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5-(Sulfonyl)oxy-tryptamines and Ethylamino Side Chain Restricted Derivatives. Structure–Affinity Relationships for h5-HT$_{1B}$ and h5-HT$_{1D}$ Receptors

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Abstract—A number of sulfonic acid ester derivatives of serotonin (5-hydroxytryptamine; 5-HT; **1**) were prepared and their affinities are compared to that of the reference compound 5-[[(trifluoromethyl)sulfonyl]oxy]-tryptamine (**8b**). The structure–affinity relationship (SAFIR) is discussed in terms of in vitro binding for cloned human h5-HT$_{1A}$, h5-HT$_{1B}$ and h5-HT$_{1D}$ receptors. All tryptamine derivatives exhibited the best affinities for h5-HT$_{1D}$ receptors but still, these were comparatively lower than that of compound **8b**. 5-Tosylated tryptamine **11b** ($K_i = 6$ nM) and the sulfamate derivatives **13b** and **14b** ($K_i = 7$ and 11 nM, respectively) were found to have the highest affinities for the h5-HT$_{1D}$ receptor. Other tryptamine derivatives displayed moderate binding for h5-HT$_{1A}$ and h5-HT$_{1B}$ receptors, along with K_i values ranging from 14–20 nM for the h5-HT$_{1D}$ sites. In addition, the syntheses of two alkylamino side chain restricted derivatives are described. 3-Amino-6-[[(trifluoromethyl)sulfonyl]oxy]-1,2,3,4-tetrahydrocarbazole **21**, as well as 4-[5-[[(trifluoromethyl)sulfonyl]oxy]-1*H*-indol-3-yl]piperidines **24** and **25**, induced a shift in selectivity in favor of the h5-HT$_{1B}$ receptor. The relatively longer distance between the basic amine and a hydrogen-bond accepting oxygen in **21**, **24** and **25** as compared to the non-restricted tryptamines, is likely responsible for this observation. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

The 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors belong to the multiple-subtype 5-HT receptor family,[1,2,31] and have been identified in various species.[3,4] Besides the presence in peripheral tissues, these receptors are among the most abundant, presently known, 5-HT$_1$ receptor subtypes in the mammalian central nervous system (CNS), existing as presynaptic heteroreceptors or terminal autoreceptors.[5] Stimulation of the centrally located receptors inhibit the release of 5-HT, which makes them interesting therapeutic targets in the treatment of mood-disorders such as aggression, anxiety and depression. In the brain, the distribution of the 5-HT$_{1B}$ receptor mRNA is shown to be consistently more widespread than that of the co-distributing 5-HT$_{1D}$ mRNA,[1] and the functional distinction between the 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor subtypes is still in progress. Human genes encoding for the h5-HT$_{1B}$ and h5-HT$_{1D}$ receptor subtypes have been cloned.[6,7] The amino acid sequence identity in the transmembrane spanning regions (TMR) is approximately 77%, whereas the h5-HT$_{1B}$ receptor differs only one—but critical—amino acid residue from its rodent analogue.[8] The successful treatment of migraine by some tryptamine derivatives, such as sumatriptan (**2**, Chart 1)[9] and recently more orally available analogues,[10] has been attributed to stimulation of (peripheral) 5-HT$_{1B/1D}$ receptors.[11]

Key words: Serotonin; 5-HT; sulfonate; h5-HT$_{1B}$; h5-HT$_{1D}$.
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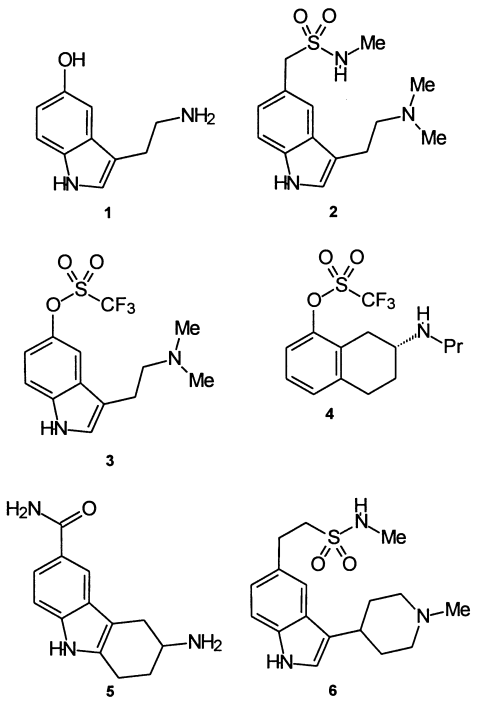


Chart 1.

The past few years, a variety of novel agents and their independent affinities for the h5-HT_{1B} and h5-HT_{1D} receptors have been reported. The majority of these ligands have 5-HT as their common ancestor. Whereas some laboratories focused lately on elongation and modification of the ethylamine moiety,[12] replacement of the 5-hydroxy group has received considerable attention.[10,13] H-bond accepting bioisosteres or rigidification of the carbon skeleton resulted in 5-$HT_{1B/1D}$ receptor ligands with different properties. Aforementioned **2** displayed low nanomolar affinities for the h5-HT_{1B} and h5-HT_{1D} sites (Table 1). Introduction of the triflate group at the 5-position of the tryptamine template (**3**) gave comparable binding results, but gave also a low nanomolar affinity for the 5-HT_{1A} site.[14] The potential antimigraine action of compound **3** was evaluated in porcine blood flow models (suggestive of therapeutic activity in migraine) and was shown to be active.[15] The electron-withdrawing triflate substituent was previously shown to enhance the affinity of conformationally restricted 2-aminotetralins (exemplified by **4**) for 5-$HT_{1B/1D}$ receptors, as compared to the hydroxy analogues.[16] The fixed 'upward' conformation of the ethylamino group in these 2-aminotetralins seemed to fit the h5-HT_{1D} receptors better than h5-HT_{1B} sites.

Locking the ethylamino side chain in a 'downward' mode, like in 3-aminocarbazole derivative **5**, was shown to produce marked effects on selectivity and affinity for 5-HT_1 receptor subtypes. King and co-workers reported

Table 1. Binding data for selected 5-HT_1 receptor subtypes

	K_i (nM)			
Compd	h5-HT_{1A}	h5-HT_{1B}	h5-HT_{1D}	Ref
2	341	22	5.7	14
3	40	32	3.2	14
4	1.3	138	6.7	16
5	500[a]		10[b]	17
6	26.4	2[c]	5[d]	19,20

[a]Reported as $pK_D = 6.3$ (piglet hippocampus).
[b]$pK_D = 8.0$ (piglet caudate).
[c]Reported as $pK_i = 8.7$.
[d]Reported as $pK_i = 8.3$.

a K_i of 10 nM and high intrinsic activity of **5** for 5-HT_{1D} receptors.[17] This finding suggests that the binding conformation of the side chain of 5-HT at the 5-HT_{1B} and/or 5-HT_{1D} receptor could be more approximate to that of 3-aminocarbazoles than of 2-aminotetralins. However, in the pharmacology experiments, the authors did not discriminate between these two receptor subtypes, which makes it difficult to draw conclusions regarding the orientation of the ethylamino group in each of these receptor subtypes. Another type of indolylalkylamine is represented by semi-rigid Naratriptan (**6**),[18] which possesses a 4-piperidino ring instead of an ethylamino side chain. This compound showed low nanomolar affinities for human 5-$HT_{1B/1D}$ receptors,[19] but is also reported to display high efficacy and marked affinity for recombinant h5-HT_{1A} sites.[20] It has superior potency as compared to **2** in both binding and functional studies, and is clinically effective in the treatment of migraine.[21]

During our previous work with aryl triflates, the question arose whether the triflate group would be the optimal sulfonic acid ester for h5-$HT_{1B/1D}$ affinity. Especially, the active site of both receptor subtypes are known to contain a pocket which can accommodate large groups, located at the five-position of the tryptamines.[13] The nature of this pocket may be explored by using sulfonate substituents with different electronic and steric properties. Thus, it was of interest to study the effects of readily available sulfonate derivatives of 5-HT on the affinity for h5-HT_{1A}, h5-HT_{1B} and h5-HT_{1D} receptors. So far, binding data on 3-aminocarbazoles and indol-3-ylpiperidines with reasonable affinity for the individual human 5-HT_1 receptor clones have respectively not or only occasionally been reported, which justifies the examination of the rigidified 5-triflated tryptamine analogues on selectivity for the h5-HT_{1A}, h5-HT_{1B} and h5-HT_{1D} receptor subtypes. The present study describes the synthesis and SAFIR of sulfonic acid ester substituted tryptamines and some restricted analogues. Throughout this series of compounds the triflate group serves as the reference substituent.

Results

Preparation of 5-sulfonyloxytryptamines. The sulfonic acid ester derivatives were prepared in moderate to high yields by treating *N*,*N*-phthalimido protected 5-HT with the appropriate sulfonyl or sulfamoyl chloride. The coupling was effected using; Et_3N as a base and dioxane as the solvent (method A); phase-transfer conditions with tetrabutyl ammonium iodide as the phase-transfer catalyst (method B); or NaH as the base and DMF as the solvent (method C). The phthalimides were converted into the primary amines upon treatment with hydrazine in ethanol (Scheme 1).

Upon crystallization from H_2O/MeOH, the mesylate derivative **9b** yielded crystals that were suitable for an X-ray single crystal analysis (Fig. 1). The compound crystallized as the hemi-oxalate in a monoclinic C2/c spacegroup with eight molecules per unit cell (a = 22.158; b = 5.791; c = 24.172 Å, β = 117.01 deg). In Table 2, selected bond distances, bond angles and torsional angles are listed. The crystal structure is stabilized by complexation between the NH of the indole portion and the oxalic acid via H-bonds at a distance of 1.834 Å (Fig. 2). This distance is comparable with that of the normal ionic interaction of the primary amine and the oxalic acid, being 1.826 Å. Furthermore, clear intermolecular H-bonds (2.034 Å) can be observed between sulfone O16 of one molecule and the ethylamino N^+H of another molecule. This is also reflected by the relative long bond length of S14-O16 (1.426 Å) as compared that of S14-O17 (1.359 Å).

Preparation of 3-aminocarbazoles. *N*,*N*-Phthalimido protected 4-aminocyclohexanol was oxidized with pyridinium chlorochromate to give the cyclohexanone derivative **16**. The 3-aminocarbazole skeleton was prepared via the Fischer-indole synthesis by refluxing **16** with 4-methoxyphenylhydrazine (**15**) in ethanol (83%).[22] Intermediate **17** was either *N*,*N*-deprotected to give **18**, or *O*-demethylated to give **19** (31%), which subsequently was triflated and converted into the primary amine to yield carbazole derivative **21** employing conditions described above (Scheme 2).

Preparation of indol-3-ylpiperidines. The *t*-BOC-protected 5-hydroxy-indol-3-ylpiperidine (**22**) was triflated in 86% yield as described before and deprotected using TFA in CH_2Cl_2, resulting in compound **24** (44% after purification). This secondary amine was *N*-methylated to give **25** (Scheme 3).

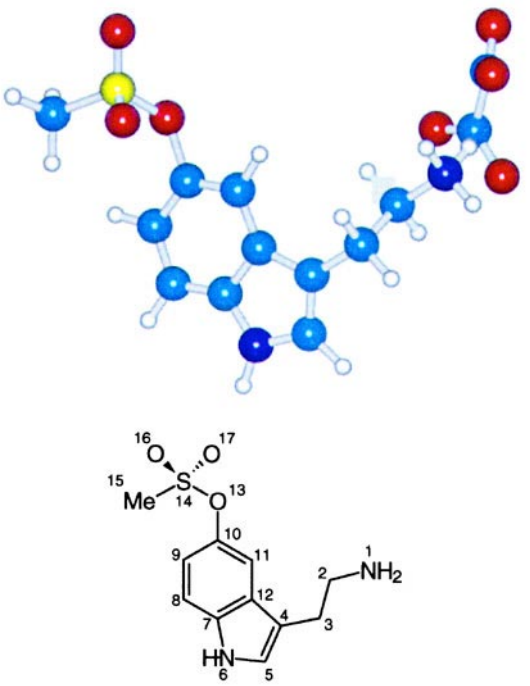
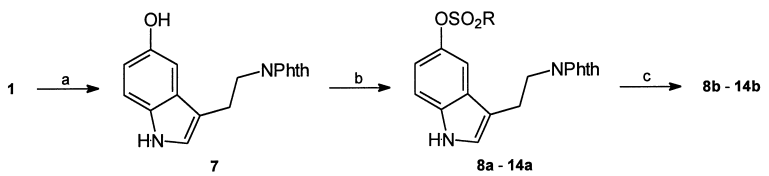


Figure 1. Crystal structure and adapted numbering of **9b**.

Receptor binding. The compounds were tested for the inhibition of [^{3}H]8-OH-DPAT (h5-HT_{1A}) or [^{3}H]5-carboxamidotryptamine ([^{3}H]5-CT) (h5-HT_{1B} and h5-HT_{1D}) binding to cloned human receptors expressed in Cos-7 cells (Table 3).

Discussion

5-Sulfonic acid ester derivatives of 5-HT. As indicated by the resolved crystal structure and the intermolecular interactions of mesylate derivative **9b**, aryl sulfonic acid esters are capable of accepting a hydrogen bond (Fig. 1). This observation may be of importance with respect to interactions with H-bond donating amino



Scheme 1. (a) *N*-Et-CO_2-phth, 10% $NaHCO_3$ (pH 8), THF:H_2O; (b) RSO_2Cl, method A, B, or C; (c) $H_2NNH_2 \cdot H_2O$, EtOH.

Table 2. Selected interatomic distances, angles and torsional angles of compound **9b**

Distance (Å)		Angle (deg)		Torsional angle (deg)	
N_1-C_2	1.498	N_1-C_2-C_3	110.2	N_1-C_2-C_3-C_4	178.4
S_{14}-C_{15}	1.744	C_2-C_3-C_4	110.3	C_2-C_3-C_4-C_5	108.9
O_{13}-S_{14}	1.550	C_{10}-O_{13}-S_{14}	120.9	C_{11}-C_{10}-O_{13}-S_{14}	−97.3
C_{10}-O_{13}	1.486	O_{13}-S_{14}-C_{15}	101.1	C_{10}-O_{13}-S_{14}-C_{15}	−84.7
$S_{14}O_{16}$	1.426	O_{13}-S_{14}-O_{16}	104.9	C_{10}-O_{13}-S_{14}-O_{16}	28.2
S_{14}-O_{17}	1.359	O_{13}-S_{14}-O_{17}	114.3	C_{10}-O_{13}-S_{14}-O_{17}	158.9

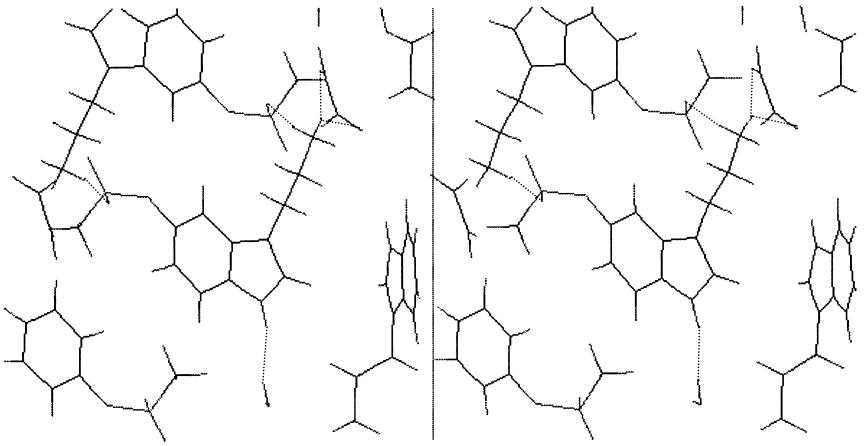
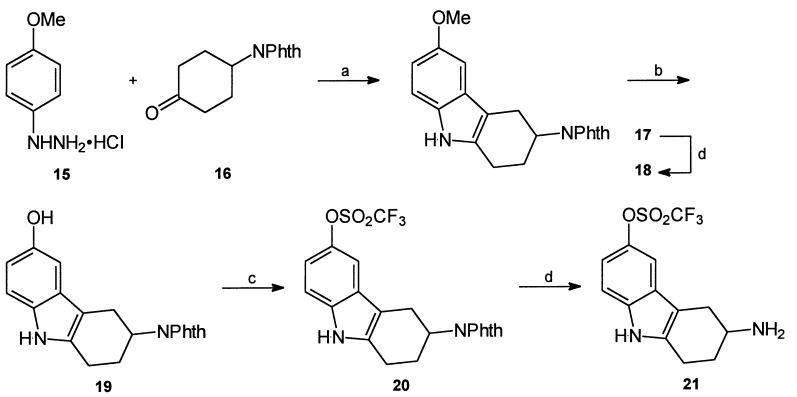


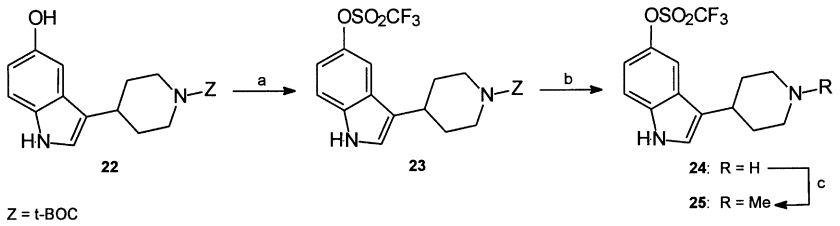
Figure 2. Stereoview of the intermolecular interactions of **9b** (indicated by a dashed line).



Scheme 2. (a) EtOH, Δ; (b) BBr_3, CH_2Cl_2, −78 °C; (c) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2; (d) $H_2NNH_2{\cdot}H_2O$, EtOH.

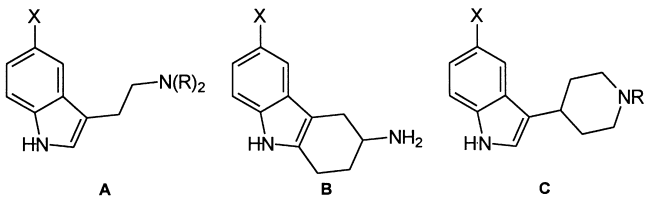
acid residues in a particular receptor. Compound **9b** binds with moderate affinity to h5-HT_{1A}, h5-HT_{1B} and h5-HT_{1D} receptors, displaying a slight preference for the h5-HT_{1D} subtype ($K_i = 17$ nM; Table 3). Since the steric interactions of **9b** and **8b** with the receptors are similar, the relatively lower affinities of **9b** have to be discussed in terms of electronic effects, which are commonly expressed as Hammett σ_p and Taft σ_I parameters. Both sulfonate groups display an electron withdrawing character, indicated by the positive signs of the σ_p and σ_I values for the mesylate (+0.33 and +0.61, respectively) and the triflate (+0.37 and +0.84, respectively).[23]

The different binding properties may be attributed to the polarizability of the triflate group, which allows participation in hydrogen bonding in the drug–receptor interaction. A phenylsulfonate ($\sigma_p = +0.33$)[23] in this position results in complete loss of selectivity. Compared



Scheme 3. (a) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2; (b) TFA, CH_2Cl_2. 0 °C; (c) 37% formaldehyde, $NaCNBH_3$, acetic acid (pH 5), acetonitrile.

Table 3. Affinities at h5-HT_{1A}, h5-HT_{1B} and h5-HT_{1D} receptors in vitro



				K_i (nM) ± SEM[a]			
Compd	Type	X	R	h5-HT_{1A}	h5-HT_{1B}	h5-HT_{1D}	h5-HT_{1B}/h5-HT_{1D}
8b[b]	**A**	OSO_2CF_3	H	41 ± 7	9 ± 1	2 ± 0	4.5
9b	**A**	OSO_2Me	H	202 ± 81	55 ± 4	17 ± 1	3.2
10b	**A**	OSO_2Ph	H	61 ± 16	37 ± 3	20 ± 1	1.9
11b	**A**	OSO_2(*p*-Tol)	H	25 ± 6	20 ± 5	6 ± 1	3.3
12b	**A**	OSO_2(2-Th)	H	39 ± 4	20 ± 0	14 ± 4	1.4
13b	**A**	OSO_2NHMe	H	59 ± 6	19 ± 1	7 ± 1	2.7
14b	**A**	$OSO_2N(Me)_2$	H	87 ± 29	20 ± 5	11 ± 1	1.8
18	**B**	OMe	–	> 1000	593 ± 98	876 ± 176	0.7
21	**B**	OSO_2CF_3	–	> 1000	60 ± 10	51 ± 5	1.2
24	**C**	OSO_2CF_3	H	107 ± 36	6 ± 1	19 ± 2	0.3
25	**C**	OSO_2CF_3	Me	71 ± 8	6 ± 0	10 ± 2	0.6

[a]K_i values (± SEM) for displacement of 5-HT_{1A} receptor agonist [^{3}H]8-OH-DPAT or non selective 5-HT receptor agonist [^{3}H]5-CT (h5-HT_{1B} or h5-HT_{1D}). Data from HeLa/h5-HT_{1A} and cloned human 5-HT_{1B} or 5-HT_{1D} receptors expressed in Cos-7 cells. The values were obtained in two to three independent experiments, each performed in duplicate.
[b]Binding data (K_i) on compound **8b** have been reported previously: 18 nM (h5-HT_{1A}), 14 nM (h5-HT_{1B}) and 2.8 nM (h5-HT_{1D}).[14]

to the mesylate, it improves the affinity threefold for the h5-HT_{1A} receptor (K_i = 61 nM) and 1.5-fold for the h5-HT_{1B} (37 nM). Interestingly, a methyl substituent on the *para*-position of the phenyl ring induces a pronounced increase in affinity for the h5-HT_{1A} (K_i = 25 nM) and the h5-HT_{1D} receptor (K_i = 6 nM), and to a lesser extend for the h5-HT_{1B} receptor (K_i = 20 nM). The Hammett σ_p and Taft σ_I values of a tosylate group are +0.28 and +0.54, respectively, and thus comparable with those of the other sulfonates.[23] The increased affinities could suggest that the methyl group favourably interacts with a lipophilic surface or pocket in each of the receptor subtypes. When considering the binding profiles of previously reported tryptamines with large 5-substituents,[13] additional drug–receptor interactions may easily be provided by extension in the direction of *para*-methyl substituent of compound **11b**. The 2-thiophene ring induces a slight improvement in affinity for all three receptor subtypes relative to the phenyl ring, which indicates that an extra hydrogen-bonding interaction in this position is to be expected. The relative position of the sulfur atom in the thiophene ring, however, may not be optimal.

Structurally, the sulfamate derivatives **13b** and **14b** are in close resemblance to **2**,[24] differing only in the 5-oxygen and the unsubstituted amine functionality. The sulfamoyl moiety has been widely utilized as an activity-modifying substituent in various classes of drugs with therapeutic potential in for instance the treatment of cancer[25] or

psychosis.[26] Compound **13b**, as well as **14b**, displays a twofold preference for h5-HT_{1D} receptors over h5-HT_{1B} receptors. Both sulfamate substituted tryptamines show a similar binding profile as compared to **2**, having higher affinity for the h5-HT_{1A} site. Presumably, the 5-oxygen of **13b** and **14b**—as in most of the other sulfonate derivatives—participates in hydrogen-bond formation with the h5-HT_{1A} receptor. Obviously, the 5-oxygen is much more important for h5-HT_{1A} receptor binding than for the h5-$HT_{1B/1D}$ receptor subtypes, since 2 and other h5-$HT_{1B/1D}$ receptor agonists lack this particular oxygen atom. This suggests that truly selective h5-HT_{1B} or h5-HT_{1D} receptor ligands are not to be expected when sulfonate substituted serotonin analogues are employed.

The homology of TMRs between the human 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is considerable (53–77%).[6] Alignment of the amino acid residues of putative helix 5 shows us that the three receptor proteins bear a serine and threonine residue in a similar position.[27] Discriminatory properties of the receptors for the tryptamine derivatives with relatively small 5-substituents may be accounted for by differential active site-surrounding amino acid residues. In addition, the potential differences in distant helical environments, in other words, the distance between the serine and/or threonine on TMR-5 and the aspartate on TMR-3, will be of importance. The affinities of conformationally restricted indolealkylamines may provide useful information regarding the size of these distances.

Alkylamino side chain restriction. While our work was in progress, Glennon and co-workers[28] reported the synthesis and binding results of 6-methoxy-3-aminocarbazole **18** for the h5-HT_{1B} receptor population ($K_i = 342$ nM). In line with their result we found a K_i of 593 nM for this receptor along with K_i values of >1000 and 867 nM for the h5-HT_{1A} and h5-HT_{1D} sites, respectively. These authors also reported K_i values of 5-methoxytryptamine for the h5-HT_{1A} (3.2 nM), h5-HT_{1B} (3.5 nM) and h5-HT_{1D} (5.4 nM) receptors. This means that a 'downward'-orientated ethylamino group is most probably not the binding conformation of serotonin itself at these receptor subtypes. Obviously, the N-O distance of compound **18** is too long for a proper interaction with the aspartate and one of the H-bond donating residues on TMR-5. This distance seems to be partially restored in carboxamido derivative **5** ($K_i = 10$ nM) in case of the 5-$HT_{1B/1D}$ receptors but is still too long for the 5-HT_{1A} receptor. Replacing the 6-carboxamido substituent by a triflate group (**21**) confirms this hypothesis. Compound **21**, like **5**, was still inactive at the h5-HT_{1A} receptor ($K_i > 1000$ nM) but displays moderate affinities for the h5-HT_{1B} (60 nM) and h5-HT_{1D} (51 nM) sites. Taken together, this leads to the assumption that in case of compound **21**, one of the sulfonyl oxygens serves as a H-bond acceptor, whereas the ester-oxygen (O_{13} in Figure 1) is no longer available for such an interaction, as compared to the non-restricted triflate derivative **8b**. Notably, the 3-aminocarbazole derivatives seem to have an equal preference for the h5-HT_{1B} and h5-HT_{1D} receptor.

The semi-rigid indolylpiperidines **24** and **25** both show an interesting receptogram. Displaying K_i values of 6 nM for the h5-HT_{1B} receptor, these compounds exhibited a clear preference for the h5-HT_{1B} site over the h5-HT_{1D} site of about threefold. The h5-HT_{1A} receptor affinities, being 107 nM for **24** and 71 nM for **25**, are comparable with that of compound **8b**, but much higher than that of **21**. The h5-HT_{1B} receptor preference again may be explained by an increased N-O distance relative to **8b**. Other factors, such as a positive lipophilic interactions of the piperidine ring with a hydrophobic part of the h5-HT_{1B} receptor may also contribute to this observation. The binding data are compatible with those found for **6**, which displayed a K_i of approximately 2 and 5 nM for 5-HT_{1B} and 5-HT_{1D} receptors, respectively, and 26.4 nM for 5-HT_{1A} sites (Table 1).

Conclusion

In our hands, the aryl triflate group seemed to be the optimal sulfonic acid ester in terms of affinity for h5-HT_{1D} and h5-HT_{1B} receptors, however, the positive contribution to binding of the *para*-methyl group of tosylate **9b** suggests that further extension is possible in this direction, providing a 'handle' for future improvements. In addition, the sulfamate derivatives **13b** and **14b** display fairly good binding to h5-HT_{1D} sites, but show less selective profiles than sumatriptan. 3-Aminocarbazole **21** exhibits moderate affinities and no preference for either the h5-HT_{1B} or h5-HT_{1D} receptor subtypes, along with a low affinity for the h5-HT_{1A} site. Notably, the indolylpiperidines display a marked preference for the h5-HT_{1B} receptor. Thus it seems that the N-O distance, roughly defined by a (semi)-rigid skeleton, primarily discriminates between the 5-HT_{1A} and 5-$HT_{1B/1D}$ receptor selectivity. Further modification and proper substituent selection may optimize the affinity for each of the receptor subtypes.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 Hz, respectively, on a Varian Gemini 200 spectrometer. $CDCl_3$ was employed as the solvent unless otherwise stated. Chemical shifts are given in δ units (ppm) and relative to TMS or deuterated solvent. Coupling

constants are given in Hz. IR spectra were obtained on a ATI-Mattson spectrometer. Elemental analyses were performed in the analytical department of Merck KGaA (Darmstadt, Germany). The chemical ionization (CI) mass spectra were obtained on a Unicam Automass 150 system using a direct-inlet probe. The high resolution mass spectra (HRMS) were generated on a AEI MS-902 mass spectrometer at the Microanalytical department of the University of Groningen (The Netherlands). Melting points were determined on a Electrothermal digital melting point apparatus and are uncorrected.

Materials. The syntheses of *N*,*N*-phthalimido protected serotonin (**7**) and compound **8b** are described elsewhere.[14] *N*-Boc-4-[(5-hydroxy)-1*H*-indol-3-yl]piperidine (**22**) was provided by Merck KGaA (Darmstadt, Germany). *N*-Methylsulfamoyl chloride was prepared according a literature procedure.[29]

Method A. *N*,*N*-Phthalimido-2-[5-[[(methyl)sulfonyl]oxy]-1*H*-indol-3-yl]ethylamine (9a). Methanesulfonyl chloride (170 μL, 2.20 mmol) was added dropwise to a solution of **7** (0.56 g, 1.83 mmol) and Et_3N (0.5 mL) in dioxane (10 mL). After 2 h of stirring anhydrous ether (30 mL) was added after which the formed precipitate was removed by filtration. The filtrate was evaporated to dryness leaving 0.71 g (100%) of a colorless oil, which was recrystallized from *i*-PrOH yielding white crystals (0.35 g, 50%): mp 167–168 °C; IR (KBr) cm^{-1} 3046 (NH), 1705 (C=O), 1398, 1360, 1180 (O-SO_2); ^1H NMR δ 3.14 (t, $J=7.69$, 2H), 3.17 (s, 3H), 3.87 (t, $J=7.79$, 2H), 7.16 (m, 2H), 7.34 (d, $J=8.74$, 1H), 7.61 (s, 1H), 7.69–7.85 (m, 4H), 8.21 (br s, NH); ^{13}C NMR δ 24.2, 36.8, 38.2, 111.6, 112.1, 113.0, 116.7, 123.2, 124.0, 127.7, 132.0, 133.9, 134.7, 143.2, 168.3; MS (EIPI) *m*/*e* 384 (M^+); Anal. calcd (obsd) for $C_{19}H_{16}N_2O_5S$: C: 59.4 (59.1), H: 4.2 (4.3) N: 7.3 (7.3).

Method A. *N*,*N*-Phthalimido-2-[5-[[(phenyl)sulfonyl]oxy]-1*H*-indol-3-yl]ethylamine (10a). Using benzenesulfonyl chloride afforded a crude yellow solid in a quantitative yield. Recrystallization from acetone gave 0.63 g (86%) of colorless plates: mp 166–168 °C; IR (KBr) cm^{-1} 3423 (NH), 1706 (C=O), 1395, 1356, 1192 (O-SO_2); ^1H NMR δ 2.98 (t, $J=7.74$, 2H), 3.85 (t, $J=7.74$, 2H), 6.82 (dd, $J_1=8.88$, $J_2=2.18$, 1H), 7.06 (d, $J=2.33$, 1H), 7.17 (s, 1H), 7.20 (d, $J=5.79$, 1H), 7.45–7.88 (m, 9H), 8.33 (br s, NH); ^{13}C NMR δ 24.1, 38.1, 111.7, 112.1, 112.8, 116.8, 123.2, 123.9, 127.4, 128.6, 129.0, 132.0, 134.0, 134.6, 135.4, 143.2, 168.2; MS (EIPI) *m*/*e* 446 (M^+); Anal. calcd (obsd) for $C_{24}H_{18}N_2O_5S$: C: 64.4 (64.4), H: 4.1 (4.1) N: 6.3 (6.3).

Method A. *N*,*N*-Phthalimido-2-[5-[[(4-toluoyl)sulfonyl]-oxy]-1*H*-indol-3-yl]ethylamine (11a). Using tosyl chloride afforded a crude yellow oil in a quantitative yield. Recrystallization from acetone gave 0.67 g (89%) of white crystals: mp 178–179 °C; IR (KBr) cm^{-1} 3416 (NH), 1718 (C=O), 1395, 1353, 1175 (O-SO_2); ^1H NMR δ 2.40 (s, 3H), 3.00 (t, $J=7.69$, 2H), 3.86 (t, $J=7.79$, 2H), 6.86 (dd, $J_1=8.74$, $J_2=2.28$, 1H), 7.08–7.32 (m, 5H), 7.70–7.87 (m, 6H), 8.15 (br s, NH); ^{13}C NMR δ 21.6, 24.1, 38.1, 111.6, 112.1, 113.0, 117.0, 123.2, 123.7, 127.4, 128.7, 129.6, 132.0, 132.5, 133.9, 134.5, 143.3, 144.9, 168.1; MS (EIPI) *m*/*e* 460 (M^+); Anal. calcd (obsd) for $C_{25}H_{20}N_2O_5S$: C: 65.2 (65.0), H: 4.4 (4.5) N: 6.1 (6.0).

Method B. *N*,*N*-Phthalimido-2-[5-[[(2-thienyl)sulfonyl]-oxy]-1*H*-indol-3-yl]ethylamine (12a). A mixture of **7** (0.45 g, 1.47 mmol), 2-thiophenesulfonyl chloride (0.32 g, mmol) and tetrabutylammonium iodide (50 mg) was magnetically stirred in CH_2Cl_2 (10 mL). 10% NaOH (20 mL) was added after which the reaction mixture was stirred for 30 min. The product was extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residual colorless oil was purified by medium-pressure liquid chromatography on SiO_2, by eluting with a gradient from *n*-hexane to EtOAc:*n*-hexane (1:4). Pure fractions were pooled and the resulting white solid (0.38 g) was recrystallized from EtOH:H_2O yielding a white crystalline material (0.26 g, 39%): mp 170–172 °C; IR (KBr) cm^{-1} 3420 (NH), 1701 (C=O), 1398, 1366, 1183 (O-SO_2); ^1H NMR δ 3.00 (t, $J=8.02$, 2H), 3.87 (t, $J=7.88$, 2H), 6.87 (dd, $J_1=8.83$, $J_2=2.23$, 1H), 7.06 (m, 2H), 7.22, (m, 2H), 7.55 (dd, $J_1=3.79$, $J_2=1.38$, 1H), 7.68–7.84 (m, 5H), 8.40 (br s, NH); ^{13}C NMR δ 24.1, 38.2, 111.8, 112.8, 116.6, 123.2, 124.0, 127.4, 132.0, 134.0, 134.4, 134.6, 134.7, 135.5, 143.3, 168.2; Anal. calcd (obsd) for $C_{22}H_{16}N_2O_5S_2$: C: 58.4 (57.5), H: 3.6 (3.1) N: 6.2 (5.9); HRMS Anal. calcd (obsd) for $C_{22}H_{16}N_2O_5S_2$: 452.050 (452.050).

Method A. *N*,*N*-Phthalimido-2-[5-[[(methylamino)sulfonyl]-oxy]-1*H*-indol-3-yl]ethylamine (13a). A similar procedure as above was employed using *N*-methylsulfamoyl chloride affording a crude yellow solid. Recrystallization from EtOH gave 0.40 g (61%) of yellow crystals: mp 184–187 °C; IR (KBr) cm^{-1} 3388, 3247 (NH), 1704 (C=O), 1400, 1359, 1184 (O-SO_2); ^1H NMR (DMSO) δ 2.74 (d, $J=4.65$, 3H), 3.00 (t, $J=6.84$, 2H), 3.38 (br s, NH), 3.84 (t, $J=6.84$, 2H), 7.00 (dd, $J_1=8.79$, $J_2=2.20$, 1H), 7.30 (d, $J=2.20$, 1H), 7.38 (d, $J=8.79$, 1H), 7.46 (d, $J=2.20$, 1H), 7.78–7.88 (m, 4H), 8.02 (m, NH); ^{13}C NMR δ 24.0, 29.5, 38.3, 111.3, 111.5, 112.4, 116.1, 123.3, 125.3, 127.4, 131.9, 134.7, 134.8, 143.2, 168.2; MS (EIPI) *m*/*e* 399 (M^+); Anal calcd (obsd) for $C_{19}H_{17}N_3O_5S$: C: 57.13 (56.98), H: 4.29 (3.91), N: 10.52 (10.41).

Method C. *N*,*N*-Phthalimido-2-[5-[[(dimethylamino)sulfonyl]oxy]-1*H*-indol-3-yl]ethylamine (14a). NaH (0.13 g; 60% oil dispersion) was washed with *n*-hexane and

taken up in dry DMF (5 mL). To this magnetically stirred suspension, **7** (0.50 g, 1.63 mmol) was added. After H_2-evolution had ceased, *N*,*N*-dimethylaminosulfamoyl chloride (210 μL, 1.96 mmol) was added dropwise to the red solution. The resulting reaction mixture was stirred for 30 min at room temperature after which time the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated at the rotavapor. The residual colorless oil was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (40:1). Identical TLC-fractions were pooled and evaporated to dryness affording the desired product (0.26 g, 38%) as a white solid and a minor amount of di-substituted product (0.04 g, 5%): mp 179–180 °C; IR (KBr) cm^{-1} 3339 (NH), 1704 (C=O), 1396, 1356, 1178 (O-SO_2); ^1H NMR δ 3.01 (s, 6H), 3.12 (t, 2H), 3.99 (t, 2H), 7.17 (m, 2H), 7.32 (d, J=8.54, 1H), 7.59 (s, 1H), 7.69–7.86 (m, 4H), 8.17 (br s, NH); ^{13}C NMR δ 24.3, 38.2, 38.8, 111.5, 111.8, 112.9, 116.6, 123.2, 123.8, 127.6, 132.1, 133.2, 133.9, 143.8, 168.3; MS (EIPI) *m*/*e* 413 (M^+); Anal. calcd (obsd) for $C_{20}H_{19}N_3O_5S$: C: 58.1 (57.8), H: 4.6 (4.7) N: 10.2 (10.1).

General procedure for deprotection of *N*,*N*-phthalimidotryptamines. The *N*,*N*-phthalimide derivative (1.0 mmol) was dissolved in absolute EtOH (10 mL) after which hydrazine hydrate (1.0 mL) was added. The reaction mixture was stirred for 0.5 h at room temperature after which time the volatiles were removed in vacuo. The residue was refluxed in $CHCl_3$ for 0.5 h, cooled to ambient temperature and filtered in order to remove the solid phthalimidohydrazine. The filtrate was evaporated in vacuo leaving the product which was converted to the oxalate and recrystallized from the appropriate solvent.

2-[5-[|(Methyl)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (9b). The oxalate salt was recrystallized from MeOH/H_2O giving 201 mg (75%) of colorless needles, suitable for X-ray single crystal analysis: mp 178–179 °C; IR (KBr) cm^{-1} 1345, 1178 (O-SO_2); ^1H NMR (DMSO-d_6) δ 2.97–3.04 (m, 4H), 3.29 (s, 3H), 7.06 (d, J=8.78, 1H), 7.31 (s, 1H), 7.43 (d, J=8.78, 1H), 7.52 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.9, 36.8, 39.1, 110.7, 111.9, 115.1, 125.1, 126.8, 134.5, 142.1, 163.9; HRMS calcd (obsd) for $C_{11}H_{14}N_2O_3S$: 254.073 (254.073).

2-[5-[|(Phenyl)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (10b). The oxalate salt was recrystallized from MeOH:H_2O giving 143 mg (53%) of white crystalline material: mp 136-138 °C; IR (KBr) cm^{-1} 3430 (NH), 1372, 1191 (O-SO_2); ^1H NMR (CH_3OD) δ 3.03 (br s, 4H), 6.68 (d, J=7.32, 1H), 7.11 (s, 1H), 7.22 (m, 2H), 7.50–7.78 (m, 5H); ^{13}C NMR (CD_3OD) δ 22.6, 39.3, 109.7, 111.0, 111.5, 115.6, 125.2, 126.6, 128.2, 128.8, 133.9, 135.1, 142.8; HRMS calcd (obsd) for $C_{16}H_{16}N_2O_3S$: 316.089 (316.089).

2-[5-[|(4-Toluoyl)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (11b). The oxalate salt was recrystallized from MeOH giving 385 mg (94%) of a white powder: mp 122–123 °C; IR (KBr) cm^{-1} 3423 (NH), 1364, 1191 (O-SO_2); ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H), 2.92 (br s, 4H), 6.64 (dd, J_1=8.73, J_2=2.28, 1H), 7.20 (d, J=2.28, 1H), 7.29 (d, J=8.73, 1H), 7.31 (s, 1H), 7.43 (AB, J=8.31, 2H) 7.69 (AB, J=8.31, 2H); ^{13}C NMR (DMSO-d_6) δ 21.1, 22.1, 39.2, 110.2, 111.3, 112.2, 115.2, 125.7, 126.7, 128.2, 130.0, 131.7, 134.6, 142.1, 145.4, 164.8; HRMS calcd (obsd) for $C_{17}H_{18}N_2O_3S$: 330.104 (330.104).

2-[5-[|(2-Thienyl)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (12b). The oxalate salt was recrystallized from MeOH:Et_2O giving 101 mg (56%) of white crystals: mp 172–173 °C; IR (KBr) cm^{-1} 3420 (NH), 1365, 1184 (O-SO_2); ^1H NMR (CD_3OD) δ 2.97–3.16 (m, 4H), 6.76 (dd, J_1=8.97, J_2=2.14, 1H), 7.16 (m, 2H), 7.27 (s, 1H), 7.29 (d, J=8.97, 1H), 7.54 (dd, J_1=3.42, J_2=1.28, 1H), 7.95 (dd, J_1=5.13, J_2=1.28, 1H); ^{13}C NMR (CD_3OD) δ 24.0, 40.7, 111.0, 112.0, 112.8, 116.6, 126.4, 127.9, 128.5, 136.1, 136.5, 136.6, 144.1; HRMS calcd (obsd) for $C_{14}H_{14}N_2O_3S_2$: 322.045 (322.045).

2-[5-[|(Methylamino)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (13b). The oxalate salt was recrystallized from acetonitrile giving 62 mg (60%) of a sticky off-white solid: IR (KBr) cm^{-1} 3420 (NH), 1347, 1184 (O-SO_2); ^1H NMR (DMSO) δ 2.72 (s, 3H), 3.01 (br s, 4H), 7.01 (dd, J_1=8.79, J_2=2.20, 1H), 7.32–7.46 (m, 3H); ^{13}C NMR (DMSO) δ 23.2, 29.5, 38.8, 110.5, 111.2, 112.5, 116.1, 125.7, 127.2, 134.8, 163.3; HRMS calcd (obsd) for $C_{11}H_{15}N_3O_3S$: 269.083 (269.083).

2-[5-[|(Dimethylamino)sulfonyl|oxy]-1*H*-indol-3-yl]ethylamine oxalate (14b). The oxalate salt was recrystallized from MeOH:Et_2O giving 73 mg (46%) of a white powder: mp 185–187 °C; IR (KBr) cm^{-1} 3294 (NH), 1357, 1181 (O-SO_2); ^1H NMR (CH_3OD) δ 2.50 (s, 6H), 2.69 (t, J=7.32, 2H), 2.83 (t, J=7.32, 2H), 6.63 (d, J=8.78, 1H), 6.68 (s, 1H), 6.99 (d, J=8.78, 1H), 7.05 (s, 1H); ^{13}C NMR (CD_3OD) δ 24.7, 39.6, 41.6, 111.7, 112.2, 113.8, 117.3, 127.1, 128.9, 145.5, 168.9; MS (EIPI) *m*/*e* 283 (M^+); Anal. calcd (obsd) for $C_{12}H_{17}N_3O_3S{\cdot}0.8\ C_2H_2O_4$: C: 45.96 (45.79), H: 5.28 (5.10) N: 11.89 (11.97); HRMS calcd (obsd) for $C_{12}H_{17}N_3O_3S$: 283.099 (283.099).

(±)-*N*,*N*-Phthalimido-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (17). *N*,*N*-Phthalimido-4-aminocyclohexanone (1.92 g, 7.9 mmol) and 4-methoxyphenylhydrazine·HCl salt (1.37 g, 7.9 mmol) were refluxed in

abs EtOH (25 mL). The title compound precipitated from solution as an off-white solid. After 1 h, the reaction mixture was cooled to ambient temperature and the solid material (2.26 g, 83%) was collected by filtration on a glass-sintered funnel: mp 213–214 °C (lit.[28] 211–213 °C); IR (KBr) cm^{-1} 1702 (C=O); ^1H NMR δ 2.01–2.11 (m, 1H), 2.86–2.98 (m, 4H), 3.43–3.56 (m, 1H), 3.83 (s, 3H), 4.62–4.76 (m, 1H), 6.80 (dd, $J_1=8.55$, $J_2=2.56$, 1H), 6.88 (d, $J=2.56$, 1H), 7.19 (d, $J=8.55$, 1H), 7.74 (dd, $J_1=5.55$, $J_2=2.99$, 2H), 7.78 (s, 1H), 7.88 (dd, $J_1=5.55$, $J_2=2.99$, 2H); ^{13}C NMR δ 23.1, 24.9, 26.8, 48.3, 55.9, 100.2, 108.5, 110.9, 111.1, 123.1, 127.9, 131.4, 132.0, 133.5, 134.0, 153.9, 168.4; MS (EIPI) *m/e* 346 (M^+).

(±)-3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (18). The deprotection was conducted according to the general method described for the *N*,*N*-phthalimido-tryptamines, yielding a browhish solid which was taken up in ethylacetate (25 mL) and washed with saturated K_2CO_3. The aqueous layer was twice extracted with ethyl acetate (25 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo leaving 226 mg (80%) of an off-white solid. Part of this material (120 mg) was converted to the HCl salt and recrystallized from EtOH/ether giving an off-white solid (103 mg; 58%): mp 108–110 °C; ^1H NMR δ 1.72–1.87 (m, 1H), 1.92–2.08 (m, 3H), 2.45 (dd, $J_1=14.96$, $J_2=8.12$, 1H), 2.75 (m, 2H), 3.00 (dd, $J_1=14.96$, $J_2=4.70$, 1H), 3.23–3.33 (m, 1H), 3.87 (s, 3H), 6.80 (dd, $J_1=8.55$, $J_2=2.56$, 1H), 6.94 (d, $J=2.56$, 1H), 7.13 (d, $J=8.55$, 1H), 8.38 (br s, NH); ^{13}C NMR δ 21.5, 31.1, 32.5, 47.8, 56.0, 100.2, 107.9, 110.6, 111.2, 128.0, 131.4, 134.1, 153.7; MS (EIPI) *m/e* 216 (M^+); HRMS calcd (obsd) for $C_{13}H_{16}N_2O$: 216.126 (216.126).

(±)-*N*,*N*-Phthalimido-3-amino-6-hydroxy-1,2,3,4-tetrahydrocarbazole (19). The title compound was prepared starting from **15** (1.23 g; 3.55 mmol) according to a previously published procedure,[28] affording a yellow solid (0.36 g, 31%): mp >270 °C (dec; lit. 270 °C dec); IR (KBr) cm^{-1} 1693 (C=O), 3352 (OH); ^1H NMR δ 2.01–2.11 (m, 1H), 2.86–2.98 (m, 4H), 3.43–3.56 (m, 1H), 3.83 (s, 3H), 4.62–4.76 (m, 1H), 6.80 (dd, $J_1=8.55$, $J_2=2.56$, 1H), 6.88 (d, $J=2.56$, 1H), 7.19 (d, $J=8.55$, 1H), 7.74 (dd, $J_1=5.55$, $J_2=2.99$, 2H), 7.78 (s, 1H), 7.88 (dd, $J_1=5.55$, $J_2=2.99$, 2H); ^{13}C NMR δ 23.1, 24.9, 26.8, 48.3, 55.9, 100.2, 108.5, 110.9, 111.1, 123.1, 127.9, 131.4, 132.0, 133.5, 134.0, 153.9, 168.4; MS (CI with NH_3) *m/e* 333 (M^+).

(±)-*N*,*N*-Phthalimido-3-amino-6-[[(trifluoromethyl)sulfonyl]-oxy]-1,2,3,4-tetrahydrocarbazole (20). A solution of **19** (227 mg, 0.68 mmol), Et_3N (0.2 mL) and $PhN(SO_2CF_3)_2$ (300 mg, 0.84 mmol) in CH_2Cl_2 (10 mL) was magnetically stirred until the reaction mixture became colorless. After 24 h, the organic layer was washed with 10% Na_2CO_3 (2×20 mL) which layers were extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The residual yellow oil was chromatographed on SiO_2 eluting with CH_2Cl_2. Pure fractions were pooled and evaporated in vacuo yielding a white solid (399 mg). This solid was recrystallized from EtOH (195 mg, 62%): mp 105–108 °C; IR (KBr) cm^{-1} 3338 (NH), 1705 (C=O), 1398, 1208 (O-SO_2); ^1H NMR δ 2.00–2.06 (m, 1H), 2.75–2.88 (m, 4H), 3.37–3.51 (m, 1H), 4.43–4.70 (m, 1H), 6.97 (dd, $J_1=8.54$, $J_2=2.44$, 1H), 7.15–7.31 m, 2H), 7.70–7.87 (m, 4H), 8.31 (br s, NH); ^{13}C NMR δ 22.7, 24.3, 26.3, 47.6, 109.1, 109.9, 111.2, 114.0, 118.7 (q, $J=321$, CF_3), 123.1, 127.6, 131.7, 134.0, 135.0, 135.5, 143.3, 168.4: HRMS calcd (obsd) for $C_{21}H_{15}N_2O_3SF_3$: 464.065 (464.065).

(±)-3-Amino-6-[[(trifluoromethyl)sulfonyl]oxy]-1,2,3,4-tetrahydrocarbazole (21). The title compound was prepared as described for the synthesis of **18**, affording 47 mg of a white foam (100%): mp 135–136 °C; ^1H NMR δ 1.65–1.83 (m, 1H), 1.92–2.12 (m, 1H), 2.41 (dd, $J_1=14.16$, $J_2=8.55$, 1H), 2.76 (m, 2H), 2.86–2.99 (m, 1H), 3.22–3.29 (m, 1H), 6.96 (dd, $J_1=8.79$, $J_2=2.44$, 1H), 7.19 (d, $J=8.79$, 1H), 7.28 (d, $J=2.44$, 1H), 8.52 (br s, NH); ^{13}C NMR δ 21.1, 30.3, 31.7, 47.1, 109.9, 111.0, 113.7, 118.7 (q, $J=320$, CF_3), 127.8, 134.9, 135.0, 143.2; HRMS calcd (obsd) for $C_{13}H_{13}N_2O_3SF_3$: 344.059 (344.059).

***N*-Boc-4-[5-[[(trifluoromethyl)sulfonyl]oxy]-1*H*-indol-3-yl]-piperidine (23).** The triflate derivative of compound **22** was prepared according to the procedure used for **20** giving 3.86 g (86%) after recrystallization from ether: *n*-hexane: mp 187–188 °C; IR (KBr) cm^{-1} 3309 (NH), 1657 (C=O), 1422, 1209 (O-SO_2); ^1H NMR δ 1.51 (s, 9H), 1.65 (dt, $J_1=12.49$, $J_2=3.84$, 2H), 2.01 (br d, $J=12.30$, 2H), 2.86–2.99 (m, 3H), 4.19 (br d, $J=12.49$, 2H), 7.04–7.10 (m, 2H), 7.37 (d, $J=8.74$, 1H), 7.50 (d, $J=2.26$, 1H), 8.70 (br s, NH); ^{13}C NMR δ 28.5, 32.7, 33.4, 44.3, 79.6, 111.4, 112.2, 115.0, 118.7 (q, $J=321$, CF_3), 121.5, 122.4, 126.7, 135.2, 143.1, 155.0; MS (CI with NH_3) *m/e* 466 ($M^{+18}NH_4^+$); anal. calcd (obsd) for $C_{19}H_{23}N_2O_5SF_3$: C: 50.89 (50.77), H: 5.17 (4.98), N: 6.25 (6.10).

4-[5-[[(Trifluoromethyl)sulfonyl]oxy]-1*H*-indol-3-yl]piperidine (24). Compound **23** (3.4 g, 7.6 mmol) was dissolved in CH_2Cl_2 (30 mL) and deprotected by adding TFA (3.5 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature. After 7 h, the volatiles were removed in vacuo giving an off-white solid which was taken up in 10% $NaHCO_3$ and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4) and reduced to dryness affording 1.95 g

(74%) of a light brown solid. Recrystallization from ethyl acetate/*n*-hexane gave an off-white solid (1.16 g, 44%). A small portion was converted in the HCl salt and recrystallized from acetonitrile: mp 249–250 °C (HCl); IR (KBr) cm^{-1} 3389 (NH), 1425, 1200 (O-SO_2); ^1H NMR (base) 2.08–2.20 (m, 2H), 2.35 (d, $J=12.82$, 2H), 3.24 (t, $J=12.09$, 3H), 3.69 (d, $J=12.09$, 2H), 7.36 (dd, $J_1=8.79$, $J_2=1.83$, 1H), 7.49 (s, 1H), 7.64 (d, $J=8.79$, 1H), 7.75 (d, $J=1.83$, 1H); ^{13}C NMR (base) δ 28.4, 29.3, 44.6, 108.5, 109.8, 112,6, 116.3 (q, $J=321$, CF_3), 123.9, 126.4, 132.5, 140.7; MS (CI with NH_3) *m/e* 349 (M^{+1}); anal. calcd (obsd) for $C_{14}H_{15}N_2O_3SF_3$·HCl: C: 43.70 (43.47), H: 4.19 (4.06), N: 7.28 (7.32).

***N*-Methyl-4-[5-[[(trifluoromethyl)sulfonyl]oxy]-1*H*-indol-3-yl]piperidine (25).** To a magnetically stirred solution of compound **24** (0.73 g, 2.1 mmol) in acetonitrile (10 mL), 37% aquous formaldehyde (1.2 mL) and $NaCNBH_3$ (0.4 g; CAUTION: poisonous) were added. The reaction mixture was acidified until pH 5 with glacial acetic acid, stirred for 2 h at room temperature and quenched with 10% NaOH (50 mL). After extraction (CH_2Cl_2, 2×50 mL), the organic layers were dried ($MgSO_4$) and evaporated in vacuo yielding 0.53 g (73%) of an oil. Conversion to the HCl salt and recrystallization from acetonitrile gave an off-white solid (165 mg, 20%): mp 247–248 °C; IR (KBr) cm^{-1} 3134 (NH), 1416, 1204 (O-SO_2); ^1H NMR (CD_3OD) δ 1.93–2.31 (m, 4H), 2.92 (s, 3H), 3.11–3.32 (m, 3H), 3.61 (br d, $J=12.21$, 2H), 7.07 (dd, $J_1=8.79$, $J_2=2.45$, 1H), 7.29 (s, 1H), 7.46 (d, $J=8.79$, 1H), 7.61 (d, $J=2.44$, 1H); ^{13}C NMR (CD_3OD) δ 30.0, 30.1, 42.4, 54.4, 110.5, 112.1, 113.9, 121.9, 123.1, 126.0, 143.0; MS (CI with NH_3) *m/e* 363 (M^{+1}); anal. calcd (obsd) for $C_{15}H_{17}N_2O_3SF_3$·HCl: C: 45.17 (45.08), H: 4.55 (4.50), N: 7.02 (7.29).

Pharmacology: Materials. The HeLa/HA_7 cell line was obtained from Tulco (Duke University, Durham, NC, USA). Cos-7 cells were purchased from ATCC (Rockville, USA). [^{3}H]5-CT (51.3 Ci/mmol) and [^{3}H]8-OH-DPAT (228 Ci/mmol) were obtained from New England Nuclear (Les Ulis, France)

Receptor binding assay. Membrane preparations of the HeLa/HA_7 cell line transfected with the h5-HT_{1A} receptor gene and transiently transfected Cos-7 cells expressing either h5-HT_{1B} or h5-HT_{1D} receptors were prepared in 50 mM Tris–HCl, pH 7.7 containing 4 mM $CaCl_2$, 10 μM pargyline and 0.1% ascorbic acid as previously described.[30] Binding assays were performed with 1 nM [^{3}H]8-OH-DPAT or 0.5 nM [^{3}H]5-CT. Incubation of mixtures consisted of 0.4 mL cell membrane preparation [200 μg (h5-HT_{1A}), and 20–80 g (h5-HT_{1B}) and 20–100 μg (h5-HT_{1D}) protein], 0.05 mL radioligand and 0.05 mL compound for inhibition or 10 μM 5-HT to determine non-specific binding. The reactions were stopped after 30 min incubation at 25 °C by adding 3.0 mL ice-cold 50 mM Tris–HCl pH 7.7 and rapid filtration over Whatman GF/B glass fiber filters using a Brandel Harvester, washed and counted as previously described.[30] Data were analyzed graphically with inhibition curves and IC_{50} values were derived. K_i values were calculated according to the equation:

$$K_i = IC_{50}/(1 + C/K_D)$$

with C the concentration and K_D the equilibrium dissociation constant of the radioactively labelled ligand. The corresponding K_D values are: 2.5 nM (h5-HT_{1A}); 0.12 nM (h5-HT_{1B}) and 0.22 nM (h5-HT_{1D}).

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31. Until recently, h5-HT_{1B} was denoted 5-$HT_{1D\beta}$ and h5-HT_{1D} was denoted 5-$HT_{1D\alpha}$. The r5-HT_{1B} receptor is the rodent homologue of the h5-HT_{1B} receptor subtype.