3-(Piperazinylpropyl)indoles: Selective, Orally Bioavailable h5-HT$_{1D}$ Receptor Agonists as Potential Antimigraine Agents

Mark S. Chambers,*,† Leslie J. Street,*,† Simon Goodacre,† Sarah C. Hobbs,† Peter Hunt,‡ Richard A. Jelley,† Victor G. Matassa,† Austin J. Reeve,† Francine Sternfeld,† Margaret S. Beer,§ Josephine A. Stanton,§ Denise Rathbone,|| Alan P. Watt,|| and Angus M. MacLeod†

Chemistry, Biochemistry, Molecular Modelling, and Bioanalytical Departments, Merck, Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

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Clinically effective antimigraine drugs such as Sumatriptan have similar affinity at h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors. In the search for a h5-HT$_{1D}$-selective agonist as an antimigraine agent, a novel series of 3-(propylpiperazinyl)indoles have been synthesized and evaluated at h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors. This class of compounds has provided subnanomolar, fully efficacious h5-HT$_{1D}$ agonists with up to 200-fold selectivity for the h5-HT$_{1D}$ receptor over the h5-HT$_{1B}$ receptor. Unlike other h5-HT$_{1D}$-selective series, several propylpiperazines demonstrate good oral bioavailability. The optimum compound was 1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-(3-fluorophenyl)ethyl)piperazine (**7f**) which has excellent selectivity for h5-HT$_{1D}$ receptors over other 5-HT receptor subtypes and good oral bioavailability in three species. Compound **7f** has been selected for further investigation as a potential development candidate in the treatment of migraine.

Introduction

The development of the 5-HT receptor agonist Sumatriptan (**1**) (Chart 1) has proven to be a significant advance in the acute treatment of migraine headaches.[1] Of the 13 currently identified 5-HT receptors,[2] Sumatriptan exhibits binding selectivity for the h5-HT$_{1D}$ and h5-HT$_{1B}$ subtypes,[3] and it has been generally accepted that its clinical efficacy is mediated through action at either one or both of these receptors.[4] Neither Sumatriptan nor the more recently developed "triptans" (Rizatriptan (**2**), Naratriptan, Zolmitriptan, Eletriptan) show significant binding selectivity for either of these two subtypes.[5] It has also been found that Sumatriptan has high affinity for the 5-HT$_{1F}$ receptor,[6] and it is therefore possible that some, or indeed all, of its effects in migraine relief are mediated through this receptor.[7] Indeed LY-334370 has been developed[8] as a selective 5-HT$_{1F}$ agonist that may test this hypothesis. Despite the clinical effectiveness of Sumatriptan, it does have some shortcomings.[9] In particular there is a potential for coronary artery constriction,[10] possibly through activation of 5-HT$_{1B}$ receptors,[11] which precludes its use in patients with known heart disease. This effect may or may not be related to chest pains experienced by some patients.[12]

In the belief that the efficacy of the "triptan" agents could be attributed to either one or the other of the 5-HT$_{1D/1B}$ receptors, we sought to identify compounds that discriminate between these two receptors, with a potentially lower side-effect profile. Although the pathogenesis of migraine is not fully understood, the efficacy of Sumatriptan has been attributed to vasoconstriction of cerebral blood vessels or inhibition of release of inflammatory neuropeptides caused by stimulation of the trigeminal ganglion.[13] Receptor mapping studies[14] have shown that the 5-HT$_{1B}$ receptor is widely distributed in the central nervous system (CNS) in neural and vascular tissues, whereas the 5-HT$_{1D}$ receptor is restricted to neural tissues including the trigeminal ganglion. This finding prompted us to investigate the possibility of developing selective h5-HT$_{1D}$ receptor agonists as potential second-generation antimigraine agents, which may lack the vasoconstrictor actions of unselective compounds such as Sumatriptan.

Screening of the Merck sample collection of 5-substituted tryptamines, synthesized during the discovery of Rizatriptan,[15] identified the pyrrolidine **4** (L-747,201) as having some binding selectivity for the h5-HT$_{1D}$ receptor over the h5-HT$_{1B}$ receptor (Table 1). Substitution on the pyrrolidine ring of **4** produced fully efficacious compounds with high binding affinity and >90-fold subtype selectivity for the h5-HT$_{1D}$ receptor (e.g., **5**);[16] however, none of the selective pyrrolidine analogues had appreciable oral bioavailability in animals, which prevented their subsequent development. In parallel to evaluating the pyrrolidine series, a program was initiated in which the basic amine was replaced by piperazine. This modification would allow the distal nitrogen to serve as a handle for substitution and so rapidly establish structure−activity relationships (SAR) within the series. This paper describes in detail the design, synthesis, and biological evaluation of a series of 3-(propylpiperazinyl)indoles as orally bioavailable h5-HT$_{1D}$ receptor-selective agonists, with up to 200-fold selectivity over the h5-HT$_{1B}$ receptor.[17]

Synthetic Chemistry

All the piperazinylindoles (with the exception of the *N*-phenyl derivative **18**) were prepared from the NH-

† Chemistry Department.
§ Biochemistry Department.
‡ Molecular Modelling Department.
|| Bioanalytical Department.

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Chart 1

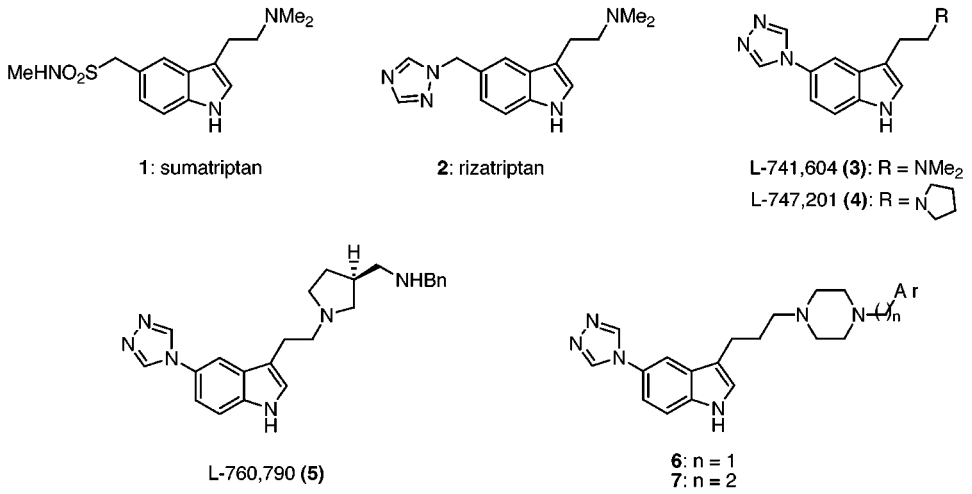
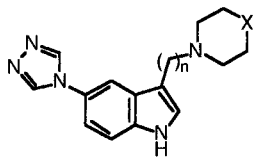


Table 1. Binding of Standard Compounds and Methylpiperazines to Cloned Human 5-HT_{1D} Receptors

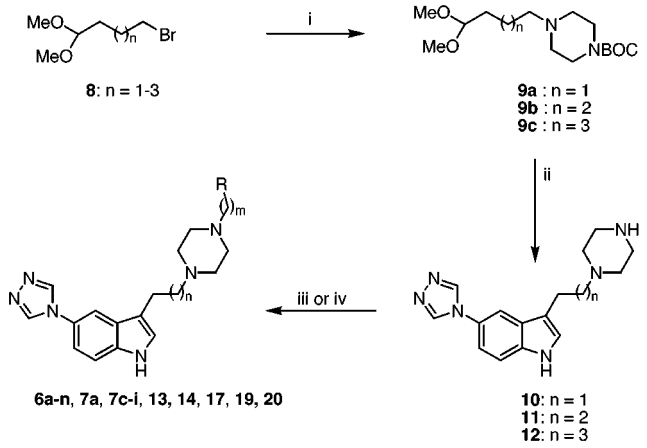


Comp[d].	n	X	IC_{50} (nM)[a] h5-HT_{1D}	IC_{50} (nM)[a] h5-HT_{1B}	selectivity 1B/1D[b]	EC_{50}(nM)[c] h5-HT_{1D}	Efficacy[d] (% 5-HT)
sumatriptan (**1**)	-	-	6.7 (7.4, 6.1)[e]	11 (13, 9)	2	14 (17, 11)	100 ± 5
L-741,604 (**3**)[f]	-	-	0.3 (0.4, 0.3)	1.3 (1.5, 1.2)	4	0.4 (0.5, 0.4)	115 ± 6
L-747,201 (**4**)	-	-	3.1 (3.8, 2.5)	28 (34, 23)	9	2.3 (3.2, 1.7)	120 ± 12
L-760,790 (**5**)	-	-	0.6 (0.7, 0.5)	37 (47, 30)	62	0.8 (1.3, 0.5)	102 ± 5
13	2	NMe	134	304	2	105 (140, 78)	61± 6
14	3	NMe	33 (42, 26)	309 (550, 174)	9	54 (69, 42)	95± 9
15	3	O	8.8	7.4	1	-	-
16	3	CH_2	24	15	2	-	-
17	4	NMe	210	5100	24	-	-

[a] Displacement of [^{3}H]-5-HT binding to cloned h5-HT_{1D} and h5-HT_{1B} receptors stably expressed in CHO cells. These results are the geometric means of ≥3 experiments. The values shown in parentheses are the upper and lower limits derived as a result of the SEM. Where these limits are not shown, the figures are the mean of two independent determinations performed in triplicate, typically with individual values within ±(10−15)% of the mean. In each case the radioligand concentration used was at the K_D for the receptor. [b] Binding selectivity for h5-HT_{1D} receptors. [c] Measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells stably transfected with h5-HT_{1D} receptors. These results are the geometric means of ≥3 experiments. The values shown in parentheses are the upper and lower limits derived as a result of the SEM. Where these limits are not shown, the figures are the mean of two independent determinations. [d] Maximum stimulation of [^{35}S]GTPγS binding expressed relative to the maximal effect produced by 5-HT. These results are the arithmetic means ± SEM of ≥3 experiments. Where SEM is not quoted, the figures are the mean of two independent determinations. [e] IC_{50}: 5HT_{1A}, 450 nM; 5-HT_{1F}, 27 nM. [f] See ref 19.

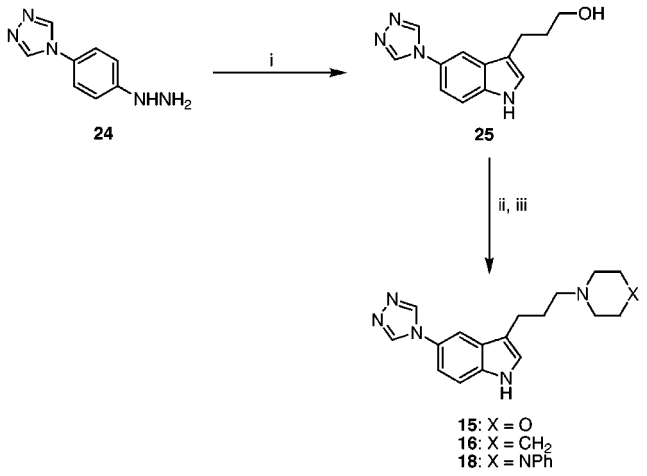
piperazines **10**−**12**. Piperazines **10**−**12** were prepared by reaction of *N*-BOC-piperazine with the bromo acetals **8**,[18] followed by Fischer cyclization of the resultant piperazine acetals **9a**−**c** with hydrazine **24**.[19] The majority of 4-substituted piperazinylindoles was prepared, as shown in Scheme 1, by reacting **10**−**12** with either the required halide (or mesylate in the case of **7d**) or aldehyde (under reductive conditions). The mesylate used for the synthesis of **7d** was prepared from the alcohol **22,** which in turn was obtained via ring closure of the amide oxime **21**. The pyridyl analogue **7b** was synthesized by coupling piperazine **11** with 3-pyridylacetic acid and reducing the resultant amide **23** with $LiAlH_4$.

Scheme 1[a]



[a] Reagents and conditions: (i) *tert*-butyl 1-piperazinecarboxylate, Na_2CO_3, DME, NaI, 100 °C; (ii) **24**, 4% H_2SO_4, reflux; (iii) $R(CH_2)_{m-1}CHO$, $NaCNBH_3$, AcOH, MeOH; (iv) $R(CH_2)_m$-X, DMF or MeOH, K_2CO_3.

Scheme 2[a]



[a] Reagents and conditions: (i) dihydropyran, 1 M HCl, reflux; (ii) $MeSO_2Cl$, Et_3N, THF; (iii) morpholine, piperidine or *N*-phenylpiperazine, K_2CO_3, DMF.

Scheme 2 outlines the synthesis of the morpholine (**15**), piperidine (**16**), and *N*-phenylpiperazine (**18**) analogues. Fischer reaction between the hydrazine **24** and dihydropyran in refluxing hydrochloric acid gave the homotryptophol **25**. Conversion to the mesylate and displacement with the appropriate amine gave the target indoles **15**, **16**, and **18**.

The benzylic substituted derivatives **6o**−**s** were synthesized as shown in Scheme 3. Reaction of piperazine **11** with methyl α-bromophenylacetate gave the ester **26**. Reduction of **26** with $LiAlH_4$ produced the alcohol **6o** which was then mesylated and converted to the aminomethyl analogue **6s**. Saponification of **26** and coupling the resultant acid with ammonia or dimethylamine gave the carboxamido and *N*,*N*-dimethylcarboxamido (**6r**) derivatives, respectively. The carboxamido analogue was resolved using a Chiralcel OD-H column to give the enantiomers **6p**,**q**.

The piperazinone **31** and thiopiperazinone **34** were prepared according to Scheme 4. The N-BOC-protected piperazinone **27** was deprotected using TFA to give **29**[20] and subsequently reacted with the mesylate of homotryptophol **25** to produce **31**. Reaction of **27** with Lawesson's reagent gave the thiopiperazinone **28**, which was then taken through in an identical manner to afford **34**.

The phenethylpiperazinone **32** was synthesized as shown in Scheme 5. 2-Phenylethylamine was converted to the N-BOC-protected diamine **35** which was then acylated, using bromoacetyl bromide, to give the amide **36**. Removal of the protecting group followed by ring closure under basic conditions gave the piperazinone **37** in high yield which was transformed to **32** as before. For synthesis of the 3-piperazinone analogue **33**, an alternative strategy was required since displacement reactions on the mesylate of **25**, using the anion of *N*-BOC-piperazinone,[21] proved unsuccessful. To circumvent this problem the piperazinone ring was constructed with the indole portion already attached.

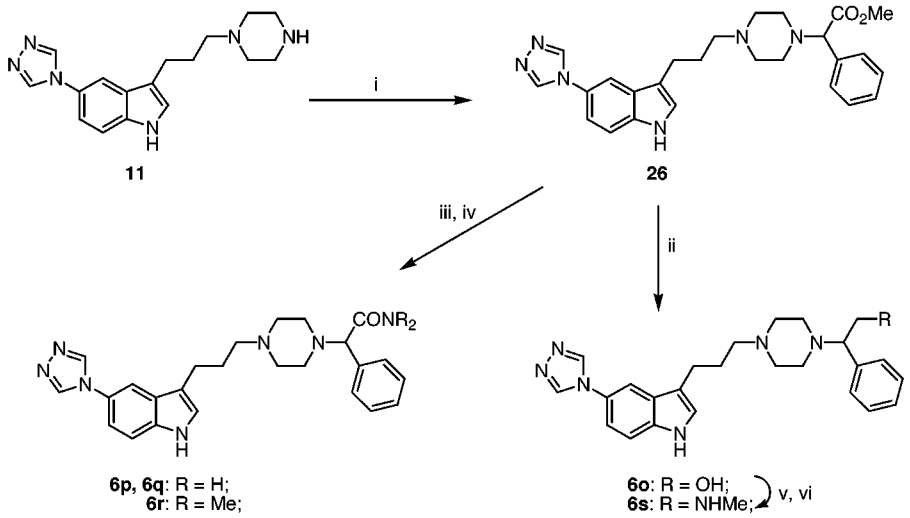
As shown in Scheme 6 the mesylate of **25** was reacted with *N*-BOC-ethylenediamine to give the indole **38**. Benzyl protection of the secondary amine followed by N-BOC removal and subsequent alkylation with ethyl bromoacetate gave the amino ester **39**. Hydrogenolysis liberated the secondary amine which was then cyclized in refluxing ethanol, in the presence of K_2CO_3, to generate the piperazinone **40**. Finally, N-benzylation gave the required analogue **33**.

Results

The h5-HT$_{1D}$ and h5-HT$_{1B}$ receptor affinities of the compounds were measured by displacement of [^{3}H]5-HT binding from cloned human 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors stably expressed in CHO cells.[22] Intrinsic efficacy (expressed as percent relative to the maximal effect produced by 5-HT) was measured in the same cell lines using the agonist-induced [^{35}S]GTPγS binding assay.[23,24]

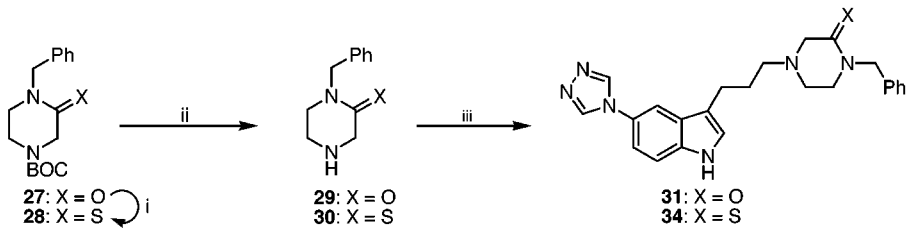
Replacement of the pyrrolidine ring of the initial lead compound **4** with *N*-methylpiperazine (**13**) was detrimental for h5-HT$_{1D}$ binding affinity (Table 1). However, extending the ethylene chain of **13** to give the propyl analogue **14** improved both h5-HT$_{1D}$ receptor affinity and binding selectivity over h5-HT$_{1B}$. Piperazine **14** was shown to be a full agonist in the [^{35}S]GTPγS binding assay. Further extension of the indole/piperazine linker to the butyl homologue **17** gave a lower affinity compound (IC_{50} 210 nM). Neither the morpholine (**15**) nor piperidine (**16**) analogues of the propylpiperazine **14** had binding selectivity for h5-HT$_{1D}$ over h5-HT$_{1B}$. Having identified **14** as a binding selective lead for the h5-HT$_{1D}$ receptor, we investigated replacement of *N*-methyl with a range of substituents to probe for increased affinity and binding selectivity (Table 2). Both the *N*-phenyl derivative **18** and pyrimidine **19** had improved affinity for the h5-HT$_{1D}$ receptor relative to **14**, although the pyrimidine was not selective. Binding selectivity could be improved in both the phenyl and heterocyclic series by introducing a methylene linker between the piperazine nitrogen and the aromatic ring. The benzyl analogue **6a** and the pyridylmethyl derivatives **6b**−**d** have high h5-HT$_{1D}$ receptor affinity and 35−85-fold binding selectivity for h5-HT$_{1D}$ over the h5-HT$_{1B}$ subtype. Replacement of the pyridine ring of **6b** with furan or imidazole gave compounds with comparable affinity and good binding selectivity. The phenethyl analogue **7a** had 10-fold lower affinity for the h5-HT$_{1D}$ receptor compared to the benzyl analogue **6a** but maintained >100-fold

Scheme 3[a]



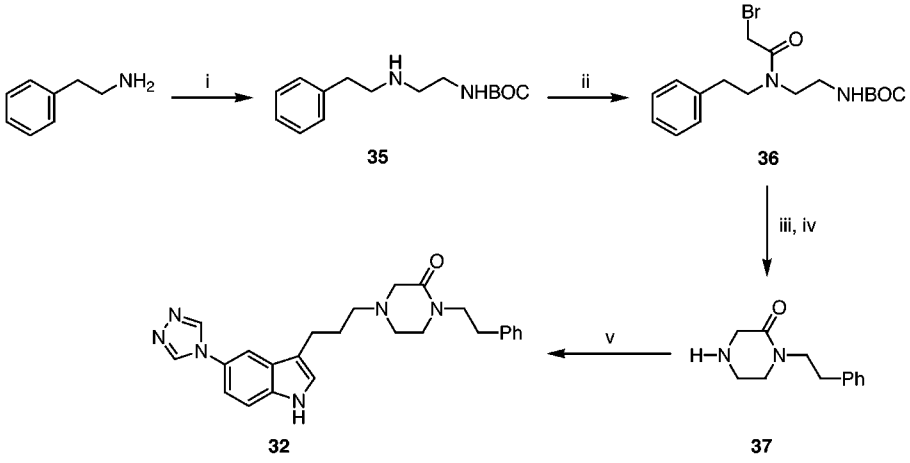
[a] Reagents and conditions: (i) methyl α-bromophenyl acetate, K_2CO_3, DMF, 60 °C; (ii) $LiAlH_4$, THF; (iii) NaOH, MeOH, H_2O; (iv) HNR_2, Et_3N, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole, DMF; (v) $MeSO_2Cl$, Et_3N, THF; (vi) H_2NMe, MeOH, THF, 65 °C.

Scheme 4[a]



[a] Reagents and conditions: (i) Lawesson's reagent, toluene, 90 °C; (ii) TFA, CH_2Cl_2; (iii) mesylate of **25**, NaI, K_2CO_3, IPA, reflux.

Scheme 5[a]

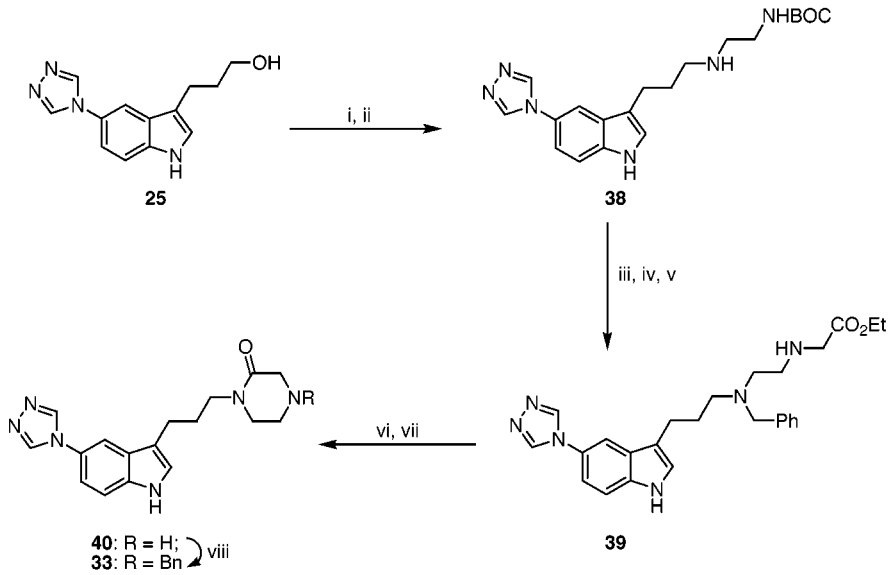


[a] Reagents and conditions: (i) 2-bromoethylcarbamic *tert*-butyl ester, K_2CO_3, DMF, 60 °C, 4 h; (ii) bromoacetyl bromide, Et_3N, DCM; (iii) TFA, DCM; (iv) K_2CO_3, EtOH, reflux; (v) mesylate of **25**, NaI, K_2CO_3, IPA, reflux.

binding selectivity, whereas further extension of the methylene linker to give the phenylpropyl derivative **20** reduced subtype selectivity. Despite the high affinity and selectivity exhibited by many of the compounds in Table 2, they all had submaximal intrinsic efficacy in the GTPγS binding assay relative to the starting leads **4** and **14**. Since there is no definitive animal model for migraine,[25] in order to fully test the hypothesis that a selective 5-HT_{1D} agonist alone is sufficient to intervene in the migraine process, we considered it essential that a development compound should have comparable efficacy to the clinically effective agents.[26]

Several strategies were employed in an attempt to improve intrinsic efficacy in the piperazine series while maintaining high affinity and h5-HT_{1D} subtype selectivity. Substituting the phenyl ring of both the benzylpiperazine **6a** and phenethylpiperazine **7a** was investigated as was substituting the methylene and ethylene chains linking the piperazine and phenyl rings. The results for the substituted benzylpiperazines **6h**−**m** and pheneth-

Scheme 6[a]



[a] Reagents and conditions: (i) $MeSO_2Cl$, Et_3N, DCM; (ii) 2-aminoethylcarbamic acid *tert*-butyl ester, K_2CO_3, NaI, reflux, IPA; (iii) PhCHO, $NaCNBH_3$, MeOH, AcOH; (iv) TFA, DCM; (v) ethyl bromoacetate, K_2CO_3, DMF; (vi) H_2, Pd on C, HCl (aq), EtOH; (vii) K_2CO_3, EtOH, reflux; (viii) benzyl bromide, K_2CO_3, DMF, 60 °C.

ylpiperazines **7c**−**h** are shown in Tables 3 and 4, respectively. In the benzyl series, *para*-substitution of the phenyl ring with small electron-withdrawing substituents, e.g., chloro (**6k**), cyano (**6l**), or fluoro (**6m**), gave compounds with high affinity and high binding selectivity for the h5-HT$_{1D}$ receptor (Table 3). In addition, both **6l**,**m** had higher intrinsic efficacy for the h5-HT$_{1D}$ receptor relative to the parent benzyl analogue **6a**. Substitution of the phenyl ring with acetamide (**6h**,**i**) resulted in lower subtype selectivity. In contrast to the benzyl series, replacing the phenyl ring of the phenethylpiperazine **7a** with 3-pyridyl (**7b**) reduced the subtype selectivity, whereas *para*-substitution with acetylamino (**7c**) gave an improvement in both selectivity (1B/1D 200) and efficacy (85% relative to 5-HT) (Table 4). Replacement of acetamide with oxadiazole to give **7d** resulted in lower affinity and selectivity. Fluoro substitution at all positions of the phenyl ring was well-tolerated to give a series of compounds, **7e**−**h**, with high affinity and selectivity for the h5-HT$_{1D}$ receptor. In addition, both the 2,4-difluorophenyl derivative **7h** and the 3-fluoro analogue **7f** (L-775,606) have efficacy for the h5-HT$_{1D}$ receptor which is comparable to that of the clinically efficacious antimigraine agents Sumatriptan and Rizatriptan.

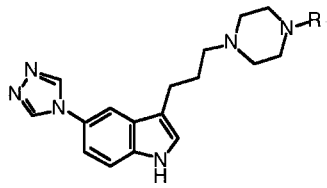
The efficacy of compounds in both the benzyl and phenethyl series could also be modulated by substituting the linking chain, although in some cases at the expense of lower affinity and subtype selectivity (Table 5). In the benzyl series substitution with methyl (**6n**), hydroxymethyl (**6o**), and *N*-methylaminomethyl (**6s**) was detrimental to h5-HT$_{1D}$ selectivity, although in the case of **6s** full agonism was achieved. Substitution of the benzylic carbon with carboxamide was also well-tolerated, and the results for the separated enantiomers, **6p**,**q**, are given in Table 5. Enantiomer **6p** had 10-fold higher h5-HT$_{1D}$ receptor affinity than its antipode **6q** (IC_{50} 0.24 and 2.3 nM, respectively), indicating that there was a stereoselective component to binding at the h5-HT$_{1D}$ receptor. This increased affinity translated into higher selectivity for the h5-HT$_{1D}$ receptor. In the phenethyl series benzylic methyl substitution resulted in the subnanomolar, fully efficacious h5-HT$_{1D}$ agonist **7i**.

The piperazinones shown in Table 6 were targeted in order to examine the effect of reducing the pK_a of the aspartate binding nitrogen. The *N*-benzylpiperazinone **31** and the thiopiperazinone analogue **34** had lower h5-HT$_{1D}$ affinity than the corresponding piperazine **6a** but demonstrated high efficacy at the h5-HT$_{1D}$ receptor. The 3-piperazinone isomer **33** had negligible h5-HT$_{1D}$ receptor affinity. In constrast to the piperazine series, N-substitution of the piperazinone ring with phenethyl (**32**) resulted in lower binding selectivity relative to the benzyl derivative **31**.

Discussion

As the results in Tables 2−6 clearly demonstrate, aryl or arylalkyl substituents on the piperazine nitrogen give enhanced binding at the h5-HT$_{1D}$ receptor compared to methyl. However, a comparison of the *N*-phenyl derivative **18** with the benzyl (**6a**) or phenethyl (**7a**) analogues indicates the importance of a linking chain between the piperazine nitrogen and the aromatic ring in order to achieve high binding selectivity. An explanation for these findings has been suggested based on the interaction of the N-substituent with important binding residues on the 5-HT$_{1D}$ receptor. Figure 1 shows the proposed docking of a phenethylpiperazine (**7f**) into the 5-HT$_{1D}$ receptor.[27] The isoleucine residue at position 113, tyrosine at position 98, and histidine at position 102 interact to form a favorable binding environment for the N-substituent at the 5-HT$_{1D}$ receptor. However, in the 5-HT$_{1B}$ receptor the isoleucine residue is phenylalanine and the histidine residue is glycine which change the side-chain arrangements in that region such that the binding of the N-substituent is no longer favorable. This proposal is supported by the observation that in a mutant 5-HT$_{1D}$ receptor[28] the change of ILE113PHE reduced the binding affinity of the selective

Table 2. Binding of Propylpiperazines to Cloned Human 5-HT_{1D} Receptors



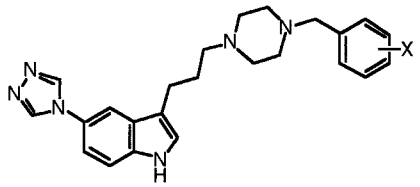
Comp[d].	R	IC_{50} (nM)[a] h5-HT_{1D}	IC_{50} (nM)[a] h5-HT_{1B}	selectivity 1B/1D[b]	EC_{50}(nM)[c] h5-HT_{1D}	Efficacy[d] (% 5-HT)
11	H	31 (36, 27)	145 (204, 102)	5	-	-
14	Me	33 (42, 26)	309 (550, 174)	9	54 (69, 42)	95 ± 9
18	Ph	1.4	13	9	-	-
19		0.6 (0.6, 0.6)	0.5 (0.6, 0.4)	1	0.6 (1.4, 0.3)	59 ± 0
6a	CH_2Ph	0.1 (0.2, 0.1)	11 (13, 9)	85	0.2 (0.4, 0.09)	57 ± 5
7a	CH_2CH_2Ph	1.4 (1.5, 1.3)	166 (191, 145)	119	1.7 (3.2, 0.9)	73 ± 8
20	$CH_2CH_2CH_2Ph$	4.9	85	17	4.0 (7.1, 2.2)	68 ± 3
6b		0.4 (0.5, 0.3)	18 (24, 13)	45	0.3	67
6c		0.3	22	73	0.3 (0.6, 0.2)	69 ± 4
6d		0.6	23	38	1.0 (1.3, 0.8)	66 ± 1
6e		0.4	18	45	0.5 (0.9, 0.3)	66 ± 6
6f		1.1	27	25	0.3 (0.4, 0.2)	70 ± 3
6g		1.6	36	23	2.0 (2.3, 1.7)	68 ± 5

[a–d] Footnotes as for Table 1.

5-HT_{1D} receptor agonists but had no effect on the affinity of the nonselective compounds, thereby indicating that this region of the receptor is important for achieving binding selectivity. In view of this explanation we wanted to determine whether the pyrrolidinylethyl series[16] could bind to the 5-HT_{1D} receptor in a similar manner. As shown in Figure 2 the low-energy conformations of the phenethylpiperazine **7f** and the pyrrolidine L-760,790 show good overlay of the ring nitrogen atoms and the aryl substituents, and it is therefore reasonable to propose a similar mode of binding for these two series. Despite either piperazine nitrogen being able to bind to the conserved aspartate in helix 3, we believe that it is the nitrogen proximal to the indole skeleton which is the main center for ionic interaction. This suggestion is based on the fact that for the very high affinity benzylpiperazine **6a** this is the most basic nitrogen and therefore the most likely to be protonated. Also, in the piperazinone series, the 3-piperazinone **33** (in which this ring nitrogen is replaced by amide) has very poor h5-HT_{1D} affinity (IC_{50} 173 nM) compared to the 2-piperazinone isomer **31** (IC_{50} 6.6 nM).

An explanation of the factors which control efficacy at the h5-HT_{1D} receptor is less obvious than those which influence binding selectivity, although substitution on either the phenyl ring or the methylene linker is clearly important in order to achieve full agonism. In particular, in the phenethyl series, fluorination at any position of the phenyl ring increased h5-HT_{1D} receptor efficacy with respect to **7a**, although these effects were not additive as demonstrated by the 3,4-difluoro analogue **7h** which had comparable efficacy to the 3-fluorophenethylpiperazine **7f**. In the benzyl series, substitution on the phenyl ring with electron-withdrawing substituents (e.g., trifluoromethyl (**6j**), cyano (**6l**), and fluoro (**6m**)) increased efficacy, although such groups are not a prerequisite for high efficacy since acetylamino (**6h** and **7c**), which is neither strongly electron-withdrawing or -donating, also has a beneficial effect. Attempts to explain the efficacy results based on the pK_a of the piperazine ring system are also undermined since the unsubstituted phenethylpiperazine **7a** (73% 5-HT) has a similar pK_a to its substituted counterparts **7f**,**h** (88–91% 5-HT). The observed change of going from a partial to a full agonist by introducing a benzylic methyl group (**7i**) in the phenethylpiperazine series may be due to a conformational change of the phenethyl side chain relative to the unsubstituted analogue **7a**. Replacing the

Table 3. Binding of Benzylpiperazines to Cloned Human 5-HT$_{1D}$ Receptors



Comp[d].	X	IC$_{50}$ (nM)[a] h5-HT$_{1D}$	IC$_{50}$ (nM)[a] h5-HT$_{1B}$	selectivity 1B/1D[b]	EC$_{50}$(nM)[c] h5-HT$_{1D}$	Efficacy[d] (% 5-HT)
6a	H	0.1 (0.2, 0.1)	11 (13, 9)	85	0.2 (0.4, 0.09)	57 ± 5
6h	4-NHCOMe	2.5 (2.7, 2.3)	56 (60, 53)	22	6.1 (7.0, 5.3)	78 ± 8
6i	3-NHCOMe	0.2	2.4	12	0.2 (0.4, 0.2)	70 ± 5
6j	4-CF$_3$	5.2	282	54	11 (17, 8)	82 ± 2
6k	4-Cl	0.5	59	118	1.2 (1.6, 0.8)	63 ± 7
6l	4-CN	0.7	130	186	1.1 (2.1, 0.6)	71 ±0
6m	4-F	0.1 (0.1, 0.1)	20 (23, 17)	167	0.3 (0.4, 0.2)	77 ± 6

[a–d] Footnotes as for Table 1.

piperazine ring with piperazinone (or thiopiperazinone) also resulted in high-efficacy compounds (cf. **6a** and **31** or **34**). This effect may be due to a direct interaction of the carbonyl (or thiocarbonyl) group with the receptor or because of the conformational change of the ring which occurs on going from piperazine to piperazinone.

An important criteria for our project was the identification of orally bioavailable h5-HT$_{1D}$ receptor-selective agonists. Most compounds in the pyrrolidine[16] and piperidine[16] series of selective h5-HT$_{1D}$ agonists showed low oral bioavailability in rats (<5%) because of either poor oral absorption or high first-pass metabolism. Benzylpiperazine **6a**, however, was shown to have 21% oral bioavailability in rats. Although the more selective phenethylpiperazine **7a** had lower oral bioavailability (7% in rats), this was improved by fluorinating the phenyl ring, and the fluoro analogues **7f**−**h** had good oral bioavailability (20−27% in rats). From this work, the 3-fluorophenylpiperazine **7f** was identified as the lead compound having oral bioavailability in three species (rat, 27% (t_{max} 2 h); dog, 25%; rhesus monkey, 24%). In addition, as well as having high binding selectivity for h5-HT$_{1D}$ over h5-HT$_{1B}$ receptors, **7f** was shown to have high selectivity over other serotonin subtypes (1A 55 nM; 1E >10 000 nM; 1F 3 800 nM; 2A 370 nM; 2C 9 000 nM; 5-HT$_3$ >10 000 nM)[17] and was >500-fold less active in a broad range of receptor and enzyme assays.[29]

In conclusion, a novel series of orally bioavailable h5-HT$_{1D}$ receptor agonists has been identified which have up to 200-fold selectivity over the h5-HT$_{1B}$ receptor. The optimum compound was shown to be the 3-fluorophenethylpiperazine **7f** which has excellent selectivity for the h5-HT$_{1D}$ receptor over other 5-HT receptor subtypes and good oral bioavailability in three species. On the basis of its in vitro and in vivo profile **7f** was selected for further investigation as a potential development candidate.

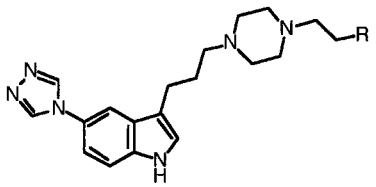
Experimental Section

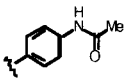
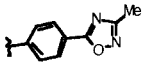
General. Unless otherwise indicated all reactions were carried out under a nitrogen atmosphere, using commercially available anhydrous solvents. Thin-layer chromatography was performed on glass-backed precoated Merck silica gel (60 F_{254}) plates, and flash column chromatography was carried out using 40−63 μm silica gel. Proton NMR spectra were measured on a Bruker AC250 or Bruker AM360 spectrometer in the solvents specified. Chemical shifts are measured in ppm downfield from TMS as an internal standard, and coupling constants are measured in hertz. Mass spectra were recorded on a VG Quattro spectrometer using positive ionization electrospray (ES^+). High-resolution mass spectra (HRMS) were carried out by M-Scan Ltd., Ascot, Berkshire, England. Combustion analyses were conducted by Butterworth Laboratories, Teddington, Middlesex, U.K. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

5-[4-(*tert*-Butyloxycarbonyl)piperazin-1-yl]pentanal Dimethyl Acetal (9b). A mixture of 5-bromovaleraldehyde dimethyl acetal[18b,c] (27.5 g, 0.13 mol), Na_2CO_3 (20.7 g, 0.2 mol), NaI (19.5 g, 0.13 mol), and *tert*-butyl 1-piperazinecarboxylate (25.5 g, 0.14 mol) in DME (250 mL) was heated at 100 °C for 3 h. The mixture was then cooled to room temperature and filtered. The filtrate was evaporated, EtOAc (50 mL) added, and the mixture filtered once again. The filtrate was removed in vacuo and the residue chromatographed on silica gel (EtOAc) to give the piperazine (25.7 g, 63%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29−1.71 (6H, m), 1.46 (9H, s), 2.31−2.39 (6H, m), 3.32 (6H, s), 3.41−3.45 (4H, m), 4.36 (1H, t, J = 6.0 Hz); HRMS calcd $C_{16}H_{32}N_2O_4$ 317.2440 $[M + H]^+$, found 317.2426.

1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4(*H*)-piperazine (11). A mixture of 4-(1,2,4-triazol-4-yl)phenylhydrazine (**24**)[19] (5.0 g, 29 mmol) and 5-[4-(*tert*-butyloxycarbonyl)-piperazin-1-yl]pentanal dimethyl acetal (9.0 g, 29 mmol) in

Table 4. Binding of Phenethylpiperazines to Cloned Human 5-HT_{1D} Receptors



Comp[d].	R	IC_{50} (nM)[a] h5-HT_{1D}	IC_{50} (nM)[a] h5-HT_{1B}	selectivity 1B/1D[b]	EC_{50}(nM)[c] h5-HT_{1D}	Efficacy[d] (% 5-HT)
7a		1.4 (1.5, 1.3)	166 (191, 145)	119	1.7 (3.2, 0.9)	73 ± 8
7b		4.9	93	19	7.8 (13, 5)	69 ± 6
7c		1.3 (1.4, 1.2)	260 (292, 232)	200	1.8 (2.1, 1.5)	85 ± 2
7d		6.9	46	7	-	-
7e		0.5	98	196	1.4	80
7f		0.5 (0.6, 0.4)	72 (83, 63)	144	1.0 (1.4, 0.8)	88 ± 3
7g		0.8	120	150	1.5 (1.6, 1.4)	81 ± 2
7h		0.9 (1.1, 0.7)	83 (105, 66)	92	0.7 (1.0, 0.5)	91 ± 4

[a–d] Footnotes as for Table 1.

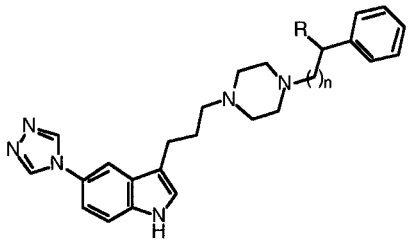
H_2SO_4 (4%, 150 mL) was heated at reflux for 48 h. The solution was cooled to 0 °C, basified (K_2CO_3), and extracted with *n*-BuOH (3 × 100 mL). The combined organic layers were evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (30:8:1)) to give the indole (3.9 g, 44%), which was converted to the hydrogen oxalate salt: mp 90−92 °C; ^{1}H NMR (D_2O) δ 2.12−2.24 (2H, m), 2.93 (2H, t, J = 7.0 Hz), 3.46−3.76 (10H, m), 7.37 (1H, dd, J = 8.7 and 1.9 Hz), 7.39 (1H, s), 7.66 (1H, d, J = 8.7 Hz), 7.82 (1H, d, J = 1.9 Hz), 9.13 (2H, s). Anal. ($C_{17}H_{22}N_6$.3.5($C_2H_2O_4$)) C, H, N.

General Procedure for the Preparation of Indoles 6a−k,m,n, 7a, 13, 14, and 17. 1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-([4-(acetylamino)phenyl]methyl)-piperazine (6h). To a solution of **11** (0.25 g, 0.81 mmol) and $NaCNBH_3$ (97 mg, 1.6 mmol) in MeOH (20 mL) was added a solution of 4-acetamidobenzaldehyde (0.16 g, 0.98 mmol) in MeOH (5 mL). The mixture was stirred for 16 h; then K_2CO_3 (saturated, 3 mL) was added. The solvents were removed, and EtOAc (50 mL) and H_2O (10 mL) were added to the residue. The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (70:8:1)) to give the title compound (0.18 g, 50%), which was converted to the hydrogen succinate salt: mp 92−94 °C; ^{1}H NMR (D_2O) δ 2.10−2.26 (2H, m), 2.28 (3H, s), 2.60 (4H, s), 2.82−3.32 (12H, m), 3.86 (2H, s), 7.35 (1H, dd, J = 8.8 and 2.1 Hz), 7.44 (1H, s), 7.46 (2H, d, J = 8.6 Hz), 7.54 (2H, d, J = 8.6 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.78 (1H, d, J = 2.1 Hz), 8.89 (2H, s). Anal. ($C_{26}H_{31}N_7O\cdot C_4H_6O_4\cdot H_2O$) C, H, N.

1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-[(4-cyanophenyl)methyl]piperazine (6l). A mixture of **11** (155 mg, 0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol), and 4-cyanobenzyl bromide (98 mg, 0.5 mmol) in DMF (5 mL) was heated at 50 °C for 45 min. The solvent was evaporated and the residue partitioned between EtOAc (25 mL) and H_2O (20 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH (95:5)) to give the title compound (190 mg, 89%), which was converted to the hydrogen oxalate salt: mp 142−144 °C; ^{1}H NMR (DMSO-d_6) δ 1.94−2.06 (2H, m), 2.42−3.20 (12H, m), 3.64 (2H, s), 7.30−7.33 (2H, m), 7.49 (1H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.79 (1H, d, J = 2.1 Hz), 7.81 (2H, d, J = 8.5 Hz), 9.01 (2H, s), 11.16 (1H, s). Anal. ($C_{25}H_{27}N_7\cdot 1.35(C_2H_2O_4)\cdot 0.25(H_2O)$) C, H, N.

1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-[4-(acetylamino)phenyl]ethyl)piperazine (7c). A mixture of **11** (0.3 g, 0.97 mmol), K_2CO_3 (0.27 g, 1.94 mmol), and (4-nitrophenyl)ethyl bromide (223 mg, 0.97 mmol) in DMF (50 mL) was stirred at room temperature for 18 h. The mixture was partitioned between EtOAc (3 × 100 mL) and H_2O (100 mL), and the combined organic extracts were washed with H_2O (2 × 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:8:1)) to give 1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-(4-nitrophenyl)ethyl)-piperazine (0.23 g, 52%), which was converted to the hydrogen oxalate salt: mp 213−215 °C; ^{1}H NMR (DMSO-d_6) δ 1.97−2.80 (2H, m), 2.70−3.20 (16H, m), 7.30−7.34 (2H, m), 7.50 (1H, d, J = 8.6 Hz), 7.54 (2H, d, J = 8.7 Hz), 7.80 (1H, d, J = 8.7 Hz), 8.15 (2H, d, J = 8.6 Hz), 9.02 (2H, s), 11.17 (1H, br s). Anal. ($C_{25}H_{29}N_7O_2\cdot 3.5(C_2H_2O_4)\cdot 0.1(H_2O)$) Calcd: C, 49.50; H, 4.70; N, 12.63. Found: C, 49.68; H, 4.90; N, 12.40.

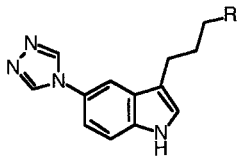
Table 5. Binding of Benzyl- and Phenethylpiperazines to Cloned Human 5-HT$_{1D}$ Receptors

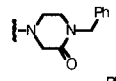
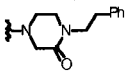
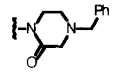
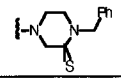


Comp[d].	n	R	IC$_{50}$ (nM)[a] h5-HT$_{1D}$	IC$_{50}$ (nM)[a] h5-HT$_{1B}$	selectivity 1B/1D[b]	EC$_{50}$(nM)[c] h5-HT$_{1D}$	Efficacy (% 5-HT)
6a	0	H	0.1(0.2, 0.1)	11 (13, 9)	85	0.2 (0.4, 0.09)	57 ± 5
6n	0	Me	1.0 (1.6, 0.6)	13 (13, 13)	13	-	-
6o	0	CH_2OH	0.7	9.5	14	0.3 (0.4, 0.2)	74 ± 6
6p	0	$CONH_2$	0.2	13	54	0.2 (0.3, 0.2)	77 ± 7
6q	0	$CONH_2$	2.3	55	24	3.8 (5.4, 2.7)	61 ± 6
6r	0	$CONMe_2$	1.0	102	102	0.8	68
6s	0	CH_2NHMe	0.9	17	19	1.7 (2.0, 1.5)	103 ± 11
7a	1	H	1.4 (1.5, 1.3)	166 (191, 145)	119	1.7 (3.2, 0.9)	73 ± 8
7i	1	Me	0.8 (0.9, 0.7)	45 (59, 34)	56	0.3 (0.5, 0.2)	94 ± 4

[a–d] Footnotes as for Table 1.

Table 6. Binding of Piperazinones and Thiopiperazinones to Cloned Human 5-HT$_{1D}$ Receptors



Comp[d].	R	IC$_{50}$ (nM)[a] h5-HT$_{1D}$	IC$_{50}$ (nM)[a] h5-HT$_{1B}$	selectivity 1B/1D[b]	EC$_{50}$(nM)[c] h5-HT$_{1D}$	Efficacy (% 5-HT)
31		6.6	282	43	7.5 (11, 5.1)	85 ± 2
32		5.2	78	15	-	-
33		173 (208, 144)	3900	22	-	-
34		0.8 (1.0, 0.6)	18 (26, 12)	23	2.3 (5.0, 1.1)	97 ± 2

[a–d] Footnotes as for Table 1.

PtO_2 (73 mg) was suspended in EtOH (40 mL) and stirred under an atmosphere of hydrogen for 1 h. The preceding (4-nitrophenylethyl)piperazine (230 mg, 0.5 mmol) was added and the mixture stirred for 15 min. The catalyst was removed by filtration, the solvent removed in vacuo, and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:8:1)) to give 1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-(4-aminophenyl)ethyl)piperazine (188 mg, 88%) which was characterized as the hydrogen oxalate salt: mp 122−125 °C; ^{1}H NMR (DMSO-d_6) δ 1.90−2.02 (2H, m), 2.62−3.06 (16H, m), 6.52 (2H, d, J = 8.3 Hz), 6.89 (2H, d, J = 8.3 Hz), 7.30−7.33 (2H, m), 7.49 (1H, d, J = 8.7 Hz), 7.79 (1H, d, J = 2.0 Hz),

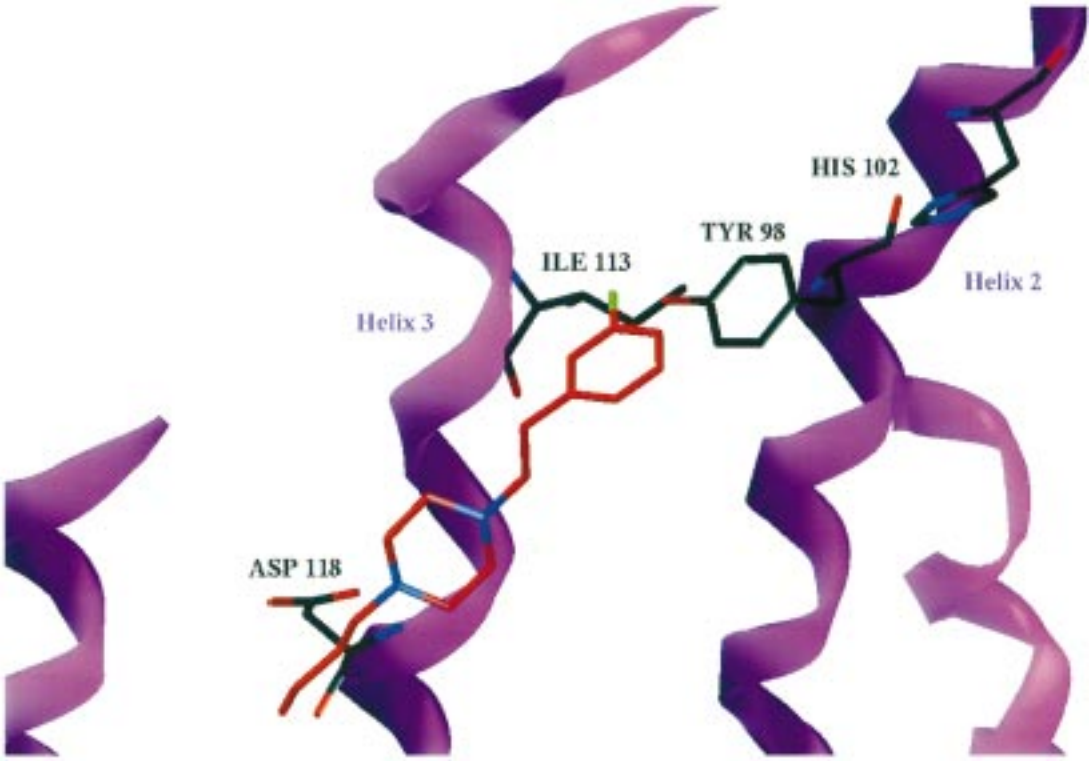


Figure 1. Proposed binding mode of the phenethylpiperazine **7f** at the 5-HT_{1D} receptor. The diagram shows interaction of the conserved aspartate in helix 3 with the piperazine nitrogen and of the aryl substituent with the isoleucine and tyrosine residues.

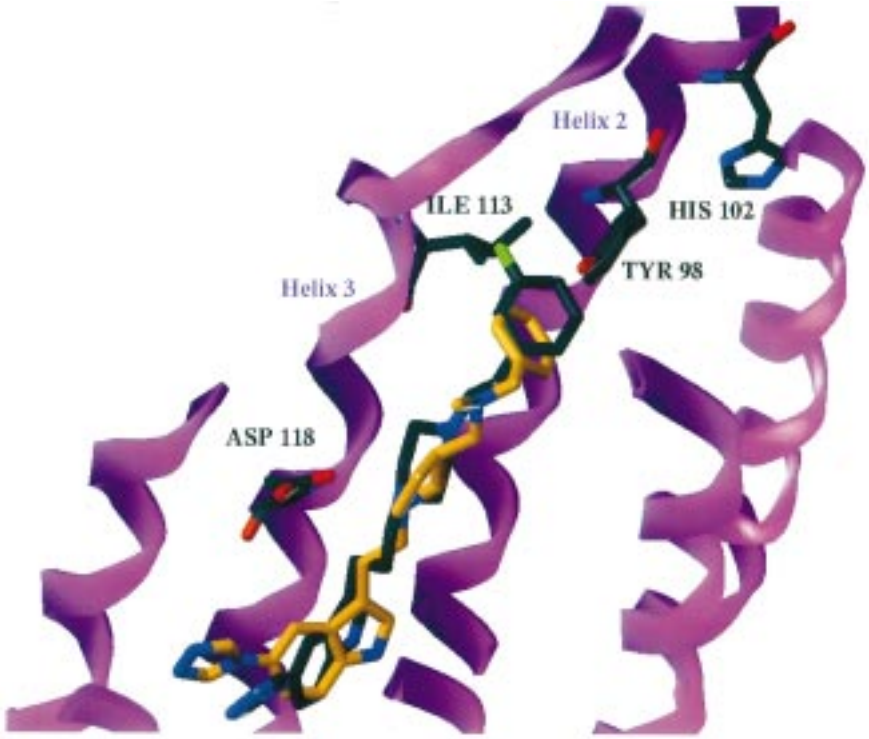


Figure 2. Overlay of the low-energy conformations of piperazine **7f** with the pyrrolidine **5** (L-760,790) at the 5-HT_{1D} receptor.

9.02 (2H, s), 11.15 (1H, s). Anal. ($C_{25}H_{31}N_7$·3.0($C_2H_2O_4$)·1.2(H_2O)) Calcd: C, 51.62; H, 5.51; N, 13.59. Found: C, 51.82, H, 5.11, 13.22.

Acetyl chloride (20 mg, 0.26 mmol) was added dropwise to a solution of the preceding aniline (100 mg, 0.23 mmol) and Et_3N (26 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was warmed to room temperature and stirred for 18 h. The solution was then diluted with CH_2Cl_2 (100 mL) and washed with H_2O (2 × 100 mL) and brine (100 mL). The organic layer was separated and dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:8:1)) to give the acetamide (78 mg, 71%) which was characterized as the hydrogen oxalate salt: mp 217−219 °C; ^{1}H NMR (DMSO-d_6) δ 1.90−2.08 (5H, m), 2.66−3.16 (16H, m), 7.15 (2H, d, J = 8.4 Hz), 7.33 (2H, m), 7.47−7.51 (3H, m), 7.79 (1H, s), 9.02 (2H, s), 9.87 (1H, s), 11.16 (1H, s). Anal. ($C_{27}H_{33}N_7O$·2.75($C_2H_2O_4$)·0.5(H_2O)) C, H, N.

General Procedure for the Preparation of Indoles 7d,e,g−i. 1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-(3,4-difluorophenyl)ethyl)piperazine (7h). To a solution of **11** (0.2 g, 0.65 mmol) in DMF (30 mL) were added Et_3N (0.13 g, 1.29 mmol), NaI (90 mg, 0.65 mmol), and (3,4-difluorophenyl)ethyl bromide (157 mg, 0.71 mmol). The mixture was heated at reflux for 16 h, then cooled to room temperature, and partitioned between EtOAc (150 mL) and H_2O (40 mL). The organic layer was separated, washed with H_2O (2 × 150 mL) and brine (150 mL), and then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:8:1)) to give the title compound (50 mg, 20%), which was converted to the hydrogen oxalate salt: mp 168−169 °C; ^{1}H NMR (DMSO-d_6) δ 1.92−2.03 (2H, m), 2.60−3.20 (16H, m), 7.06−7.10 (1H, m), 7.29−9.37 (4H, m), 7.49 (1H, d, J = 8.6 Hz), 7.80 (1H, d, J = 2.0 Hz), 9.01 (2H, s), 11.16 (1H, s). Anal. ($C_{25}H_{28}FN_6$·1.15($C_2H_2O_4$)·0.3(H_2O)) C, H, N.

1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(2-(3-fluorophenyl)ethyl)piperazine (7f). Phenyllithium (98 mL of a 1.8 M solution in cyclohexane/diethyl ether, 57 mmol) was added to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (60.8 g, 177 mmol) in ether (500 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and then at room temperature for 30 min. The mixture was cooled to −20 °C and 3-fluorobenzaldehyde (20 g, 161 mmol) added. The mixture was warmed to room temperature and stirred for 16 h. Saturated NH_4Cl (250 mL) was added and the organic layer separated. The aqueous phase was extracted with ether (2 × 250 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was distilled (60 °C/1.3 mbar) and the distillate chromatographed on silica gel (hexane:EtOAc (98:2)) to give 1-(3-fluorophenyl)-2-methoxyethene (10.7 g, 44%) as an *E*:*Z* mixture.

Concentrated HCl (45 mL) was added to a stirred solution of the preceding enol ether (7.2 g, 47 mmol) in THF (225 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min and then at room temperature for 3 h. Water was added, and the volatiles were evaporated in vacuo. Ether (100 mL) was added to the residue, and the organic layer was separated. The ethereal layer was washed with H_2O (2 × 100 mL), $NaHCO_3$ (saturated, 100 mL), and H_2O (100 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated (30 mmHg) to give 3-fluorophenylacetaldeyde[30] (5.8 g, 89%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 3.71 (2H, d, J = 2.2 Hz), 6.93−7.39 (4H, m), 9.76 (1H, t, J = 2.1 Hz).

To a stirred solution of **11** (7.6 g, 24 mmol), AcOH (3.5 mL, 61 mmol), and $NaCNBH_3$ (1.92 g, 31 mmol) in MeOH (300 mL) at 0 °C was added a solution of 3-fluoroacetaldehyde (4.2 g, 31 mmol) in MeOH (100 mL). The solution was warmed to room temperature and then stirred for 16 h. K_2CO_3 (saturated, 150 mL) was added and the solution decanted away from the solids and evaporated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The organic layer was separated, washed with K_2CO_3 (saturated, 200 mL) and brine (200 mL), then separated, and dried ($MgSO_4$). The solvent was removed in vacuo and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (80:8:1)) to give the title piperazine (8.3 g, 79%). The piperazine was converted to the bis-hydrogen maleate salt: mp 184 °C; ^{1}H NMR (MeOH-d_4 + TFA) δ 2.19−2.25 (2H, m), 2.93 (2H, t, J = 7.5 Hz), 3.07−3.11 (2H, m), 3.29−3.32 (6H, m), 3.45−3.48 (2H, m), 3.70 (4H, br s), 6.30 (4H, s), 7.01−7.10 (3H, m), 7.31−7.41 (3H, m), 7.59 (1H, d, J = 8.5 Hz), 7.94 (1H, d, J = 2.0 Hz), 9.83 (2H, s). Anal. ($C_{25}H_{29}FN_6$·2.0($C_4H_4O_4$)·0.4(H_2O)) C, H, N.

1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-(pyrimidin-2-yl)piperazine (19). A mixture of **11** (150 mg, 0.48 mmol), 2-chloropyrimidine (66 mg, 0.58 mmol), and Na_2CO_3 (72 mg, 0.68 mmol) in MeOH (20 mL) was heated at reflux for 16 h. The solvent was removed in vacuo and the residue partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was separated, washed with H_2O (20 mL) and brine (20 mL), and then dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed (CH_2Cl_2:MeOH:NH_3(60:8:1)) to give the title piperazine (25 mg, 13%), which was converted to the hydrogen oxalate salt: mp 79−81 °C; ^{1}H NMR (D_2O) δ 2.12−2.26 (2H, m), 2.86−2.98 (2H, m), 3.08−3.80 (8H, m), 4.58−4.70 (2H, m), 7.01 (1H, t, J = 5.0 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.41 (1H, s), 7.67 (1H, d, J = 8.6 Hz), 7.87 (1H, s), 8.52 (2H, d, J = 5.0 Hz), 9.47 (2H, s). Anal. ($C_{21}H_{24}N_8$·2.2($C_2H_2O_4$)·0.25(H_2O)) C, H, N.

4-(2-Hydroxyethyl)phenyl Amide Oxime (21). Sodium (0.23 g, 10 mmol) was dissolved in MeOH (30 mL), and hydroxylamine hydrochloride (0.7 g, 10 mmol) was added. The mixture was stirred at room temperature for 15 min; then 2-(4-cyanophenyl)ethanol (1.47 g, 10 mmol) was added. The mixture was stirred for 72 h; then the solvent was removed in vacuo. The residue was treated with EtOAc and filtered and the filtrate evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH (90:10)) to give the amide oxime (1.0 g, 56%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 2.73 (2H, t, J = 7.0 Hz), 3.56−3.64 (2H, m), 4.64−4.68 (1H, br t, J = 5.0 Hz), 5.76 (2H, br s), 7.21 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 9.55 (1H, s).

2-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]ethyl Alcohol (22). Sodium (130 mg, 5.6 mmol) was dissolved in MeOH (40 mL), **21** (1.0 g, 5.6 mmol) was added, and the mixture was stirred at room temperature for 15 min. EtOAc (5.3 mL, 56 mmol) was added and the mixture heated at reflux for 24 h. The solvent was removed in vacuo and the residue chromatographed on silica gel (CH_2Cl_2:MeOH (95:5)) to give the oxadiazole (0.48 g, 43%) as a colorless oil, which solidified on standing: mp 68−70 °C; ^{1}H NMR (DMSO-d_6) δ 2.66 (3H, s), 2.80 (2H, t, J = 6.8 Hz), 3.60−3.70 (2H, m), 4.68−4.77 (1H, m), 7.40 (2H, d, J = 8.3 Hz), 7.90 (2H, d, J = 8.3 Hz); HRMS calcd $C_{11}H_{12}N_2O_2$ 205.0977 $[M + H]^+$, found 205.0960.

4-[(Pyrid-3-yl)methylcarbonyl]-1-[3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl]piperazine (23). A solution of **11** (0.5 g, 1.6 mmol), 3-pyridylacetic acid hydrochloride (336 mg, 1.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (371 mg, 1.9 mmol), 1-hydroxybenzotriazole (262 mg, 1.94 mmol), and Et_3N (0.54 mL, 3.9 mmol) in DMF (10 mL) was stirred at room temperature for 18 h. The mixture was poured into H_2O (20 mL) and extracted with butanol (3 × 20 mL). The organic extracts were combined and evaporated and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)). The amide (0.6 g, 87%) was converted to the hydrogen oxalate salt: mp 99−100 °C; ^{1}H NMR (DMSO-d_6) δ 1.99−2.11 (2H, m), 2.75−2.81 (2H, m), 3.00−3.21 (6H, m), 3.61−3.85 (6H, m), 7.31−7.36 (3H, m), 7.50 (1H, d, J = 8.6 Hz), 7.59−7.62 (1H, m), 7.81 (1H, s), 8.40 (1H, d, J = 2.0 Hz), 8.43−8.45 (1H, m), 9.02 (2H, s), 11.17 (1H, br s). Anal. ($C_{24}H_{26}N_7O$·4.0($C_2H_2O_4$)) C, H, N.

4-(2-(Pyrid-3-yl)ethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)piperazine (7b). To a solution of **23** (0.3 g, 0.7 mmol) in THF (10 mL) was added $LiAlH_4$ (2.2 mL of a 1.0 M solution in ether, 2.2 mmol), and the mixture was stirred at room temperature for 30 min. After this time H_2O (0.2 mL) was added followed by NaOH (0.2 mL of a 4.0 M solution) and H_2O (5 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:H_2O (90:10:1)) to give the title piperazine (70 mg, 24%), which was converted to the hydrogen oxalate salt: mp 192−195 °C; ^{1}H NMR (DMSO-d_6) δ 1.87−2.11 (2H, m), 2.70−3.22 (16H, m), 7.28−7.37 (3H, m), 7.49 (1H, d, J = 8.6 Hz), 7.67−7.71 (1H, m), 7.80 (1H, d, J = 2.0 Hz), 8.40−8.46 (1H, m), 8.47−8.50 (1H, d, J = 2.0 Hz), 9.03 (2H, s), 11.19 (1H, br s). Anal. ($C_{24}H_{29}N_7$·3.85($C_2H_2O_4$)) C, H, N.

3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol (25). A solution of 4-(1,2,4-triazol-4-yl)phenylhydrazine (**24**) (25 g, 0.14 mol) and dihydropyran (24 g, 0.29 mol) in 1 M HCl (150 mL) was heated at reflux for 18 h. The mixture was evaporated in vacuo and the residue treated with MeOH and acetonitrile. The mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH (9:

1−4:1)) to afford **25** (10.3 g, 30%) as a colorless solid: mp 205−207 °C; ^{1}H NMR (DMSO-d_6) δ 1.81 (2H, quintet, J = 7.0 Hz), 2.75 (2H, t, J = 8.0 Hz), 3.46 (2H, d of t, J = 6.0 and 5.0 Hz), 4.43 (1H, t, J = 5.0 Hz), 7.26 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 9.0 and 2.0 Hz), 7.47 (1H, d, J = 9.0 Hz), 7.77 (1H, d, J = 2.0 Hz), 9.01 (2H, s), 11.05 (1H, s). Anal. ($C_{13}H_{14}N_4O$) C, H, N.

General Procedure for the Preparation of Morpholine 15, Piperidine 16, and Piperazine 18. 1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-4-phenylpiperazine (18). To a suspension of **25** (0.25 g, 1.0 mmol) in THF (75 mL) were added Et_3N (0.29 mL, 2.1 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol). The mixture was stirred for 1 h; then more Et_3N (73μL, 0.7 mmol) and methanesulfonyl chloride (40 μL, 0.5 mmol) were added. The reaction mixture was stirred for a further 1 h and then filtered and the solvent evaporated to afford the crude mesylate as a yellow gum. The mesylate was used in the subsequent reaction without further purification.

To a solution of *N*-phenylpiperazine (1.6 mL, 10.3 mmol) in DMF (5 mL) were added K_2CO_3 (214 mg, 1.6 mmol) and a solution of the preceding mesylate in DMF (10 mL). The mixture was heated at 50 °C for 4 h; then the solvent was evaporated. The residue was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The organic layer was separated and the aqueous phase washed further with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH (90:10)) to give the title piperazine (183 mg, 46%), which was converted to the hydrogen oxalate salt: mp 125 °C; ^{1}H NMR (DMSO-d_6) δ 1.99−2.10 (2H, m), 2.78 (2H, t, J = 7.3 Hz), 2.97−3.02 (2H, m), 3.10−3.21 (4H, m), 3.30−3.40 (4H, m), 6.83 (1H, t, J = 7.3 Hz), 6.97 (2H, d, J = 8.0 Hz), 7.24 (2H, t, J = 7.4 Hz), 7.30−7.34 (2H, m), 7.50 (1H, d, J = 8.6 Hz), 7.81 (1H, d, J = 1.9 Hz), 9.02 (2H, s), 11,17 (1H, br s). Anal. ($C_{23}H_{26}N_6$·1.2($C_2H_2O_4$)) C, H, N.

(±)-Methyl 2-(1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]-propyl)piperazin-4-yl)phenylacetate (26). To a solution of **11** (200 mg, 0.64 mmol) in DMF (5 mL) were added K_2CO_3 (98 mg, 0.71 mmol) and methyl α-bromophenyl acetate (112 μL, 0.71 mmol). The mixture was heated at 60 °C for 90 min, then the solvent evaporated, and the residue chromatographed on silica gel (CH_2Cl_2:MeOH (93:7)). The ester (205 mg, 70%) was isolated as a cream-colored foam: ^{1}H NMR ($CDCl_3$) δ 1.92−2.02 (2H, m), 2.42−2.70 (10H, m), 2.78 (2H, t, J = 7.4 Hz), 3.67 (3H, s), 4.00 (1H, s), 7.10−7.18 (2H, m), 7.27−7.41 (5H, m), 7.48 (1H, d, J = 8.5 Hz), 7.54 (1H, d, J = 2.0 Hz) 8.47 (2H, s), 9.05 (1H, br s); HRMS calcd $C_{26}H_{30}N_6O_2$ 459.2430 [M + H]$^+$, found 459.2526.

(±)-4-(2-Hydroxy-1-phenylethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)piperazine (6o). To a solution of **26** (620 mg, 1.4 mmol) in THF (20 mL) at −10 °C was added $LiAlH_4$ (1.6 mL of a 1.0 M solution in ether, 1.62 mmol) dropwise. After 2 h at −10 °C Na_2SO_4 (saturated, 5 mL) was added and the mixture warmed to room temperature. After 15 min the solid was removed by filtration and the filtrate evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)) to afford the alcohol (485 mg, 84%), which was converted to the hydrogen oxalate salt: mp 130−132 °C; ^{1}H NMR (DMSO-d_6) δ 2.16−2.28 (2H, m), 2.90−3.52 (12H, m), 3.76−3.82 (1H, m), 3.85−3.95 (1H, m), 3.87−4.08 (1H, m), 7.48−7.63 (7H, m), 7.72 (1H, d, J = 8.6 Hz), 8.02 (1H, s), 9.24 (2H, m), 11.42 (1H, br s). Anal. ($C_{25}H_{30}N_6O$·3.5($C_2H_2O_4$)·0.75 (diethyl ether)) C, H, N.

(±)-4-(2-(Methylamino)-1-phenylethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)piperazine (6s). To a solution of **6o** (132 mg, 0.31 mmol) in THF (10 mL) at 0 °C were added Et_3N (64 μL, 0.46 mmol) and methanesulfonyl chloride (36 μL, 0.46 mmol). After stirring at 0 °C for 45 min the mixture was filtered and the solvent volume reduced. The crude mesylate (in 5 mL THF) was then treated with methylamine (0.76 mL of a 8.0 M solution in EtOH, 6.1 mmol) and the mixture heated at 65 °C in a sealed tube for 30 min. The solvents were removed in vacuo and the residue chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)) to give the amine (87 mg, 64%), which was converted to the hydrogen oxalate salt: mp 180 °C; ^{1}H NMR (DMSO-d_6 + TFA) δ 2.01−2.17 (2H, m), 2.40 (3H, s), 2.40−3.20 (12H, m), 3.42−3.57 (2H, m), 4.41−4.50 (1H, m), 7.37−7.50 (6H, m), 7.58 (2H, d, J = 8.6 Hz), 7.96 (1H, s), 9.80 (2H, s), 11.34 (1H, s). Anal. ($C_{26}H_{33}N_7$·1.5($C_2H_2O_4$)·0.9(H_2O)) C, H, N.

Resolution of (±)-2-(1-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)piperazin-4-yl)phenylacetamide (6p,q). A solution of **26** (205 mg, 0.45 mmol) and NaOH (36 mg, 0.89 mmol) in MeOH (6 mL) and H_2O (1 mL) was heated at 60 °C for 10 h. The solvent was evaporated and the residue dissolved in H_2O (20 mL). The aqueous phase was neutralized using 1 M HCl and then the solvent removed in vacuo. The residue was azeotroped with toluene (2 × 7 mL) and the crude acid used without further purification.

To a solution of this acid in DMF (7 mL) were added Et_3N (77 μL, 0.55 mmol), 1-hydroxybenzotriazole (72 mg, 0.54 mmol), ammonia (573 μL of a 2 M solution in MeOH, 1.1 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (106 mg, 0.55 mmol). The mixture was stirred at room temperature for 24 h before the solvent was removed in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)) to afford the racemic carboxamide (158 mg, 80%), which was characterized as the hydrogen oxalate salt: mp 153 °C; ^{1}H NMR (DMSO-d_6) δ 1.90−2.06 (2H, m), 2.48−3.26 (12H, m), 3.87 (1H, s), 7.18 (1H, s), 7.29−7.38 (7H, m), 7.49 (1H, d, J = 8.6 Hz), 7.62 (1H, br s), 7.79 (1H, d, J = 2.0 Hz), 9.02 (2H, s), 11.18 (1H, br s). Anal. ($C_{25}H_{29}N_7O$·1.5($C_2H_2O_4$))

The racemic amide (121 mg, 0.27 mmol) was dissolved in EtOH (50 mg/mL), and the solution (50 μL/run) was injected onto a Chiralcel OD-H column (250- × 4.6-mm i.d., 5 μm) using EtOH:hexane (1:1) as the mobile phase. Using a flow rate of 1 mL/min and UV detection at 285 nM, the two enantiomers were efficiently separated (purity >99.5%). The fractions containing each separate enantiomer were combined and evaporated in vacuo.

Enantiomer 6p (40 mg): mp 148−150 °C. Anal. ($C_{25}H_{29}N_7O$·1.5($C_2H_2O_4$)) C, H, N.

Enantiomer 6q (41 mg): mp 150−153 °C. Anal. ($C_{25}H_{29}N_7O$·1.5($C_2H_2O_4$)) C, H, N.

4-(*tert*-Butyloxycarbonyl)-1-(phenylmethyl)piperazine-2-thione (28). A mixture of **27**[20] (1.0 g, 3.4 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) (0.84 g, 2.1 mmol) in toluene (10 mL) was heated at 90 °C for 45 min. The mixture was then partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated and the aqueous phase washed further with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:EtOAc (95:5)). The thioamide (0.85 g, 82%) was isolated as a colorless solid: mp 126−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, m), 3.40−3.44 (2H, m), 3.60−3.65 (2H, m), 4.67 (2H, s), 5.31 (2H, s), 7.31−7.39 (5H, m). Anal. ($C_{16}H_{22}N_2O_2S$·0.1(H_2O)) C, H, N.

1-(Phenylmethyl)piperazine-2-thione (30). To a solution of **28** (0.93 g, 3.0 mmol) in CH_2Cl_2 (25 mL) was added TFA (2.5 mL), and the mixture was stirred for 2 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (50 mL) and Na_2CO_3 (10% (w/v), 40 mL). The organic layer was separated and the aqueous phase washed further with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH (95:5)). 1-(Phenylmethyl)piperazine-2-thione (0.54 g, 87%) was isolated as a cream-colored solid: mp 70−73 °C; ^{1}H NMR ($CDCl_3$) δ 3.11−3.16 (2H, m), 3.29−3.33 (2H, m), 4.10 (2H, m), 5.31 (2H, s), 7.30−7.37 (5H, m). Anal. ($C_{11}H_{14}N_2S$·0.1(H_2O)) C, H, N.

2-(2-Phenylethylamino)ethylcarbamic Acid *tert*-Butyl Ester (35). A mixture of phenylethylamine hydrochloride (2.88 g, 18 mmol), 2-bromoethylcarbamic acid *tert*-butyl ester[31] (4.1 g, 18 mmol), and K_2CO_3 (5.0 g, 36 mmol) in DMF (50 mL) was heated at 60 °C for 4 h. The mixture was cooled to room temperature and filtered and the filtrate evaporated in vacuo.

The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel (CH_2Cl_2:MeOH (90:10)). The title compound (1.44 g, 30%) was isolated as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.74 (2H, t, J = 6.0 Hz), 2.79 (2H, m), 2.88 (2H, m), 3.19 (2H, m), 4.87 (1H, br s), 7.19−7.22 (3H, m), 7.26−7.31 (2H, m). Anal. ($C_{15}H_{24}N_2O_2$·0.2(H_2O)) C, H, N.

1-(2-Phenylethyl)piperazin-2-one (37). To a solution of bromoacetyl bromide (0.25 mL, 2.9 mmol) in CH_2Cl_2 (10 mL) at −10 °C was added a solution of **35** (0.7 g, 2.7 mmol) and Et_3N (0.41 mL, 2.9 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at −10 °C for 30 min; then the solvent was removed in vacuo. The residue was partitioned between EtOAc (30 mL) and H_2O (30 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (hexane:EtOAc (2:1)) to afford the amide **36** (0.81 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.86−2.94 (2H, m), 3.10−3.94 (8H, m), 4.59 and 4.92 (1H, br s), 7.15−7.37 (5H, m); MS (ES^+) 385/387 (M^+).

A solution of **36** (0.81 g, 2.1 mmol) and TFA (2.5 mL) in CH_2Cl_2 (25 mL) was stirred at room temperature for 1 h. The solvent was removed in vacuo; the resultant amine trifluoroacetate dissolved in EtOH (50 mL) and K_2CO_3 (0.58 g, 4.2 mmol) was added. The mixture was heated at reflux for 20 h, cooled to room temperature, and filtered. The filtrate was evaporated and the residue partitioned between CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)). The piperazinone **37** (0.36 g, 84%) was isolated as a colorless solid: mp 75−78 °C; ^{1}H NMR ($CDCl_3$) δ 2.89 (2H, t, J = 7.1 Hz), 2.97 (2H, m), 3.14 (2H, m), 3.51 (2H, s), 3.59 (2H, t, J = 7.2 Hz), 7.19−7.33 (5H, m). Anal. ($C_{12}H_{16}N_2O$) C, H, N.

General Procedure for the Preparation of Piperazinones 31 and 32 and Thiopiperazinone 34. 1-(Phenylmethyl)-4-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-piperazine-2-thione (34). To a suspension of **25** (150 mg, 0.62 mmol) in THF (80 mL) were added Et_3N (172 μL, 1.24 mmol) and methanesulfonyl chloride (96 μL, 1.24 mmol). The mixture was stirred for 90 min; then more Et_3N (86 μL, 0.62 mmol) and methanesulfonyl chloride (48 μL, 0.62 mmol) were added. The mixture was stirred for a further 1 h and then filtered and the filtrate evaporated. The resultant crude mesylate was treated with **30** (255 mg, 1.24 mmol), K_2CO_3 (257 mg, 1.9 mmol), and NaI (93 mg, 0.62 mmol) in isopropanol (20 mL) and the mixture heated at reflux for 20 h. The mixture was then cooled to room temperature and filtered and the filtrate evaporated. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (95:5:1)). The title piperazine (47 mg, 18%) was isolated as a colorless solid: mp (MeOH) 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.81−1.92 (2H, m), 2.42 (2H, t, J = 7.1 Hz), 2.70−2.76 (4H, m), 3.37−3.42 (2H, m), 3.61 (2H, s), 5.24 (2H, s), 7.27−7.38 (7H, m), 7.47 (1H, d, 8.6 Hz), 7.77 (1H, s), 9.01 (2H, s), 11.07 (1H, br s). Anal. ($C_{24}H_{26}N_6S$·0.3(H_2O)) C, H, N.

2-[3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propylamino]-ethylcarbamic Acid *tert*-Butyl Ester (38). To a suspension of **25** (0.8 g, 3.3 mmol) in THF (250 mL) were added Et_3N (0.51 mL, 6.6 mmol) and methanesulfonyl chloride (0.92 mL, 6.6 mmol). The mixture was stirred for 90 min, then filtered, and evaporated. The crude mesylate was dissolved in 2-propanol (130 mL), and K_2CO_3 (1.4 g, 9.9 mmol), NaI (0.5 g, 3.3 mmol), and 2-aminoethylcarbamic acid *tert*-butyl ester (1.3 g, 8.3 mmol) were added. The mixture was heated at reflux in the dark for 9 h. After cooling the mixture was filtered and the filtrate evaporated. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (90:10:1)) to afford the title compound (0.42 g, 33%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.84−1.96 (2H, m), 2.68−2.85 (6H, m), 3.16−3.26 (2H, m), 4.91 (1H, br s), 7.13−7.17 (2H, m), 7.48 (1H, d, J = 8.6 Hz), 7.56 (1H, d, J = 2.1 Hz), 8.48 (2H, s), 8.53 (1H, br s). Anal. ($C_{20}H_{28}N_6O_2$·1.2(H_2O)) C, H, N.

Ethyl 2-[(Phenylmethyl)-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)amino]ethylaminoacetate (39). To a solution of **38** (0.42 g, 1.1 mmol) in MeOH (10 mL) at 0 °C were added benzaldehyde (133 μL, 1.3 mmol), AcOH (189 μL, 3.3 mmol), and $NaCNBH_3$ (137 mg, 2.2 mmol). The cooling bath was removed and the mixture stirred at room temperature for 4 h. More benzaldehyde (220 μL, 2.2 mmol) was added and the mixture stirred for an additional 18 h. The solvents were evaporated, and the residue was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (95:5:1)) to give 2-(phenylmethyl-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-amino)ethylcarbamic acid *tert*-butyl ester (0.44 g, 85%) as a pale-yellow foam: ^{1}H NMR ($CDCl_3$) δ 1.41 (9H, s), 1.84−1.96 (2H, m), 2.52−2.58 (4H, m), 2.75 (2H, t, J = 7.5 Hz), 3.12−3.20 (2H, m), 3.58 (2H, s), 4.78 (1H, br s), 7.03 (1H, s), 7.14 (1H, dd, J = 8.5 and 2.0 Hz), 7.21−7.36 (5H, m), 7.45 (1H, d, J = 8.5 Hz), 7.51 (1H, d, J = 2.0 Hz), 8.29 (1H, br s), 8.45 (2H, s); MS (ES^+) 475 (M + 1).

A solution of the preceding N-benzylated derivative (440 mg, 0.93 mmol) and TFA (3 mL) in CH_2Cl_2 (20 mL) was stirred at room temperature for 5 h. After this time the solvent was evaporated and the residue partitioned between CH_2Cl_2 (30 mL) and K_2CO_3 (10% (w/v), 20 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. *N*-(Phenylmethyl)-*N*-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)-1,2-diaminoethane (287 mg, 83%) was isolated as a colorless foam and used without further purification: ^{1}H NMR ($CDCl_3$ + MeOH-d_4) δ 1.83−1.99 (2H, m), 2.44−2.59 (4H, m), 2.61−2.79 (4H, m), 3.58 (2H, s), 7.07 (1H, s), 7.11 (1H, dd, J = 8.6 and 2.1 Hz), 7.20−7.32 (5H, m), 7.48 (1H, d, J = 8.6 Hz), 7.51 (1H, d, J = 2.1 Hz), 8.49 (2H, s); HRMS calcd: $C_{22}H_{26}N_6$ 375.2219 $[M + H]^+$, found 375.2307.

To a mixture of the preceding diamine (125 mg, 0.33 mmol) and K_2CO_3 (46 mg, 0.33 mmol) in DMF (10 mL) was added ethyl bromoacetate (37 μL, 0.33 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h, then the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous phase extracted further with CH_2Cl_2 (30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH (90:10)). The ester (94 mg, 62%) was isolated as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 1.84−1.99 (2H, m), 2.52−2.80 (6H, m), 3.31 (2H, s), 3.60 (2H, s), 4.15 (2H, q, J = 7.2 Hz), 7.01 (1H, s), 7.14 (1H, dd, J = 8.5 and 2.1 Hz), 7.21−7.30 (5H, m), 7.45 (1H, d, J = 8.5 Hz), 7.58 (1H, d, J = 2.1 Hz), 8.35 (1H, br s), 8.48 (2H, s); MS (ES^+) 461 (M + 1).

1(*H*)-4-(3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl)-piperazin-3-one (40). A solution of **39** (94 mg, 0.25 mmol) and 1 M HCl (2 mL) in EtOH (20 mL) was hydrogenated at 40 psi for 3 h in the presence of palladium on carbon (10%, 121 mg). The catalyst was removed by filtration and the filtrate evaporated and azeotroped with EtOH (20 mL) The resultant foam was dissolved in EtOH (8 mL), K_2CO_3 (56 mg, 0.41 mmol) added, and the mixture heated at reflux for 2 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer extracted with BuOH (3 × 15 mL). The combined BuOH layers were evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH:NH_3 (60:8:1)) to give the piperazinone (42 mg, 40%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.94−2.07 (2H, m), 2.80 (2H, t, J = 7.2 Hz), 3.02 (2H, t, J = 5.7 Hz), 3.31−3.37 (2H, m), 3.41−3.45 (4H, m),

7.13 (1H, dd, J = 8.6 and 2.1 Hz), 7.23 (1H, s), 7.49 (1H, d, J = 8.6 Hz), 7.58 (1H, d, J = 2.1 Hz), 8.60 (2H, s); MS (ES^+) 325 (M + 1). Anal. ($C_{17}H_{20}N_6O \cdot 1.6(H_2O)$) C, H, N.

1-(Phenylmethyl)-4-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl)piperazin-3-one (33). A mixture of **40** (44 mg, 0.14 mmol), K_2CO_3 (19 mg, 0.14 mmol), and benzyl bromide (16 μL, 0.14 mmol) in DMF (7 mL) was heated at 60 °C for 2 h. The solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH (95:5)) to afford **33** (34 mg, 61%), which was converted to the hydrogen oxalate salt: mp 130−132 °C; ^{1}H NMR (DMSO-d_6) δ 1.83−1.96 (2H, m), 2.65−2.76 (4H, m), 3.03 (2H, s), 3.27−3.43 (4H, m), 3.61 (2H, s), 7.28−7.35 (7H, m), 7.47 (1H, d, J = 8.9 Hz), 7.77 (1H, s), 9.01 (2H, s), 11.08 (1H, br s). Anal. ($C_{24}H_{26}N_6O \cdot 1.2(C_2H_2O_4) \cdot H_2O$) C, H, N.

Bioavailability Method. A serial sampling protocol using surgically cannulated rats was chosen for this study. Following overnight food deprivation, six male Sprague−Dawley rats (approximate weight 310 g) were anesthetized with Isoflurane and their tail arteries were surgically cannulated. The animals were pretreated with a 100-unit dose of heparin (0.1 mL, 1000 units/mL) and allowed to recover for a period of at least 30 min prior to dosing with **7f**. The HCl salt of the compound was administered iv to three rats as a solution (1.27 mL/kg of a 2.36 mg/mL solution; 3 mg/kg) in dilute HCl/PEG300 (75/25 (v/v)) via a bolus injection into the tail vein. The compound was also dosed orally to three rats as a solution (5 mL/kg of a 0.6 mg/mL solution; 3 mg/kg) in dilute HCl (pH 2.8) via a gavage to the stomach. Blood samples (approximately 600 μL) were taken from each rat via the tail artery cannula at times out to 6 h postdose. After each sample an equivalent volume of heparinized saline (10 units/mL) was injected into the rat via the cannula. Plasma samples, prepared by centrifugation of whole blood, were stored frozen (−20 °C) prior to analysis. Concentrations of **7f** in plasma were quantified by method of internal standard using a nonvalidated HPLC fluorescence assay (ex = 234 nm, em = 370 nm), and phamacokinetic analysis was model-independent, calculated using standard formulas in an EXCEL spreadsheet.

Biochemical Methods. 1. h5-HT$_{1D}$/h5-HT$_{1B}$ Radioligand Binding. Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors were harvested in PBS, homogenized in ice-cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron, and centrifuged at 48000g at 4 °C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10-min incubation at 37 °C. Finally the tissue was recentrifuged at 48000g, 4 °C for 11 min, and the pellet resuspended in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, $CaCl_2$ 4, ascorbate 0.1%, pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg of protein/mL). Incubations were carried out for 30 min at 37 °C in the presence of 0.02−150 nM [^{3}H]-5-HT for saturation studies or 2−5 nM [^{3}H]-5-HT for displacement studies. The final assay volume was 1 mL. 5-HT (10 μM) was used to define nonspecific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/0.5% Triton X) followed by 2 × 4-mL washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by nonlinear, least-squares regression analysis using an iterative curve fitting routine, from which IC$_{50}$ (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound.

2. h5-HT$_{1D}$/h5-HT$_{1B}$ GTPγS Binding. Studies were performed essentially as described in ref 24. CHO clonal cell lines expressing the human cloned 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors were harvested in PBS and homogenized using a Kinematica polytron in ice-cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40000g, 4 °C for 15 min. The pellet was then resuspended in ice-cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature, and recentrifuged at 40000g, 4 °C for 15−25 min. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, $MgCl_2$ 10, pargyline 0.01, ascorbate 0.1%, pH 7.4 at room temperature) at a concentration of 40 μg of protein/mL for the h5-HT$_{1D}$ receptor transfected cells and 40−50 μg of protein/mL for the h5-HT$_{1B}$ receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 mL, with GDP (100 μM for h5-HT$_{1D}$ receptor transfected cells, 30 μM for the h5-HT$_{1B}$ receptor transfected cells) and test compound at 30 °C for 20 min and then transferred to ice for a further 15 min. [^{35}S]GTPγS was then added at a final concentration of 100 pM, and the samples were incubated for 30 min at 30 °C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters, washed with 5 mL of water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a nonlinear, least-squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC$_{50}$ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound.

Supporting Information Available: Information describing the computer-generated model of the 5-HT$_{1D}$ receptor. This material is available free of charge via the Internet at http://pubs.acs.org.

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