Synthesis and Serotonergic Activity of 5-(Oxadiazolyl)tryptamines: Potent Agonists for 5-HT$_{1D}$ Receptors

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The synthesis and 5-HT$_{1D}$ receptor activity of a novel series of 5-(oxadiazolyl)tryptamines is described. Modifications of the oxadiazole 3-substituent, length of the linking chain (*n*), and the amine substituents are explored and reveal a large binding pocket in the 5-HT$_{1D}$ receptor domain. Oxadiazole substituents such as benzyl are accommodated without loss of agonist potency or efficacy. The incorporation of polar functionality on a phenyl or benzyl spacer group results in a 10-fold increase in affinity and functional potency. Optimal 5-HT$_{1D}$ activity is observed when the heterocycle is conjugated with the indole and the benzyl sulfonamides **20t** and **20u** represent some of the most potent 5-HT$_{1D}$ agonists known. Replacement of O for S in the heterocycle leads to a further increase in potency. Deletion of oxadiazole N-2 does not reduce activity, suggesting the requirement for only one H-bond acceptor in this location. The selectivity of these compounds for 5-HT$_{1D}$ receptors over other serotonergic receptors is discussed. Sulfonamide **20t** shows ≥1000-fold selectivity for 5-HT$_{1D}$ over 5-HT$_2$, 5-HT$_{1C}$, and 5-HT$_3$ receptors and 10-fold selectivity with respect to 5-HT$_{1A}$ receptors. The functional activity of this series of compounds is studied and demonstrates high 5-HT$_{1D}$ receptor potency and efficacy comparable to that of 5-HT.

Introduction

During the last decade, the serotonin (5-HT) (**1**) (Chart I) superfamily of receptors has provided a rich source of targets for drug therapy.[1] 5-HT receptors have been classified into four main families, 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, and 5-HT$_4$, and receptor subtypes have been identified.[2a,b] The recent cloning of several human 5-HT receptors has added further impetus to the search for 5-HT receptor subtype specific ligands for use as pharmacological tools to study the function and physiological importance of 5-HT receptors and as novel therapy for conditions associated with 5-HT neurotransmission dysfunction.[3a–c,4] Of the 5-HT receptor families, the 5-HT$_1$ group appears to be the most complex with the existence of at least four subtypes:[5] 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1E}$.[2a,6,7] The first three of these receptors are characterized by high affinity for the selective 5-HT$_1$ agonist 5-carboxamido-tryptamine (5-CT) (**2**). 5-CT however shows no selectivity between the 5-HT$_1$ receptor subtypes. The 5-HT$_{1D}$ receptor is one of the most recently discovered subtypes,[8] and there have been few reports of selective ligands.[9a,b,10a,b] Two 5-HT$_1$ selective agonists which show selectivity for 5-HT$_{1D}$ over the other 5-HT$_1$ subtypes are the amide AH 25086B (**3**) and the sulfonamide sumatriptan (**4**). These compounds have been shown to be selective vasoconstrictors of cranial blood vessels,[11] and **4** has proven efficacy in the acute treatment of migraine.[12a–c]

A simple comparison of the 5-HT$_{1D}$ agonists **1–4** would suggest that the key groups required for binding and efficacy are a basic amine, an indole ring (the NH of which may bind by a hydrogen bond), and a 5-substituent capable of participating in hydrogen-bonding interactions as an acceptor and/or donor. However, the structural features required for binding selectivity to the 5-HT$_{1D}$ receptor

Chart I

5-HT **1**

5-CT **2**

AH 25086B **3**

Sumatriptan **4**

5:　n = 0,1,2,or 3;　R' = H or Me
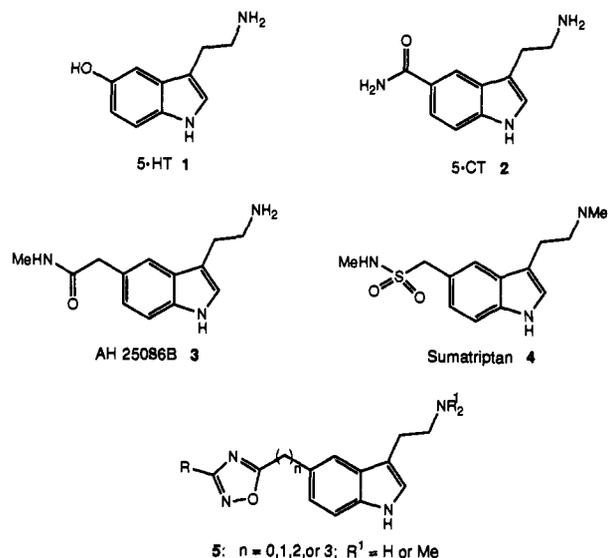
subtype are less clear because of the limited ligands available. A program was initiated in our laboratories with the objective of identifying novel series of 5-HT$_{1D}$ agonists for use both as novel agents for migraine therapy and as tools to study the physiological function of the 5-HT$_{1D}$ receptor. Compounds were sought which had high potency and receptor selectivity, high oral bioavailability, and low central nervous system (CNS) penetration.[12c] In so doing it was anticipated that we would identify structural requirements for effective binding to the 5-HT$_{1D}$ receptor and thus aid the delineation of a pharmacophore of the 5-HT$_{1D}$ agonist binding site. We have recently shown in series of both muscarinic[13] and 5-HT$_3$[14] receptor ligands that 5-membered heteroaromatic rings, in particular 1,2,4-oxadiazole, are excellent stable bioisosteric replacements for ester and amide groups. Our initial strategy in this program was to identify heterocyclic

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Scheme I[a]
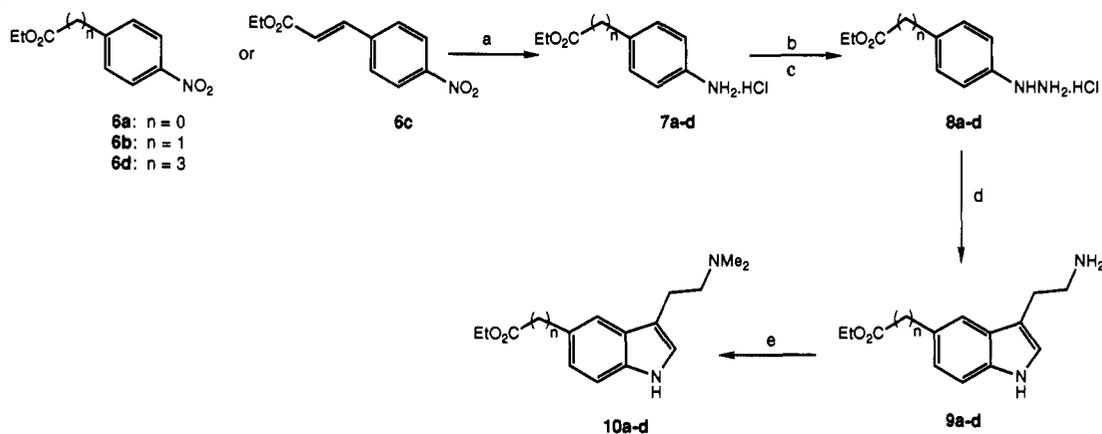
[a] Reagents: (a) H_2, 10% Pd/C, EtOH, 2 N HCl; (b) $NaNO_2$, H_2O, concentrated HCl, -10 °C; (c) $SnCl_2 \cdot 2H_2O$, concentrated HCl; (d) 4-chlorobutanal dimethyl acetal, EtOH/H_2O (5:1), reflux, 2 h; (e) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C.

Scheme II[a]
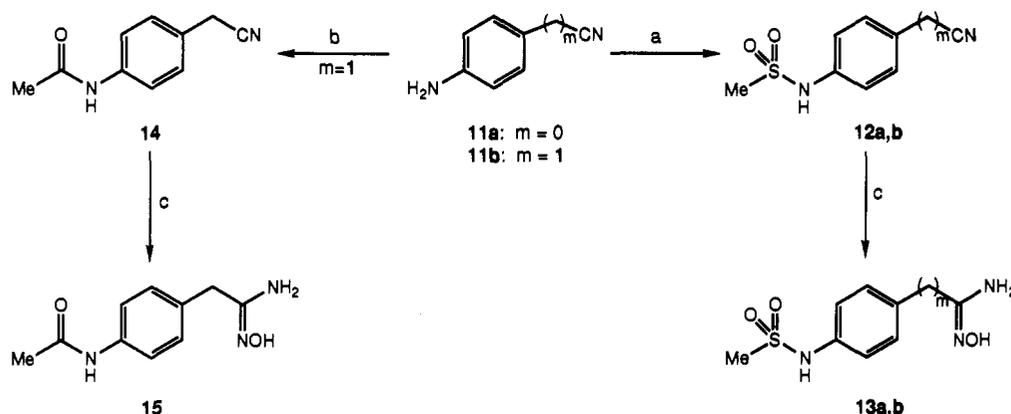
[a] Reagents: (a) $MeSO_2Cl$, CH_2Cl_2, triethylamine; (b) Ac_2O, CH_2Cl_2, triethylamine; (c) $NH_2OH \cdot HCl$, Na, MeOH.

replacements for the amide of the 5-HT_1 agonist 5-CT (2) and to probe for 5-HT_{1D} receptor selectivity within these series.

We describe in this paper the synthesis, 5-HT_{1D} activity, and 5-HT receptor selectivity profile of a series of 5-(oxadiazolyl)tryptamines, 5, and related analogues. To explore the pharmacophore of the 5-HT_{1D} recognition site we have studied changes in the amine substituent (R^1), the length of the linking chain (n), and the nature of the oxadiazole 3-substituent (R).

Synthetic Chemistry

The tryptamine esters 9a–d were prepared from the 4-nitrophenyl esters 6a–d (Scheme I). Hydrogenation of 6a–d over Pd–C gave the anilines 7a–d, which were isolated as their hydrochloride salts. Treatment of 7a–d with $NaNO_2$ followed by reduction of the intermediate diazonium salts with $SnCl_2 \cdot 2H_2O$ gave the hydrazines 8a–d. Fischer reaction[15] of 8a–d with 4-chlorobutanal dimethyl acetal,[16] in refluxing EtOH/H_2O (5:1), afforded the tryptamines 9a–d which were purified by silica gel chromatography. N,N-Dimethylation of 9a–d using $NaCNBH_3$/CH_2O/$MeCO_2H$ gave 10a–d in high yield. The 4-substituted benzyl and phenyl amide oximes 13a,b, 15, and 19a–e were prepared as shown in Schemes II and III. Reaction of 4-aminobenzonitrile, 11a, and 4-aminobenzyl cyanide, 11b, with methanesulfonyl chloride gave the crystalline sulfonamides 12a and 12b, respectively (Scheme II). Similarly, the acetamide 14 was prepared from 11b by treatment with Ac_2O/NEt_3. The nitrile 18a was

Scheme III[a]
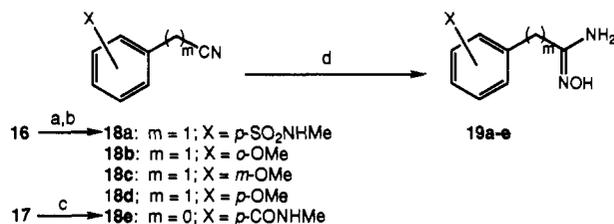
[a] Reagents: 16 = N-methyl-p-toluenesulfonamide; (a) N-bromosuccinimide, CCl_4, benzoyl peroxide; (b) KCN, EtOH, H_2O, reflux; 17 = 4-cyanobenzoyl chloride; (c) NH_2Me(gas), CH_2Cl_2; (d) $NH_2OH \cdot HCl$, Na, MeOH.

prepared from N-methyl-p-toluenesulfonamide by bromination with NBS followed by displacement with KCN (Scheme III). Reaction of 4-cyanobenzoyl chloride with methylamine gas afforded 18e. Treatment of the nitriles 12a,b, 14, and 18a–e with hydroxylamine hydrochloride and NaOMe gave the amide oximes 13a,b, 15, and 19a–e, respectively. Oxadiazoles 20a–x and 21a–k were prepared by one of two general procedures (Scheme IV).[17] Tryptamines 20a–c, 20e, 20f, 20h, 20j, 20k and 20m–r, and N,N-dimethyltryptamines 21b, 21d, and 21j were prepared by refluxing a solution of the appropriate ester and amide oxime (3 equiv) in THF for 2 h, using NaH as base. Tryptamines 20d, 20g, 20i, 20l, and 20s–x and N,N-dimethyltryptamines 21a, 21c, 21e, and 21f–i were prepared by reaction of the ester and amide oxime in refluxing EtOH (3–24 h), using NaOEt as base. All compounds were purified by column chromatography on silica gel.

The synthetic route to aminothiadiazole 28[20] is shown

Scheme IV[a]

9a–d: R¹ = H
10a–d: R¹ = Me

20a–x: R¹ = H
21a–k: R¹ = Me
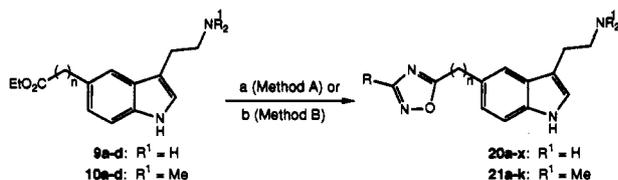
[a] Reagents: (a) NaH, THF, RC(=NOH)NH₂, reflux, 3 h; (b) Na, EtOH, RC(=NOH)NH₂, reflux 2–24 h.

in Scheme V. 4-Aminobenzyl cyanide was converted to tryptamine **22** by conversion to the hydrazine followed by Fischer reaction with 4-chlorobutanal dimethyl acetal. N,N-Dimethylation of **22** gave **23** which was hydrolyzed, and the intermediate acid was esterified to give methyl ester **24**. Treatment of **24** with the lithium salt of 4-methoxybenzyl alcohol, in THF, gave 4-methoxybenzyl ester **25** in 89% yield. Boc protection of **25** using (Boc)₂O in MeCN and 4-DMAP as catalyst gave **26** which, upon treatment with NaH in DMF followed by addition of 3-amino-5-chloro-1,2,4-thiadiazole,[18] afforded the alkylation product **27**, in 33% yield. Reaction of **27** with TFA in CH₂Cl₂/H₂O resulted in removal of the Boc group and debenzylation. Decarboxylation of the intermediate acid was achieved by refluxing in MeOH to give the aminothiadiazole **28**, in 45% yield.

Oxazole **31** was prepared in three steps from ester **10a** (Scheme VI). Saponification of **10a** with LiOH gave acid **29** which was coupled with propargylamine using water soluble carbodiimide to give amide **30**. Cyclization of **30** was achieved using Hg(OAc)₂ in acetic acid, to afford oxazole **31**, in 57% yield.

Results and Discussion

Structure–Affinity Relationships. The 5-HT₁D receptor affinities of compounds were measured by displacement of [³H]-5-HT from bovine caudate membranes, in the presence of cyanopindolol and mesulergine to block interactions with 5-HT₁A, 5-HT₁B, and 5-HT₁C sites.[8,19] The data is presented in Tables I–III and V.

The methyloxadiazole **20a**, in which the heterocyclic ring is conjugated to the indole ring, has affinity for the 5-HT₁D binding site similar to that of the endogenous ligand 5-HT (Table I). More bulky alkyl groups, e.g., Et, **20b**, and ᶜPr, **20c**, can be accommodated without compromising affinity. However, the amino derivative **20d** has reduced affinity, suggesting that a H bond to N-2 of the heterocycle may not be important in binding to the 5-HT₁D receptor since 3-amino substitution in an oxadiazole ring has been shown to improve the H-bond acceptor ability of N-2.[13] Although the phenyl analogue **20e** has reduced affinity compared to **20a**, the benzyl analogue **20f** has activity comparable to 5-CT. In the amino- and phenyloxadiazole series, incorporation of a methylene chain between the indole and heterocycle improved binding to the 5-HT₁D receptor, although affinity was reduced in the benzyl series. Extending the chain to ethylene and propylene generally increased 5-HT₁D affinity over the methylene-linked analogues. The effect on log *D* of incorporating a methylene spacer group between the heterocycle and indole ring is also illustrated in Table I. In general log *D* was reduced by 1 order of magnitude by removing the conjugation, e.g., compare **20i**, log *D* –1.90, and **20d**, log *D* –0.72. This effect is important to consider when attempting to design ligands which will not penetrate

the blood–brain barrier. After identifying benzyl as an optimal substituent, substitution of the phenyl ring was explored (Table II). Methoxy substitution around the phenyl ring identified the para position to be optimum. Further improvements in binding could be achieved by modifying the para substituent. Thus, the sulfonamides **20t** and **20u** are 10-fold more potent than **20f** and 50–100-fold more potent than **4**. These compounds represent the most potent 5-HT₁D ligands reported to date. Similar improvements in affinity were achieved in the phenyl series by para substitution, e.g., **20v**. As with the unsubstituted compounds, incorporation of a methylene spacer group between the oxadiazole and indole rings reduced activity, in this case by 1 order of magnitude, e.g., **20t** (pIC₅₀ 9.5 ± 0.19) and **20x** (pIC₅₀ 8.5). The beneficial effect of the phenyl ring in this series can be seen by comparison of the benzylacetamide **20s** (pIC₅₀ 9.3) (Table II) and methylacetamide **20g** (pIC₅₀ 7.7) (Table I). N,N-Dimethylation of the tryptamines generally resulted in reduced affinity for the 5-HT₁D recognition site in all series (Table III),[10] although high affinity was retained for certain 4-substituted phenyl (**21f**) and benzyl (**21c**) derivatives. The oxazole **31** has affinity comparable to methyloxadiazole **20a** (Tables I and III). Interestingly, the aminothiadiazole **28** displays 10-fold higher affinity for 5-HT₁D receptors than its oxadiazole analogue **21e** (Table V).[20]

The binding results for the alkyl- and benzyl-substituted oxadiazoles would suggest that the critical pharmacophoric element at the indole C5-position, for high affinity binding to the 5-HT₁D receptor, is an H-bond acceptor, not a donor, since these compounds do not possess an H-bond donor group. Secondly, the high affinity observed for oxazole **31** implies that the H bond of primary importance is to the N-4 lone pair of the oxadiazole ring and that N-2 in these compounds may not be required for binding. However, it should not be ruled out that in the absence of N-4 an H bond to N-2 of the resultant isoxazole may suffice for binding. The relative position of this H-bond acceptor does not appear to be critical since extension of the linking chain to two and three methylene units does not compromise 5-HT₁D activity. The fact that a benzyl group can be accommodated in all series, *n* = 0 → 3, suggests that an extended pocket exists in the binding domain of the receptor, although hydrophobic interaction of the phenyl ring with the receptor may not be important because the methyl (**20a**) and benzyl (**20f**) analogues have equal affinity. However, a dramatic increase in affinity (>10-fold) is observed when an additional H-bond acceptor group is introduced into the para position of the phenyl ring, which suggests the existence of additional binding sites in the 5-HT₁D receptor binding pocket. This activity is optimal when the oxadiazole and indole rings are conjugated (e.g., **20r–u**), possibly as a result of lower conformational flexibility. In addition, conjugated delocalization from the indole nitrogen atom lone pair into the conjugated oxadiazole ring would be expected to improve both the H-bond acceptor ability of N-4 of the oxadiazole, and the H-bond donor ability of the indole NH proton. As seen previously,[10] N,N-dialkylation of the tryptamine resulted in reduced affinity, suggesting that the preferred electrostatic interaction at the receptor is with the protonated primary amine which is found in the endogenous ligand and 5-CT. The increased affinity observed on replacing O by S in going from oxadiazole **21e** to thiadiazole **28** is intriguing and may be a consequence of

Scheme V[a]
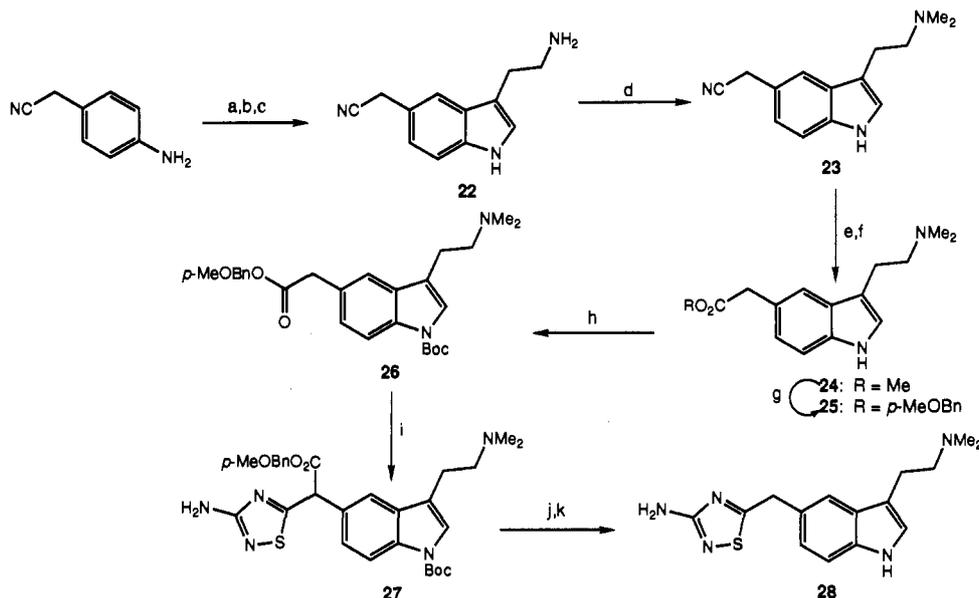
[a] Reagents: (a) $NaNO_2$, H_2O, concentrated HCl, -10 °C; (b) $SnCl_2 \cdot 2H_2O$, concentrated HCl, -10 °C; (c) 4-chlorobutanal dimethyl acetal, EtOH/H_2O (5:1), reflux, 2 h; (d) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C; (e) 2 N NaOH; (f) $SOCl_2$, MeOH; (g) 4-methoxybenzyl alcohol, THF, [n]BuLi; (h) MeCN, $(Boc)_2O$, 4-DMAP; (i) NaH, 3-amino-5-chloro-1,2,4-thiadiazole; (j) TFA, CH_2Cl_2, H_2O, +25 °C, 1 h; (k) MeOH, reflux, 0.1 h.

Scheme VI[a]
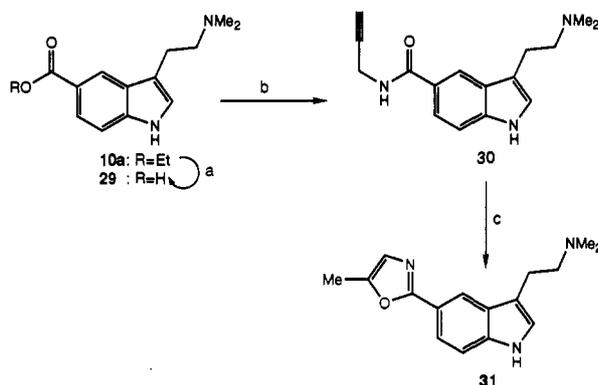
[a] Reagents: (a) LiOH, EtOH–H_2O, 60 °C, 8 h; (b) propargylamine, N-methylmorpholine, 1-hydroxybenzotriazole, water-soluble carbodiimide, CH_2Cl_2–DMF (1:1), 18 h; (c) Hg(OAc)$_2$, $MeCO_2H$, reflux, 3 h.

the differences in electrostatic distributions in the two molecules.[20]

Receptor Selectivity. In order to determine the pharmacological specificity of the compounds of this study for 5-HT$_{1D}$ recognition sites, the affinity of a range of oxadiazoles, and the thiadiazole 28, for 5-HT$_{1A}$,[21] 5-HT$_2$,[22] 5-HT$_{1C}$,[23] and 5-HT$_3$[24] receptors, was measured. The results are summarized in Tables IV and V. All compounds showed selectivity for 5-HT$_{1D}$ receptors over the other serotonin receptors, although the degree of selectivity was dependent on the nature of the oxadiazole substituent and the length of the linking chain. In general all compounds showed 10-fold selectivity for 5-HT$_{1D}$ over 5-HT$_{1A}$ receptors with the exception of highly lipophilic compounds such as 20f (log D = +1.32). Compounds with very high affinity for 5-HT$_{1D}$ recognition sites such as 20r–t showed excellent receptor selectivity with ≥1000-fold selectivity over 5-HT$_{1C}$, 5-HT$_2$, and 5-HT$_3$ receptors. Thus 20r–t represent some of the most potent and selective 5-HT$_{1D}$ receptor ligands identified. In general, all compounds showed ≥100-fold selectivity for 5-HT$_{1D}$ receptors over 5-HT$_{1C}$ and 5-HT$_2$ receptors and very low affinity for the 5-HT$_3$ recognition site.

Table I. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by 5-(Oxadiazolyl)tryptamines and Standard 5-HT$_{1D}$ Agonists

compd	n	R	pIC$_{50}$ ± SEM[a]	log D[b]
5-HT (1)			8.0 ± 0.09	
5-CT (2)			8.4 ± 0.1	
sumatriptan (4)			7.7 ± 0.08	-1.17
20a	0	Me	8.0 ± 0.25	-0.37
20b	0	Et	7.9	+0.13
20c	0	[c]Pr	8.1 ± 0.16	+0.60
20d	0	NH$_2$	7.3	-0.72
20e	0	Ph	7.1	
20f	0	CH$_2$Ph	8.2 ± 0.12	+1.32
20g	0	MeCONHCH$_2$	7.7	
20h	1	Me	7.5 ± 0.16	-1.70
20i	1	NH$_2$	7.7 ± 0.09	-1.90
20j	1	Ph	7.7 ± 0.13	
20k	1	CH$_2$Ph	7.5 ± 0.12	+0.42
20l	2	NH$_2$	8.0	-1.51
20m	2	CH$_2$Ph	8.3 ± 0.07	
20n	3	Me	8.3 ± 0.29	
20o	3	CH$_2$Ph	8.8	

[a] SEM = standard error of the mean from $n \geq 3$. Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10–15% of the mean. [b] log P measured at pH 7.4.

Functional Activity. The functional serotonergic activity of a selection of compounds was assessed *in vitro* on the New Zealand white rabbit saphenous vein preparation. In this model, contractions evoked by agonists are considered to be mediated by 5-HT$_{1-like}$ receptors.[25] Agonist potencies were calculated as pEC$_{50}$ values from plots of percentage 5-HT (1 μM) response against concentration of the agonist. The results are presented in Table VI. All compounds caused contraction of the saphenous vein and had efficacy comparable to 5-HT. The high affinity of the acetamide 20s and sulfonamides 20t and 20u for 5-HT$_{1D}$ receptors was reflected in the

Table II. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by Benzyl- and Phenyl-Substituted Oxadiazoles
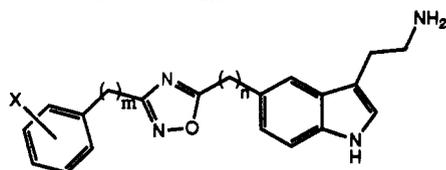
compd	n	m	X	pIC$_{50}$ ± SEM^a	log D^b
20p	0	1	*o*-OMe	7.8	+1.38
20q	0	1	*m*-OMe	8.9	
20r	0	1	*p*-OMe	9.1 ± 0.12	
20s	0	1	*p*-NHCOMe	9.3	+0.48
20t	0	1	*p*-NHSO$_2$Me	9.5 ± 0.19	+0.25
20u	0	1	*p*-SO$_2$NHMe	9.6	+0.25
20v	0	0	*p*-CONHMe	9.1 ± 0.23	
20w	1	1	*p*-NHCOMe	8.6	-0.36
20x	1	1	*p*-NHSO$_2$Me	8.5	-0.54

^{a} SEM = standard error of the mean from $n \geq 3$. Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10–15% of the mean. ^{b} log P measured at pH 7.4.

Table III. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by *N,N*-Dimethyltryptamines
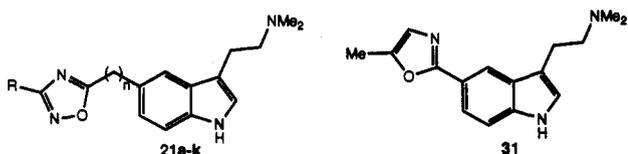
compd	n	R	pIC$_{50}$ ± SEM^a	log D^b
21a	0	NH$_2$	7.1	+0.20
21b	0	PhCH$_2$	8.2	
21c	0	*p*-(MeSO$_2$NH)Bn	8.9 ± 0.17	+1.25
21d	1	Me	7.3 ± 0.18	+0.04
21e	1	NH$_2$	7.6 ± 0.21	-0.67
21f	1	*p*-(MeNHCO)Ph	8.7	+1.45
21g	1	*p*-(MeSO$_2$NH)Ph	8.0	+1.22
21h	1	*p*-(MeSO$_2$NH)Bn	7.5	+0.50
21i	2	NH$_2$	7.9 ± 0.1	-0.40
21j	2	PhCH$_2$	7.9	
21k	3	PhCH$_2$	7.9 ± 0.12	
31			8.1	

^{a} SEM = standard error of the mean from ≥ 3. Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10–15% of the mean. ^{b} log P measured at pH 7.4.

functional assay. These compounds were 10-fold more potent in the saphenous vein assay than 5-HT. The thiadiazole **28** has unusually high potency and again mirrors the high affinity of this compound for 5-HT$_{1D}$ receptors.[26]

Conclusions

A novel series of 5-HT$_{1D}$ receptor agonists has been identified which contains some of the most potent and selective agonists reported to date. It can be concluded that an H-bond acceptor group and not a donor group is required at C-5 of the indole for effective binding to 5-HT$_{1D}$ receptors, and this could be the function of the hydroxyl and carboxamide groups of 5-HT and 5-CT, respectively. An additional H-bond binding site has been identified which results in a 10-fold increase in 5-HT$_{1D}$ agonist potency. A large pocket is available in the binding domain of the 5-HT$_{1D}$ receptor which will accommodate relatively bulky groups, positioned at C5 of the indole, without loss

of affinity or efficacy. Optimal potency was found when the heterocycle is conjugated to the indole ring, analogous to 5-CT, and may be a consequence of the imposed conformational rigidity and/or a more favorable electrostatic distribution. The activity of these compounds in *in vivo* models of migraine[11,27] will be presented shortly.

Experimental Section

Chemical Methods: General Directions. Except where otherwise stated, the following procedures were adopted: all ^{1}H NMR spectra were recorded at 360 MHz on a Brucker AM 360 instrument and mass spectra with a VG70-250 mass spectrometer. Organic solvents were purified when necessary by the methods described by Perrin *et al.* (Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1966) or were purchased from The Aldrich Chemical Co., Sureseal. All solutions were dried over sodium sulfate and evaporated on a Büchi rotary evaporator at reduced pressure. Thin-layer chromatography and preparative chromatography were performed on silica, with use of plates (Merck Art No. 5719) and columns (Merck Art No. 7734). log D's were determined using 1-octanol and pH 7.4 buffer by the shake flask method. Melting points are uncorrected.

General Procedure for the Preparation of Anilines 7a–d. Ethyl 3-(4-Aminophenyl)propionate Hydrochloride (7c). A suspension of ethyl 4-nitrocinnamate (50 g, 0.23 mol) in EtOH (500 mL) and 5 N HCl (46 mL) was hydrogenated over 10% Pd/C (5 g) in a Parr shake apparatus at 50 psi for 0.5 h. The product remaining after filtration through hyflo and evaporation of the solvent was recrystallized from EtOAc/EtOH to give 7c (50.4 g, 97%): mp 170–173 °C; MS *m/z* 194 (M + 1)$^+$; ^{1}H NMR (D$_2$O) δ 1.17 (3H, t, J = 7.1 Hz, CH$_3$), 2.73 (2H, t, J = 7.2 Hz, 2-CH$_2$), 2.99 (2H, t, J = 7.2 Hz, 1-CH$_2$), 4.09 (2H, q, J = 7.1 Hz, CH$_2$O), 7.34 and 7.41 (each 2H, each d, J = 8.6 Hz, 3'-CH and 5'-CH, and 2'-CH and 6'-CH). Anal. (C$_{11}$H$_{15}$NO$_2$·HCl) C, H, N.

General Procedure for the Preparation of Tryptamines 9a–d, and 22. 2-(5-Carbethoxy-1*H*-indol-3-yl)ethylamine Hydrogen Maleate (9a). A solution of NaNO$_2$ (17.0 g, 0.25 mol) in H$_2$O (90 mL) was added to a cooled (–10 °C) solution of ethyl 4-aminobenzoate (40.0 g, 0.24 mol) in concentrated HCl (225 mL), at such a rate that the temperature did not exceed 0 °C. The mixture was stirred at 0 °C for 0.1 h and then added portionwise to a cooled (–10 °C) and rapidly stirred solution of SnCl$_2$·2H$_2$O (202.0 g, 0.90 mol) in concentrated HCl (135 mL), at such a rate that the temperature did not exceed –5 °C. The resulting cream-colored suspension was warmed to 25 °C, filtered under vacuum, and washed with Et$_2$O. The product was dried at 80 °C under vacuum to give ethyl 4-hydrazinobenzoate hydrochloride, **8a** (32.1 g, 61%): mp 202–203 °C (EtOH); MS *m/z* 180 (M$^+$); ^{1}H NMR (D$_2$O) δ 1.38 (3H, t, J = 7.1 Hz, CH$_3$), 4.37 (2H, q, J = 7.1 Hz, CH$_2$O), 7.06 (2H, d, J = 9.0 Hz, 3-CH and 5-CH), 8.03 (2H, d, J = 9.0 Hz, 2-CH and 6-CH). Anal. (C$_9$H$_{12}$N$_2$O$_2$·HCl) C, H, N.

To a solution of **8a** (10.0 g, 46.2 mmol) in EtOH/H$_2$O (5:1, 500 mL) was added 4-chlorobutanal dimethyl acetal[16] (7.0 g, 46.0 mmol) and the mixture heated at reflux for 2 h. The solvent was evaporated and the residue chromatographed on silica gel, eluting with CH$_2$Cl$_2$/EtOH/NH$_3$ (40:8:1) to give **9a** (3.69 g, 34.4%). The hydrogen maleate salt was prepared: mp 127 °C; MS *m/z* 232 (M$^+$); ^{1}H NMR (D$_2$O) δ 1.43 (3H, t, J = 7.1 Hz, CH$_3$), 3.21 and 3.37 (each 2H, each t, J = 7.0 Hz, 1-CH$_2$ and 2-CH$_2$), 4.42 (2H, q, J = 7.1 Hz, CH$_2$O), 6.23 (2H, s, maleate H), 7.40 (1H, s, 2'-CH), 7.56 (1H, d, J = 8.6 Hz, 7'-CH), 7.88 (1H, dd, J = 1.6 and 8.6 Hz, 6'-CH), 8.38 (1H, d, J = 1.6 Hz, 4'-CH). Anal. (C$_{13}$H$_{18}$N$_2$O$_2$·(CHCOOH)$_2$) C, H, N.

General Procedure for the Preparation of *N,N*-Dimethyltryptamines 10a–d, and 23. *N,N*-Dimethyl-2-(5-(carbethoxymethyl)-1*H*-indol-3-yl)ethylamine (10b). A solution of formaldehyde (1.1g of a 37% w/w solution, 13.6 mmol) in MeOH (20 mL) was added dropwise to a stirred solution of 2-(5-(carbethoxymethyl)-1*H*-indol-3-yl)ethylamine, **9b** (1.0 g, 4.07 mmol), glacial acetic acid (0.65 g, 10.8 mmol), and NaCNBH$_3$ (0.45 g, 7.2 mmol) in MeOH (20 mL) at 0 °C. The solution was warmed to 25 °C and stirred for 2.5 h before adding saturated

Table IV. Selectivity of 5-(Oxadiazolyl)tryptamines in Binding to 5-HT$_{1D}$ Serotonin Receptors
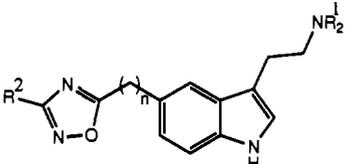
compd	n	R^1	R^2	pIC$_{50}$ ± SEM^a 5-HT$_{1D}$^{b}	5-HT$_{1A}$^{c}	5-HT$_{1C}$^{d}	5-HT$_2$^{e}	5-HT$_3$^{f}
20a	0	H	Me	8.0 ± 0.25	7.2 ± 0.04	5.9	5.8	<5.0
20c	0	H	^{c}Pr	8.1 ± 0.16	7.5	6.0	5.6	<5.0
20f	0	H	PhCH$_2$	8.2 ± 0.12	7.9 ± 0.10	5.4	5.9	<5.0
20r	0	H	p-(MeO)Bn	9.1 ± 0.12	8.3 ± 0.20	6.1	6.0	<5.0
20s	0	H	p-(MeCONH)Bn	9.3	8.3	5.8^g	6.4	<5.0^g
20t	0	H	p-(MeSO$_2$NH)Bn	9.5 ± 0.19	8.5	6.5 ± 0.27	6.5	<5.0
20h	1	H	Me	7.5 ± 0.16	6.4	5.9	5.5	<5.0
20i	1	H	NH$_2$	7.7 ± 0.09	6.5	5.5	6.1	<5.0
21d	1	Me	Me	7.3 ± 0.18	6.3	6.0 ± 0.38	5.6	5.4
21e	1	Me	NH$_2$	7.6 ± 0.21	6.5 ± 0.05	5.9 ± 0.09	6.4	5.6
21i	2	Me	NH$_2$	7.9 ± 0.10	7.3	6.0	6.7	5.2
20m	2	H	PhCH$_2$	8.3 ± 0.07	7.8 ± 0.14	6.1	6.6	<5.0

^{a} SEM = standard error of the mean from $n \geq 3$. Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10–15% of the mean. ^{b} Displacement of [^{3}H]-5-HT binding to 5-HT$_{1D}$ recognition sites in pig caudate membranes. ^{c} Displacment of [^{3}H]-8-OH-DPAT from pig cortex. ^{d} Displacement of [^{3}H]mesulergine from pig cortex. ^{e} Displacement of [^{3}H]DOB from rat cortex homogenates. ^{f} Displacement of [^{3}H]-Q-ICS 205–930 from rat cortex homogenates. ^{g} Value derived from a single determination.

Table V. Comparison of the in Vitro Binding Profiles of Aminooxadiazole (21e) and Aminothiadiazole (28)
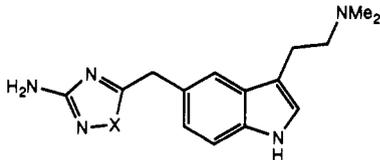
compd	X	pIC$_{50}$ ± SEM^a 5-HT$_{1D}$^{b}	5-HT$_{1A}$^{c}	5-HT$_{1C}$^{d}	5-HT$_2$^{e}	5-HT$_3$^{f}
21e	O	7.6 ± 0.21	6.5 ± 0.05	5.9 ± 0.09	6.4	5.6
28	S	8.7 ± 0.12	7.3 ± 0.1	6.6	6.9 ± 0.10	5.62 ± 0.07

$^{a-f}$ See corresponding footnotes of Table IV.

Table VI. In Vitro Functional Activity of 5-(Oxadiazolyl)- and 5-(Thiadiazolyl)tryptamines
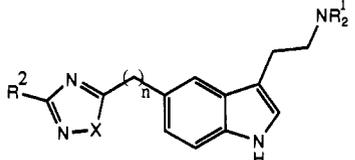
compd	n	X	R^1	R^2	pEC$_{50}$^{a}	relative^b maximum
5-HT (1)					6.8	1.0
20a	0	O	H	Me	6.6	1.0
20s	0	O	H	p-(MeCONH)Bn	7.9	1.0
20t	0	O	H	p-(MeSO$_2$NH)Bn	7.8	1.0
20u	0	O	H	p-(MeNHSO$_2$)Bn	7.9	0.9
20i	1	O	H	NH$_2$	6.8	1.1
21e	1	O	Me	NH$_2$	6.3	0.9
21i	2	O	Me	NH$_2$	6.7	1.0
28	1	S	Me	NH$_2$	8.0	1.1

^{a} Contraction of the New Zealand white rabbit saphenous vein. The figures are the mean of two independent determinations typically with individual values within ±10–15% of the mean. ^{b} Relative maximum = relative efficacy of the agonist with respect to 1 μM 5-HT.

K$_2$CO$_3$ solution (5 mL). The MeOH was removed under vacuum, and H$_2$O (15 mL) was added to the residue and extracted with EtOAc (3×). The crude product was chromatographed on silica gel, eluting with CH$_2$Cl$_2$/EtOH/NH$_3$ (40:8:1) to give **10b** (0.81 g, 73%) as a low melting solid: mp 35 °C; MS m/z 274 (M$^+$); ^{1}H

NMR (CDCl$_3$) δ 1.24 (3H, t, J = 7.0 Hz, CH$_3$), 2.34 (6H, s, N(CH$_3$)$_2$), 2.64 and 2.92 (each 2H, each t, J = 7.5 Hz, 1-CH$_2$ and 2-CH$_2$), 3.71 (2H, s, CH$_2$CO$_2$Et), 4.15 (2H, q, J = 7.0 Hz, CH$_2$O), 7.00 (1H, d, J = 2.2 Hz, 4'-CH), 7.11 (1H, dd, J = 2.2 and 8.4 Hz, 6'-CH), 7.29 (1H, d, J = 8.4 Hz, 7'-CH), 7.49 (1H, s, 2'-CH), 8.00 (1H, br s, NH). Anal. (C$_{16}$H$_{22}$N$_2$O$_2$·0.25H$_2$O) C, H, N.

4-((Methylsulfonyl)amino)benzonitrile (12a). A solution of methanesulfonyl chloride (11.45 g, 0.1 mol) in CH$_2$Cl$_2$ (20 mL) was added dropwise to a stirred solution of 4-aminobenzonitrile (11.8 g, 0.1 mol) and pyridine (7.9 g, 0.1 mol) in CH$_2$Cl$_2$ (100 mL), at 0 °C. The solution was stirred at room temperature for 1.0 h before adding H$_2$O (150 mL) and stirring for 0.1 h. The precipitated product was filtered off, washed with H$_2$O, and dried under vacuum over P$_2$O$_5$ to give **12a** (15.0 g, 76.5%): mp 195–196 °C; MS m/z 196 (M$^+$); ^{1}H NMR (CD$_3$OD) δ 2.98 (3H, s, CH$_3$), 7.27 and 7.60 (each 2H, each d, J = 8.7 Hz, Ar-H). Anal. (C$_8$H$_8$N$_2$O$_2$S) C, H, N.

4-((Methylsulfonyl)amino)benzyl Cyanide (12b). Methanesulfonyl chloride (17.3 g, 0.15 mol) was added to a mixture of 4-aminobenzyl cyanide hydrochloride (25.5 g, 0.15 mol) and NEt$_3$ (30.5 g, 0.30 mol) in CH$_2$Cl$_2$ (250 mL) and stirred at 25 °C for 4 h. The solution was washed with NaHCO$_3$ solution (2×), 0.1 N HCl (1×), and brine (1×), dried, and evaporated. The product was purified by crystallization from EtOH/H$_2$O (15.09 g, 48%): mp 118 °C; MS m/z 210 (M$^+$); ^{1}H NMR (CD$_3$OD) δ 2.86 (3H, s, CH$_3$), 3.76 (2H, s, CH$_2$CN), 7.17 and 7.24 (each 2H, each d, J = 8.6 Hz, Ar-H). Anal. (C$_9$H$_{10}$N$_2$O$_2$S) C, H, N.

4-(Acetylamino)benzyl Cyanide (14). A solution of 4-aminobenzyl cyanide (15.0 g, 0.11 mol), NEt$_3$ (15 mL), and acetic anhydride (15 mL) in CH$_2$Cl$_2$ (250 mL) was stirred for 16 h at room temperature. The solvents were evaporated, and the crude product was purified by crystallization from H$_2$O (140 g, 71%): mp 85–87 °C; ^{1}H NMR (CDCl$_3$) δ 2.18 (3H, s, CH$_3$), 3.71 (2H, s, CH$_2$CN), 7.26 and 7.54 (each 2H, each d, J = 8.4 Hz, Ar-H), 7.63 (1H, br s, NH). Anal. (C$_{10}$H$_{10}$N$_2$O·0.5H$_2$O) C, H, N.

4-((N-Methylamino)sulfonyl)benzyl Cyanide (18a). To a mixture of N-methyl-p-toluenesulfonamide (23.9 g, 0.13 mol) in CCl$_4$ (250 mL) was added N-bromosuccinimide (22.9 g, 0.13 mol), and the mixture was purged with N$_2$ for 0.1 h. Benzoyl peroxide (0.1 g) was added, and the mixture was irradiated (800-W lamp) and heated at reflux for 3 h. The reaction mixture was stirred at room temperature for 16 h. The resulting succinimide was removed by filtration and the filtrate evaporated to give $\cong$ 1:2 mixture of N-methyl-p-toluenesulfonamide and the desired 4-((methylamino)sulfonyl)benzyl bromide, respectively (32.1 g), which coeluted on TLC (EtOAc/hexane, 1:1). This material was used without further purification: ^{1}H NMR (DMSO-d_6) δ 2.39

Table VII. Physical Data for 5-(Oxadiazolyl)tryptamines^a

no.	empirical formula	mp, °C	no.	empirical formula	mp, °C
20a	$C_{13}H_{14}N_4O\cdot1.2(COOH)_2$	230	20l	$C_{14}H_{17}N_5O\text{-cis-}(CHCOOH)_2\cdot0.75H_2O$	147–148
20b	$C_{14}H_{16}N_4O\cdot2(COOH)_2\cdot0.5H_2O$	195–197	20m	$C_{21}H_{22}N_4O\cdot0.5cis\text{-}(CHCOOH)_2$	113–114
20c	$C_{15}H_{16}N_3O\cdot0.5(CH_2COOH)_2\cdot0.15H_2O$	205–207	20n	$C_{16}H_{20}N_4O\cdot0.9cis\text{-}(CHCOOH)_2$	136–137
20d	$C_{12}H_{13}N_5O\cdot2(COOH)_2\cdot0.75H_2O$	160–164	20p	$C_{20}H_{20}N_4O_2\cdot0.6(COOH)_2$	244–245
20e	$C_{18}H_{16}N_4O\cdot0.85(COOH)_2$	212–213	20q	$C_{20}H_{20}N_4O_2\text{-cis-}(CHCOOH)_2\cdot0.1H_2O$	173–175
20f	$C_{19}H_{18}N_4O\cdot(COOH)_2\cdot0.85H_2O$	229	20r	$C_{20}H_{20}N_4O_2\text{-cis-}(CHCOOH)_2$	195–196
20g	$C_{15}H_{17}N_5O_2\cdot0.5(CH_2COOH)_2\cdot1.0H_2O\cdot0.2(iPA)^b$	107–110	20s	$C_{21}H_{21}N_5O_2\cdot2(COOH)_2\cdot0.25H_2O$	113–115
20h	$C_{14}H_{16}N_4O\cdot(COOH)_2\cdot0.75H_2O$	72–74	20u	$C_{20}H_{21}N_5O_3S\cdot2(CH_2COOH)_2\cdot0.75H_2O$	49–50^c
20i	$C_{13}H_{15}N_5O\cdot(COOH)_2\cdot1.2H_2O$	85–87	20v	$C_{20}H_{19}N_5O_2\cdot(CH_2COOH)_2\cdot0.75H_2O$	126–128
20j	$C_{19}H_{18}N_4O\cdot(COOH)_2\cdot0.3(EtOH)^b$	82–84	20w	$C_{22}H_{23}N_5O_2\cdot1.5HCl$	147
20k	$C_{20}H_{20}N_4O\cdot(COOH)_2$	176–178	20x	$C_{21}H_{23}N_5O_3S\cdot1.25(COOH)_2\cdot0.33(EtOH)^b$	110–112

^{a} All compounds were crystallized from either ^{i}PrOH/Et$_2$O or EtOH and gave satisfactory microanalyses for C, H, and N. ^{b} ^{1}H NMR of these compounds suggested that the salt had crystallized with solvent. ^{c} Hygroscopic salt.

Table VIII. Physical Data for N,N-Dimethyl-5-(oxadiazolyl)tryptamines^a

no.	empirical formula	mp, °C	no.	empirical formula	mp, °C
21a	$C_{14}H_{17}N_5O\cdot1.8(COOH)_2\cdot1.0H_2O$	156–158	21g	$C_{22}H_{25}N_5O_3S\cdot(COOH)_2\cdot0.4(Et_2O)^b$	213–215
21b	$C_{21}H_{22}N_4O\cdot1.6(COOH)_2$	157–158	21h	$C_{23}H_{27}N_5O_3S\cdot(COOH)_2\cdot0.25H_2O$	156–159
21c	$C_{22}H_{25}N_5O_3S\cdot(CH_2COOH)_2\cdot1.75H_2O$	65–66	21i	$C_{16}H_{21}N_5O\cdot1.1(COOH)_2$	164–167
21d	$C_{16}H_{20}N_4O\cdot1.5(COOH)_2\cdot0.1H_2O$	159–160	21k	$C_{24}H_{28}N_4O\cdot(CH_2COOH)_2\cdot0.35H_2O$	132–135
21f	$C_{23}H_{25}N_5O_2\cdot(COOH)_2\cdot0.5H_2O$	205–207			

^{a} All compounds were crystallized from ^{i}PrOH/Et$_2$O and gave satisfactory microanalyses for C, H, and N. ^{b} ^{1}H NMR of this compound suggested that the salt had crystallized with solvent.

(3H, s, CH$_3$), 4.58 (2H, s, CH$_2$Br), 7.53 and 7.66 (each 2H, each d, J = 8.3 Hz, Ar-H).

A solution of the product from stage 1 (32.1 g) in EtOH (100 mL) was added to a solution of KCN (5.45 g, 84.0 mmol) in EtOH/H$_2$O (1:1, 250 mL) at 100 °C, and the mixture was heated at reflux for 4 h. The solvents were evaporated, and the residue was partitioned between CH$_2$Cl$_2$ (250 mL) and brine (200 mL). The aqueous layer was further extracted with CH$_2$Cl$_2$ (3×), and the resulting crude product was chromatographed on silica gel, eluting with EtOAc/hexane (1:3 → 2:1) to give 18a (8.58 g): ^{1}H NMR (CDCl$_3$) δ 2.68 (3H, d, J = 7.7 Hz, CH$_3$), 3.85 (2H, s, CH$_2$-CN), 4.42 (1H, br q, NH), 7.52 (2H, d, J = 8.7 Hz, 2-CH and 6-CH), 7.89 (2H, d, J = 8.7 Hz, 3-CH and 5-CH); MS m/z 210 (M$^+$).

4-(N-Methylcarbamoyl)phenyl Cyanide (18e). Methylamine (gas) was bubbled through a solution of 4-cyanobenzoyl chloride (10.0 g, 60.4 mmol) in CH$_2$Cl$_2$ (150 mL) until the solution was saturated. The precipitate was filtered off, washed with H$_2$O, and dried over P$_2$O$_5$ to give 18e (8.5 g, 88%): mp 158–160 °C; ^{1}H NMR (CD$_3$OD) δ 2.83 (3H, s, CH$_3$), 7.74 and 7.85 (each 2H, each d, J = 8.6 Hz, Ar-H). Anal. (C$_9$H$_8$N$_2$O·0.125H$_2$O) C, H, N.

General Procedure for the Preparation of Amide Oximes 13a,b, 15, and 19a-e. 4-((Methylsulfonyl)amino)benzenecarboxamide Oxime (13a). Hydroxylamine hydrochloride (3.48 g, 50.0 mmol) was added to a solution of Na metal (1.15 g, 50 mmol) in MeOH (100 mL), and the mixture was stirred at 25 °C for 0.1 h. 12a (9.8 g, 50 mmol) was added, and the mixture was refluxed for 2 h and then stirred at 25 °C for 16 h. The resulting precipitate was filtered off, washed with H$_2$O, and dried under vacuum to give 13a (7.5 g, 65.5%): mp 197 °C; ^{1}H NMR (CD$_3$OD) δ 2.89 (3H, s, CH$_3$), 7.16 and 7.52 (each 2H, each d, J = 8.7 Hz, Ar-H). Anal. (C$_8$H$_{11}$N$_3$O$_3$S) C, H, N.

General Procedures for the Preparation of 5-(Oxadiazolyl)tryptamines 20a-x. General Method A. 2-[5-[3-(3-Benzyl-1,2,4-oxadiazol-5-yl)propyl]-1H-indol-3-yl]ethylamine Oxalate (20o). This procedure illustrates the general method for preparation of 20a-c,e,f,h,j,k,m-r. NaH (0.34 g of an 80% dispersion in oil, 11.3 mmol) was added to a solution of benzeneacetamide oxime^{13} (1.64 g, 10.9 mmol), in THF (25 mL), and heated at 60 °C for 0.25 h. A solution of 9d (1.0 g, 3.7 mmol) in THF (10 mL) was added and the mixture heated at reflux for 2 h. The solvent was evaporated and the residue partitioned between CH$_2$Cl$_2$ (100 mL) and H$_2$O (100 mL). The aqueous portion was further extracted with CH$_2$Cl$_2$ (4×) and the resultant crude product chromatographed on silica gel, eluting with CH$_2$-Cl$_2$/EtOH/NH$_3$ (60:8:1) to give 20o (0.74 g, 56.3%). The oxalate salt was prepared: mp 188–189 °C (^{i}PrOH/Et$_2$O); ^{1}H NMR

(DMSO-d_6) δ 1.98–2.07 (2H, m, CH$_2$CH_2CH$_2$), 2.70 (2H, t, J = 7.3 Hz, 2-CH$_2$), 2.83–2.96 (6H, m, 1-CH$_2$ and CH_2CH$_2$CH_2), 4.05 (2H, s, CH_2Ph), 6.91 (1H, d, J = 8.3 Hz, 7′-CH), 7.14 (1H, s, 2′-CH), 7.22–7.34 (7H, m, 4′-CH, 6′-CH, and Ph). Anal. (C$_{22}$H$_{24}$N$_4$O·0.5(COOH)$_2$) C, H, N.

General Method B. 2-[5-[3-[4-[(Methylsulfonyl)amino]benzyl]-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl]ethylamine Sesquioxalate (20t). This procedure illustrates the general method for preparation of 20d,g,i,l,s-x. 4-[(Methylsulfonyl)amino]benzeneacetamide oxime, 13b (1.83 g, 7.5 mmol), was added to a solution of Na (0.4g, 17.4mmol) in EtOH (50 mL), and the mixture was stirred under reflux for 0.5 h. 9a (9.5 g, 2.2 mmol) was added and the mixture refluxed for 24 h. The solvent was evaporated and the residue chromatographed on silica gel, eluting with CH$_2$Cl$_2$/EtOH/NH$_3$ (30:8:1) to give 20t (0.16 g, 18.6%). The sesquioxalate salt was prepared: mp 219–220 °C (^{i}PrOH/Et$_2$O); MS m/z 412 (M + 1)$^+$; ^{1}H NMR (DMSO-d_6) δ 2.97 (3H, s, CH$_3$), 3.06 (4H, br s, 1-CH$_2$ and 2-CH$_2$), 4.10 (2H, s, CH_2Ph), 7.18 and 7.32 (each 2H, each d, J = 8.4 Hz, Ar-H), 7.42 (1H, s, 2′-CH), 7.55 (1H, d, J = 8.6 Hz, 7′-CH), 7.81 (1H, dd, J = 1.6 and 8.6 Hz, 6′-CH), 8.36 (1H, d, J = 1.6 Hz, 4′-CH), 11.50 (1H, s, NH). Anal. (C$_{20}$H$_{21}$N$_5$O$_3$S·1.5(COOH)$_2$) C, H, N.

General Procedures for the Preparation of N,N-Dimethyl-5-(oxadiazolyl)tryptamines 21a-k. General Method A. N,N-Dimethyl-2-[5-[2-(3-benzyl-1,2,4-oxadiazol-5-yl)ethyl]-1H-indol-3-yl]ethylamine Hydrogen Oxalate (21j). This procedure illustrates the general method for preparation of 21b,d,j. NaH (0.4 g, 13.3 mmol) was added to a solution of benzeneacetamide oxime (1.8 g, 12.0 mmol), in THF (40 mL), and stirred at 60 °C for 0.25 h. A solution of 10c (1.1 g, 3.82 mmol) in THF (10 mL) was added, and the mixture was refluxed for 2 h. The solvent was evaporated and the residue partitioned between CH$_2$Cl$_2$ (200 mL) and H$_2$O (50 mL). The aqueous portion was separated and further extracted with CH$_2$Cl$_2$ (3×). The crude product was chromatographed on silica gel, eluting with CH$_2$-Cl$_2$/EtOH/NH$_3$ (60:8:1) to give 21j (0.4 g, 28%). The hydrogen oxalate salt was prepared: mp 141–143 °C (^{i}PrOH); ^{1}H NMR (D$_2$O) δ 2.84 (6H, s, N(CH$_3$)$_2$), 3.04–3.30 (8H, m, 1-CH$_2$, 2-CH$_2$, and (CH$_2$)$_2$), 3.96 (2H, s, CH_2Ph), 6.95–7.00 (3H, m, 2′-CH, 4′-CH, and 7′-CH), 7.17–7.26 (5H, m, Ph), 7.34 (1H, d, J = 8.4 Hz, 6′-CH). Anal. (C$_{23}$H$_{26}$N$_4$O·(COOH)$_2$) C, H, N.

General Method B. N,N-Dimethyl-2-[5-[(3-Amino-1,2,4-oxadiazol-5-yl)methyl]-1H-indol-3-yl]ethylamine Hydrochloride (21e). This procedure illustrates the general method for preparation of 21a,c,e,f-i. Hydroxyguanidine sulfate (56.3 g, 0.21 mol) was added to a solution of Na (16.2 g, 0.7 mol) in EtOH (900 mL) and the mixture refluxed for 0.2 h before adding a solution of 10b (19.3 g, 70.5 mmol) in EtOH (50 mL) and

refluxing for 3 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (700 mL) and H_2O (200 mL). The aqueous portion was separated and further extracted (4×). The crude product was chromatographed on silica gel, eluting with $CH_2Cl_2/EtOH/NH_3$ (30:8:1) to give **21e** (6.84 g, 34%). The hydrochloride salt was prepared: mp 186–188 °C (MeOH/Et_2O); MS m/z 286 (M^+); ^{1}H NMR (D_2O) δ 2.92 (6H, s, $N(CH_3)_2$), 3.22 (2H, t, J = 7.4 Hz, 2-CH_2), 3.47 (2H, t, J = 7.4 Hz, 2-CH_2), 4.28 (2H, s, CH_2), 7.22 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.35 (1H, s, 2'-CH), 7.52 (1H, d, J = 8.4 Hz, 7'-CH), 7.62 (1H, s, 4'-CH). Anal. ($C_{15}H_{19}N_5O \cdot HCl$) C, H, N.

N,N-Dimethyl-2-[5-[[[(4-methoxybenzyl)oxy]carbonyl]-methyl]-1H-indol-3-yl]ethylamine (25). A solution of **23** (16.4 g, 72.3 mmol) in MeOH (25 mL) and 2 N NaOH (250 mL) was heated at 80 °C for 16 h. The solvents were evaporated, and the residue was dried by azeotroping with toluene (3×). $SOCl_2$ (12.9 g, 0.11 mol) was added to a rapidly stirred suspension of the residue in MeOH (750 mL) and the mixture stirred for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (400 mL) and saturated K_2CO_3 solution (100 mL). The aqueous layer was further extracted with EtOAc (3 × 200 mL) and dried and the solvent evaporated to give **24** (18.4 g, 98%). [n]BuLi (20 mL of a 1.6 M solution in hexane, 32.0 mmol) was added dropwise, over 0.2 h, to a cooled (–70 °C) and stirred solution of 4-methoxybenzyl alcohol (6.3 g, 45.6 mmol) in THF (50 mL). A solution of **24** (2.5 g, 9.6 mmol) in THF (20 mL) was added dropwise and the solution allowed to warm to room temperature and stir for 1 h. The solvent was evaporated, H_2O (50 mL) was added, and the mixture was extracted with Et_2O (2×). The combined extracts were washed with brine (50 mL), dried, and evaporated. Flash chromatography of the resulting oil, eluting with $CH_2Cl_2/MeOH/NH_3$ (90:10:1), gave **25** (3.1 g, 89%); ^{1}H NMR ($CDCl_3$) δ 2.33 (6H, s, $N(CH_3)_2$), 2.59–2.65 and 2.87–2.94 (each 2H, each m, 1-CH_2 and 2-CH_2), 3.74 (2H, s, CH_2-Ar), 3.80 (3H, s, OCH_3), 5.07 (2H, s, CH_2O), 6.83–6.88 (2H, m, ArH), 6.99 (1H, d, J = 2.5 Hz, 4'-CH), 7.10 (1H, dd, J = 1.7 and 8.4 Hz, 6'-CH), 7.23–7.29 (3H, m, 7'-CH and ArH), 7.48 (1H, s, 2'-CH), 8.04 (1H, br s, NH); MS m/z 366 (M^+); HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1967.

N,N-Dimethyl-2-[5-[[[(4-methoxybenzyl)oxy]carbonyl]-methyl]-1-(tert-butoxycarbonyl)indol-3-yl]ethylamine (26). Di-tert-butyl dicarbonate (2.63 g, 12.06 mmol) and 4-DMAP (0.11 g) were added to a solution of **25** (3.4 g, 9.27 mmol) in MeCN (25 mL), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue chromatographed on silica gel, eluting with $CH_2Cl_2/MeOH$ (95:5) to give **26** (3.33 g, 77%): ^{1}H NMR ($CDCl_3$) δ 1.66 (9H, s, $(CH_3)_3$), 2.32 (6H, s, $N(CH_3)_2$), 2.58–2.65 and 2.80–2.88 (each 2H, each m, 1-CH_2 and 2-CH_2), 3.74 (2H, s, CH_2Ar), 3.80 (3H, s, OCH_3), 5.07 (2H, s, CH_2O), 6.84–6.89 (2H, m, ArH), 7.18–7.28 (3H, m, 6'-CH and ArH), 7.38 (1H, s, 2'-CH), 7.41 (1H, d, J = 1.2 Hz, 4'-CH), 8.03 (1H, br d, J = 8.1 Hz, 7'-CH); MS m/z 466 (M^+); HRMS calcd for $C_{27}H_{34}N_2O_5$ 466.2467, found 466.2456.

N,N-Dimethyl-2-[5-[(3-amino-1,2,4-thiadiazol-5-yl)meth-yl]-1H-indol-3-yl]ethylamine Hydrogen Oxalate (28). To a solution of **26** (2.0 g, 4.28 mmol) in DMF (25 mL) was added NaH (0.43 g of a 60% dispersion in oil, 10.70 mmol), and the mixture was stirred for 0.25 h before a solution of 3-amino-5-chloro-1,2,4-thiadiazole[18] (1.22 g, 8.99 mmol) in DMF (5 mL) was added. The mixture was stirred for 2.5 h, H_2O (50 mL) and brine (40 mL) were added, and the mixture was extracted into EtOAc (3×). The combined extracts were washed with brine (1×), dried, and evaporated. The crude product was chromatographed on silica gel, eluting with $CH_2Cl_2/MeOH$ (84:16) to give **27** (0.8 g, 33%): MS m/z 566 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.65 (9H, s, $(CH_3)_3$), 2.32 (6H, s, $N(CH_3)_2$), 2.57–2.64 and 2.78–2.84 (each 2H, each m, 1-CH_2 and 2-CH_2), 3.78 (3H, s, OCH_3), 4.83 (2H, s, NH_2), 5.08 (1H, d, J = 11.9 Hz, 1 of CH_2O), 5.19 (1H, d, J = 11.9 Hz, one of CH_2O), 5.35 (1H, s, $CHCO_2$), 6.79–6.84 and 7.16–7.21 (each 2H, each m, ArH), 7.28 (1H, dd, J = 1.9 and 8.7 Hz, 6'-CH), 7.41 (1H, s, 2'-CH), 7.50 (1H, d, J = 1.9 Hz, 4'-CH), 8.06 (1H, d, J = 8.7 Hz, 7'-CH).

A solution of **27** (0.8 g, 1.41 mmol) in CH_2Cl_2 (120 mL), H_2O (5 mL), and trifluoroacetic acid (21 mL) was stirred at room temperature for 1 h. The solvents were evaporated, and the residue was dried by azeotroping with toluene–MeOH. The

product was dissolved in MeOH (50 mL) and refluxed for 0.1 h. The solvent was evaporated, saturated K_2CO_3 solution (20 mL) was added, and the mixture was extracted into EtOAc (2×). The crude product was chromatographed on silica gel, eluting with $CH_2Cl_2/MeOH/NH_3$ (90:10:1.5) to give **28** (0.19 g, 44.8%). The hydrogen oxalate salt was prepared: mp 185–188 °C (MeOH/Et_2O); MS m/z 301 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.75 (6H, s, $N(CH_3)_2$), 3.00–3.05 and 3.20–3.25 (each 2H, each m, 1-CH_2 and 2-CH_2), 4.32 (2H, s, CH_2Ar), 6.55 (2H, s, NH_2), 7.08 (1H, dd, J = 1.5 and 8.3 Hz, 6'-CH), 7.25 (1H, d, J = 1.5 Hz, 4'-CH), 7.34 (1H, d, J = 8.3 Hz, 7'-CH), 7.57 (1H, s, 2'-CH), 10.99 (1H, br s, NH). Anal. ($C_{15}H_{19}N_5S \cdot (COOH)_2$) C, H, N.

N,N-Dimethyl-2-[5-(5-methyl-1,3-oxazol-2-yl)-1H-indol-3-yl]ethylamine Sesquioxalate (31). A solution of **10a** (1.4 g, 5.4 mmol) and LiOH (0.45 g, 10.8 mmol) in EtOH/H_2O (10:1, 40 mL) was heated at 60 °C for 8 h and then stirred at room temperature for 16 h. The solvent was evaporated and the residue chromatographed on silica gel, eluting with $Et_2O/EtOH/H_2O/$ NH_3 (20:15:5:1) to give **29** (0.94 g, 75%). To a solution of **29** (0.2 g, 0.86 mmol), 1-hydroxybenzotriazole (0.14 g, 1.0 mmol), N-methylmorpholine (0.2 mL, 1.7 mmol), and propargylamine (71 μL, 1.0 mmol) in CH_2Cl_2–DMF (1:1, 25 mL), at 0 °C, was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (98 mg, 1.03 mmol). The solution was stirred for 18 h and washed with water (50 mL), and the aqueous layer was separated and extracted with CH_2Cl_2 (4×). The combined extracts were dried and evaporated, and the residue was chromatographed on silica gel, eluting with $CH_2Cl_2/EtOH/NH_3$ (40:8:1) to give the propargylamide **30** (88 mg, 38%): ^{1}H NMR ($CDCl_3$) δ 2.33 (7H, m, $CH\equiv C$ and $N(CH_3)_2$), 2.65 and 2.92 (each 2H, each t, J = 7.0 Hz, 1-CH_2 and 2-CH_2), 4.32 (2H, dd, J = 1.0 and 7.0 Hz, CH_2NHCO), 6.50 (1H, br t, NHCO), 7.02 (1H, s, 2'-CH), 7.24 (1H, d, J = 9.0 Hz, 7'-CH), 7.54 (1H, dd, J = 1.0 and 9.0 Hz, 6'-CH), 8.09 (1H, s, 4'-CH), 8.79 (1H, br s, NH).

A solution of **30** (88 mg, 0.33 mmol) and Hg(OAc)$_2$ (7 mg, 0.02 mmol) in acetic acid (4 mL) was refluxed for 3 h. The solvent was evaporated, saturated K_2CO_3 solution (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (5×). The crude product obtained was chromatographed on silica gel, eluting with $CH_2Cl_2/EtOH/NH_3$ (60:8:1) to give the desired oxazole **31** (50 mg, 57%). The sesquioxalate salt was prepared: mp 164–166 °C; MS m/z 269 (M^+); ^{1}H NMR (D_2O) δ 2.49 (3H, s, CH_3), 2.93 (6H, s, $N(CH_3)_2$), 3.25 and 3.51 (each 2H, each t, J = 7.0 Hz, 1-CH_2 and 2-CH_2), 7.30 (1H, s, oxazole-CH), 7.43 (1H, s, 2'-CH), 7.61 (1H, d, J = 9.0 Hz, 7'-CH), 7.72 (1H, dd, J = 1.0 and 9.0 Hz, 6'-CH), 8.20 (1H, d, J = 1.0 Hz, 4'-CH). Anal. ($C_{16}H_{19}N_3O \cdot 1.6 \cdot (COOH)_2$) C, H, N.

Biochemical Methods. Binding Experiments: (a) Brain Membrane Preparations. Crude membrane homogenates were prepared from pig cerebral cortex for 5-HT$_{1A}$ and 5-HT$_{1C}$ assays and from pig caudate for the 5-HT$_{1D}$ assay.[19] Thawed material was homogenized in 10–15 volumes of ice-cold 50 mM TRIS·HCl (pH 7.7 at room temperature) using a Kinematica polytron and centrifuged at 48000g at 4 °C for 11 min. The supernatant was discarded and the pellet resuspended in the same volume of ice-cold TRIS·HCl buffer and recentrifuged at 48000g at 4 °C for a further 11 min. The pellet was then resuspended in 10 volumes of 50 mM TRIS·HCl followed by a 10-min incubation at 37 °C to remove any endogenous 5-HT. Finally the tissue was recentrifuged at 48000g, 4 °C for 11 min, and the pellet resuspended in assay buffer (see below) to give the required volume for the assay, immediately prior to use. Crude P2 pellet homogenates were prepared from rat frontal cortex for the 5-HT$_2$ assay and from rat whole cortex for the 5-HT$_3$ assay. Brains of male Sprague–Dawley rats (250–300 g) were dissected on ice and promptly transferred to 10–15 volumes of ice-cold 0.32 mM sucrose. The tissue was then homogenized using 10 strokes of a motor-driven Teflon/glass homogenizer (Janke and Kunkel) at 500 rpm. The homogenate was centrifuged at 1000g, 4 °C for 10 min, and the supernatant recentrifuged at 48000g, 4 °C for 21 min. The resulting pellet was resuspended in 10–15 volumes of 50 mM TRIS·HCl, pH 7.7 at room temperature (5-HT$_2$), 2.5 mM Hepes, pH 7.4 at room temperature (5-HT$_3$), to remove endogenous 5-HT. Finally, the homogenates were recentrifuged for a further 21 min at 48000g, 4 °C, and the resulting pellet was stored

on ice. Immediately prior to use the pellet was made up to the required volume in assay buffer (see below).

(b) Binding Assays. Membranes, ligand, and drugs were prepared, in duplicate, in assay buffer which consisted of 50 mM TRIS·HCl containing 10 μM pargyline, 0.1% ascorbate, 5.7 mM CaCl₂, pH 7.7 at room temperature for the 5-HT₁A assay, 50 mM TRIS·HCl containing 10 μM pargyline, 0.1% ascorbate, 4.0 mM CaCl₂, pH 7.7 at room temperature for the 5-HT₁C and 5-HT₁D assays, 50 mM TRIS·HCl containing 10 μM pargyline, 0.1% ascorbate, 10 mM MgCl₂, 0.5 mM EDTA, pH 7.4 at room temperature for the 5-HT₂ assay, and 10 mM Hepes containing 10 μM pargyline, 0.1% ascorbate, pH 7.1 at room temperature for the 5-HT₃ assay. Test compound was incubated with appropriate radioligand to give a final volume of 1 mL with the exception of the 5-HT₂ assay which was carried out in a total volume of 2 mL. [³H]-8-OH-DPAT (1.5 nM), [³H]mesulergine (1.5 nM), [³H]-5-HT (2 nM) in the presence of 100 nM cyanopindolol and 100 nM mesulergine, [³H]DOB (0.6 nM), and [³H]-Q-ICS 205-930 (0.5 nM) were used to label 5-HT₁A, 5-HT₁C, 5-HT₁D, 5-HT₂, and 5-HT₃ binding sites, respectively. 5-HT (10 μM) was used to define nonspecific binding in the 5-HT₁A, 5-HT₁C, and 5-HT₁D assays, cyproheptidine (1 μM) in the 5-HT₂ assay, and MDL 72222 (10 μM) in the 5-HT₃ assay. 5-HT₁A, 5-HT₁C, 5-HT₁D, and 5-HT₂ assay incubations were carried out in a shaking water bath at 37 °C for 20, 30, 30, and 15 min, respectively. 5-HT₃ assay incubations were carried out on ice for 15 min. In all cases the reaction was started by the addition of the membrane solution and terminated by rapid filtration through Whatman G/FB glass fibre filters (ice cold for the 5-HT₁C assay) using a Brandel cell harvester, followed by 2 × 4-mL washes with 50 mM TRIS·HCl (5 mM HEPES for the 5-HT₃ assay). The filters had previously been soaked in 0.3% poly(ethylenimine) (PEI)/0.5% Triton X to minimize nonspecific binding. The filter were then transferred to scintillation vials containing 10 mL of Hydrofluor, and the radioactivity was determined by liquid scintillation spectrometry at 30–40% efficiency.

(c) Data Analysis. Experiments were performed on two to three separate occasions in duplicate. Each displacement curve consisted of 18 (5-HT₁D), 10 (5-HT₁A), or 9 (all other assays) separate concentrations ranging from 100 μM to 30 pM. The data represent in all cases specific binding (total–nonspecific) only. Each inhibition curve was analyzed by nonlinear regression analysis using the function fitting routine provided by the data manipulation software RS/1. All curves were analyzed based on the assumption of a one-site model. 5-HT₁D displacement curves were also fitted to a two-site model, and improvement of the fit was assessed using the partial *F*-test procedure.[28] A two-site model was only accepted if the probability of the models being the same was less than 1:20 (*P* < 0.05). All compounds, with exception of 5-HT, tested for 5-HT₁D receptor activity yielded displacement curves best fit to a two-site model, and the pIC₅₀ values quoted refer to the high affinity component only.

Functional Experiment: New Zealand White Rabbit Saphenous Vein Preparation. Rabbits were anaesthetized with 45 mg/kg pentobarbitone (intravenously) and decapitated, and the saphenous veins were cannulated and removed. The vessels were cleared of connective and adipose tissue, cut into 5-mm sections, and placed on tissue holders in organ baths containing Krebs-Henseleit solution at 37 °C. Tension was set at 2 g and reset regularly over a period of at least 30 min while the tissues were exposed to phenoxybenzamine (0.3 μM) and pargyline (500 μM). After the tissues were washed to remove excess inhibitors, 1 μM 5-HT was added from which relative efficacy values were calculated. Agonist potencies were calculated as pEC₅₀ values from plots of percentage 5-HT (1 μM) response against concentration of the agonist.[25]

Supplementary Material Available: A table of microanalytical data for novel compounds and table of HRMS data for novel compounds (4 pages). Ordering information is given on any current masthead page.

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