5-HT Reuptake Inhibitors with 5-HT$_{1B/1D}$ Antagonistic Activity: A New Approach toward Efficient Antidepressants

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Received October 14, 1998

As part of our research program toward new, potential antidepressants, a series of unsymmetrical ureas has been prepared and evaluated as 5-HT reuptake inhibitors with 5-HT$_{1B/1D}$ antagonistic activities. The design of these compounds was based on coupling of various indole derivatives, previously shown to inhibit 5-HT reuptake, to three different aniline moieties, which are part of known 5-HT$_{1B/1D}$ ligands. Binding experiments in rat frontal cortex using [^{125}I]iodocyanopindolol, in calf striatum using [^{3}H]5-HT, and in rat hippocampus using [^{3}H]8-OH-DPAT as radioligands, respectively, revealed significantly higher affinity at the 5-HT$_{1B}$ receptor as compared to the affinities for the 5-HT$_{1A}$ and 5-HT$_{1D}$ receptors for a number of compounds, among them 4-(5-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (**5**), the corresponding 4-fluoro-1*H*-indol-3-yl analogue **21a,** and the corresponding 6-fluoro-1*H*-indol-3-yl analogue **21b**. Conformational restriction of the aniline moiety in **5** only slightly enhanced the 5-HT$_{1B}$ affinity, whereas introduction of an aniline moiety with higher conformational flexibility resulted in a less potent 5-HT$_{1B}$ receptor ligand as compared to **5**. The functional 5-HT$_{1B/1D}$ antagonistic activity was investigated using the rabbit saphenous vein model as well as the [^{3}H]5-HT release from guinea pig cortical slices. All new compounds tested in the rabbit saphenous vein model were shown to antagonize the sumatriptan-evoked contractile responses with pA_2 values ranging from 7.3 to 8.7. These observations were consistent with the results of the cortical slice model, in which the ureas were found to block the sumatriptan-induced inhibition of potassium-evoked [^{3}H]5-HT release. The 5-HT reuptake inhibition of the ureas determined in rat brain synaptosomes was found to be either increased or decreased as compared to the uncoupled indole derivatives indicating that the reuptake inhibition shown by the ureas is not only due to the indole part but also affected by the aniline moiety of the molecule. Among this series of compounds described the ureas **5**, **21a,** and **21b** seem to be the most interesting candidates showing both 5-HT reuptake inhibition and 5-HT$_{1B/1D}$ antagonism in vitro. This dual pharmacological profile should in theory lead to a pronounced enhancement in serotonergic neurotransmission and consequently to a more efficient treatment of depression.

Introduction

Serotonin (5-HT, **1**; Chart 1), a biogenic amine neurotransmitter with diverse physiological actions in both the central and peripheral nervous systems, operates through various distinct membrane receptors.[1−4] Disturbances in the central serotonin system have been associated with the pathogenesis of depression, and the antidepressant effect of the selective 5-HT reuptake inhibitors (SSRIs) is believed to be due to an enhancement of postsynaptic 5-HT levels.[5−11] Although SSRIs are effective in the treatment of depression, clinical improvement is first obtained after several weeks. Thus, the delayed onset of therapeutic action of SSRIs needs to be improved.[12]

One of the hypotheses proposed to explain the delayed onset of the antidepressant action of SSRIs is the time required for desensitization of somatodendritic 5-HT$_{1A}$ receptors and terminal 5-HT$_{1B/1D}$ autoreceptors.[8,9,11] The terminal 5-HT$_{1B/1D}$ autoreceptors modulate the 5-HT release and are inhibitory such that agonists decrease extracellular 5-HT.[13,14] SSRIs lead to an increase in 5-HT levels, and the extracellular 5-HT counteracts the desired increase by activation of terminal 5-HT$_{1B/1D}$ receptors resulting in a decreased 5-HT release. Thus, the therapeutic action of SSRIs is believed to set in after desensitization of the terminal 5-HT$_{1B/1D}$ receptors. However, blockade of terminal 5-HT$_{1B/1D}$ receptors by selective antagonists would in theory prevent the initial decrease in 5-HT release.[12,15] It is therefore anticipated that coadministration of a SSRI and a 5-HT$_{1B/1D}$ antagonist would lead to a potentiation of the SSRI effect and produce a large increase in extracellular 5-HT concentrations. As a consequence, the time of onset of therapeutic action would be diminished and the clinical efficacy in the treatment of depressive disorders improved.[12,14] However the role of 5-HT$_{1B/1D}$ receptors in depression is still not clear and needs further evaluation.

GR 127935 (**2a**; Chart 1) has been reported as the first example of a selective 5HT$_{1D/1B}$ antagonist.[16] However, later investigations have shown that **2a** acts as a partial agonist at human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.[17]

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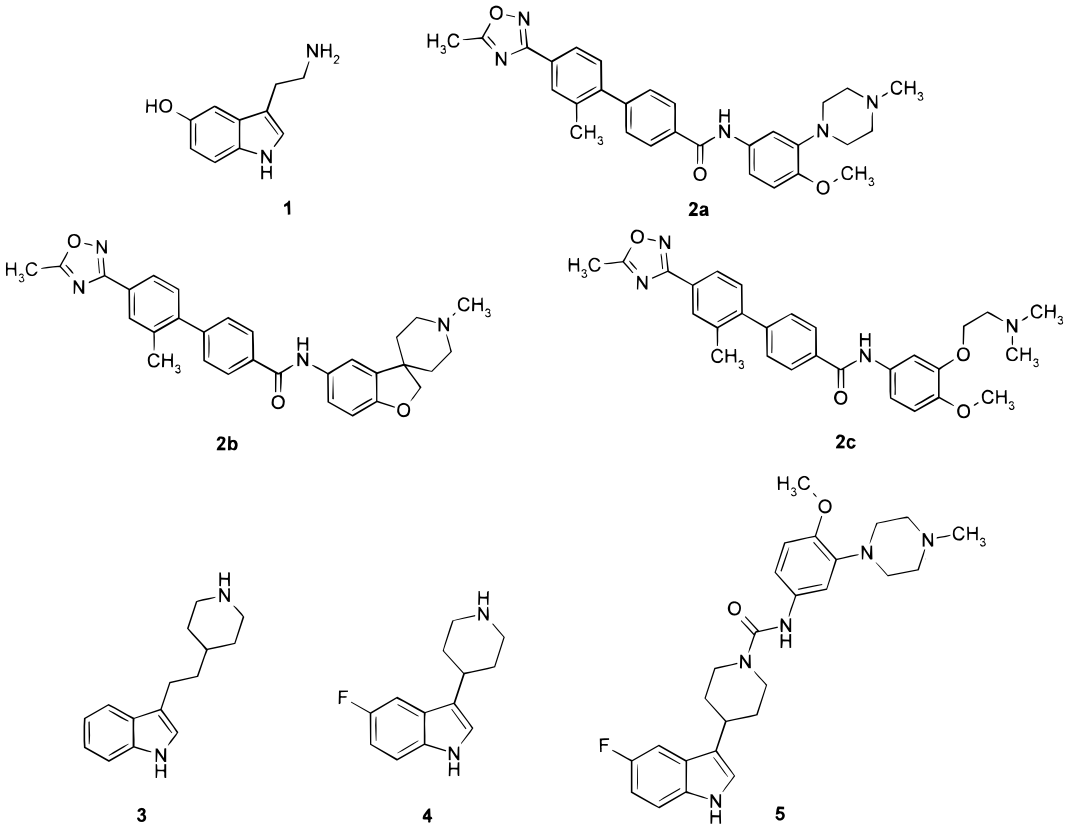
10.1021/jm9811054 CCC: $19.00
Published on Web 02/29/2000

Chart 1. Chemical Structures of Serotonin (**1**), the Partial 5-$HT_{1B/1D}$ Agonist GR 127935 (**2a**), the Inverse 5-HT_{1B} Agonist **2b**, the Partial 5-HT_{1B} Agonist **2c**, the 5-HT Reuptake Inhibitors Indalpine (**3**) and **4**, and the Lead Structure **5**



Interestingly, two structurally closely related analogues of **2a**, **2b** and **2c** (Chart 1), have recently been identified as an inverse agonist and a partial agonist for the 5-HT_{1B} receptor, respectively, both with significant selectivity over the 5-HT_{1D} receptor.[18]

Microdialysis data published for **2a** have been controversial. Thus, local perfusion of **2a** into the guinea pig frontal cortex increased 5-HT levels whereas 5-HT levels were decreased after ip administration.[19] In a microdialysis study performed by Rollema et al.,[14] combined sc administration of **2a** and the SSRI sertraline resulted in a pronounced, long-lasting increase in 5-HT levels in guinea pig hypothalamus indicating that **2a** potentiates the effects of SSRIs on terminal 5-HT levels and enhances extracellular 5-HT concentration more effectively when 5-HT tone is increased.[14] Instead of combining a SSRI with a 5-$HT_{1B/1D}$ antagonist to potentiate the postsynaptic 5-HT level, our research program directed toward new, efficient, and fast-acting antidepressive drugs has aimed at compounds with a dual pharmacological profile showing both 5-HT reuptake inhibition and 5-$HT_{1B/1D}$ antagonism within a single molecule.

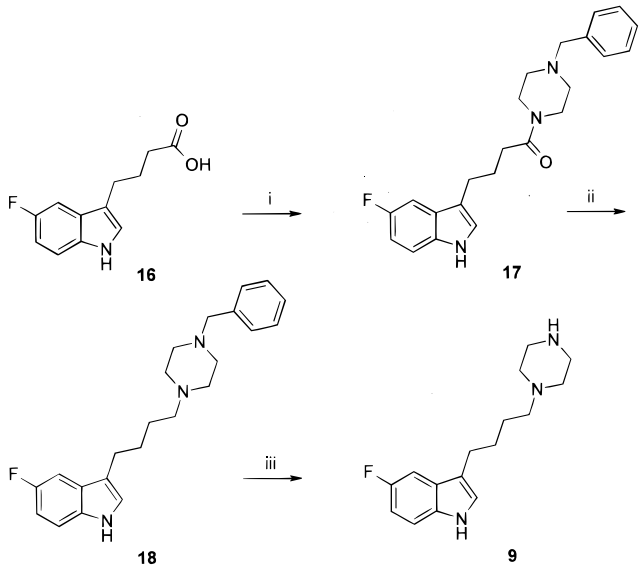
Many compounds of various structures have been described as selective inhibitors of 5-HT reuptake, among them 3-(alkylpiperidin-4-yl)indoles (e.g. indalpine, **3**; Chart 1).[20] In connection with our previous work in the field of antidepressants we have identified a number of substituted 4-(indol-3-yl)piperidines such as **4** (Chart 1), which were shown to act as potent inhibitors of 5-HT reuptake.

Aiming at compounds with a mixed pharmacological profile containing both 5-HT reuptake inhibition and 5-$HT_{1B/1D}$ antagonistic properties, we have coupled structural moieties believed to induce 5-$HT_{1B/1D}$ antagonism to the above-mentioned 4-(indol-3-yl)piperidines, inhibiting 5-HT reuptake. Coupling of 4-(5-fluoro-*1H*-indol-3-yl)piperidine (**4**) to the arylpiperazine moiety of **2a** resulted in the urea **5** (Chart 1) which was found to inhibit [^{3}H]5-HT uptake in rat brain synaptosomes and to have affinity for the 5-HT_{1B} receptor (Table 2). Using **5** as a lead structure this publication reports on the synthesis and the in vitro pharmacology of a series of new indole derivatives. Similar ureas have been reported earlier.[34] The pharmacological characterization includes binding studies at the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} receptor sites − in rat frontal cortex using [^{125}I]-iodocyanopindolol, in calf striatum using [^{3}H]5-HT, and in rat hippocampus using [^{3}H]8-OH-DPAT as radioligands, respectively. [^{3}H]5-HT release experiments in guinea pig cortex slices as well as the determination of the effect on sumatriptan-induced contractile responses in rabbit saphenous vein were performed to study the 5-$HT_{1B/1D}$ antagonistic activity in vitro. The [^{3}H]5-HT reuptake inhibition was determined in rat brain synaptosomes.

Results and Discussion

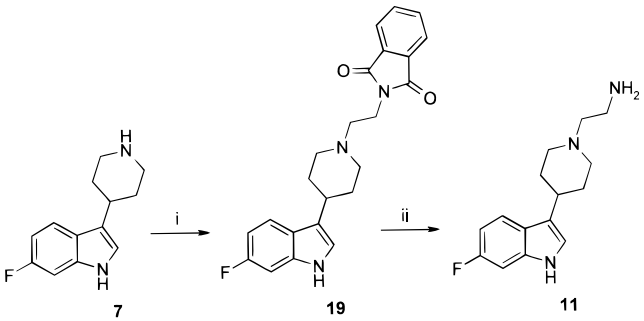
Chemistry. The 4-(indol-3-yl)piperidines (**4**, **6**, **7**, **13**−**15**) and the 3-(indol-3-yl)pyrrolidine (**10**) (Table 1) were obtained according to a published method by condensation of the respective indole with 1-benzyl-4-piperidone or 1-benzyl-3-pyrrolidone in alkaline medium, followed by hydrogenation and *N*-debenzylation.[21] The carboline derivative **12**,[22] indalpine **(3),**[20] and tryptamine **(8)**[32] were prepared as described before.

Scheme 1[a]



[a] (i) 1-Benzylpiperazine, CDI; (ii) sodium bis(2-methoxyethoxy)-aluminum dihydride; (iii) H_2, Pd−C 5%.

Scheme 2[a]



[a] (i) *N*-(2-Bromoethyl)phthalimide; (ii) hydrazine hydrate.

The piperazine analogue **9** was prepared from **16**[23] by acylation with 1-benzylpiperazine using 1,1′-carbonyldiimidazole (CDI) as a coupling reagent to give the amide **17** in 60% yield (Scheme 1). Reduction of the amide by treatment with sodium bis(2-methoxyethoxy)-aluminum dihydride resulted in 85% of **18**, which was *N*-debenzylated to give **9** in 73% yield.

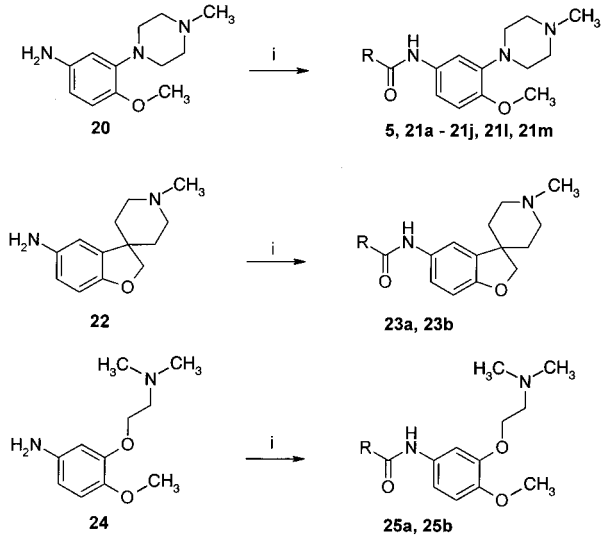
The piperidine analogue **11** was synthesized by alkylation of **7** with commercially available *N*-(2-bromoethyl)phthalimide to give **19** in 80% yield. Treatment of **19** with hydrazine resulted in 92% of **11** (Scheme 2).

The arylpiperazine moiety **20** of GR 127935 (**2a**)[24] as well as the conformationally restricted analogue **22**[18] and the aniline **24**[18] were synthesized as described before.

The unsymmetrical ureas **5**, **21a**−**21j**, **21m**, **23a**, **23b**, **25a,** and **25b** were prepared by treatment of the anilines **20**, **22,** and **24**, respectively, with CDI in the presence of triethylamine (TEA) to give an intermediate which upon addition of the respective indole (Table 1) gave the ureas in moderate to good yields (Scheme 3 and Table 2). Compound **21l** was obtained after hydrogenation of the respective benzyl derivative **21k.**

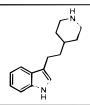
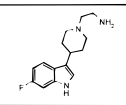
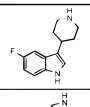
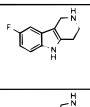
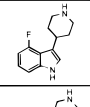
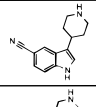
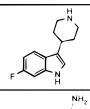
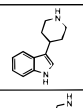
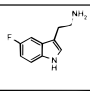
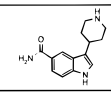
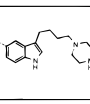
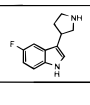
Biology. The binding affinities for the 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1A}$ receptor sites were determined in rat frontal cortex using [^{125}I]iodocyanopindolol,[25] in calf striatum using [^{3}H]5-HT,[26] and in rat hippocampus using [^{3}H]8-OH-DPAT[27] as radioligands, respectively (Table 2). The 5-HT$_{1B/1D}$ antagonist potency was evaluated in vitro by measuring the effect on the sumatriptan-induced contractile response of rabbit saphenous vein (RSV)[28] and by determining the extent of antagonism against sumatriptan-induced inhibition of potassium-evoked [^{3}H]5-HT release in slices of guinea pig cortex (Table 2).[29] The in vitro inhibitory effects of the new compounds on 5-HT reuptake were measured using rat brain synaptosomes (Tables 1 and 2).[30]

Scheme 3[a]



[a] (i) (1) CDI, TEA, (2) **3**−**15** and 5-benzyloxytryptamine, TEA.

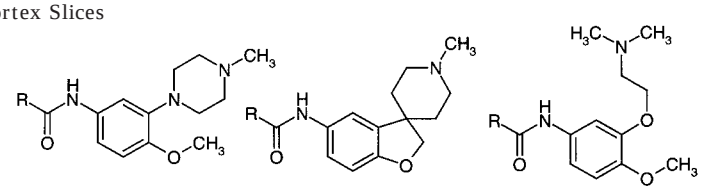
Table 1. 5-HT RUI in Rat Brain Synaptosomes

Compd	Structure	5-HT RUI[a] IC$_{50}$ (nM)	Compd	Structure	5-HT RUI[a] IC$_{50}$ (nM)
3		1 ± 0.04	**11**		11 ± 2
4		55 ± 8	**12**		> 100
6		60 ± 6	**13**		58 ± 2
7		20 ± 0.3	**14**		60 ± 10
8		130 ± 4	**15**		> 100
9		0.15 ± 0.05	**20**		>1000
			22		>1000
10		45 ± 2	**24**		>1000

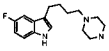
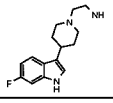
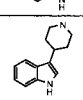
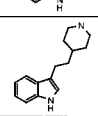
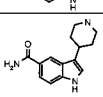
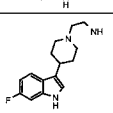
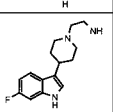
[a] n = 2−3.

Receptor Binding. The indole analogues **3**−**4** and **6**−**15** (Table 1) were inactive in the 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1A}$ receptor binding assays (results not shown). The affinities for the 5-HT$_{1B}$ receptor of the ureas **5**, **21a**−**21j**, **21l**, **21m**, **23a**, **23b**, **25a,** and **25b** ranged from low to modest affinities, none of the new compounds being more potent than **2a** and **2b** (Table 2). In the series of

Table 2. Receptor Binding Affinities at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} Receptors, 5-HT RUI in Rat Brain Synaptosomes, Inhibitory Activities on Sumatriptan-Induced Contractile Responses in RSV, and Antagonism of Sumatriptan-Induced Inhibition of K^+-Evoked [^{3}H]5-HT Release in Guinea Pig Cortex Slices



21 23 25

Compd	R	Receptor Binding, IC_{50} (nM)[a] 5-HT_{1D}	5-HT_{1B}	5-HT_{1A}	5-HT RUI[a] IC_{50} (nM)	RSV app. pA_2	Release[b] % (300 nM)
2a		53 ± 24	1.6 ± 0.7	360 ± 75	1000	9.4[c]	114 ± 12
2b		>1000	2.1 ± 1.1	>1000	>1000	N.T.	134 ± 14
5		233 ± 33	85 ± 12	367 ± 67	21 ± 5	7.8	151 ± 18
21a		300 ± 0	50 ± 6	300 ± 58	65 ± 4	8.7	145 ± 36
21b		200 ± 0	80 ± 12	667 ± 145	49 ± 1	7.6	169 ± 8
21c		167 ± 33	63 ± 20	27 ± 9	387 ± 8	7.7	134 ± 36
21d		367 ± 67	77 ± 15	50 ± 10	0.7 ± 0.05	7.7	120 ± 15
21e		233 ± 33	233 ± 33	100 ± 0	106 ± 6	N.T.	N.T.
21f		200 ± 0	233 ± 33	160 ± 40	1.9 ± 0.3	N.T.	N.T.
21g		667 ± 120	567 ± 13	>800	469 ± 15	N.T.	N.T.
21h		400 ± 0	267 ± 88	233 ± 67	1.9 ± 0.06	8.0	167 ± 15
21i		233 ± 33	50 ± 12	400 ± 100	200 ± 11	7.7	127 ± 4
21j		200 ± 0	120 ± 40	>300	10 ± 10.8	7.7	121 ± 5
21l		200 ± 0	467 ± 33	57 ± 3	314 ± 54	N.T.	N.T.
21m		100 ± 0	113 ± 43	17 ± 3	472 ± 14	7.8	217 ± 18
23a		900	23 ± 3	>200	0.2 ± 0.05	7.3	125 ± 11
23b		900	300 ± 58	700 ± 115	2.2 ± 0.25	N.T.	N.T.
25a		>1000	633 ± 145	>500	4.0 ± 0.49	N.T.	N.T.
25b		433 ± 33	133 ± 33	233 ± 33	1.2 ± 0.2	N.T.	N.T.

[a] $n = 3–5$. [b] $n = 3–4$. N.T. = not tested.

ureas containing the arylpiperazine **20,** the compounds **5**, **21a**−**21d**, **21i**, **21j**, and **21m** were shown to have IC_{50} values of 50−120 nM in the 5-HT$_{1B}$ binding assay. The substitution pattern of the indole in **5**, **21a,** and **21b** did not seem to play a role in the 5-HT$_{1B}$ affinity. However, replacement of the 5-fluoro substituent in **5** by a cyano group lowered the 5-HT$_{1B}$ receptor affinity of **21h,** whereas replacement by a carboxamido group to give **21m** decreased selectivity versus the 5-HT$_{1A}$ receptor. Replacement of the piperidine of **5** by pyrrolidine to give **21e** led to a decrease in 5-HT$_{1B}$ affinity. A similar effect was observed upon conformational restriction of the 4-(5-fluoro-1*H*-indol-3-yl)piperidine ring system of **5** resulting in **21g**. Decreasing the conformational flexibility of the arylpiperazine moiety **20** did not change or only slightly improved the 5-HT$_{1B}$ affinity (compare **21f**/**23b** and **5**/**23a,** respectively). Replacement of **20** by **24** resulted in a less potent 5-HT$_{1B}$ ligand and a ligand with slightly higher 5-HT$_{1B}$ affinity (compare **5**/**25a** and **21f**/**25b,** respectively). None of the compounds tested displayed significant affinity for the 5-HT$_{1D}$ receptor. On the other hand, the tryptamines **21c** and **21l** as well as the piperazine **21d** and the piperidine **21m** turned out to be quite potent ligands for the 5-HT$_{1A}$ receptor sites, although attempts to determine any agonistic or antagonistic activity of **21m** in a functional 5-HT$_{1A}$ system[33] (data not shown) failed. The most promising compounds with both high affinity at the 5-HT$_{1B}$ receptor and some selectivity over the 5-HT$_{1A}$ and 5-HT$_{1D}$ receptors were **5**, **21a**, **21b**, **21i**, **21j,** and **23a**.

Rabbit Saphenous Vein (RSV). The results of the RSV model are shown in Table 2. All ureas tested antagonized the contractile responses evoked by sumatriptan although with lower potency than **2a**. The level of 5-HT$_{1B/1D}$ antagonistic activity displayed by the new compounds was shown to be modest but significant, the apparent pA_2 values ranging from 7.3 to 8.7. None of the new compounds showed intrinsic activity in this model, neither did **2a** nor **2b**.

[^{3}H]5-HT Release Test. The results displayed in Table 2 demonstrate that all compounds tested in this model were able to antagonize the sumatriptan-induced inhibition of potassium-evoked [^{3}H]5-HT release from guinea pig cortex slices. The fluoro analogues **5**, **21a**, and **21b**, the 5-cyano analogue **21h,** and the carboxamide analogue **21m** turned out to be the most potent antagonists enhancing the 5-HT release by 145−217% as compared to the release observed with sumatriptan in the absence of test compound. Interestingly, all ureas tested in the release model showed equal or better potency than the reference compounds **2a** and **2b**. The new compounds displayed no instrinsic activity on potassium-induced [^{3}H]5-HT release in the absence of sumatriptan (results not shown), which is consistent with the results obtained from the RSV model.

[^{3}H]5-HT Reuptake Inhibition (5-HT RUI). The results of the rat brain synaptosomes experiments are summarized in Tables 1 and 2. In the series of the substituted 4-(indol-3-yl)piperidines, **4**, **6**, **7**, **13**, **14,** and the pyrrolidine derivative **10** were equally potent in inhibiting the reuptake of 5-HT (Table 1). However, the carboxamido-substituted compound **15** as well as the anilines **20**, **22,** and **24** were found to be inactive in this test.

It is obvious from the results obtained that the distance between the indole moiety and the basic nitrogen atom is critical to the activity as a 5-HT reuptake inhibitor. Thus, the compounds **3** and **9** displayed improved 5-HT inhibitory activity as compared to the 3-(piperidin-4-yl)indoles. Conformational restriction of **4** resulted in a decrease of 5-HT reuptake inhibition, as demonstrated by **12**.

Coupling of the indole moieties **3**, **4,** and **6**−**15** to **20** led to an increased activity as 5-HT reuptake inhibitors for the compounds **5**, **21f**, and **21h** as compared to the corresponding indoles (Tables 1 and 2). In contrast, the compounds **21a**−**21c**, **21e**, **21i,** and **21j** were shown to be weaker 5-HT reuptake inhibitors than the corresponding indoles.

Compounds in which the arylpiperazine moiety **20** was replaced by **22** and **24**, respectively, displayed higher potency as compared to the uncoupled indoles (Tables 1 and 2). In addition, the compounds **23a** and **25a** turned out to be more potent 5-HT reuptake inhibitors than the analogue **5,** whereas **23b** and **25b** were equipotent to **21f**.

These observations indicate that the indole part of the molecule may not be sufficient to account for the 5-HT reuptake inhibition and that the mode of interaction of the indole part with the 5-HT reuptake site probably is modulated by the nature of the aniline moiety.

Conclusion

As mentioned in the Introduction coadministration of a SSRI and a 5-HT$_{1B/1D}$ receptor antagonist should in theory immediately increase serotonergic neurotransmission avoiding the time required for desensitization of the terminal 5-HT$_{1B/1D}$ autoreceptors and so decreasing the time of onset of antidepressive action. Instead of coadministration of two separate molecules to improve the delayed onset of therapeutic action, this new approach describes the development of a series of novel compounds with mixed pharmacological profiles showing both 5-HT reuptake inhibition and 5-HT$_{1B/1D}$ receptor antagonism within a single molecule. The new compounds contain various indole moieties shown to inhibit 5-HT reuptake and the aniline part of **2a**, **2b,** and **2c** (**20, 22**, and **24**, respectively) believed to introduce 5-HT$_{1B/1D}$ receptor activity. Coupling of the indole moieties **3**, **4**, and **6**−**15** to the anilines **20, 22**, and **24**, respectively, resulted in an increased or decreased 5-HT reuptake inhibition indicating that the 5-HT reuptake inhibitory activity is not only due to the indole part of the molecule but also modulated by the aniline moieties **20, 22,** and **24**, although they were not inhibitory by themselves (Table 1). On the other hand, combination of the different indole moieties with the anilines **20, 22,** and **24** diminished the activity in the 5-HT$_{1B}$ binding assay in all cases as compared to **2a** and **2b**. However, the ureas **5**, **21a**, **21b**, **21i**, **21j**, and **23a** still maintained a significant affinity for the 5-HT$_{1B}$ receptor and showed some selectivity versus the 5-HT$_{1A}$ and 5-HT$_{1D}$ receptors.

In the RSV test the new compounds inhibited the constrictor effects of sumatriptan indicating 5-HT$_{1B/1D}$ receptor antagonistic properties. In guinea pig cortical slices all ureas tested were found to block the sumatriptan-induced inhibition of [^{3}H]5-HT release.

The 5-HT_{1B} receptor binding affinities do not always correlate to the results obtained in the rabbit saphenous vein preparation and in the [^{3}H]5-HT release model. The differences between the function of the 5-$HT_{1B/1D}$ receptors in rat frontal cortex, rabbit saphenous vein, and guinea pig cortex still need to be evaluated. In addition the affinity to other 5-HT receptor subtypes such as 5-HT_{1F} and 5-HT_2 (not tested) could disturb the correlation of the results obtained in the functional models and the binding data.

Interestingly, the ureas antagonized the inhibition of [^{3}H]5-HT release with equal or better potency than **2a** or **2b,** although having weaker affinity to the 5-HT_{1B} receptor. This may be due to the additional 5-HT reuptake inhibition of these compounds. The high potency of **21m** in the release model may be due to the combination of 5-HT_{1B} and 5-HT_{1A} effects, but this still has to be evaluated further.

Among the new compounds presented the ureas **5**, **21a,** and **21b** appear to be the most promising new 5-HT reuptake inhibitors with 5-$HT_{1B/1D}$ antagonistic activity. To our knowledge, this is the first report describing compounds which contain these activities within a single molecule. Their mixed profile should facilitate serotonergic transmission, and their further pharmacological characterization will be of primary importance to evaluate the antidepressive potential of these novel compounds.

Experimental Section

Chemistry. General Procedures. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses are within ±0.4% of the calculated values, unless otherwise stated. Analytical HPLC was conducted on a LiChrospher RP Select B column 5 μm (4 mm i.d. × 250 mm) using a gradient of water (with 0.1% TFA) and acetonitrile (with 0.08% TFA) for elution, with UV monitoring at 220 nm. ^{1}H NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz using DMSO-d_6 as solvent. Unless otherwise stated, chemical shift values (δ) are expressed in ppm relative to TMS. The following abbreviations are used for multiplicity of NMR signals: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet. Mass spectra were obtained on a VG-70 SE spectrometer from VG-Instruments to get molecular weight information ($(M + H)^+$) for FAB-MS and on a 70-70E spectrometer from VG-Instruments to get molecular weight information ($(M)^+$) for EI-MS. Drying of organic phases was performed using Na_2SO_4. Column chromatography (CC) and TLC were performed on silica gel 60 (70−230 mesh, Merck) and silica gel F_{254} plates (Merck), respectively.

1-(4-Benzylpiperazin-1-yl)-4-(5-fluoro-1*H*-indol-3-yl)-butan-1-one (17). A solution of 4-(5-fluoro-1*H*-indol-3-yl)-butyric acid **(16)**[23] (20.0 g, 90.0 mmol) and carbonyldiimidazole (CDI) (14.6 g, 90 mmol) in THF (100 mL) was stirred for 1 h at room temperature. A solution of 1-benzylpiperazine (15.9 g, 90 mmol) in THF (50 mL) was added and stirring was continued for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in EtOAc (100 mL), washed with H_2O (2 × 100 mL), dried and evaporated. CC [eluent: EtOAc] gave **17** (20.4 g, 60%): mp 85−87 °C; ^{1}H NMR (DMSO-d_6) δ 10.81 (s, 1 H), 7.28 (m, 7 H), 7.16 (d, 1 H, J = 2.2 Hz), 7.86 (dt, 1 H, J = 8.8 Hz and J = 1.3 Hz), 3.49 (s, 2 H), 3.42 (d, 4 H, J = 12.0 Hz), 2.65 (t, 2 H, J = 8.0 Hz), 2.31 (m, 6 H), 1.87 (quintet, 2 H, J = 6.6 Hz); EI-MS $(M)^+$ m/z 380.

3-[4-(Benzylpiperazin-1-yl)butyl]-5-fluoro-1*H*-indole Dihydrochloride (18). To a solution of **17** (20.0 g, 53.0 mmol) in THF (350 mL) was added a 65% solution of sodium bis(2-methoxyethoxy)aluminum dihydride in toluene (43.0 mL, 132 mmol) dropwise at 5−10 °C in N_2 atmosphere. After stirring for 4 h at room temperature H_2O (40 mL) was added. The reaction mixture was filtered, evaporated, dissolved in EtOAc (300 mL), washed with H_2O (2 × 200 mL), dried and evaporated. Dissolution of the residue in acetone and addition of 1 M HCl in EtOH resulted in a precipitate which was collected and dried to give **18** (23.2 g, 85%): mp 233−235 °C; ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1 H), 7.65 (br s, 2 H), 7.44 (br s, 3 H), 7.29 (m, 3 H), 6.86 (dt, 1 H, J = 8.8 Hz and J = 2.0 Hz), 4.37 (br s, 2 H), 3.79−3.30 (m, 8 H), 3.17 (br s, 2 H), 2.69 (t, 2 H, J = 6.6 Hz), 1.72 (m, 4 H); FAB-MS ($(M + H)^+$) m/z 366.

5-Fluoro-3-(4-piperazin-1-ylbutyl)-1*H*-indole Oxalate (9). A solution of **18** (19.7 g, 44.9 mmol) in MeOH (300 mL) was hydrogenated using Pd−C 5% (3.5 g) as catalyst. Filtration, evaporation and CC [eluent: CH_2Cl_2−MeOH (9:1)] gave an oily residue. Upon dissolution in acetone and addition of a solution of oxalic acid in acetone a precipitate formed. The precipitate was collected and dried to give **9** (12.0 g, 73%): mp 175−176 °C; ^{1}H NMR (DMSO-d_6) δ 10.84 (s, 1H), 8.75 (br s, 1 H), 7.29 (dd, 1 H, J = 11.0 Hz and J = 2.4 Hz), 7.21 (dd, 1 H, J = 11.0 Hz and J = 2.2 Hz), 7.12 (d, 1 H, J = 1.5 Hz), 6.87 (dt, 1 H, J = 8.8 Hz and J = 2.0 Hz), 3.16 (m, 4 H), 2.78 (m, 4 H), 2.66 (t, 2 H, J = 6.6 Hz), 2.59 (t, 2 H, J = 6.6 Hz), 1.61 (m, 4 H); EI-MS $(M)^+$ m/z 275.

2-{2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl}-isoindole-1,3-dione Hydrobromide (19). A mixture of 4-(6-fluoro-1*H*-indol-3-yl)piperidine (**7**) (21.8 g, 100 mmol) and *N*-(2-bromoethyl)phthalimide (25.4 g, 100 mmol; purchased from Merck #820178) in 500 mL acetonitrile was stirred under reflux for 48 h. The crystalline precipitate formed was collected and dried to give **19** (33.2 g, 80%): ^{1}H NMR (DMSO-d_6) δ 10.81 (s, 1 H), 7.85 (d, 1 H, J = 8.8 Hz), 7.56 (m, 3 H), 7.33 (br s, 1 H), 7.06 (m, 2 H), 6.82 (t, 1 H, J = 8.7 Hz), 4.64 (br s, 1 H), 4.35 (t, 2 H, J = 7.5 Hz), 3.98 (t, 2 H, J = 7.5 Hz), 3.20−2.65 (m, 5 H), 1.68 (br s, 3 H); FAB-MS ($(M + H)^+$) m/z 393.

2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl)ethylamine (11). A mixture of **19** (33.2 g, 70 mmol) and hydrazine hydrate (5.0 mL, 100 mmol) in MeOH (500 mL) was stirred under reflux for 2 h. After cooling the reaction mixture was filtered and evaporated. Dissolution of the residue in 1 M NaOH (300 mL), extraction with EtOAc (3 × 300 mL), drying and evaporation gave **11** (16.8 g, 92%): mp 165−166 °C; ^{1}H NMR (DMSO-d_6) δ 10.91 (s, 1 H), 7.52 (dd, 1 H, J = 7.0 Hz and J = 3.5 Hz), 7.11 (m, 2 H), 6.82 (m, 1 H), 2.93 (d, 2 H, J = 13.7 Hz), 2.66 (t, 2 H, J = 7.0 Hz), 2.35 (t, 2 H, J = 7.0 Hz), 1.50−2.12 (m, 9 H); FAB-MS ($(M + H)^+$) m/z 262.

General Method for the Synthesis of Unsymmetrical Ureas. 4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-amide Hydrochloride Hydrate (5). A solution of 4-methoxy-3-(4-methylpiperazin-1-yl)aniline dihydrochloride (**20**)[24] (2.7 g, 9.2 mmol), TEA (4.6 mL, 32.2 mmol) and CDI (1.6 g, 10.1 mmol) in acetonitrile (100 mL) was stirred at room temperature for 4 h. A suspension of 4-(5-fluoro-1*H*-indol-3-yl)piperidine (**4**) (2.0 g, 9.2 mmol) and TEA (1.3 mL, 9.2 mmol) in acetonitrile (100 mL) was added and stirring was continued for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in EtOAc (100 mL), washed with H_2O (2 × 100 mL), dried and evaporated. The residue was dissolved in acetone (100 mL) and stirred with 1 M HCl. Collection of the precipitate followed by recrystallization (EtOH−Et_2O) gave **5** (2.2 g, 35%): mp 230−231 °C; ^{1}H NMR (DMSO-d_6) δ 11.18 (s, 1 H), 10.93 (s, 1 H), 8.35 (s, 1 H), 7.30 (d, 1 H, J = 9.0 Hz), 7.24 (d, 1 H, J = 10.0 Hz), 7.21 (d, 1 H, J = 2.1 Hz), 7.17 (1 H, s), 6.90 (d, 1 H, J = 9.0 Hz), 6.85 (d, 1 H, J = 10.0 Hz), 4.26 (d, 2 H, J = 12.0 Hz), 3.74 (s, 3 H), 3.55 (m, 4 H), 3.55−2.85 (m, 7 H), 2.78 (s, 3 H), 1.95 (d, 2 H, J = 12.1 Hz), 1.57 (m, 2 H); FAB-MS ($(M + H)^+$) m/z 466. Anal. ($C_{26}H_{32}FN_5O_2$·HCl·H_2O) C, H, N; Cl: calcd, 6.82%; found, 7.45%.

4-(4-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide Dihydrochloride (21a). Compound **21a** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 4-(4-fluoro-1*H*-indol-3-yl)piperidine (**6**) (895 mg, 4.1 mmol) in acetonitrile (75 mL).

CC [eluent: toluene−MeOH−TEA (7:2:1)] and preparation of the dihydrochloride followed by recrystallization (2-propanol−light petroleum) gave **21a** (640 mg, 30%): mp 205 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.68 (s, 1 H), 11.11 (s, 1 H), 8.33 (s, 1 H), 7.17 (m, 3 H), 7.05 (m, 1 H), 6.60 (d, 1 H, J = 8.8 Hz), 6.67 (dd, 1 H, J = 12.0 Hz and J = 9.0 Hz), 4.25 (d, 2H, J = 12.0 Hz), 3.73 (s, 3 H), 3.45 (d, 4 H, J = 11.0 Hz), 3.39−2.85 (m, 7 H), 2.55 (s, 3 H), 1.96 (d, 2 H, J = 11.1 Hz), 1.57 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 466. Anal. ($C_{26}H_{32}FN_5O_2$·2HCl) C, H, N; Cl: calcd, 13.17%; found, 12.30%.

4-(6-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide Dihydrate (21b). Compound **21b** was synthesized as described for **5** using **20**[24] (588 mg, 2.0 mmol), TEA (1.3 mL, 9 mmol), CDI (357 mg, 2.2 mmol) and 4-(6-fluoro-1*H*-indol-3-yl)piperidine (**7**) (437 mg, 2.0 mmol) in acetonitrile (50 mL). CC [eluent: toluene−MeOH−TEA (7:2:1)] followed by recrystallization (EtOAc−light petroleum) gave **21b** (126 mg, 14%): mp 135−137 °C; ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1 H), 8.23 (s, 1 H), 7.55 (m, 1 H), 7.10 (m, 3 H), 7.03 (s, 1 H), 6.83 (d, 1 H, J = 8.3 Hz), 6.72 (d, 1 H, J = 9.0 Hz), 4.25 (d, 2H, J = 12.1 Hz), 3.72 (s, 3 H), 2.92 (m, 7 H), 2.38 (br s, 4 H), 2.20 (s, 3 H), 1.92 (d, 2 H, J = 11.3 Hz), 1.57 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 466. Anal. ($C_{26}H_{32}FN_5O_2$·2H_2O) C, H; N: calcd, 14.22%; found, 13.70%.

1-[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Hemihydrate (21c). Compound **21c** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (3.3 mL, 22.6 mmol), CDI (730 mg, 4.5 mmol) and 5-fluorotryptamine hydrochloride **(8)**[32] (880 mg, 4.1 mmol) in acetonitrile (75 mL). Recrystallization (EtOAc−light petroleum) gave **21c** (1.27 g, 75%): mp 97−98 °C; ^{1}H NMR (DMSO-d_6) δ 10.91 (s, 1 H), 8.22 (s, 1 H), 7.32 (m, 2 H), 7.23 (d, 1 H, J = 2.2 Hz), 6.92 (m, 3 H), 6.75 (d, 1 H, J = 8.8 Hz), 5.95 (t, 1 H, J = 6.6 Hz), 3.69 (s, 3H), 3.40 (t, 2 H, J = 6.6 Hz), 2.94 (br s, 4 H), 2.80 (t, 2 H, J = 6.6 Hz), 2.43 (br s, 4 H), 2.20 (s, 3 H); FAB-MS ((M + H)$^+$) m/z 426. Anal. ($C_{23}H_{28}FN_5O_2$·0.5H_2O) C, H; N: calcd, 16.12%; found, 14.28%.

4-[4-(5-Fluoro-1*H*-indol-3-yl)butyl]piperazine-1-carboxylic Acid [4-Methoxy-3-(4-methyl-1-piperazin-1-yl)-phenyl]amide Dihydrochloride Hydrate (21d). Compound **21d** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (3.9 mL, 26.7 mmol), CDI (730 mg, 4.5 mmol) and 5-fluoro-3-(4-piperazin-1-ylbutyl)-1*H*-indole oxalate (**9**) (1.5 g, 4.1 mmol) in acetonitrile (75 mL). Preparation of the dihydrochloride followed by recrystallization (EtOH−Et_2O) gave **21d** (1.0 g, 42%): mp 220 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1 H), 8.59 (s, 1 H), 7.32 (m, 2 H), 7.25 (br s, 1 H), 7.14 (m, 2 H), 6.82 (d, 2 H, J = 8.2 Hz), 4.23 (br s, 6 H), 3.75 (s, 3H), 3.46 (br, 2 H), 3.40−2.93 (m, 10 H), 2.81 (s, 3 H), 2.70 (t, 2 H, J = 5.1 Hz), 1.88−1.60 (m, 4 H); FAB-MS ((M + H)$^+$) m/z 523. Anal. ($C_{29}H_{39}FN_6O_2$·2HCl·H_2O) H, Cl; C: calcd, 56.76%; found, 56.24%. N: calcd, 13.96%; found, 13.13%.

3-(5-Fluoro-1*H*-indol-3-yl)pyrrolidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (21e). Compound **21e** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (3.3 mL, 23.1 mmol), CDI (730 mg, 4.5 mmol) and (*R*,*S*)-3-(5-fluoro-1*H*-indol-3-yl)pyrrolidine (**10**) (987 mg, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc−MeOH−TEA (5:2:1)] followed by recrystallization (EtOAc−light petroleum) gave **21e** (1.0 g, 30%): mp 210−213 °C; ^{1}H NMR (DMSO-d_6) δ 10.97 (s, 1 H), 7.88 (s, 1 H), 7.35 (m, 2 H), 7.28 (d, 1 H, J = 2.2 Hz), 7.14 (m, 2 H), 6.91 (dt, 1 H, J = 8.8 Hz and J = 2.2 Hz), 6.76 (d, 1 H, J = 8.8 Hz), 3.93 (t, 1 H, J = 6.6 Hz), 3.73 (s, 3 H), 3.62 (m, 2 H), 3.55−3.25 (m, 2 H), 2.93 (br s, 4H), 2.45 (br s, 4 H), 2.30 (m, 1H), 2.23 (s, 3H), 2.10 (m, 1 H); FAB-MS ((M + H)$^+$) m/z 452. Anal. ($C_{25}H_{30}FN_5O_2$) C, H, N.

1-{2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl}-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Dihydrochloride Hydrate (21f). Compound **21f** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.6 mmol), CDI (730 mg, 4.5 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (**11**) (1.1 g, 4.1 mmol) in acetonitrile (75 mL). Collection of the precipitate, dissolution in acetone and preparation of the dihydrochloride gave **21f** (1.5 g, 61%): mp 189−192 °C; ^{1}H NMR (DMSO-d_6) δ 10.82 (s, 1 H), 8.39 (s, 1 H), 7.52 (t, 1 H, J = 6.6 Hz), 7.10 (d, 1 H, J = 8.8 Hz), 7.05 (s, 1 H), 6.98 (s, 1 H), 6.92 (d, 1 H, J = 8.8 Hz), 6.75 (m, 2 H), 5.93 (br s, 1 H), 3.70 (s, 3 H), 3.29 (br s, 2 H), 3.22 (m, 2 H), 2.95 (br s, 6 H), 2.74 (m, 1 H), 2.44 (br s, 4 H), 2.21 (s, 3 H), 2.12 (t, 2 H, J = 9.3 Hz), 1.95 (m, 2 H), 1.72 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 509. Anal. ($C_{28}H_{37}FN_6O_2$·2HCl·H_2O) C, H, Cl; N: calcd, 14.02%; found, 13.35%.

8-Fluoro-1,3,4,5-tetrahydropyrido[4,3-*b*]indole-2-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (21g). Compound **21g** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 8-fluoro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**12**)[22] (780 mg, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc−MeOH−TEA (5:2:1)] followed by recrystallization (EtOAc) gave **21g** (1.1 g, 61%): mp 243−245 °C; ^{1}H NMR (DMSO-d_6) δ 10.97 (s, 1 H), 8.60 (s, 1 H), 7.28 (dd, 1 H, J = 8.5 Hz and H = 4.4 Hz), 7.09 (m, 3 H), 6.86 (dt, 1 H, J = 8.8 Hz and J = 2.2 Hz), 6.77 (d, 1 H, J = 8.8 Hz), 4.60 (s, 2 H), 3.81 (t, 2H, J = 6.6 Hz), 3.73 (s, 3 H), 2.95 (br s, 4 H), 2.64 (m, 2 H), 2.45 (br s, 4 H), 2.23 (s, 3 H); FAB-MS ((M + H)$^+$) m/z 438. Anal. ($C_{24}H_{28}FN_5O_2$) C, H, N.

4-(5-Cyano-1*H*-indol-3-yl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide·0.25H_2O (21h). Compound **21h** was synthesized as described for **5** using **20**[24] (647 mg, 2.2 mmol), TEA (1.4 mL, 9.9 mmol), CDI (392 mg, 2.4 mmol) and 4-(5-cyano-1*H*-indol-3-yl)piperidine (**13**) (496 mg, 2.2 mmol) in acetonitrile (50 mL). CC [eluent: toluene−MeOH−TEA (7:2:1)] followed by recrystallization (acetonitrile−Et_2O) gave **21h** (100 mg, 10%): mp 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 11.44 (s, 1H), 8.23 (s, 1 H), 8.15 (s, 1 H), 7.49 (d, 1 H, J = 8.8 Hz), 7.38 (d, 1 H, J = 8.8 Hz), 7.33 (br s, 1 H), 7.05 (m, 2 H), 6.72 (d, 1 H, J = 9.0 Hz), 4.26 (d, 2 H, J = 12.5 Hz), 3.70 (s, 3 H), 3.32 (m, 3 H), 2.95 (m, 8 H), 2.20 (s, 3 H), 1.97 (m, 2 H), 1.55 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 489. Anal. ($C_{27}H_{32}N_6O_2$·0.25H_2O) C, H; N: calcd, 17.62%; found, 17.09%.

4-(3-Indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]piperidine-1-carboxamide Dihydrochloride (21i). Compound **21i** was synthesized as described for **5** using **20**[24] (1.8 g, 6.1 mmol), TEA (4.0 mL, 27.5 mmol), CDI (1.1 g, 6.7 mmol) and 4-(1*H*-indol-3-yl)piperidine (**14**) (1.2 g, 4.1 mmol) in acetonitrile (100 mL). CC [eluent: EtOAc−MeOH−TEA (5:2:1)] followed by preparation of the dihydrochloride gave **21i** (1.4 g, 44%): mp 203−205 °C; ^{1}H NMR (DMSO-d_6) δ 10.79 (s, 1 H), 8.35 (s, 1 H), 7.57 (d, 1 H, J = 8.8 Hz), 7.29 (d, 1 H, J = 8.8 Hz), 7.18 (m, 2 H), 7.11 (d, 1 H, J = 3.0 Hz), 7.06 (t, 1 H, J = 8.2 Hz), 6.97 (t, 1 H, J = 89.2 Hz), 6.85 (d, 1 H, J = 8.8 Hz), 4.24 (d, 2 H, J = 13.2 Hz), 3.75 (s, 3 H), 3.44 (d, 4 H, J = 13.2 Hz), 3.17 (q, 2 H, J = 9.0 Hz), 2.99 (m, 5 H), 2.75 (s, 3 H), 1.99 (d, 2 H, 13.2 Hz), 1.59 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 448. Anal. ($C_{26}H_{33}N_5O_2$·2HCl) C, H, N; Cl: calcd, 13.45%; found, 12.34%.

4-[2-(3-Indolyl)ethyl]-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide (21j). Compound **21j** was synthesized as described for **5** using **20**[24] (588 mg, 2.0 mmol), TEA (1.3 mL, 9.0 mmol), CDI (357 mg, 2.2 mmol) and indalpine (**3**)[20] (457 mg, 2.0 mmol) in acetonitrile (50 mL). Recrystallization (acetonitrile) gave **21j** (700 mg, 76%): mp 200−202 °C; ^{1}H NMR (DMSO-d_6) δ 10.68 (s, 1 H), 8.16 (s, 1 H), 7.50 (d, 1 H, J = 7.7 Hz), 7.33 (d, 1 H, J = 7.7 Hz), 7.07 (m, 4 H), 6.95 (t, 1 H, J = 7.8 Hz), 6,76 (d, 1 H, J = 8.8 Hz), 4.09 (d, 2 H, J = 13.2 Hz), 3.71 (s, 3 H), 2.94 (br s, 4 H), 2.74 (m, 4 H), 2.45 (br s, 4 H), 2.20 (s, 3 H), 1.76 (d, 2 H, J = 13.2 Hz), 1.67 (m, 2 H), 1.50 (m, 1 H),1.10 (m, 2 H); FAB-MS ((M + H)$^+$) m/z 476. Anal. ($C_{28}H_{37}N_5O_2$) C, H; N: calcd, 14.72%; found, 15.35%.

1-(2-(5-Benzyloxy-1*H*-indol-3-yl)ethyl)-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea·0.25H_2O (21k). Compound **21k** was synthesized as described for **5** using **20**[24] (1.8 g, 6.1 mmol), TEA (4.9 mL, 33.6 mmol), CDI (1.1 g, 6.7 mmol) and 5-benzyloxytryptamine (1.8 g, 6.1 mmol) in acetonitrile

(100 mL). CC [eluent: toluene−MeOH−TEA (7:2:1)] followed by recrystallization (EtOAc−light petroleum) gave **21k** (2.4 g, 77%): mp 153−154 °C; ^{1}H NMR (DMSO-d_6) δ 10.70 (s, 1 H), 8.24 (s, 1 H), 7.42 (m, 2 H), 7.38 (t, 2 H, J = 6.0 Hz), 7.30 (t, 1 H, J = 6.1 Hz), 7.20 (d, 1 H, J = 9.0 Hz), 7.15 (s, 1 H), 7.09 (s, 1 H), 6.99 (s, 1 H), 6.86 (d, 1 H, J = 8.8 Hz), 6.75 (m, 2 H), 5.92 (t, 1 H, J = 5.0 Hz), 5.05 (s, 2 H), 3.67 (s, 3 H), 3.42 (m, 3 H), 2.91 (s, 4 H), 2.80 (t, 2 H, J = 7.0 Hz), 2.39 (br s, 3 H), 2.15 (s, 3 H); MS (M^+) m/z 513. Anal. ($C_{30}H_{35}N_5O_3 \cdot 0.25H_2O$) C, H, N.

1-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Hemihydrate (21l). A solution of **21k** (1.1 g, 21. mmol) in MeOH (100 mL) was hydrogenated using Pd−C 5% (1.0 g) as catalyst. Filtration, CC [EtOAc−MeOH−TEA (5:2:1)] gave **21l** (200 mg, 25%): mp 140−142 °C; ^{1}H NMR (DMSO-d_6) δ 10.46 (s, 1 H), 8.55 (s, 1 H), 8.19 (s, 1 H), 7.12 (d, 1 H, J = 8.8 Hz), 7.05 (d, 1 H, J = 3.0 Hz), 6.97 (d, 1 H, J = 3.0 Hz), 6.91 (dd, 1 H, J = 8.9 Hz and J = 3.1 Hz), 6.87 (d, 1 H, J = 3.0 Hz), 6.78 (d, 1 H, J = 8.9 Hz), 6.57 (dd, 1 H, J = 8.7 Hz and J = 3.3 Hz), 5.93 (t, 1 H, J = 6.6 Hz), 3.70 (s, 3 H), 3.43 (d, 4 H, J = 13.2 Hz), 2.91 (br s, 4 H), 2.75 (t, 2 H, J = 6.7 Hz), 2.40 (m, 2 H), 2.25 (s, 3 H); FAB-MS (($M + H)^+$) m/z 424. Anal. ($C_{23}H_{29}N_5O_3 \cdot 0.5H_2O$) C; H: calcd, 6.99%; found, 8.19%. N: calcd, 16.19%; found, 15.37%.

3-{1-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenylaminocarbonyl]-4-piperidyl}indole-5-carboxamide Hydrate (21m). Compound **21m** was synthesized as described for **5** using **20**[24] (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 4-(5-carboxamido-1*H*-indol-3-yl)-piperidine monohydrate (**15**) (1.1 g, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: toluene−MeOH−TEA (7:2:1)] followed by recrystallization (acetonitrile) gave **21m** (241 mg, 12%): mp 179 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1 H), 8.29 (s, 1 H), 8.22 (s, 1 H), 7.80 (br s, 1 H), 7.63 (d, 1 H, J = 8.8 Hz), 7.33 (d, 1 H, J = 8.8 Hz), 7.20 (d, 1 H, J = 2.2 Hz), 7.11 (m, 2H), 7.02 (br s, 1 H), 6.79 (d, 1 H, J = 8.8 Hz), 4.26 (d, 2 H, J = 12.8 Hz), 3.72 (s, 3 H), 3.05 (m, 7 H), 2.66 (br s, 4 H), 2.35 (s, 3 H), 2.03 (d, 2 H, J = 13.0 Hz), 1.60 (m, 2 H); FAB-MS (($M + H)^+$) m/z 491. Anal. ($C_{27}H_{34}N_6O_3 \cdot H_2O$) C, H, N.

4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [2,3-Dihydro-1′-methylspiro(benzofuran-3,4′-piperidine)]-amide Hemihydrate (23a). Compound **23a** was synthesized as described for **5** using 5-amino-2,3-dihydro-1′-methylspiro-(benzofuran-3,4′-piperidine) (**22**)[18] (300 mg, 1.4 mmol), TEA (0.5 mL, 3.5 mmol), CDI (243 mg, 1.5 mmol) and 4-(5-fluoro-1*H*-indol-3-yl)piperidine (**4**) (306 mg, 1.4 mmol) in acetonitrile (50 mL). CC [toluene−MeOH−TEA (7:2:1)] followed by recrystallization (EE−light petroleum) gave **23a** (300 mg, 47%): mp 213−215 °C; ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1 H), 8.27 (s, 1 H), 7.32 (dd, 1H, J = 9.7 Hz and J = 2.2 Hz), 7.25 (d, 1 H, J = 2.2 Hz), 7.19 (dd, 1 H, J = 9.7 Hz and J = 2.2 Hz), 7.13 (m, 2 H), 6.81 (dt, 1 H, J = 9.8 Hz and J = 2.2 Hz), 6.62 (d, 1 H, J = 8.8 Hz), 4.55 (s, 2 H), 4.44 (d, 2 H, J = 11.9 Hz), 2.97 (m, 3 H), 2.73 (d, 2 H, J = 11.9 Hz), 2.42 (s, 3 H), 1.95 (m, 4 H), 1.80 (dt, 2 H, J = 12.5 Hz and J = 4.4 Hz), 1.60 (m, 4 H); FAB-MS (($M + H)^+$) m/z 463. Anal. ($C_{27}H_{31}FN_4O_2 \cdot 0.5H_2O$) C, H, N.

1-{2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl}-[2,3-dihydro-1′-methylspiro(benzofuran-3,4′-piperidine)]-amide (23b). Compound **23b** was synthesized as described for **5** using **22**[18] (349 mg, 1.6 mmol), TEA (0.58 mL, 4.0 mmol), CDI (292 mg, 1.8 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)-piperidin-1-yl]ethylamine (**11**) (418 mg, 1.6 mmol) in acetonitrile (50 mL). Recrystallization (EE−light petroleum) gave **23b** (170 mg, 21%): mp 237−239 °C; ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1 H), 8.37 (s, 1 H), 7.52 (dd, 1 H, J = 8.8 Hz and J = 4.4 Hz), 7.23 (d, 1 H, J = 3.0 Hz), 7.07 (m, 3 H), 6.80 (dt, 1 H, J = 8.7 Hz and J = 3.0 Hz), 6.60 (d, 1 H, J = 8.9 Hz), 5.91 (t, 1 H, J = 7.0 Hz), 4.29 (s, 2 H), 3.21 (m, 2 H), 2.99 (d, 2 H, J = 11.0 Hz), 2.69 (d, 3 H, J = 10.09 Hz), 2.43 (t, 2 H, J = 6.6 Hz), 2.17 (s, 3 H), 2.11 (m, 2 H), 1.98−1.55 (m, 10 H); FAB-MS (($M + H)^+$) m/z 506. Anal. ($C_{29}H_{36}FN_5O_2$) C, H, N.

4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [3-(2-(Dimethylamino)ethoxy)-4-methoxyphenyl]amide Hydrochloride (25a). Compound **25a** was synthesized as described for **5** using 3-(2-(dimethylamino)ethoxy)-4-methoxyaniline (**24**)[18] (631 mg, 3.0 mmol), TEA (1.1 mL, 8.0 mmol), CDI (535 mg, 3.3 mmol) and 4-(5-fluoro-1*H*-indol-3-yl)piperidine (**4**) (655 mg, 3.0 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc−MeOH−TEA (5:2:1)] and preparation of the dihydrochloride gave **25a** (900 mg, 61%): mp 210−211 °C; ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1 H), 8.41 (s, 1 H), 7.33 (m, 2 H), 7.19 (d, 1 H, J = 2.2 Hz), 7.08 (dd, 1 H, J = 11.0 Hz and J = 2.2 Hz), 6.90 (m, 3 H), 4.30 (m, 4 H), 3.75 (s, 3H), 3.49 (t, 2 H, J = 5.3 Hz), 3.02 (m, 3 H), 2.90 (6 H, s), 1.95 (d, 2 H, J = 11.9 Hz), 1.55 (m, 2 H); FAB-MS (($M + H)^+$) m/z 455 Anal. ($C_{25}H_{31}N_4O_3 \cdot HCl$) C, H; Cl: calcd, 7.22%; found, 7.88%. N: calcd, 11.41%; found, 11.88%.

1-[3-(2-(Dimethylamino)ethoxy)-4-methoxyphenyl]-3-{2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl}urea Dihydrochloride Hydrate (25b). Compound **25b** was synthesized as described for **5** using **24**[18] (631 mg, 3.0 mmol), TEA (1.1 mL, 8.0 mmol), CDI (535 mg, 3.3 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (**11**)[24] (758 mg, 2.9 mmol) in acetonitrile (75 mL). CC [eluent: EE−MeOH−TEA (5:2:1)] followed by preparation of the dihydrochloride gave **25b** (850 mg, 52%): mp 130−131 °C; ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1 H), 8.91 (s, 1 H), 7.68 (m, 1 H), 7.50 (d, 1H, J = 2.2 Hz), 7.14 (2H, m), 645−7.00 (4 H, m), 4.42 (t, 2 H, J = 6.0 Hz), 3.75 (s, 3 H); 3.70−3.40 (m, 6 H), 2.76 (m, 5 H), 2.82 (6H, s), 2.12 (br s, 4 H); FAB-MS (($M + H)^+$) m/z 498. Anal. ($C_{27}H_{36}N_5O_3 \cdot 2HCl \cdot H_2O$) C, H, Cl, N.

Receptor Binding Assays. Affinities for 5-HT_{1B} receptors were determined in rat frontal cortex using [^{125}I]iodocyanopindolol as radioligand, final concentration 0.1 nM.[25] The 5-HT_{1D} assays were performed according to Peroutka et al.[26] using membranes prepared from calf striatum and 1.7 nM [^{3}H]-serotonin in the presence of 100 nM 8-OH-DPAT and 100 nM mesulergine to mask 5-HT_{1A} and 5-HT_{2C} binding sites. Non-specific binding was determined in the presence of 10 μM serotonin. Inhibition by drugs of the binding of 0.5 nM [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in membranes from rat hippocampus was determined according to the reported method.[27]

Rabbit Saphenous Vein (RSV). The inhibition of the contractile responses elicited by sumatriptan in rabbit saphenous vein was determined according to a published method.[28] For determining of 5-$HT_{1B/1D}$ antagonistic activity, segments of isolated rabbit saphenous veins were suspended in organ baths and subjected to two concentration−response curves to sumatriptan, the second challenge being performed in the presence of the antagonist or control vehicle (incubated for 60 min). Apparent pA_2 values were calculated using a single antagonist concentration in at least 3 preparations.

[^{3}H]5-HT Release. The effect on the sumatriptan-induced inhibition of potassium-evoked [^{3}H]5-HT release from guinea pig cortex slices was determined according to a method published by Ormandy.[29] Cerebral cortices were removed from male Dunkin−Hartley guinea pigs, cross-chopped into slices, and then incubated 30 min with [^{3}H]5-HT. Slices were placed into chambers of a superfusion apparatus and superfused with oxygenated Krebs's solution. Superfusate was collected in 4-min periods beginning 60 min after the slices were placed in the chambers. The slices were exposed to two periods (4 min) of 30 mM K^+ at 68- and 108-min superfusion (S1 and S2, respectively). Sumatriptan at a concentration of 3 μM (controls) and sumatriptan plus test compounds (30 nM, 300 nM, and 3 μM, respectively) were superfused prior to and during the S2 stimulation period. Released radioactivity in each sample was measured, and after basal release was subtracted, the S2/S1 ratio was calculated. Results represent the mean (±SEM) of 3−4 determinations. The effects of drugs were expressed as a percent of control, i.e. purely sumatriptan perfused S2/S1 ratio.

[^{3}H]5-HT Reuptake Inhibition. Crude synaptosomal fraction (P_2 fraction) of rat cerebral tissue was prepared according to Whittaker[31] giving a suspension enriched in synaptosomes of 3 mg protein/mL. The synaptosomal uptake was performed

in a total volume of 570 μL, which contained 12 nM [^{3}H]5-HT. Incubation was performed at 37 °C for 4 min in Krebs-Ringer buffer (126 mM NaCl, 1.4 mM $MgCl_2$, 4.8 mM KCl, 15.8 mM Na_2HPO_4, 11 mM glucose, 0.9 mM $CaCl_2$, pH 7.4, 346 mOsM).[30]

Acknowledgment. We thank Uwe Eckert and Kurt Schuster for the synthesis of some of the building blocks mentioned in this publication; Sylke Rebscher, Doris Seeger, Dagmar Wolf, Hermann Kaiser, Andreas Tiglmann, and Waldemar Walter for the determination of the biological data; and Karin Rölfing for assistance in preparing the manuscript.

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JM9811054