4.03 (ϕt, 2H), 3.83 (s, 3H), 2.94 (m, 4H),

2.75 (t, 2H, $J = 6.6$ Hz), 2.68 (t, 2H, $J = 6.4$ Hz), 2.45 (m, 4H), 2.34 (t, 2H $J = 6.6$ Hz), 1.87 (m, 2H), 1.69 (m, 2H), 1.52 (m, 2H). Anal. ($C_{27}H_{33}N_3O_3$) C, H, N. A solution of 5.5 g (13 mmol) of the previously prepared methyl ester in 50 mL of dioxane was heated with 52 mL (52 mmol) of 1 N NaOH to 80 °C for 2 h. After the solution had cooled to room temperature concentrated HCl was added, leading to precipitation. Precipitation was completed at 7 °C for 12 h, and after filtration and drying 5.8 g (98%) of fawn crystals of 3-[4-(4-chroman-6-ylpiperazin-1-yl)butyl]-1*H*-indole-5-carboxylic acid hydrochloride were collected: mp 245−247 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.30 (br s, 1H), 11.18 (s, 1H), 10.55 (br s, 1H), 8.20 (s, 1H), 7.69 (dd, 1H, $J = 1.5$ Hz and $J = 8.5$ Hz), 7.38 (d, 1H, $J = 8.5$ Hz), 7.26 (d, 1H, $J = 1.8$ Hz), 6.72 (dd, 1H, $J = 2.8$ Hz and $J = 8.8$ Hz), 6.63 (m, 2H), 4.04 (ϕt, 2H), 3.29 (m, 4H), 3.06 (m, 4H), 2.77 (t, 2H, $J = 6.5$ Hz), 2.69 (t, 4H, $J = 6.4$ Hz), 1.87 (m, 2H), 1.71 (m, 4H). Anal. ($C_{25}H_{29}N_3O_3$·HCl) H, Cl. C: calcd, 65.9; found, 64.8. N: calcd, 9.2; found, 9.9. A solution of 5.6 g (11 mmol) of the previously prepared acid and 5.6 g (22 mmol) of 1-methyl-2-chloropyridinium iodide (CMPJ) in 50 mL of 1-methylpyrrolidin-2-one (NMP) was stirred at room temperature, and 7.3 mL (44 mmol) of *N*,*N*-diisopropylethylamine (DIPEA) were added drop by drop before NH_3 gas was introduced for 2 h. The mixture reached 63 °C and cooled to room temperature after completion. Then 50 mL of 1 N NaOH and 100 mL of water were added. The precipitate (4.4 g) was collected and recrystallized from 100 mL of ethanol, yielding 2.6 g (55%) **50**: mp 177−179 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (br s, 1H), 8.15 (s, 1H), 7.80 (br s, 1H), 7.64 (dd, 1H, $J = 1.6$ Hz and $J = 8.5$ Hz), 7.32 (d, 1H, $J = 8.5$ Hz), 7.17 (d, 1H, $J = 2.2$ Hz), 7.02 (br s, 1H), 6.66 (dd, 1H, $J = 2.8$ Hz and $J = 8.8$ Hz), 6.58 (s, 1H), 6.57 (d, 1H, $J = 8.8$ Hz), 4.03 (t, 2H, $J = 5.1$ Hz), 2.94 (t, 4H, $J = 4.7$ Hz), 2.74 (t, 2H, $J = 7.5$ Hz), 2.68 (t, 2H, $J = 6.5$ Hz), 2.45 (t, 4H, $J = 4.8$ Hz), 2.35 (t, 2H, $J = 7.4$ Hz), 1.86 (m, 2H), 1.69 (m, 2H), 1.53 (m, 2H). Anal. ($C_{26}H_{34}N_4O_2$) C, H, N.

3-{4-[4-(4-Carbamoylphenyl)piperazin-1-yl]butyl}-1*H*-indole-5-carboxamide (54). A suspension of 5 g (19 mmol) of methyl 3-(4-chloro-butyl)-1*H*-indole-5-carboxylate,[14] 4.6 g (12 mmol) of 4-piperazin-1-ylbenzamide,[25] 5.2 g (38 mmol) of potassium carbonate, and 5 mL (38 mmol) of triethylamine in 200 mL of acetonitrile was coupled as described above, yielding 1.7 g (20%) of methyl 3-{4-[4-(carbamoylphenyl)piperazin-1-yl]butyl}-1*H*-indole-5-carboxylate. Without further purification the ester (1.7 g, 4 mmol) was hydrolyzed with 1 N NaOH (12 mL) as described above, yielding 1.2 g (67%) of 3-{4-[4-(carbamoylphenyl)piperazin-1-yl]butyl}-1*H*-indole-5-carboxylic acid hydrochloride as colorless crystals: mp 288−290 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (br s, 1H), 11.14 (s, 1H), 9.76 (br s, 1H), 8.19 (s, 1H), 7.77 (d, 2H, $J = 8.8$ Hz), 7.68 (dd, 2H, $J = 1.8$ Hz, $J = 8.6$ Hz), 7.38 (d, 1H $J = 8.6$ Hz), 7.25 (d, 1H, $J = 1.8$ Hz), 7.00 (br m, 3H), 3.95 (m, 2H), 3.54 (m, 2H), 3.19 (m, 2H), 3.08 (m, 4H), 2.77 (m, 2H), 1.71 (m, 4H). Anal. ($C_{24}H_{28}N_4O_3$·HCl) H, Cl. C: calcd, 63.1; found, 61.2. N: calcd, 12.3; found, 11.8. The previously prepared acid (1.1 g, 2.4 mmol), 1.5 g (6 mmol) of CMPJ, and 1.7 mL (9 mmol) of DIPEA in 30 mL of NMP were reacted as described above, giving 0.9 g (90%) of the corresponding carboxamide semihydrate **54** as colorless crystals: mp 138−140 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.89 (d, 1H, $J = 2.2$ Hz), 8.19 (d, 1H, $J = 1.7$ Hz), 7.86 (br s, 2H), 7.76 (d, 2H, $J = 8.9$ Hz), 7.67 (dd, 1H, $J = 1.7$ Hz and $J = 8.5$ Hz), 7.36 (d, 1H, $J = 8.5$ Hz), 7.21 (d, 1H, $J = 2.3$ Hz), 7.04 (br s, 2H), 6.93 (d, 1H, $J = 8.9$ Hz), 3.24 (m, 4H), 2.77 (t, 2H, $J = 7.0$ Hz), 2.48 (m, 4H), 2.38 (t, 2H, $J = 7.0$ Hz), 1.77−1.56 (m, 4H). Anal. ($C_{24}H_{29}N_5O_2$·0.5 H_2O) C, H, N.

Pharmacological Methods. Receptor Binding Assays. The affinity of compounds for dopamine receptors were determined in a total volume of 2 mL containing 0.1 nM [^{3}H]-spiperone and 0.3−1.0 mg of protein of rat striatal membranes per milliliter. Assay buffer was 50 mol/L Tris-HCl, pH 7.1, 120 mmol/L NaCl, 5 mmol/L KCl, 1 mmol/L $CaCl_2$, 1 mmol/L $MgCl_2$, 50 mmol Tris/HCl, pH 7.7, and 0.1% ascorbic acid. Incubations were carried out at 37 °C for 15 min and terminated by rapid filtration (Whatman GF/B) and three washes with ice-cold buffer. Nonspecific binding was determined in the presence of 1 mmol/L (+)-butaclamol.[17]

Radioligand Binding Assay at Rat Hippocampus 5-HT$_{1A}$ Serotonergic Receptors. The method was adapted from Cossery et al.[26] Rat hippocampus membranes (0.2 mg protein/tube) were incubated with 0.5 nM [^{3}H]-8-OH-DPAT in a total volume of 0.5 mL at 25 °C for 30 min. Nonspecific binding was determined in the presence of 1 μM serotonin.

Stimulation of [^{35}S]GTPγS binding at Cloned 5-HT$_{1A}$ Receptors. The effects of different compounds tested on [^{35}S]-GTPγS binding were evaluated according to a method of Newman-Tancredi et al.[19] with modifications. Membranes of CHO cells stably expressing the recombinant human 5-HT$_{1A}$ receptor were obtained from NEN (catalog no. CRM035, GenBank no. X13556). The membranes were stored at −70 °C. Prior to use, membranes were thawed and rehomogenized in assay buffer ($MgCl_2$, NaCl, and EDTA in Tris-HCl, pH 7.4). Membranes (~10 μg of protein) were incubated at 37 °C for 30 min (shaking water bath) in duplicate in a total volume of 800 μL of buffer containing $MgCl_2$ (3 mM), NaCl (120 mM), EDTA (0.2 mM), GDP (10 μM), [^{35}S]GTPγS (0.1 nM), Tris (50 mM), and test compounds. Prior to addition to the incubation mixture, the test compounds were dissolved in twice distilled water. DMSO was used to aid in solubilizing certain compounds. Nonspecific binding was defined with 0.1 μM GTPγS. 5-HT was tested as standard in each experiment at concentrations of 100, 30, and 10 nM. Experiments were terminated by rapid filtration through Whatman GF/B filters using a Brandel cell harvester. Subsequently, the filters were rinsed twice with 5 mL of ice-cold Tris-HCl and placed in scintillation vials. Radioactivity was extracted in 4 mL of scintillation fluid (Ultima Gold, Packard Instruments, Frankfurt, Germany) and determined by liquid scintillation counting. Binding isotherms were analyzed by nonlinear regression. Agonist efficacy (=E_{max}) is expressed relative to that of 5-HT (=100%), which was tested at a maximally active concentration (0.1 mM) in each experiment. EC_{50} values were defined as the concentration of the compound at which 50% of its own maximal stimulation was obtained.

Ultrasonic Vocalization Test. Male rats weighing 180−280 g from Charles River (Sulzfeld, Germany) were used. Ultrasonic vocalization was measured in a sound-attenuated test chamber (W 24 cm, L 22 cm, H 22 cm) with a grid floor for delivery of foot shock (scrambled shock of 0.2 mA for 0.5 s, shocker Getra BN 2002). Ultrasonic vocalization was recorded (microphone 4004, Bruel and Kjær) and processed by an interface (developed at Merck KGaA, Darmstadt) to select 22 ± 4 kHz signals and to digitize the resulting signals for automatic processing in a personal computer. In a priming phase, each rat was placed in the test chamber. After a 2 min time period, a series of at most 10 shocks (trials), 1.8 mA for 0.3 s, separated by 20 s shock-free intervals, was delivered via the grid floor of the test chamber. In the shock-free intervals the occurrence of ultrasonic vocalization was automatically recorded, and the duration of ultrasonic vocalization was calculated immediately. The priming session was terminated either when the rat constantly vocalized at least for 10 s on three consecutive trials or after the tenth trial. Rats that did not respond with ultrasonic vocalization on three consecutive trials were excluded from further testing. In the actual test performed on the next day, each rat received five initial shocks (1.8 mA for 0.3 s, separated by 20 s shock-free intervals) in the test chamber, and the duration of ultrasonic vocalization was recorded during the following 3 min period. Animals were tested 2 h after administration of compounds. ID_{50} values (=calculated dose for half-maximal inhibition of ultrasonic vocalization) were determined from the dose−response curves.

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Supporting Information Available: Spectral data, elemental analyses, and melting points for compounds **1** and **10**−**59**. This material is available free of charge via the Internet at http://pubs.acs.org.

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