Synthesis and Serotonergic Activity of *N,N*-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine and Analogues: Potent Agonists for 5-HT_{1D} Receptors[1]

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The synthesis and the 5-HT receptor activity of a novel series of *N,N*-dimethyltryptamines substituted in the 5-position with an imidazole, triazole, or tetrazole ring are described. The objective of this work was to identify potent and selective 5-HT_{1D} receptor agonists with high oral bioavailability and low central nervous system penetration. Compounds have been prepared in which the azole ring is attached through either nitrogen or carbon to the indole. Conjugated and methylene-bridged derivatives have been studied ($n = 0$ or 1). Substitution of the azole ring has been explored either α or β to the point of attachment to indole. In a series of N-linked azoles (X = N), simple unsubstituted compounds have high affinity and selectivity for 5-HT_{1D} receptors. It is proposed that for good affinity and selectivity a hydrogen bond acceptor interaction with the 5-HT_{1D} receptor, through a β-nitrogen in the azole ring, is required. In a series of C-linked triazoles and tetrazoles (X = C), optimal affinity and selectivity for the 5-HT_{1D} receptor was observed when the azole ring is substituted at the 1-position with a methyl or ethyl group. This study has led to the discovery of the 1,2,4-triazole **10a** (MK-462) as a potent and selective 5-HT_{1D} receptor agonist which has high oral bioavailability and rapid oral absorption. The *in vitro* activity and the preliminary pharmacokinetics of compounds in this series are presented.

Introduction

During the last 5 years, molecular biology has revealed the immense diversity of serotonin (5-HT, **1**) (Chart 1) receptors. At this point in time, seven 5-HT receptor families have been identified of which 5-$HT_{1,2,4-7}$ are G-protein-coupled receptors.[2-8] For many of these 5-HT families, receptor subtypes have been identified and classified on the basis of a combination of amino acid sequence homology in the seven transmembrane domains, the signal transduction mechanism, and classical pharmacology.[9] The most recently cloned subtypes hold promise for the discovery of new selective drug candidates in the next 5–10 years. The 5-HT_1 family appears to have the highest multiplicity, and to date five human 5-HT_1-like receptors have been cloned, 5-HT_{1A}, 5-$HT_{1B/1D\beta}$, 5-$HT_{1D\alpha}$, 5-HT_{1E}, and 5-HT_{1F}.[2,3] Much work recently has focused on 5-HT_{1D} receptors,[10] originally characterized in bovine brain membranes[11] and shown to have high affinity for the 5-HT_1 selective agonist 5-carbamoyltryptamine (5-CT, **2**).[12] The introduction of the 5-HT_{1D} receptor agonist sumatriptan (**3**), for the acute treatment of migraine,[13] has sparked an intense research effort to discover more potent and selective 5-HT_{1D} receptor agonists with improved pharmacokinetic profiles.[14-18] Sumatriptan selectively constricts intracranial vascular smooth muscle and inhibits neuropeptide release from perivascular trigeminal sensory neurones, and both mechanisms have been proposed to be important in eliciting its antimigraine action.[19,20]

We have recently reported that the carboxamide and sulfonamide groups of **2** and **3**, respectively, can be replaced with substituted 1,2,4-oxadiazole and 1,2,4-thiadiazole rings to give potent and selective 5-HT_{1D} receptor agonists, and we concluded that the H-bond acceptor ability of these rings was important for 5-HT_{1D} receptor affinity and selectivity.[21,22] Structure–activity studies in these series led to the discovery of the benzylsulfonamide **4a** (L-694,247) as a highly potent 5-HT_{1D} receptor agonist with good selectivity for 5-HT_{1D} receptors.[23] Pharmacokinetic studies on compounds such as **4a**, however, suggested low oral bioavailability. In the oxadiazole series, it was generally found that primary tryptamines had low oral bioavailability, probably as a result of metabolism by monoamine oxidase. The *N,N*-dimethyltryptamine **4b** (L-695,894) however, showed 40% oral bioavailability in rats but had significant affinity for 5-HT_{2A} and 5-HT_{2C} receptors.[21] In order to improve the 5-HT_{1D} receptor selectivity and oral bioavailability, we have extended this work to explore alternative 5-membered heteroaromatic rings which are also capable of functioning as H-bond acceptors. Compounds were sought which had log *D*'s < -0.5 to minimize central nervous system (CNS) penetration.[13] We describe herein the synthesis, serotonergic activity, and preliminary pharmacokinetics of a series of *N,N*-

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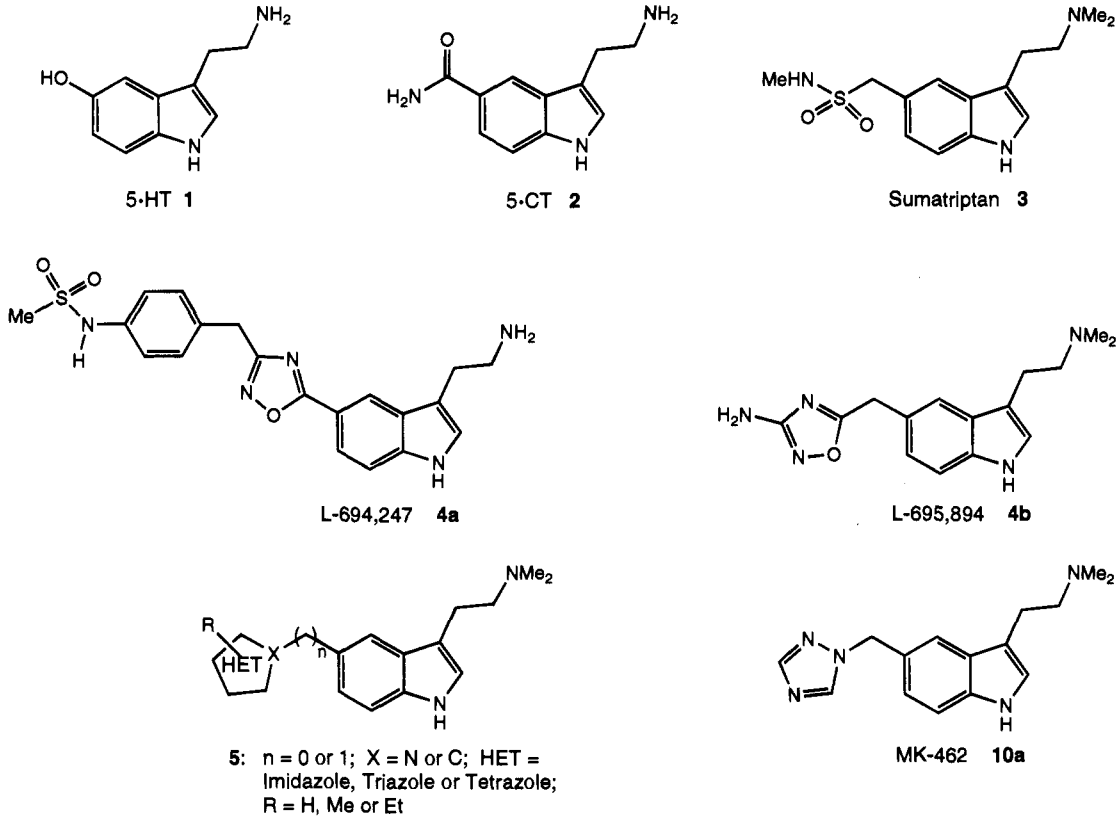
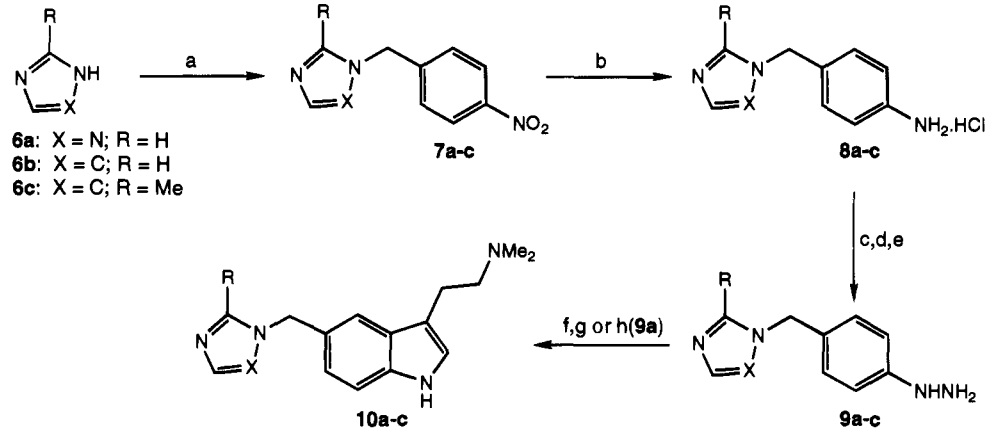
Chart 1



Scheme 1[a]



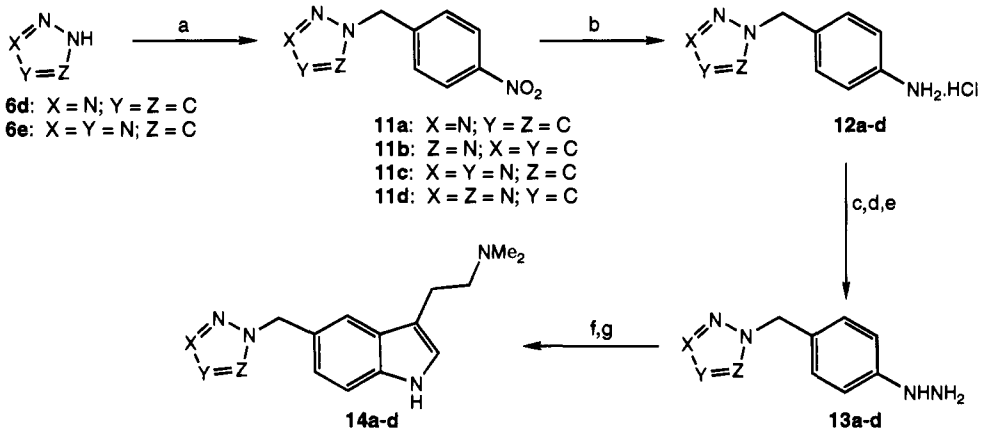
[a] Reagents: (a) NaH, DMF, 4-nitrobenzyl bromide; (b) H_2, 10% Pd–C, EtOH, 2 N HCl; (c) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (d) $SnCl_2 \cdot 2H_2O$, concentrated HCl; (e) NaOH (aq)/EtOAc; (f) 4-chlorobutanal dimethyl acetal, EtOH/H_2O (5:1), 5 N HCl (1.2 equiv), reflux, 4 h; (g) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C; (h) 4-(*N,N*-dimethylamino)butanal dimethyl acetal, 4% H_2SO_4, reflux, 2 h.

dimethyltryptamines (**5**), substituted in the 5-position of indole with imidazole, triazole, or tetrazole and linked through either N or C in the ring. The choice of these heterocycles also allowed a study of the effect of substitution in the ring, either α or β to the point of attachment to indole, on 5-HT_{1D} receptor affinity and selectivity. This work has led to the discovery of the 1,2,4-triazole **10a** (L-705,126, MK-462) as a potent and selective 5-HT_{1D} receptor agonist with high oral bioavailability and good *in vivo* activity predictive of antimigraine action.[24]

Synthetic Chemistry

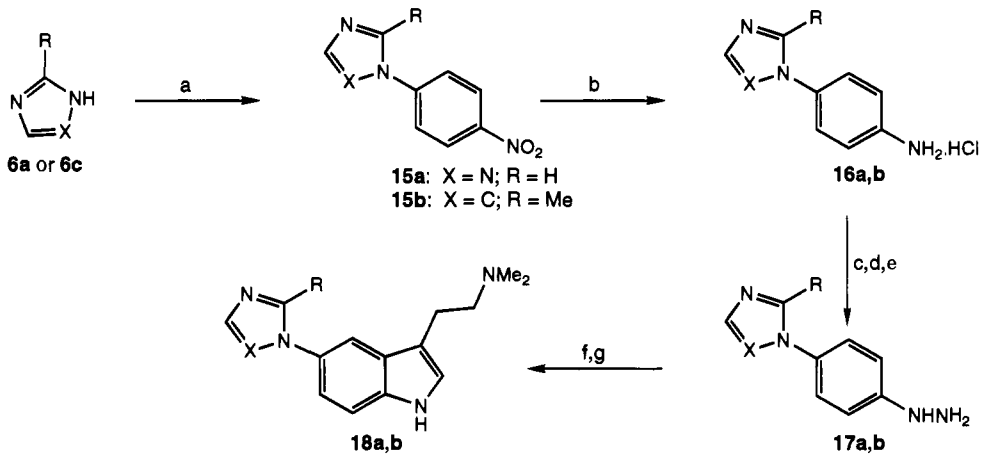
The imidazole-, triazole-, and tetrazole-substituted *N,N*-dimethyltryptamines **10a–c** and **14a–d** were prepared starting from 4-nitrobenzyl bromide (Schemes 1 and 2). Reaction of the sodium derivative of 1,2,4-triazole with 4-nitrobenzyl bromide gave 4-nitrobenzyl triazole **7a** as a crystalline solid and, as expected, as a single isomer[25a] (Scheme 1). Similar treatment of 4-nitrobenzyl bromide with imidazole and 2-methylimidazole gave the 4-nitrobenzyl imidazoles **7b,c**, respectively. Alkylation of 1-*H*-1,2,3-triazole with 4-nitrobenzyl bromide gave a 6:1 mixture of **11a:b** which were separated by silica gel chromatography (Scheme 2). Reaction of 1-*H*-tetrazole with 4-nitrobenzyl bromide under the same conditions gave the alkylation products **11c** (75%) and **11d** (17%). The regiochemical assignments for **11a–d** were made on the basis of NOE enhancement experiments. Saturation of the H-5 imidazole and tetrazole protons in **11a,c**, respectively, gave an NOE enhancement of CH_2 thus defining N-1 as the

Scheme 2[a]



[a] Reagents: (a) NEt_3, MeCN, 4-nitrobenzyl bromide; (b) H_2, 10% Pd–C, EtOH, 2 N HCl; (c) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (d) $SnCl_2 \cdot 2H_2O$, concentrated HCl; (e) NaOH (aq)/EtOAc; (f) 4-chlorobutanal dimethyl acetal, EtOH/H_2O (5:1), 5 N HCl (1.2 equiv), reflux, 4 h; (g) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C.

Scheme 3[a]



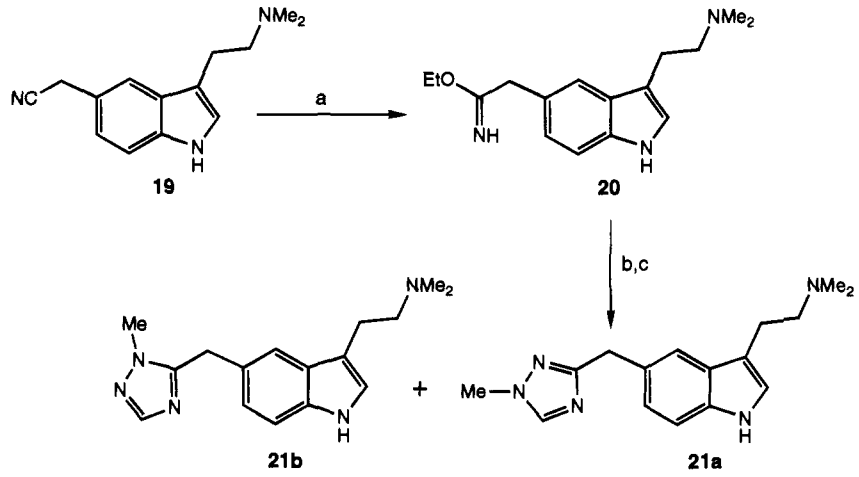
[a] Reagents: (a) NaH, DMF, 4-fluoronitrobenzene; (b) H_2, 10% Pd–C, EtOH, 2 N HCl; (c) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (d) $SnCl_2 \cdot 2H_2O$, concentrated HCl; (e) NaOH (aq)/EtOAc; (f) 4-chlorobutanal dimethyl acetal, EtOH/H_2O (5:1), 5 N HCl (1.2 equiv), reflux, 4 h; (g) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C.

position of alkylation of the heterocycles. Hydrogenation of **7a–c** and **11a–d** over Pd–C gave the anilines **8a–c** and **12a–d** which were isolated as their hydrochloride salts. Treatment of **8a–c** and **12a–d** with $NaNO_2$ followed by reduction of the intermediate diazonium salts with $SnCl_2 \cdot 2H_2O$ gave the hydrazines **9a–c** and **13a–d**. Fischer reaction[25b] of **9a–c** and **13a–d** with 4-chlorobutanal dimethyl acetal,[26] in refluxing EtOH/H_2O (5:1) and 5 N HCl (1.2 equiv), afforded the corresponding tryptamines which were treated with $NaCNBH_3/CH_2O/MeCO_2H$ to give the *N,N*-dimethyltryptamines **10a–c** and **14a–d** respectively, in moderate yields (Schemes 1 and 2).[27] An alternative procedure for the preparation of triazole **10a** was to treat the hydrochloride salt of hydrazine **9a** with 4-(*N,N*-dimethylamino)butanal dimethyl acetal,[28] in refluxing 4% sulfuric acid, to give *N,N*-dimethyltryptamine **10a** directly.

The route to the conjugated triazole **18a** and imidazole **18b** is shown in Scheme 3. Reaction of the sodium salt of 1,2,4-triazole with 1-fluoro-4-nitrobenzene, in DMF, gave a high yield of the N-1 alkylation product **15a** together with a trace amount of the N-4 adduct. Similar reaction of 2-methylimidazole with 1-fluoro-4-nitrobenzene gave **15b**. Hydrogenation of **15a,b** gave the anilines **16a,b** which were converted to the hydrazines **17a,b** using $NaNO_2/SnCl_2 \cdot 2H_2O$. Fischer reaction of **17a,b** with 4-chlorobutanal dimethyl acetal followed by N,N-dimethylation of the resultant tryptamines afforded **18a,b**.

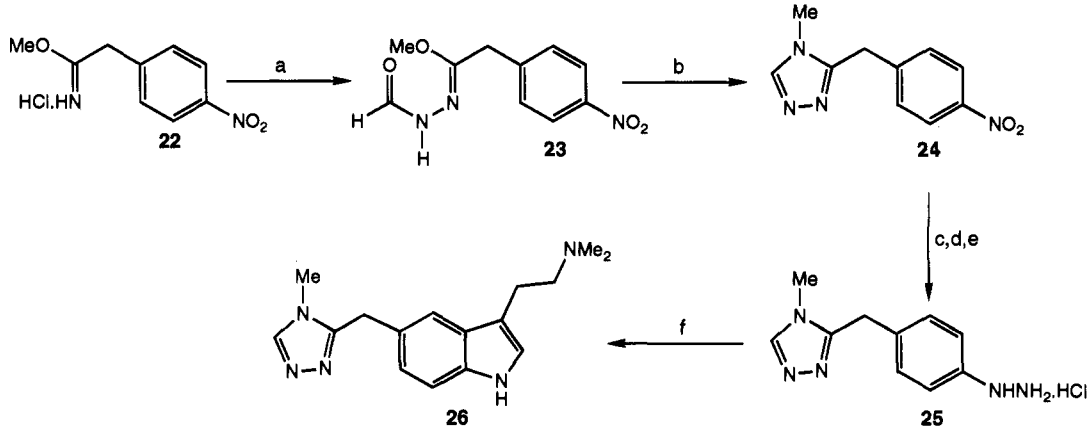
The *N*-methyl-1,2,4-triazoles **21a,b** and **26** were prepared as illustrated in Schemes 4 and 5. The imino ether **20** was prepared by treatment of *N,N*-dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine, **19**,[21] with EtOH/HCl (gas). Treatment of **20** with methylhydrazine followed by refluxing in formic acid gave the *N*-methyl-1,2,4-triazoles **21a,b** in a 1:2 ratio, respectively, in low yield. Regiochemical assignments were again based on NOE enhancement experiments. Saturation of the methyl of **21a,b** gave NOE enhancements of the triazole proton and methylene bridge, respectively, thus defining the regiochemistry. The 4-methyl-1,2,4-triazole **26** was prepared starting from the methyl imino ether **22** (Scheme 5). Addition of formylhydrazine to **22** gave the formylhydrazone **23** which was reacted with methylamine to give the desired 4-methyl-1,2,4-triazole **24**, in 87% yield, after silica gel chromatography. Hydrogenation followed by diazotization and reduction gave the hydrazine **25**. Fischer reaction of **25** with 4-(*N,N*-dimethylamino)butanal dimethyl acetal, in refluxing 4% H_2SO_4, gave **26** in moderate yield.

Scheme 4[a]



[a] Reagents: (a) EtOH/HCl; (b) $MeNHNH_2$, EtOH, NEt_3; (c) HCO_2H, reflux, 2 h.

Scheme 5[a]



[a] Reagents: (a) NH_2NHCHO, MeOH; (b) $MeNH_2$ (g), MeOH; (c) H_2, 10% Pd–C, EtOH, 2 N HCl; (d) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (e) $SnCl_2 \cdot 2H_2O$, concentrated HCl; (f) 4-(*N,N*-dimethylamino)butanal dimethyl acetal, 4% H_2SO_4, reflux, 2 h.

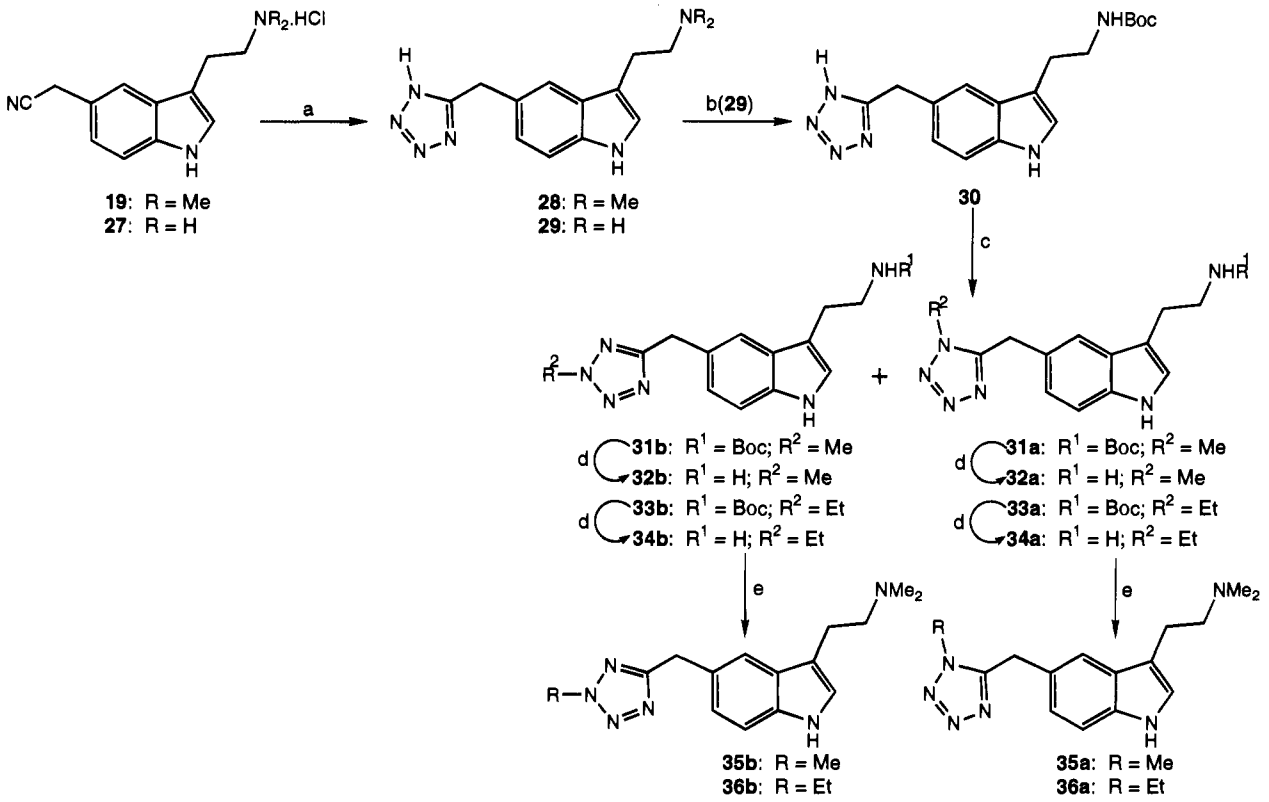
A series of tetrazoles substituted on either N-1 or N-2 was prepared (Scheme 6). The tetrazole ring of *N,N*-dimethyltryptamine **28** and tryptamine **29** was constructed by reaction of the corresponding nitriles **19** and **27**, respectively, with sodium azide, in *N*-methyl-2-pyrrolidinone, using triethylamine hydrochloride as catalyst. Tetrazoles **28** and **29** were obtained in 76% and 69% yield, respectively. Tetrazole formation was not observed when the free bases of **19** and **27** were used. In order to alkylate the tetrazole ring of **29**, protection of the tryptamine as the Boc derivative **30** was necessary. Reaction of **30** with methyl iodide gave a mixture of the N-1 and N-2 alkylation products **31a,b** in a 1.9:1 ratio which were separated by silica gel chromatography. Similar reaction of **30** with ethyl iodide gave the ethyl tetrazoles **33a,b** in 43% and 37% yields, respectively. In each case, the N-1 alkylation products were more polar than the N-2 adducts on silica gel and the structural assignments were made by NOE enhancement experiments. Thus, saturation of the methyl of **31a** and the CH_2CH_3 of **33a** gave NOE enhancement of the methylene bridge in each compound, thus defining the position of alkylation as N-1. Removal of the Boc group of **31a,b** and **33a,b** was achieved using trifluoroacetic acid to give the tryptamines **32a,b** and **34a,b**, respectively. Reaction of **32a,b** and **34a,b** with $NaCNBH_3$/HCHO/CH_3CO_2H in MeOH gave the *N,N*-dimethyltryptamines **35a,b**, and **36a,b** respectively (Scheme 6).

Results and Discussion

Structure–Affinity Relationships. The 5-HT_{1D} receptor affinities of compounds were measured by displacement of [^{3}H]-5-HT from bovine caudate membranes, in the presence of cyanopindolol and mesulergine to block interactions with 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} sites.[11,21,29] The data is presented in Tables 1–3.

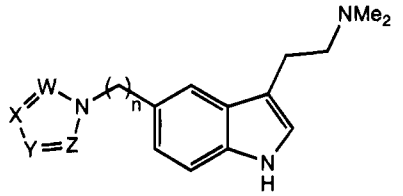
The 5-HT_{1D} receptor affinities of a series of imidazoles, triazoles, and tetrazoles, attached to indole through a ring N, are shown in Table 1. The 1-substituted 1,2,4-triazole **10a** has good affinity for the 5-HT_{1D} receptor and is comparable to the 1-substituted 1,2,3-triazole **14a**. Both compounds have low log *D*'s, predictive of low CNS penetration (cf. sumatriptan log $D = -1.17$) which is important for potential antimigraine agents of this class.[13a,b] The 2-substituted 1,2,3-triazole **14b** has reduced affinity compared to **10a** and **14a**, suggesting that a ring N, β to the position of substitution (X or Y = N), is important for binding to the 5-HT_{1D} receptor in this series. The 4-substituted 1,2,4-triazole analogue of **10a** could not be prepared because of stability problems. Imidazole **10b** and tetrazoles **14c,d** have comparable 5-HT_{1D} receptor affinities to triazole **10a** although log *D* is optimal for **10a** reflecting the higher

Scheme 6[a]



[a] Reagents: (a) NaN_3, *N*-methyl-2-pyrrolidinone, $Et_3N{\cdot}HCl$, 160 °C, 8–16 h; (b) $(Boc)_2O$, NEt_3, CH_2Cl_2; (c) R^2I, NEt_3, MeCN; (d) trifluoroacetic acid, CH_2Cl_2; (e) HCHO, $NaCNBH_3$, $MeCO_2H$, MeOH, 0 °C.

Table 1. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by N-Linked Imidazoles, Triazoles, and Tetrazoles and Standard 5-HT$_{1D}$ Agonists



compd	*n*	W	X	Y	Z	pIC$_{50}$ ± SEM[a]	log *D*[b]
5-HT (**1**)						8.0 ± 0.09	
5-CT (**2**)						8.4 ± 0.1	
sumatriptan (**3**)						7.7 ± 0.08	−1.17
4a						9.5 ± 0.19	0.25
4b						7.6 ± 0.21	−0.67
10a	1	N	C	N	C	7.3 ± 0.08	−0.74
10b	1	C	N	C	C	7.5 ± 0.06	−0.53
10c	1	C-Me	N	C	C	7.2 ± 0.13	−0.74
14a	1	N	N	C	C	7.3	−0.70
14b	1	N	C	C	N	6.6 ± 0.06	−0.20
14c	1	N	N	N	C	7.4 ± 0.10	−0.64
14d	1	N	N	C	N	7.4 ± 0.08	−0.34
18a	0	N	C	N	C	7.7 ± 0.03	−0.34
18b	0	C-Me	N	C	C	8.1 ± 0.10	−0.13

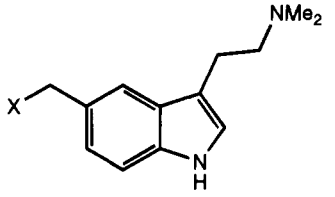
[a] SEM = standard error of the mean from $n \geq 3$. Where SEM is not quoted, the figures are the mean of two independent determinations typically with individual values within ±(10–15)% of the mean. [b] log *P* measured at pH 7.4.

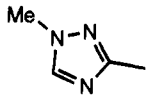
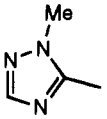
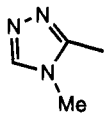
basicity of this system. 2-Methyl substitution of the imidazole ring, to give **10c**, resulted in slightly lower affinity for 5-HT$_{1D}$ receptors compared to the unsubstituted analogue **10b**. The effect of conjugation of the 5-ring heterocycle with indole on 5-HT$_{1D}$ receptor affinity, in this series, was demonstrated by preparation of triazole **18a** and 2-methylimidazole **18b**. Both compounds have 5–10-fold higher affinity for the 5-HT$_{1D}$ receptor than the methylene-linked analogues **10a,c**. This result parallels that we reported for a series of 3-substituted 1,2,4-oxadiazoles which led to the identification of the highly potent 5-HT$_{1D}$ receptor agonist L-694,247.[21,23] Unfortunately, a second consequence of conjugation is increased hydrophobicity, e.g., compare **10c**, log $D = -0.74$, and **18b**, log $D = -0.13$, resulting in greater penetration into the CNS.

The three regioisomers of *N*-methyl-1,2,4-triazole, **21a,b** and **26**, were prepared to determine the effect of changing the position of methyl substitution on 5-HT$_{1D}$ receptor binding and log *D* (Table 2). The 1,3-substituted triazole **21a** has 10-fold lower affinity for 5-HT$_{1D}$ receptors compared with sumatriptan. One order of magnitude improvement in activity was seen for the 4-methyltriazole **26**, whereas the 1,5-substituted triazole **21b** has intermediate 5-HT$_{1D}$ receptor affinity. Triazole **26** also has optimal hydrophilicity, again reflecting the higher basicity of this pattern of substitution in the 1,2,4-triazole ring.

Data for an analogous series of substituted tetrazoles are shown in Table 3. Here both the position of substitution in the ring and the size of the substituent were studied. The zwitterionic 1*H*-tetrazole **28** has poor affinity for the 5-HT$_{1D}$ recognition site suggesting that charged fragments at this position are not well tolerated by the receptor. Alkylation of the tetrazole ring gave up to 100-fold improvement in receptor affinity. In a series of methyl- and ethyl-substituted tetrazoles, the highest 5-HT$_{1D}$ receptor affinity was observed for the 1-substituted derivatives. Thus, 1-methyltetrazole **35a** has 5-fold higher affinity than the 2-methyl analogue **35b**.

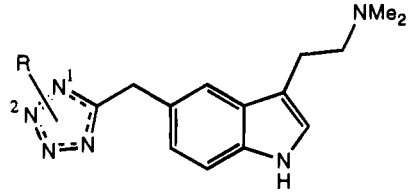
Table 2. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by C-Linked Triazoles



compd	X	pIC$_{50}$ ± SEM[a]	Log D[b]
21a		6.7	-1.01
21b		7.0 ± 0.14	-0.75
26		7.6	-1.44

[a,b] See corresponding footnotes of Table 1.

Table 3. Displacement of [^{3}H]-5-HT Binding to 5-HT$_{1D}$ Recognition Sites in Pig Caudate Membranes by C-Linked Tetrazoles



compd	R	position of substitution	pIC$_{50}$ ± SEM[a]	log D[b]
28	H		5.4	
35a	Me	1	7.6	−0.94
36a	Et	1	7.6 ± 0.16	−0.43
35b	Me	2	7.1 ± 0.05	−0.51
36b	Et	2	6.9 ± 0.17	0.02

[a,b] See corresponding footnotes of Table 1.

The ethyltetrazoles **36a,b** have comparable activity to the methyl derivatives **35a,b**, respectively. Structure–activity in the tetrazole series therefore parallels that seen in the methyl triazole series with substitution of the heteroaromatic ring at the α-position leading to higher affinity compounds.

The 5-HT$_{1D}$ binding results for the N-linked imidazoles, triazoles, and tetrazoles **10a–c**, **14a–d**, and **18a,b** (Table 1) demonstrate that unsubstituted 5-membered heteroaromatic rings are well tolerated at the 5-HT$_{1D}$ recognition site. It is predicted that the critical role of the azole ring at the receptor is to act as a H-bond acceptor. The lower affinity of the 2-substituted 1,2,3-triazole **14b** would suggest that this interaction is primarily through the β-nitrogen (X or Y in Table 1) of the azole ring in compounds **10a–c**, **14a,c,d**, and **18a,b**. The importance of this interaction is also reflected in the results for the C-linked 1,2,4-triazoles and tetrazoles. The 5–10-fold higher affinity of 4-methyltriazole **26** and 1-methyltetrazole **35a**, compared to the triazole **21a** and 2-methyltetrazole **35b**, can also be rationalized on the basis of the degree to which the β-nitrogen in the azole ring can participate in a H-bond interaction. This would be more favorable for compounds **26** and **35a**. However, in these systems a more favorable hydrophobic interaction of the receptor with the α-methyl substituent cannot be ruled out.

Receptor Selectivity. The pharmacological specificity of the compounds for 5-HT$_{1D}$ receptors was determined by measuring affinities for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_3$ receptors. The data are presented in Table 4. The 1,2,4-triazole **10a** has good selectivity for 5-HT$_{1D}$ receptors over 5-HT$_{1A}$ receptors (6-fold) and 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_3$ receptors (all ≥100-fold) and has an improved selectivity profile over the aminooxadiazole **4b**. Imidazoles **10b,c** have comparable selectivity to **10a**. In the N-linked series, introduction of more than three nitrogen atoms into the heterocycle led to a reduction in receptor selectivity. Thus, tetrazole **14d** has 8-fold higher affinity for 5-HT$_{2C}$ receptors than triazole **10a** and has generally lower receptor selectivity. Removal of the methylene bridge of **10a** to give the conjugated triazole **18a** reduced selectivity for 5-HT$_{1D}$ receptors over 5-HT$_{1A}$ and 5-HT$_{2C}$, but ≥100-fold selectivity over 5-HT$_{2A}$ and 5-HT$_3$ was maintained. The conjugated 2-methylimidazole **18b**, however, has improved selectivity for 5-HT$_{1D}$ over all the other serotonin receptors measured, compared with the methylene-bridged analogue **10c**. In the carbon-linked triazole series, the 4-methyl-1,2,4-triazole **26** has the optimal 5-HT$_{1D}$ receptor selectivity profile and is comparable to the nitrogen-linked triazole **10a**. Interestingly, although the acidic N-*H* tetrazole **28** showed poor affinity for 5-HT$_{1D}$ receptors, it has high affinity and selectivity for 5-HT$_{1A}$ receptors. The N-1 alkyltetrazoles **35a** and **36a** have higher selectivity for 5-HT$_{1D}$ receptors than the N-2 alkylation adducts **35b** and **36b**, with the ethyl tetrazole **36a** having the best profile. Therefore, across the triazole and tetrazole series, substitution of the azole ring α to the methylene bridge always gives compounds with higher affinity and selectivity for 5-HT$_{1D}$ receptors, compared with the β-substituted products. Triazole **26** and tetrazoles **35a** and **36a** are more selective than analogous compounds in the previously reported 1,2,4-oxadiazole series in which only substitution β to the methylene bridge was possible.[21] The binding selectivity of **10a** for 5-HT$_{1D}$ receptors in human cortical membranes was compared with sumatriptan, and the results are shown in Table 5. Triazole **10a** and sumatriptan have comparable 5-HT$_{1D}$ receptor selectivity in human brain cortex.

Functional Activity. The *in vitro* functional activity of the compounds for 5-HT$_{1D}$ receptors was assessed 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.[30] 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 shown in Table 6. Triazole **10a** is a potent agonist in the preparation with potency and efficacy comparable to that of 5-HT. Compound **10a** is more potent in this assay than the aminooxadiazole **4b** and sumatriptan. The increased affinity observed on conjugating the heterocycle with indole, for compounds **18a,b**, is reflected in the higher potency of these compounds in the functional assay. Similarly, the 1-substituted tetrazoles **35a** and **36a** are more potent than the 2-substituted

Table 4. Selectivity of Imidazole, Triazole, and Tetrazole Derivativies in Binding to 5-HT$_{1D}$ Serotonin Receptors

compd	pIC$_{50}$ ± SEM[a]				
	5-HT$_{1D}$[b]	5-HT$_{1A}$[c]	5-HT$_{2C}$[d]	5-HT$_{2A}$[e]	5-HT$_3$[f]
sumatriptan (**3**)	7.7 ± 0.1	6.3 ± 0.2	5.1	<5.0	<5.0
L-695,894 (**4b**)	7.6 ± 0.21	6.5 ± 0.05	5.9 ± 0.09	6.4	5.6
MK-462 (**10a**)	7.3 ± 0.08	6.5 ± 0.08	5.1 ± 0.02	5.2 ± 0.06	5.4 ± 0.06
10b	7.5 ± 0.06	6.8 ± 0.02	5.4 ± 0.14	5.5	5.9
10c	7.2 ± 0.03	6.5	5.5 ± 0.02	5.1	5.8
14a	7.3	6.9		5.2	
14c	7.4 ± 0.01	6.8 ± 0.07	5.7 ± 0.10	5.3	5.9
14d	7.4 ± 0.08	6.7	6.0 ± 0.14	5.7	5.5
18a	7.7 ± 0.03	7.6	6.3	5.0	5.0
18b	8.1 ± 0.01	7.2	5.5	<5.0	5.5
21b	7.0 ± 0.14	6.5	<5.0	5.4	5.0
26	7.6	6.5	5.1	<5.0	5.1
28	5.4	7.2	<5.0	<5.0	<5.0
35a	7.6	6.7 ± 0.19	5.3 ± 0.21	<5.0	5.3[g]
36a	7.6 ± 0.16	6.5	<5.0	<5.0	<5.0
35b	7.1 ± 0.05	6.2 ± 0.09	5.6 ± 0.23	5.6	5.6
36b	6.9	6.3	5.6	5.8	5.6

[a] SEM = standard error of the mean from n ≥ 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] Displacement 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 5. Selectivity of **10a** in Binding to 5-HT Receptors in Human Brain Cortex

compd	pIC$_{50}$ ± SEM[a]				
	5-HT$_{1D}$	5-HT$_{1A}$	5-HT$_{2C}$	5-HT$_{2A}$	5-HT$_3$
10a	7.1 ± 0.2	6.4 ± 0.07	<5.0	5.1 ± 0.2	<5.0
sumatriptan (**3**)	7.4 ± 0.2	6.4 ± 0.04	<5.0	5.1 ± 0.12	<5.0

[a] See corresponding footnote of Table 4. The radioligands used are as shown in Table 4.

Table 6. *In Vitro* Functional Activity of Imidazole, Triazole, and Tetrazole Derivatives

compd	pEC$_{50}$[a]	relative maximum[b]
5-HT (**1**)	6.8	1.0
sumatriptan (**3**)	6.2	1.0
4b	6.3	0.9
10a	6.6	1.0
10b	6.3	0.8
10c	6.2	0.7
14a	6.0	1.0
14c	6.7	1.0
14d	6.7	0.8
18a	7.2	1.2
18b	6.8	1.0
21b	6.2	0.7
35a	6.6	1.0
36a	6.4	1.0
35b	6.0	1.0
36b	6.2	0.7

[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.

analogues **35b** and **36b**. A detailed description of the *in vitro* and *in vivo* functional activity of these compounds, in particular for triazole **10a**, will be presented shortly.[31]

Pharmacokinetics. Conclusions from pharmacokinetic studies in the 1,2,4-oxadiazole series were (a) all compounds containing benzyl substituents showed low oral bioavailability and small substituents on the heterocycle, e.g., methyl and amino, were best; (b) primary tryptamines gave low oral bioavailability presumably because of extensive metabolism by monoamine oxidase; and (c) measurement of brain/plasma ratios suggested

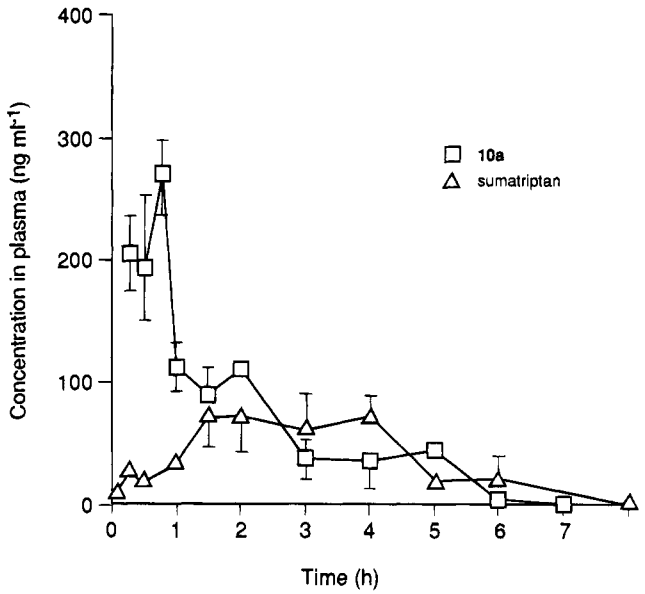


Figure 1. Concentrations of **10a** benzoate and sumatriptan succinate in plasma after oral administration (3 mg kg^{-1}) to rats.

that conjugated heterocycles show greater CNS penetration than the methylene-linked analogues, presumably because of the higher hydrophobicity of these compounds.

With these results in mind, the compounds of this study were designed to identify an optimal oral absorption profile in combination with low brain penetration. Triazole **10a** was shown to have the most desired pharmacokinetic profile in rats, following oral administration (see Figure 1), with high bioavailability (76%; cf. sumatriptan, 44%) and rapid absorption (t_{max} = 0.75 h). The plasma half-life ($t_{1/2}$) of **10a** in rat was shown to be 0.8 h (cf. sumatriptan, 1.1 h) and the steady state volume of distribution (V_{ss}) 6.3 L/kg (cf. sumatriptan, 4.6 L/kg). After oral administration, triazole **10a** could not be detected in rat brain at any time point (<20 ng/mL). Following intravenous administration (iv), the brain/plasma ratios for **10a** were as follows: at 0.083 h, 0.07; at 0.25 h, 0.1; and at 0.5 h, 0.14 (cf. sumatriptan,

0.04, 0.09, and 0.1, respectively). This datum suggests that **10a** only poorly penetrates the CNS after iv dosing.[32] Both the C-linked triazole **26** and the 1-methyltetrazole **35a** showed poor oral absorption in rats. On the basis of its 5-HT_{1D} receptor selectivity profile and oral bioavailability, **10a** was chosen as the clinical candidate to investigate efficacy as an antimigraine agent, and results from these studies will be published in due course.

Conclusions

A novel series of imidazole-, triazole-, and tetrazole-substituted indoles has been identified which are potent and selective agonists for the 5-HT_{1D} receptor. The heterocycle can be linked to indole through either N or C, and in the N-linked series, simple unsubstituted imidazoles, triazoles, and tetrazoles have high affinity and good selectivity for the 5-HT_{1D} receptor. The results suggest that for high affinity a H-bond acceptor interaction with a β-N in the azole ring is required. As reported for the oxadiazole series, directly linking the heterocycle to indole leads to a 5–10-fold increase in affinity. In a series of *N*-methyl-substituted triazoles and tetrazoles, linked to indole through C, optimal potency and selectivity were found when the heterocycle is substituted α to the methylene bridge. This may be a consequence of either a more favorable H-bond interaction or a more positive hydrophobic interaction. The 1,2,4-triazole **10a** was shown to have the optimal pharmacokinetic profile with rapid oral absorption and high bioavailability and is currently undergoing clinical trials for the treatment of migraine.

Experimental Section

Chemical Methods: General Directions. Except where otherwise stated, the following procedures were adopted. ^{1}H NMR spectra were recorded at 360 MHz on a Brucker AM360 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 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 gel, 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. Microanalyses were performed by Butterworth Laboratories Ltd., Middlesex, U.K., and are within ±0.4 unless otherwise noted. Melting points are uncorrected.

General Procedure for the Preparation of 1-(Triazolylmethyl)- and 1-(Imidazolylmethyl)-4-nitrobenzenes 7a–c. 1-(1,2,4-Triazol-1-ylmethyl)-4-nitrobenzene (7a). 4-Nitrobenzyl bromide (21.6 g, 0.1 mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1 g, 0.1 mol) in anhydrous DMF (100 mL) and the mixture stirred at 25 °C for 16 h. Ethyl acetate (400 mL) and water (250 mL) were added to the reaction mixture and the layers separated. The organic phase was washed with water (3×), dried, and evaporated. The crude product was chromatographed on silica gel, eluting with ethyl acetate, to give **7a** (10.6 g, 52%): mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 5.47 (2H, s, CH_2), 7.40 (2H, d, J = 9.0 Hz, Ar-H), 8.02 and 8.18 (each 1H, each s, triazole-H), 8.23 (2H, d, J = 9.0 Hz, Ar-H). Anal. ($C_9H_8N_4O_2$) H, N; C: calcd, 52.9; found, 53.4.

7b: 18%; mp 55–56 °C; ^{1}H NMR ($CDCl_3$) δ 5.26 (2H, s, CH_2), 6.92 (1H, s, imidazole-H), 7.16 (1H, s, imidazole-H), 7.28 (2H, d, J = 9.5 Hz, Ar-H), 7.62 (1H, s, imidazole-H), 8.22 (2H, d, J = 9.5 Hz, Ar-H).

7c: 10.5%; ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s, CH_3), 5.16 (2H, s, CH_2), 6.67 (1H, d, J = 1.3 Hz, imidazole-H), 7.03 (1H, d, J = 1.3 Hz, imidazole-H), 7.19 (2H, d, J = 9.5 Hz, Ar-H), 8.22 (2H, d, J = 9.5 Hz, Ar-H).

1-(1,2,3-Triazol-1-ylmethyl)-4-nitrobenzene (11a) and 1-(1,2,3-Triazol-2-ylmethyl)-4-nitrobenzene (11b). 4-Nitrobenzyl bromide (25.4 g, 0.12 mol) was added to a solution of 1*H*-1,2,3-triazole (8.12 g, 0.12 mol) and triethylamine (11.88 g, 0.12 mol) in anhydrous acetonitrile (150 mL). The mixture was refluxed for 1 h and then cooled to room temperature and the precipitated triethylamine hydrobromide filtered off. The solvent was evaporated and the resultant crude product chromatographed on silica gel eluting with CH_2Cl_2/MeOH (100:0 → 95:5) to give **11a** (13 g, 54%) and **11b** (2.25 g, 9%). **11a** was isolated as the more polar isomer: mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 5.72 (2H, s, CH_2), 7.38 (2H, d, J = 9.0 Hz, Ar-H), 7.64 and 7.78 (each 1H, each s, triazole-H), 8.18 (2H, d, J = 9.0 Hz, Ar-H). Anal. ($C_9H_8N_4O_2$) C, H, N.

11b: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 5.72 (2H, s, CH_2), 7.40 (2H, d, J = 9.0 Hz, Ar-H), 7.66 (2H, s, triazole-H), 8.18 (2H, d, J = 9.0 Hz, Ar-H). Anal. ($C_9H_8N_4O_2$) C, H, N.

1-(Tetrazol-1-ylmethyl)-4-nitrobenzene (11c) and 1-(Tetrazol-2-ylmethyl)-4-nitrobenzene (11d). The title compounds were prepared from 4-nitrobenzyl bromide and 1*H*-tetrazole using the procedure described for **11a,b**. The more polar, major product was identified as **11c** (75%): mp 93 °C; ^{1}H NMR ($CDCl_3$) δ 5.73 (2H, s, CH_2), 7.46 and 8.27 (each 2H, each d, J = 8.7 Hz, Ar-H), 8.64 (1H, s, tetrazole-H). Anal. ($C_8H_7N_5O_2$) C, H; N: calcd, 34.1; found, 34.6.

11d: 17%; mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 5.92 (2H, s, CH_2), 7.53 and 8.25 (each 2H, each d, J = 8.7 Hz, Ar-H), 8.56 (1H, s, tetrazole-H). Anal. ($C_8H_7N_5O_2$) C, H, N.

General Procedure for the Preparation of *N,N*-Dimethyltryptamines 10a–c and 14a–d. *N,N*-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine Benzoate (10a). A solution of **7a** (10.0 g, 49.0 mmol) in EtOH (50 mL), ethyl acetate (50 mL), and 2 N HCl (20 mL) was hydrogenated over 10% Pd–C (1.0 g) in a Parr shake apparatus at 40 psi for 0.2 h. The catalyst was removed by filtration through Hyflo, the solvent evaporated, and the residue azeotroped with EtOH (3×) to give **8a** (10.6 g, 100%) which was characterized as the free base: mp 126–128 °C; ^{1}H NMR (CD_3OD) δ 5.23 (2H, s, CH_2), 6.68 and 7.08 (each 2H, each d, J = 9.0 Hz, Ar-H), 7.95 and 8.39 (each 1H, each s, triazole-H). Anal. ($C_9H_{10}N_4$) C, H, N.

A solution of $NaNO_2$ (3.28 g, 48.0 mmol) in H_2O (20 mL) was added to a cooled (−10 °C) solution of **8a** (10.0 g, 48.0 mmol) in concentrated HCl (40 mL), at a 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 $SnCl_2 \cdot 2H_2O$ (40.0 g, 0.18 mol) in concentrated HCl (40 mL), at such a rate that the temperature did not exceed −5 °C. The solution was warmed to room temperature, basified with 20% aqueous NaOH solution, and extracted with ethyl acetate (3×). The combined extracts were dried and evaporated to give **9a** (5.0 g, 56%): mp 109–112 °C; ^{1}H NMR (DMSO-d_6) δ 3.93 (2H, br s, NH_2), 5.20 (2H, s, CH_2), 6.73 and 7.08 (each 2H, each d, J = 8.0 Hz, Ar-H), 7.92 and 8.57 (each 1H, each s, triazole-H).

To a solution of **9a** (5.0 g, 26.4 mmol) in EtOH/H_2O (5:1, 180 mL) and 5 N HCl (4.5 mL) was added 4-chlorobutanal dimethyl acetal[26] (3.22 g, 21.1 mmol), and the solution was refluxed for 4 h. The solvents were evaporated and the residue chromatographed on silica gel, eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1), to give 2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]-ethylamine (2.4 g, 38%). A solution of formaldehyde (0.30 g of a 37%, w/v, solution, 3.7 mmol) in MeOH (10 mL) was added to a stirred mixture of 2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine (0.36 g, 1.5 mmol), $NaCNBH_3$ (0.225 g, 3.6 mmol), and glacial acetic acid (0.45 g, 7.5 mmol), in MeOH (10 mL), at 0 °C. The solution was warmed to 25 °C and stirred for 2 h before adding saturated K_2CO_3 solution (5 mL). The MeOH was removed under vacuum, H_2O (10 mL) was added, and the mixture was extracted with ethyl acetate (3×).

The combined extracts were washed with brine (1×) and dried and the solvent evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give **10a** (0.21 g, 52%). The benzoate salt was prepared. **10a:** mp 178–180 °C; MS *m/z* 269 (M^+); ^{1}H NMR (D_2O) δ 2.91 (6H, s, $N(CH_3)_2$), 3.19 and 3.43 (each 2H, each t, J = 7.0 Hz, 1-CH_2 and 2-CH_2), 5.49 (2H, s, CH_2), 7.20 (1H, dd, J = 1.6 and 8.4 Hz, 6′-CH), 7.34 (1H, s, 2′-CH), 7.52 (1H, d, J = 8.4 Hz, 7′-CH), 7.43–7.53 (3H, m, benzoic acid-H), 7.62 (1H, d, J = 1.6 Hz, 4′-CH), 7.87–7.90 (2H, m, benzoic acid-H), 8.05 (1H, s, triazole-H), 8.52 (1H, s, triazole-H). Anal. ($C_{15}H_{19}N_5 \cdot C_6H_5COOH$) C, H, N.

The following *N,N*-dimethyltryptamines were prepared using the general procedure.

***N,N*-Dimethyl-2-[5-(imidazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine dioxalate (10b):** mp 165-166 °C (MeOH/Et_2O); ^{1}H NMR (D_2O) δ 2.92 (6H, s, $N(CH_3)_2$), 3.24 and 3.48 (each 2H, each t, J = 7.7 Hz, 1-CH_2 and 2-CH_2), 5.50 (2H, s, CH_2), 7.27 (1H, dd, J = 1.5 and 8.4 Hz, 6′-CH), 7.37 (1H, s, 2′-CH), 7.45 and 7.49 (each 1H, each s, imidazole-H), 7.56 (1H, d, J = 8.4 Hz, 7′-CH), 7.75 (1H, s, 4′-CH), 8.78 (1H, s, imidazole-H). Anal. ($C_{16}H_{20}N_4 \cdot 2.05(COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-[(2-methylimidazol-1-yl)methyl]-1*H*-indol-3-yl]ethylamine trioxalate (10c):** mp 160–163 °C (MeOH/Et_2O); MS *m/z* 282 (M^+); ^{1}H NMR (D_2O) δ 2.65 (3H, s, CH_3), 2.92 (6H, s, $N(CH_3)_2$), 3.25 and 3.50 (each 2H, each t, J = 7.3 Hz, 1-CH_2 and 2-CH_2), 5.42 (2H, s, CH_2), 7.18 (1H, d, J = 8.4 Hz, 6′-CH), 7.31–7.40 (3H, m, imidazole-H and 2′-CH), 7.56 (1H, d, J = 8.4 Hz, 7′-CH), 7.66 (1H, s, 4′-CH). Anal. ($C_{17}H_{22}N_4 \cdot 2.8(COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine hydrogen oxalate (14a):** mp 210–212 °C; ^{1}H NMR (D_2O) δ 2.90 (6H, s, $N(CH_3)_2$), 3.22 and 3.46 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 5.72 (2H, s, CH_2), 7.24 (1H, dd, J = 1.6 and 8.4 Hz, 6′-CH), 7.36 (1H, s, 2′-CH), 7.52 (1H, d, J = 8.4 Hz, 7′-CH), 7.66 and 7.79 (each 1H, each s, triazole-H), 8.00 (1H, d, J = 1.6 Hz, 4′-CH). Anal. ($C_{15}H_{19}N_5 \cdot 1.1(COOH)_2 \cdot 0.15H_2O$) C, H, N.

***N,N*-Dimethyl-2-[5-(1,2,3-triazol-2-ylmethyl)-1*H*-indol-3-yl]ethylamine hydrogen oxalate (14b):** mp 204–205 °C; ^{1}H NMR (D_2O) δ 2.90 (6H, s, $N(CH_3)_2$), 3.21 and 3.46 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 5.74 (2H, s, CH_2), 7.22 (1H, dd, J = 1.6 and 8.4 Hz, 6′-CH), 7.34 (1H, s, 2′-CH), 7.50 (1H, d, J = 8.4 Hz, 7′-CH), 7.64 (1H, s, 4′-CH), 7.78 (2H, s, triazole-H). Anal. ($C_{15}H_{19}N_5(COOH)_2 \cdot 0.25H_2O$) C, H, N.

***N,N*-Dimethyl-2-[5-(tetrazol-1-ylmethyl)-1*H*-indol-3-yl]-ethylamine succinate (14c):** mp 55–56 °C (hygroscopic); ^{1}H NMR (D_2O) δ 2.93 (6H, s, $N(CH_3)_2$), 3.23 and 3.48 (each 2H, each t, J = 7.5 Hz, 1-CH_2 and 2-CH_2), 5.81 (2H, s, CH_2), 7.28 (1H, dd, J = 1.7 and 8.4 Hz, 6′-CH), 7.39 (1H, s, 2′-CH), 7.56 (1H, d, J = 8.4 Hz, 7′-CH), 7.75 (1H, s, 4′-CH), 9.20 (1H, s, tetrazole-H). Anal. ($C_{14}H_{18}N_6 \cdot 0.75(CH_2COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-(tetrazol-2-ylmethyl)-1*H*-indol-3-yl]-ethylamine hydrogen oxalate (14d):** mp 198–199 °C (EtOH/Et_2O); ^{1}H NMR (D_2O) δ 2.91 (6H, s, $N(CH_3)_2$), 3.23 and 3.48 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 6.01 (2H, s, CH_2), 7.30 (1H, dd, J = 1.6 and 8.4 Hz, 6′-CH), 7.37 (1H, s, 2′-CH), 7.53 (1H, d, J = 8.4 Hz, 7′-CH), 7.76 (1H, s, 4′-CH), 8.74 (1H, s, tetrazole-H). Anal. ($C_{14}H_{18}N_6 \cdot (COOH)_2 \cdot 0.2C_2H_5OH$) C, H, N.

Alternative Procedure for the Preparation of 10a. To a solution of the hydrochloride salt of **9a** (5.0 g, 22.2 mmol) in 4% H_2SO_4 (190 mL) was added 4-(*N,N*-dimethylamino)butanal dimethyl acetal[28] (5.35 g, 33.2 mmol), and the solution was refluxed for 2 h. The mixture was cooled to room temperature, ethyl acetate (400 mL) was added, and the aqueous was basified with 5 N NaOH solution. The aqueous was separated and extracted with ethyl acetate (2×), and the combined extracts were dried and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give **10a** (2.2 g, 37%).

1-(1,2,4-Triazol-1-yl)-4-nitrobenzene (15a). 1-Fluoro-4-nitrobenzene (25.0 g, 0.18 mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (17.7 g, 0.19 mol) in anhydrous DMF (150 mL) and the mixture stirred at room temperature for 16 h. Ethyl acetate (500 mL) and water (300 mL) were added to the reaction mixture which was then stirred for 0.1 h and the layers separated. The organic phase was washed with water (3×) and dried and the solvent evaporated to give **15a** (24.8 g, 74%): mp 197–198 °C; MS *m/z* 190 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 9.1 Hz, Ar-H), 8.17 (1H, s, triazole-H), 8.40 (2H, d, J = 9.1 Hz, Ar-H), 8.48 (1H, s, triazole-H). Anal. ($C_8H_6N_4O_2$) H, N; C: calcd, 50.5; found, 51.2.

1-(2-Methylimidazol-1-yl)-4-nitrobenzene (15b). Sodium hydride (60% dispersion in oil, 4.87 g, 0.122 mol) was added to a solution of 2-methylimidazole (10.0 g, 0.122 mol) in DMF (100 mL) and the mixture stirred for 0.1 h. 1-Fluoro-4-nitrobenzene (17.18 g, 0.122 mol) was added and the mixture stirred at room temperature for 16 h. Water (150 mL) and ethyl acetate (250 mL) were added to the mixture, which was stirred for 0.1 h, and the layers separated. The aqueous phase was extracted with ethyl acetate (3×), and the combined extracts were washed with H_2O (3×), dried, and evaporated to give **15b** (11.5 g, 47%): mp 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s, CH_3), 7.06 and 7.10 (each 1H, each d, J = 1.5 Hz, imidazole-H), 7.50 and 8.38 (each 2H, each d, J = 9.5 Hz, Ar-H). Anal. ($C_{10}H_9N_3O_2$) C, H, N.

***N,N*-Dimethyl-2-[5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl]ethylamine Dioxalate (18a).** The title compound was prepared from **15a** using the general procedure described for **10a**: mp 210 °C (MeOH/Et_2O); ^{1}H NMR (D_2O) δ 2.92 (6H, s, $N(CH_3)_2$), 3.25 and 3.50 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 7.44 (1H, s, 2′-CH), 7.47 (1H, dd, J = 2.0 and 8.7 Hz, 6′-CH), 7.63 (1H, d, J = 8.7 Hz, 7′-CH), 7.88 (1H, d, J = 2.0 Hz, 4′-CH), 8.36 and 9.05 (each 1H, each s, triazole-H). Anal. ($C_{14}H_{17}N_5 \cdot 1.9(COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1*H*-indol-3-yl]ethylamine Sesquioxalate (18b).** The title compound was prepared from **15b** using the general procedures: mp 185–186 °C; ^{1}H NMR (D_2O) δ 2.55 (3H, s, CH_3), 2.93 (6H, s, $N(CH_3)_2$), 3.26 and 3.51 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 7.30 (1H, dd, J = 2.0 and 8.7 Hz, 6′-CH), 7.48 (1H, d, J = 2.1 Hz, imidazole-H), 7.51–7.53 (2H, m, imidazole-H and 2′-CH), 7.70 (1H, d, J = 8.7 Hz, 7′-CH), 7.79 (1H, d, J = 2.0 Hz, 4′-CH). Anal. ($C_{16}H_{20}N_4 \cdot 1.55(COOH)_2 \cdot 0.1EtOH$) C, H, N.

***N,N*-Dimethyl-2-[5-[(1-methyl-1,2,4-triazol-3-yl)methyl]-1*H*-indol-3-yl]ethylamine Trihydrochloride (21a) and *N,N*-Dimethyl-2-[5-[(1-methyl-1,2,4-triazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine Dioxalate (21b).** A solution of *N,N*-dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine[21] (**19**) (5.0 g, 22.0 mmol) in EtOH (50 mL) was saturated with HCl (gas) and stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure to give **20** (6.0 g, 92%): ^{1}H NMR (DMSO-d_6) δ 1.29 (3H, t, J = 7.0 Hz, CH_3), 2.83 (6H, s, $N(CH_3)_2$), 3.13 and 3.31 (each 2H, each t, J = 7.5 Hz, 1-CH_2 and 2-CH_2), 4.04 (2H, s, CH_2), 4.42 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.08 (1H, dd, J = 1.5 and 8.4 Hz, 6′-CH), 7.27 (1H, s, 2′-CH), 7.37 (1H, d, J = 8.4 Hz, 7′-CH), 7.48 (1H, br s, NH), 7.71 (1H, s, 4′-CH).

A mixture of **20** (3.0 g, 10.15 mmol), methylhydrazine (0.69 g, 15.0 mmol), and triethylamine (2.6 g, 25.4 mmol) in EtOH (30 mL) was stirred at room temperature for 3 h. The solvent was evaporated and the product dissolved in formic acid (98%, 3.3 mL). The solution was stirred at room temperature for 0.5 h and then at reflux for 2 h. After cooling to room temperature, the mixture was poured into K_2CO_3 solution (75 mL) and extracted with ethyl acetate (4×). The combined extracts were dried, the solvent was evaporated, and the crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give two products. The less polar isomer was identified as **21b** (0.36 g, 12.5%) and the dioxalate salt was prepared. **21b:** mp 135–137 °C; ^{1}H NMR (D_2O) δ 2.91 (6H, s, $N(CH_3)_2$), 3.23 and 3.48 (each 2H, each t, J = 7.3 Hz, 1-CH_2 and 2-CH_2), 3.95 (3H, s, CH_3), 4.48 (2H, s, CH_2), 7.13 (1H, dd, J = 1.5 and 8.4 Hz, 6′-CH), 7.37 (1H, s, 2′-CH), 7.53 (1H, d, J = 8.4 Hz, 7′-CH), 7.57 (1H, s, 4′-CH), 8.32 (1H, s, triazole-H). Anal. ($C_{16}H_{21}N_5 \cdot 2.25(COOH)_2$) C, H; N: calcd, 14.4; found, 13.9.

The more polar product was identified as **21a** (0.18 g, 6.3%). Treatment of **21a** with ethereal HCl gave the trihydrochloride salt: mp <40 °C (hygroscopic); ^{1}H NMR (D_2O) δ 2.91 (6H, s,

$N(CH_3)_2$), 3.23 and 3.49 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 3.95 (3H, s, CH_3), 4.27 (2H, s, CH_2), 7.17 (1H, dd, J = 1.5 and 8.5 Hz, 6'-CH), 7.34 (1H, s, 2'-CH), 7.50 (1H, d, J = 8.5 Hz, 7'-CH), 7.60 (1H, s, 4'-CH), 8.88 (1H, s, triazole-H). Anal. ($C_{16}H_{21}N_5 \cdot 3HCl \cdot 0.35Et_2O$) C, H, N.

1-[(4-Methyl-1,2,4-triazol-3-yl)methyl]-4-nitrobenzene (24). A mixture of **22** (10.0 g, 43.0 mmol) and formylhydrazine (2.6 g, 43.0 mmol) in anhydrous MeOH (175 mL) was stirred at room temperature for 3 days. The solvent was removed under vacuum, the residue triturated with ether, and the precipitate filtered off. The filtrate was concentrated under reduced pressure and the resultant crude product chromatographed on silica gel eluting with CH_2Cl_2/MeOH (9:1) to give **23** (2.25 g, 22%). Methylamine (gas) was bubbled through a solution of **23** (1.25 g, 5.3 mmol) in anhydrous MeOH (30 mL), for 0.25 h, and the mixture then stirred for 72 h at room temperature. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH (9:1) to give **24** (1.0 g, 87%) as a white crystalline solid: mp 168–170 °C; MS m/z 218 (M^+); ^1H NMR ($CDCl_3$) δ 3.51 (3H, s, CH_3), 4.31 (2H, s, CH_2), 7.42 (2H, d, J = 8.7 Hz, Ar-H), 8.11 (1H, s, triazole-H), 8.20 (2H, d, J = 8.7 Hz, Ar-H). Anal. ($C_{10}H_{10}N_4O_2$) C, H, N.

***N,N*-Dimethyl-2-[5-[(4-methyl-1,2,4-triazol-3-yl)methyl]-1*H*-indol-3-yl]ethylamine Hydrogen Oxalate Hemihydrate (26).** The title compound was prepared from **24** using the procedures described for **10a.** The hydrogen oxalate hemihydrate salt was prepared. **26:** mp <40 °C (hygroscopic); MS m/z 283 (M^+); ^1H NMR (D_2O) δ 2.89 (6H, s, $N(CH_3)_2$), 3.20 and 3.45 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 3.64 (3H, s, CH_3), 4.37 (2H, s, CH_2), 7.12 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.34 (1H, s, 2'-CH), 7.50 (1H, d, J = 8.4 Hz, 7'-CH), 7.52 (1H, s, 4'-CH), 8.55 (1H, s, triazole-H). Anal. ($C_{16}H_{21}N_5 \cdot 1.2(COOH)_2 \cdot 0.5H_2O$) C, H, N.

***N,N*-Dimethyl-2-[5-(tetrazol-5-ylmethyl)-1*H*-indol-3-yl]ethylamine Hydrochloride (28).** A solution of the hydrochloride salt of **19** (0.58 g, 2.2 mmol), sodium azide (0.43 g, 6.6 mmol) and triethylamine hydrochloride (0.45 g, 3.3 mmol), in *N*-methylpyrrolidin-2-one (10 mL) was heated at 160 °C for 8 h; 5 N HCl (2 mL) was added, and the solvents were removed by distillation under high vacuum. Inorganic salts were removed by addition of MeOH (20 mL) and ether (30 mL). The filtrate was concentrated and the crude product chromatographed on silica gel eluting with EtOH/Et_2O/H_2O/NH_3 (20:40:8:1) to give **28** (0.45 g, 76%). The hydrochloride salt was prepared. **28:** mp 223–225 °C (MeOH/Et_2O); ^1H NMR (D_2O) δ 2.90 (6H, s, $N(CH_3)_2$), 3.20 and 3.45 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.43 (2H, s, CH_2), 7.18 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.33 (1H, s, 2'-CH), 7.49 (1H, d, J = 8.4 Hz, 7'-CH), 7.56 (1H, s, 4'-CH). Anal. ($C_{14}H_{18}N_6 \cdot HCl \cdot 0.1H_2O$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-2-[5-(tetrazol-5-ylmethyl)-1*H*-indol-3-yl]ethylamine (30).** A solution of 2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine hydrochloride (**27**) (2.5 g, 10.6 mmol), triethylamine hydrochloride (2.2 g, 16.0 mmol), and sodium azide (2.1 g, 32.3 mmol) in *N*-methylpyrrolidin-2-one (30 mL) was heated at 140 °C for 8 h; 5 N HCl (3 mL) was added, and the solvents were removed by distillation under vacuum. The residue was chromatographed on silica gel eluting with EtOH/Et_2O/H_2O/NH_3 (20:30:8:1) to give **29** (1.76 g, 69%). Triethylamine (1.5 g, 14.9 mmol) and di-*tert*-butyl dicarbonate (1.9 g, 7.3 mmol) were added to a stirred suspension of **29** (1.76 g, 7.27 mmol) in CH_2Cl_2 (40 mL), and the mixture was stirred for 16 h at room temperature. The solvent was removed under vacuum and the crude product chromatographed on silica gel eluting with EtOH/Et_2O/H_2O/NH_3 (20:60:8:1) to give **30** (1.6 g, 64%): mp 95–98 °C; ^1H NMR (CD_3OD) δ 1.41 (9H, s, $(CH_3)_3$), 2.87 and 3.30 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.32 (2H, s, CH_2), 6.99 (1H, d, J = 8.3 Hz, 6'-CH), 7.04 (1H, s, 2'-CH), 7.26 (1H, d, J = 8.3 Hz, 7'-CH), 7.49 (1H, s, 4'-CH). Anal. ($C_{17}H_{22}N_6O_2 \cdot 0.8H_2O$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-2-[5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine (31a) and *N*-(*tert*-Butyloxycarbonyl)-2-[5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine (31b).** Methyl iodide (2.49 g, 17.5 mmol) was added to a stirred solution of **30** (1.0 g, 2.93 mmol) and triethylamine (0.59 g, 5.85 mmol), in acetonitrile (50 mL), and the mixture stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 (100 mL), washed with H_2O (2×), dried, and evaporated. The crude product was chromatographed on silica gel eluting with MeOH/CH_2Cl_2 (5:95) to give two separated products. The more polar major isomer was identified as the N-1 methylation product **31a** (0.20 g, 19%): mp 65 °C; ^1H NMR ($CDCl_3$) δ 1.43 (9H, s, $(CH_3)_3$), 2.90 (2H, t, J = 6.9 Hz, 2-CH_2), 3.42 (2H, br s, 1-CH_2), 3.83 (3H, s, CH_3), 4.40 (2H, s, CH_2), 6.98 (1H, dd, J = 1.4 and 8.2 Hz, 6'-CH), 7.05 (1H, s, 2'-CH), 7.31 (1H, d, J = 8.2 Hz, 7'-CH), 7.43 (1H, s, 4'-CH), 8.18 (1H, br s, NH). Anal. ($C_{18}H_{24}N_6O_2$) C, H, N.

The less polar isomer was identified as the N-2 methylation product **31b** (0.10 g 10%): mp 65 °C; ^1H NMR ($CDCl_3$) δ 1.43 (9H, s, $(CH_3)_3$), 2.88 (2H, t, J = 6.8 Hz, 2-CH_2), 3.38–3.46 (2H, m, 1-CH_2), 4.25 (3H, s, CH_3), 4.32 (2H, s, CH_2), 6.91 (1H, s, 2'-CH), 7.13 (1H, dd, J = 1.6 and 8.3 Hz, 6'-CH), 7.26 (1H, d, J = 8.3 Hz, 7'-CH), 7.52 (1H, s, 4'-CH), 8.43 (1H, br s, NH). Anal. ($C_{18}H_{24}N_6O_2 \cdot 0.2H_2O$) C, H; N: calcd, 23.3; found, 22.6.

***N*-(*tert*-Butyloxycarbonyl)-2-[5-[(1-ethyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine (33a) and *N*-(*tert*-Butyloxycarbonyl)-2-[5-[(2-ethyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine (33b).** Ethyl iodide (7.64 mL, 95.5 mmol) was added to a stirred solution of **30** (5.74 g, 16.8 mmol) and triethylamine (4.67 mL, 33.5 mmol), in acetonitrile (220 mL), and the mixture stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure, CH_2Cl_2 (150 mL) added, and the mixture washed with H_2O (2×). The crude product obtained was chromatographed on silica gel eluting with Et_2O/hexane (80:20) → Et_2O (100%) → EtOAc (100%) to give two products. The more polar isomer was identified as the N-1 alkylation product **33a** (2.7 g, 43%): mp 52–54 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.3 Hz, CH_3CH_2), 1.43 (9H, s, $(CH_3)_3$), 2.90 (2H, t, J = 7.0 Hz, 2-CH_2), 3.41 (2H, br s, 1-CH_2), 4.17 (2H, q, J = 7.3 Hz, CH_2CH_3), 4.39 (2H, s, CH_2), 6.98 (1H, dd, J = 1.4 and 8.3 Hz, 6'-CH), 7.05 (1H, s, 2'-CH), 7.30 (1H, d, J = 8.3 Hz, 7'-CH), 7.42 (1H, s, 4'-CH), 8.18 (1H, br s, NH). Anal. ($C_{19}H_{26}N_6O_2$) H, N; C: calcd, 61.6; found, 62.2.

The less polar isomer was identified as the N-2 alkylation product **33b** (2.27 g, 37%): mp 108–110 °C; ^1H NMR ($CDCl_3$) δ 1.43 (9H, s, $(CH_3)_3$), 1.59 (3H, t, J = 7.3 Hz, CH_3CH_2), 2.92 (2H, t, J = 6.8 Hz, 2-CH_2), 3.38–3.48 (2H, m, 1-CH_2), 4.33 (2H, s, CH_2), 4.58 (2H, q, J = 6.8 Hz, CH_2CH_3), 7.00 (1H, s, 2'-CH), 7.18 (1H, dd, J = 1.4 and 8.3 Hz, 6'-CH), 7.29 (1H, d, J = 8.3 Hz, 7'-CH), 7.54 (1H, s, 4'-CH), 8.04 (1H, br s, NH). Anal. ($C_{19}H_{28}N_6O_2$) C, H, N.

General Procedure for the Preparation of Methyltetrazoles 35a,b and Ethyltetrazoles 36a,b. *N,N*-Dimethyl-2-[5-[(2-ethyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine Hydrogen Oxalate (36b). Trifluoroacetic acid (1.5 mL) was added dropwise to a stirred solution of **33b** (0.164 g, 0.44 mmol) in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 0.75 h, and the solvents were then evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give **34b** (0.103 g, 86%). A solution of formaldehyde (0.081 g of a 38%, w/v, solution, 1.0 mmol) in MeOH (11 mL) was added to a stirred solution of **34b** (0.097 g, 0.36 mmol), $NaCNBH_3$ (0.05 g, 0.80 mmol), and glacial acetic acid (0.103 mL, 1.8 mmol), in MeOH (11 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. Saturated K_2CO_3 solution (5 mL) was added, the MeOH evaporated under reduced pressure, and the residue taken up into ethyl acetate (30 mL) and washed with brine (2×). The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give **36b** (0.075 g, 70%). The hydrogen oxalate salt was prepared. **36b:** mp 140–142 °C (MeOH/Et_2O); ^1H NMR (D_2O) δ 1.54 (3H, t, J = 7.4 Hz, CH_2CH_3), 2.91 (6H, s, $N(CH_3)_2$), 3.21 and 3.47 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.34 (2H, s, CH_2), 4.64 (2H, q, J = 7.4 Hz, CH_2CH_3), 7.17 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.33 (1H, s, 2'-CH), 7.48 (1H, d, J = 8.4 Hz, 7'-CH), 7.59 (1H, s, 4'-CH). Anal. ($C_{16}H_{22}N_6 \cdot (COOH)_2$) C, H, N.

The following tetrazoles were prepared using the general procedure described for **36b**.

***N,N*-Dimethyl-2-[5-[(1-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine hydrogen oxalate (35a)**: mp 176–177 °C (MeOH/Et_2O); ^1H NMR (D_2O) δ 2.91 (6H, s, $N(CH_3)_2$), 3.21 and 3.40 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.00 (3H, s, CH_3), 4.43 (2H, s, CH_2), 7.13 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.35 (1H, s, 2'-CH), 7.50 (1H, d, J = 8.4 Hz, 7'-CH), 7.54 (1H, s, 4'-CH). Anal. ($C_{15}H_{20}N_6 \cdot (COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-[(2-methyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine hydrogen oxalate (35b)**: mp 185–186 °C (MeOH/Et_2O); ^1H NMR (D_2O) δ 2.91 (6H, s, $N(CH_3)_2$), 3.21 and 3.47 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.30 (3H, s, CH_3), 4.34 (2H, s, CH_2), 7.17 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.33 (1H, s, 2'-CH), 7.48 (1H, d, J = 8.4 Hz, 7'-CH), 7.59 (1H, s, 4'-CH). Anal. ($C_{15}H_{20}N_6 \cdot (COOH)_2$) C, H, N.

***N,N*-Dimethyl-2-[5-[(1-ethyltetrazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine hydrogen oxalate (36a)**: mp 175–178 °C (MeOH/Et_2O); ^1H NMR (D_2O) δ 1.32 (3H, t, J = 7.4 Hz, CH_2CH_3), 2.90 (6H, s, $N(CH_3)_2$), 3.21 and 3.46 (each 2H, each t, J = 7.4 Hz, 1-CH_2 and 2-CH_2), 4.38 (2H, q, J = 7.4 Hz, CH_2CH_3), 4.47 (2H, s, CH_2), 7.14 (1H, dd, J = 1.5 and 8.4 Hz, 6'-CH), 7.35 (1H, s, 2'-CH), 7.50 (1H, d, J = 8.4 Hz, 7'-CH), 7.53 (1H, s, 4'-CH). Anal. ($C_{16}H_{22}N_6 \cdot 1.05(COOH)_2$) C, H, N.

Biochemical Methods. Biochemical methods for both the binding and functional experiments have previously been described.[21]

Pharmacokinetic Methods. For each compound studied, each one of a number of rats (36–72 rats having been deprived of food overnight and typically weighing between 175 and 250 g) was allocated to one of a range of blood sampling time points, the latest point being between 4 and 8 h after drug administration. Six rats were allocated to each time point, of which three were dosed intravenously (iv) and three were dosed orally. The dose was always 3 mg of free base (or free base equivalent)/kg of body weight. Each rat was anesthetized with isoflurane at its preselected blood sampling time point, and a large sample of blood (>5 mL) was drawn into a lithium heparin blood tube by cardiac puncture. Plasma was separated from the blood by centrifugation and stored at −20 °C until analysis. Extracts of plasma were prepared either by liquid–liquid or solid phase extraction and analyzed by reversed phase HPLC employing UV or fluorescence detection. The average plasma concentration value at each dose route/sampling time combination was calculated from the three individual data points, and pharmacokinetic parameters were calculated from the mean data by standard model-independent methods.

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Supplementary Material Available: Table of microanalytical data for novel compounds (2 pages). Ordering information is given on any current masthead page.

References

(1) This work was presented in part at the Groupe D'etude Structure Activite XXIII, Annecy, France, May 1993, the 7th RSC-SCI Medicinal Chemistry Symposium, Cambridge, U.K., Sept. 1993 (P15), and the 208th National ACS Meeting, Washington, DC, Aug. 1994 (MEDI 180).

(2) Branchek, T. More Serotonin Receptors? *Curr. Biol.* **1993**, *3* (5), 315–317.

(3) (a) Beer, M. S.; Middlemiss, D. N.; McAllister, G. 5-HT$_{1\text{-like}}$ Receptors: Six Down and Still Counting. *Trends Pharmacol. Sci.* **1993**, *14*, 228–231. (b) Hartig, P. R.; Adham, N.; Zgombick, J.; Weinshank, R.; Branchek, T. Molecular Biology of the 5-HT$_1$ Receptor Subfamily. *Drug Dev. Res.* **1992**, *26*, 215–224. (c) Weinshank, R. L.; Zgombick, J. M.; Macchi, M.; Branchek, T. A.; Hartig, P. R. Human Serotonin 1D Receptor is Encoded by a Subfamily of Two Distinct Genes: 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3630–3634. (d) Hartig, P. R.; Branchek, T. A.; Weinshank, R. L. A Subfamily of 5-HT$_{1D}$ Receptor Genes. *Trends Pharmacol. Sci.* **1992**, *13*, 152–159. (e) McAllister, G.; Charlesworth, A.; Snodin, C.; Beer, M. S.; Noble, A. J.; Middlemiss, D. N.; Iversen, L. L.; Whiting, P. Molecular Cloning of a Serotonin Receptor From Human Brain (5-HT$_{1E}$): A Fifth 5-HT$_{1\text{-like}}$ Subtype. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5517–5521. (f) Adham, N.; Kao, H.-T.; Schechter, L. E.; Bard, J.; Olsen, M.; Urquhart, D.; Durkin, M.; Hartig, P. R.; Weinshank, R. L.; Branchek, T. A. Cloning of Another Human Serotonin Receptor (5-HT$_{1F}$): A Fifth 5-HT$_1$ Receptor Subtype Coupled to the Inhibition of Adenylate Cyclase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 408–412.

(4) Bockaert, J.; Fozard, J. R.; Dumuis, A.; Clarke, D. E. The 5-HT$_4$ Receptor. A Place in the Sun. *Trends Pharmacol. Sci.* **1992**, *13*, 141–145.

(5) Matthes, H.; Boschert, U.; Nourdine, A.; Grailhe, R.; Plassat, J.-L.; Muscatelli, F.; Mattei, M.-G.; Hen, R. Mouse 5-Hydroxytryptamine$_{5A}$ and 5-Hydroxytryptamine$_{5B}$ Receptors Define a New Family of Serotonin Receptors: Cloning, Functional Expression, and Chromosomal Localization. *Mol. Pharmacol.* **1993**, *43*, 313–319.

(6) Monsma, F. J., Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. Cloning and Expression of a Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs. *Mol. Pharmacol.* **1993**, *43*, 320–327.

(7) (a) Shen, Y.; Monsma, F. J., Jr.; Metcalf, M. A.; Jose, P. A.; Hamblin, M. W.; Sibley, D. R. Molecular Cloning and Expression of a 5-Hydroxytryptamine$_7$ Serotonin Receptor Subtype. *J. Biol. Chem.* **1993**, *268* (24), 18200–18204. (b) Bard, J. A.; Zgombick, J.; Adham, N.; Vayasse, P.; Branchek, T. A.; Weinshank, R. L. Cloning of a Novel Human Serotonin Receptor (5-HT$_7$) Positively Linked to Adenylate Cyclase. *J. Biol. Chem.* **1993**, *268* (31), 23422–23426.

(8) Plassat, J.-L.; Amlaiky, N.; Hen, R. Molecular Cloning of a Mammalian Serotonin Receptor That Activates Adenylate Cyclase. *Mol. Pharmacol.* **1993**, *44*, 229–236.

(9) Humphrey, P. P. A.; Hartig, P.; Hoyer, D. A Proposed New Nomenclature for 5-HT Receptors. *Trends Pharmacol. Sci.* **1993**, *14*, 233–236.

(10) Glennon, R. A.; Westkaemper, R. B. 5-HT$_{1D}$ Receptors: A Serotonin Receptor Population for the 1990s. *Drug News Perspect.* **1993**, *6* (6), 390–405.

(11) Heuring, R. E.; Peroutka, S. J. Characterisation of a Novel ^{3}H-5-Hydroxytryptamine Binding Site Subtype in Bovine Brain Membranes. *J. Neurosci.* **1987**, *7* (3), 894–903.

(12) Nowak, H. P.; Mahle, C. D.; Yocca, F. D. [^{3}H]-5-carboxamidotryptamine labels 5-HT$_{1D}$ binding sites in bovine substantia nigra. *Br. J. Pharmacol.* **1993**, *109*, 1206–1211.

(13) (a) Feniuk, W.; Humphrey, P. P. A. The Development of a Highly Selective 5-HT$_1$ Receptor Agonist, Sumatriptan, for the Treatment of Migraine. *Drug Dev. Res.* **1992**, *26*, 235–240. (b) Dechant, K. L.; Clissold, S. P. Sumatriptan: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in the Acute Treatment of Migraine and Cluster Headache. *Drugs* **1992**, *43* (5), 776–798.

(14) Glennon, R. A.; Ismaiel, A. M.; Chaurasia, C.; Titeler, M. 5-HT$_{1D}$ Serotonin Receptors: Results of a Structure-Affinity Investigation. *Drug Dev. Res.* **1991**, *22*, 25–36.

(15) King, F. D.; Brown, M. A.; Gaster, M. L.; Kaumann, A. J.; Medhurst, A. D.; Parker, S. G.; Parsons, A. A.; Patch, T. L.; Raval, P. (±) 3-Amino-6-carboxamido-1,2,3-tetrahydrocarbazole: A Conformationally Restricted Analogue of 5-Carboxamidotryptamine with Selectivity for the Serotonin 5-HT$_{1D}$ Receptor. *J. Med. Chem.* **1993**, *36*, 1918–1919.

(16) (a) Glen, R. C.; Hill, A. P.; Martin, G. R.; Robertson, A. D. Molecular Design of 5-HT$_{1D}$ Agonists for the Acute Treatment of Migraine. *Headache* **1994**, *34*, 307. (b) Hill, A. P.; Hyde, R. M.; Robertson, A. D.; Wollard, P. M.; Glen, R. C.; Martin, G. R. Oral Delivery of 5-HT$_{1D}$ Receptor Agonists: Towards the Discovery of 311C90, a Novel Anti-Migraine Agent. *Headache* **1994**, *34*, 308.

(17) Macor, J. E.; Blank, D. H.; Post, R. J.; Ryan, K. The Synthesis of a Conformationally Restricted Analog of the Anti-Migraine Drug Sumatriptan. *Tetrahedron Lett.* **1992**, *33* (52), 8011–8014.

(18) Ward, T. J. 5-HT$_1$-Like and 5-HT$_{1D}$ Agonists as Treatments for Migraine. *Curr. Opin. Ther. Pat.* **1993**, 417–423.

(19) (a) Feniuk, W.; Humphrey, P. P. A.; Perren, J. J. The Selective Carotid Arterial Vasoconstrictor Action of GR 43175 in Anaesthetized Dogs. *Br. J. Pharmacol.* **1989**, *96*, 83–90. (b) Saxena, P. R.; Ferrari, M. D. 5-HT$_{1\text{-Like}}$ Receptor Agonists and the Pathophysiology of Migraine. *Trends Pharmacol. Sci.* **1989**, *10*, 200–204.

(20) (a) Gabriella Buzzi, M.; Moskowitz, M. A. The Antimigraine Drug, Sumatriptan (GR 43175), Selectively Blocks Neurogenic Plasma Extravasation from Blood Vessels in Dura Mater. *Br. J. Pharmacol.* **1990**, *99*, 202–206. (b) Moskowitz, M. A. Neurogenic versus Vascular Mechanisms of Sumatriptan and Ergot Alkaloids in Migraine. *Trends Pharmacol. Sci.* **1992**, *13*, 307–311.

(21) Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.;

Hargreaves, R. J. Synthesis and Serotonergic Activity of 5-(Oxadiazolyl)tryptamines : Potent Agonists for 5-HT_{1D} Receptors. *J. Med. Chem.* **1993**, *36*, 1529–1538.
(22) Castro, J. L.; Matassa, V. G.; Broughton, H. B.; Mosley, R. T.; Street, L. J.; Baker, R. Synthesis, Biological Activity and Electrostatic Properties of 3-[2-(Dimethylamino)ethyl]-5-[(3-amino-1,2,4-thiadiazol-5-yl)methyl]-1H-indole, a Novel 5-HT_{1D} Receptor Agonist. *Bioorg. Med. Chem. Lett.* **1993**, *3* (6), 993–997.
(23) Beer, M. S.; Stanton, J. A.; Bevan, Y.; Heald, A.; Reeve, A. J.; Street, L. J.; Matassa, V. G.; Hargreaves, R. J.; Middlemiss, D. N. L-694,247 : a Potent 5-HT_{1D} Receptor Agonist. *Br. J. Pharmacol.* **1993**, *110*, 1196–1200.
(24) A preliminary account of the profile of the triazole **10a** was presented at the 3rd IUPHAR Satellite Meeting on Serotonin, Chicago, IL, July 1994.
(25) (a) Polya, J. B. 1,2,4-Triazoles. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: New York, 1984; Vol. 5, p 733. (b) This is the Grandberg modification of the Fischer Indole Synthesis. Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: New York, 1982; pp 487–495.
(26) Fleming, I.; Pearce, A. Controlling the Outcome of a Carbocation-Initiated Cyclisation. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251–255.
(27) Baker, R.; Matassa, V. G.; Street, L. J. Imidazole, Triazole and Tetrazole Derivatives. European Patent Appl. 0497512, 1992.
(28) Chen, C.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Improved Fischer-Indole Reaction for the Preparation of *N,N*-Dimethyltryptamines : Synthesis of L-695,894, a Potent 5-HT_{1D} Receptor Agonist. *J. Org. Chem.* **1994**, *59*, 3738–3741.
(29) Beer, M. S.; Stanton, J. A.; Bevan, Y.; Chauhan, N. S.; Middlemiss, D. N. An Investigation of the 5-HT_{1D} Receptor Binding Affinity of 5-Hydroxytryptamine, 5-Carboxamidotryptamine and Sumatriptan in the Central Nervous System of Seven Species. *Eur. J. Pharmacol.* **1992**, *213*, 193–197.
(30) Martin, G. R.; MacLennan, S. J. Analysis of the 5-HT Receptors in Rabbit Saphenous Vein Exemplifies the Problem of Using Exclusion Criteria for Receptor Classification. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1990**, *342*, 111–119.
(31) Hargreaves, R. J.; Shepheard, S.; Beer, M. S.; Stanton, J. A.; Middlemiss, D. N.; et al. Unpublished results.
(32) A detailed description of the pharmacokinetic profile of triazole **10a** (MK-462) shall be the subject of a forthcoming publication. Hargreaves, R. J.; Graham, M. I.; Sohal, B.; et al. Unpublished results.

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