Discovery of 4-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (4991W93), a $5HT_{1B/1D}$ Receptor Partial Agonist and a Potent Inhibitor of Electrically Induced Plasma Extravasation

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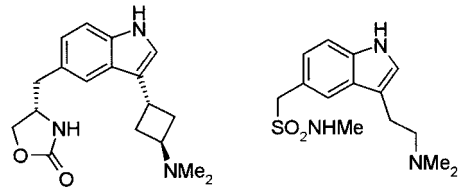
Utilizing a pharmacophoric model of binding of 3-(2-aminoethyl)indoles to $5HT_{1B/1D}$ receptors, we identified the 3-aminocyclobutyl group as a potential ethylamine isostere. A novel multidimensional chemometric approach was used to predict the intrinsic activity (degree of agonism) at the receptor. A qualitative model for pharmacokinetic properties was then used to guide the synthesis toward molecules likely to have oral bioavailability in humans. A novel synthetic route to 3-(3-dimethylaminocyclobutyl)indoles was developed. Analogues showed generally lower intrinsic activity at $5HT_{1B/1D}$ receptors than their ethylamine counterparts. 4-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (4991W93, **1**) was identified as a partial agonist against $5HT_{1B/1D}$ receptors, with low intrinsic activity. This molecule also has significant activity against $5HT_{1F}$ receptors but is selective over other 5HT receptors. In addition this compound was found to be an exceptionally potent inhibitor of electrically induced plasma extravasation. Compound **1** may have utility in the treatment and prophylaxis of migraine.

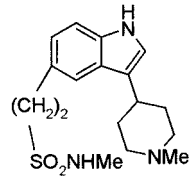
Introduction

We report the design, synthesis, and pharmacological evaluation of 4-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (4991W93, **1**), a novel 3-(3-dimethylaminocyclobutyl)indole $5HT_{1B/1D}$ receptor partial agonist with potential for the treatment and prophylaxis of migraine. This compound demonstrates potent inhibition of electrically evoked plasma extravasation. Migraine is a debilitating condition afflicting some 5−10% of the population with the majority being women of young to middle age. In recent years several $5HT_{1B/1D}$ receptor[1] agonists have been developed by pharmaceutical companies as antimigraine agents. The first of these was sumatriptan **2**, which has been followed to the market by a series of other "triptans".[2] These molecules such as naratriptan[3] **3** and zolmitriptan[4] **4**, are in general more lipophilic than sumatriptan and may have improved clinical effectiveness as a result of increased blood−brain barrier penetration and activation of $5HT_{1B/1D}$ receptor or other receptors within the CNS.[5] All of these molecules were developed as selective vasoconstrictors of the cranial vasculature, though several workers, notably Moskowitz[6] and Goadsby,[7] have proposed additional direct neuronal actions for these molecules. In Moskowitz's model the $5HT_{1B/1D}$ receptor agonists act on prejunctional 5HT heteroreceptors to inhibit the release of vasoactive peptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP). Recent studies on the localization of

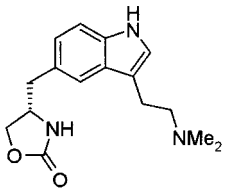


1 4991W93

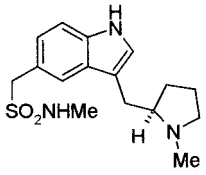
2 sumatriptan



3 naratriptan



4 zolmitriptan



5 CP-122,288

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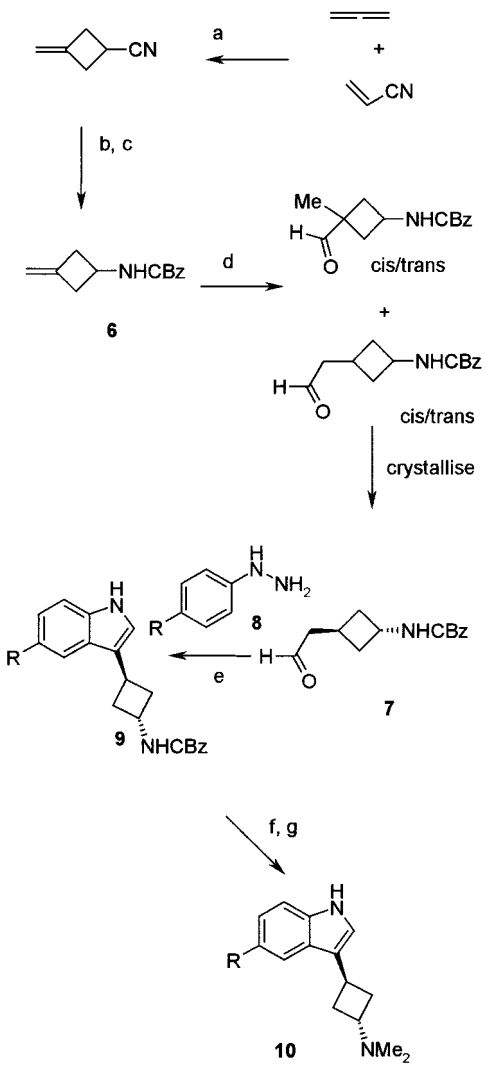
$5HT_{1D}$ and $5HT_{1B}$ receptors have indicated that only $5HT_{1D}$ receptors are located on human trigeminal sensory neurons whereas only $5HT_{1B}$ receptors were detected on dural arteries.[8] A refinement to the model suggests that stimulation of C fibers causes release of SP and leads to extravasation while stimulation of Aδ fibers causes release of CGRP and leads to vasodilation.[9] A further complication arose with the report of the potent activity of CP-122,288 **5**: this novel pyrrolidinylmethylindole exhibits potent inhibition of electrically stimulated plasma extravasation which is not consistent with its $5HT_{1B/1D}$ receptor activity. The existence of an undiscovered 5HT receptor has been invoked to explain the potency of inhibition.[10] CP-122,288 itself is reported to be ineffective in the treatment of migraine.[11] Despite a decade of research the precise involvement of the various receptors in the mechanism of action of the $5HT_{1B/1D}$ agonists is still unclear,[12] though more information is expected from the clinical testing of selective $5HT_{1D}$ receptor agonists. In the case of the $5HT_{1F}$ receptor the selective agonist LY334370 has been proposed to have a central action blocking noiciception.[13] It may be that both $5HT_{1B}$ and $5HT_{1D}$ receptor activities are necessary for clinical effectiveness. Clearly inhibition of extravasation alone does not account for the action of sumatriptan as NK_1 antagonists are ineffective in the treatment of acute migraine.[14]

In our program to develop novel analogues with potential antimigraine properties, we sought a novel ethylamine isostere with reduced susceptibility to monoamine oxidase (MAO), acceptable oral bioavailability, and significantly lower intrinsic activity, i.e., very low partial agonism at $5HT_{1B/1D}$ receptors. We also needed to maintain activity at the receptors thought to be important to the antimigraine action ($5HT_{1B}$ and $5HT_{1D}$). Selectivity over $5HT_{2A}$ receptors is required or the molecule should be functionally silent at this receptor.

Chemistry

A combination of molecular modeling and pharmacokinetic considerations identified the 3-cyclobutylamine indoles as strong candidates for selective $5HT_{1B/1D}$ receptor ligands likely to have low intrinsic activity (vide infra). Scheme 1 shows the general synthetic route used for most of the analogues. In all cases the Fischer indole synthesis was utilized to construct the indole core. The use of the *trans*-cyclobutyl moiety as an ethylamine isostere was dependent on achieving a viable synthetic route. Initially a synthetic scheme utilizing a cycloalkylation of diethyl malonate with 1,3-dibromo-2-benzyloxypropane was attempted (data not shown).[15] Although this route did provide small amounts of the desired analogues, it did not form the basis for a medicinal chemistry program. The key novel chemistry concerned the preparation of the cyclobutyl aldehyde precursor for the Fischer indole. Using the known cyclobutane olefin[16] **6** we were able to conduct a hydroformylation reaction using $(Ph_3P)_3RhCl$ as catalyst in the presence of 1:1 CO/H_2 to give a 3:1 mixture of straight chain and branched aldehydes which were separated by flash chromatography. The predominant *trans* product **7** could be crystallized from the mixture of straight chain aldehydes in 20% yield. A literature report[17] indicates that increased

Scheme 1. General Synthetic Methods for Cyclobutylindoles[a]

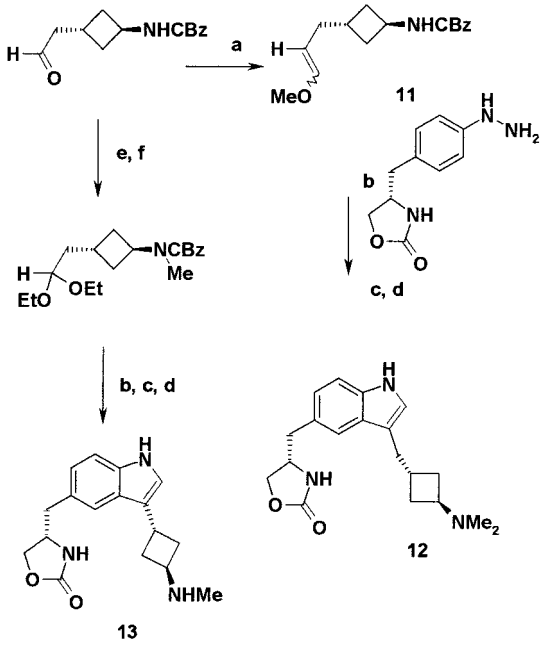


[a] Reagents and conditions: (a) 200 °C; (b) KOH/H_2O; (c) DPPA/BnOH; (d) $(Ph_3P)_3RhCl/CO/H_2$; (e) 1% aq H_2SO_4/EtOH; (f) $Pd(OH)_2$/C/HCOOH; (g) $NaCNBH_3/AcOH/CH_2O$. For structures of R, see Table 1.

PPh_3 and H_2 concentrations increase the proportion of normal/branched aldehyde. However, this is at the cost of greatly increased amounts of reduced olefin side products. The simple 1:1 ratio of reactants provided the best compromise of yield versus normal/branched ratio.

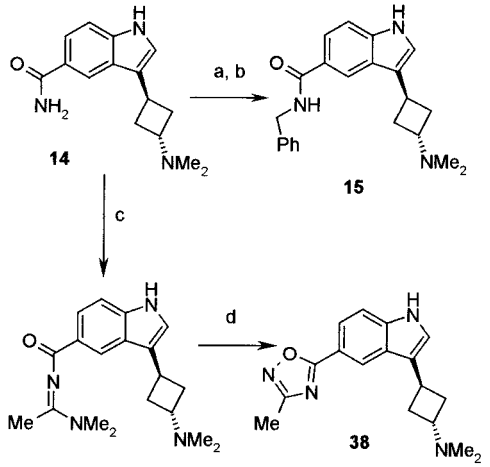
With quantities of the desired aldehyde available we could for the first time explore the structure−activity relationships (SARs) for 5HT ligands containing this novel ethylamine isostere. 5-Methylheterocyclic hydrazines **8** were prepared by methods reported previously[18,23] for 2-(indol-3-yl)ethylamine 5HT receptor ligands. The CBz-protected amines **9** were cleaved using $Pd(OH)_2/C$ in formic acid at reflux and the primary amines directly dimethylated using $NaCNBH_3$ and formaldehyde to give the 5-substituted analogues **10**. Scheme 2 details the synthesis of a chain-extended and also a monomethylated analogue. The homologation of the aldehyde proceeded smoothly with Ph_3PCH_2OMe/NaH to give the enol ether **11**, which was utilized directly in the Fischer indole synthesis and dimethylation strategy to give **12**. The formation of **13** involved conversion of the aldehyde to the diethyl acetal using triethyl orthoformate/pTsOH.

Scheme 2. Synthesis of Homocyclobutyl- and Monomethylindole Analogues[a]



[a] Reagents and conditions: (a) Ph_3PCH_2OMe/NaH; (b) 1% aq H_2SO_4/EtOH; (c) $Pd(OH)_2$/C/HCOOH; (d) $NaCNBH_3$/AcOH/CH_2O; (e) $(EtO)_3CH$/pTsOH; (f) NaH/MeI/DMF.

Scheme 3. Synthesis of 5-Amide and 5-Heterocyclic Cyclobutylindoles[a]

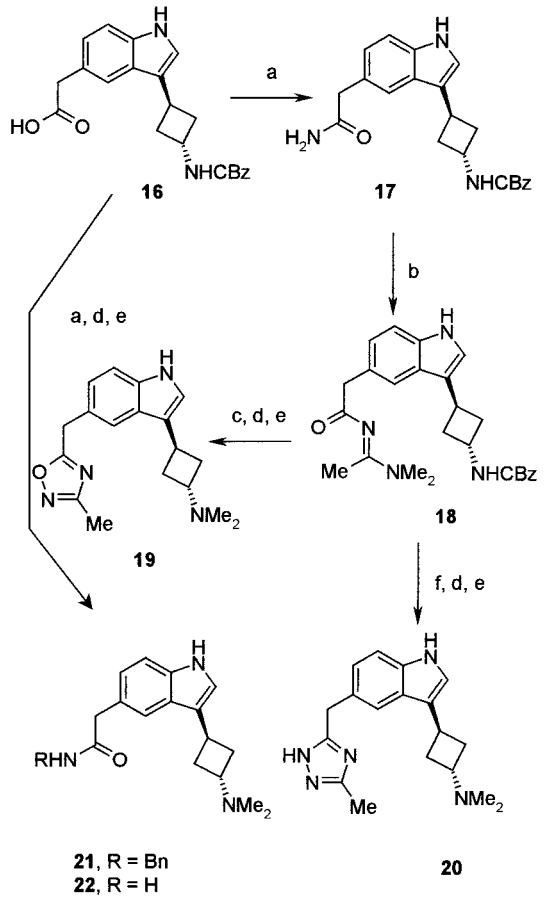


[a] Reagents and conditions: (a) NaOH; (b) $BnNH_2$/TBTU; (c) $(MeO)_2CMeNMe_2$/PhMe/120 °C; (d) H_2NOH/70% aq AcOH/*p*-dioxane.

This product was alkylated using NaH/MeI then treated as above to give the monomethylated analogue **13**.

Schemes 3 and 4 show the strategy adopted for the synthesis of various amides and heteroaryls at the 5-position. In these cases it was found to be more convenient to modify the pre-formed indole rather than synthesize the individual hydrazines. Thus, the primary amide **14**, formed from the 4-carboxamidophenylhydrazine, was hydrolyzed to the acid and coupled with benzylamine using TBTU to give **15** (Scheme 3). The 5-acetic acid **16** (Scheme 4), prepared from the corresponding hydrazine, was similarly converted to the amide **17** using *0*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*^{1},*N*^{1}-tetramethyluronium tetrafluoroborate (TBTU) coupling. In the case of the oxadiazole and triazole analogues these

Scheme 4. Synthesis of Methylene-Linked 5-Amide and 5-Heterocyclic Cyclobutylindoles[a]



[a] Reagents and conditions: (a) liq NH_3/TBTU; (b) $(MeO)_2CMeNMe_2$/PhMe/120 °C; (c) H_2NOH/70% aq AcOH/*p*-dioxane; (d) $Pd(OH)_2$/C/HCOOH; (e) $NaCNBH_3$/AcOH/CH_2O; (f) H_2NNH_2/70% aq AcOH/120 °C.

were synthesized using the methodology of Lin.[19] Reaction of the primary amide **17** with *N*,*N*-dimethylacetamide dimethyl acetal gave the intermediate acylamidine **18** which was reacted with hydroxylamine or hydrazine to give the oxadiazole **19** and triazole **20**, respectively. In a similar fashion the ethylene-linked oxadiazole **38** was prepared from the primary amide **14**. Finally the intermediate acid **16** (Scheme 3) was also coupled with benzylamine to provide the benzylamide **21** or with ammonia to give the primary amide **22**.

Design Features

The factors considered in seeking to employ a novel ethylamine isostere were (i) resistance to monoamine oxidase attack and cleavage to the inactive indole acetic acid metabolite, (ii) good oral absorption, and (iii) high affinity and good selectivity over $5HT_{2A}$ and other monoamine receptors together with reduced intrinsic activity at the $5HT_{1B/1D}$ receptors represented by functional activity in the rabbit saphenous vein. This last feature was intended to counter the ability of triptan molecules to constrict the coronary vasculature. This pharmacological action contraindicates the use of such agents in patients with coronary heart disease.

(i) The initial metabolite of the related compound zolmitriptan is the 3-(2-methylaminoethyl) derivative.

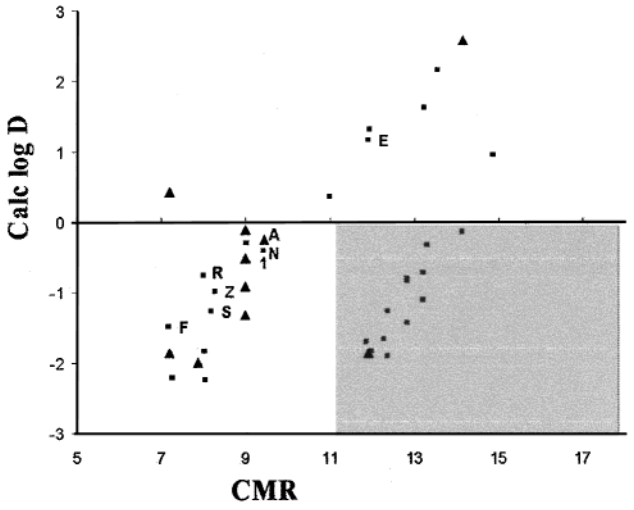


Figure 1. Relationship between CMR and calculated log $D_{pH7.4}$ for a range of triptan and tryptamine analogue values. Average plasma concentrations (at 0.5 and 2 h) after oral administration (10 mg/kg) to rats were determined and compounds with >25% of the level for sumatriptan are indicated as triangles. Other triptans known to be bioavailable in humans are indicated by single letters: A = almotriptan, E = eletriptan, F = frovitriptan, R = rizatriptan, N = naratriptan, S = sumatriptan, and Z = zolmitriptan. Gray shading indicates a zone of physicochemical properties where little oral absorption was observed.

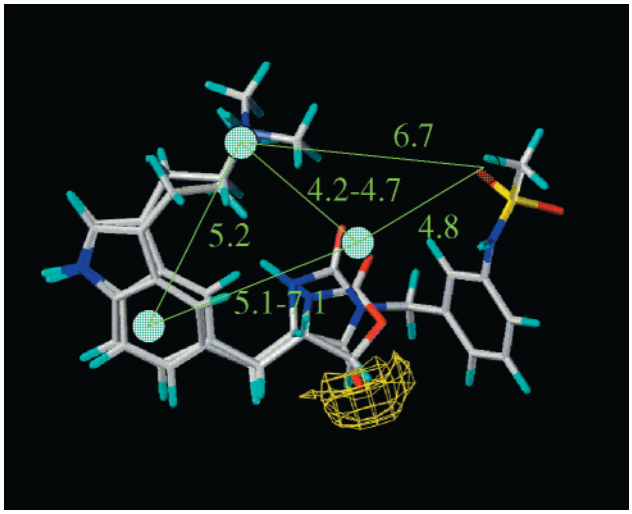


Figure 2. Pharmacophore model used to overlay novel analogues. Distance ranges are in Ångstroms, selectivity volume in yellow.

This conversion has been shown to be CYP1A2-mediated.[20] Cleavage to the monomethyl derivatives results in an *active* metabolite. That the 3-(3-dimethylaminocyclobutyl) moiety cannot be cleaved to the indole acetic acid is reasonable to expect, although the compound could still be demethylated.

(ii) To establish that our planned analogues would have a reasonable chance of oral absorption we utilized the model previously employed by our group to predict oral absorption for a range of $5HT_{1B/1D}$ agonists.[21] In this model oral absorption for these relatively hydrophilic molecules is thought to occur *via* a paracellular route, i.e., crossing of the intestinal membrane through aqueous pores. We observed that a relationship existed between the molecular size of the molecule, as measured by the calculated molar refractivity (CMR) and absorption. Larger hydrophilic molecules tended to have poor absorption. Our findings were derived from a study, which estimated the plasma levels in rats following oral dosing in rats. The plot of calculated log *D* versus CMR is shown in Figure 1 with compound **1** highlighted. Average plasma concentrations (at 0.5 and 2 h) after oral administration (10 mg/kg) to rats were determined, and compounds with >25% of the level for sumatriptan (0.2 μg/L) are indicated. By way of validation other triptans known to be bioavailable in humans are indicated by single letters: A = almotriptan, E = eletriptan, F = frovitriptan, R = rizatriptan, N = naratriptan, S = sumatriptan, and Z =zolmitriptan. Gray shading indicates a zone of physicochemical properties where little oral absorption was observed. Eletriptan appears to be very different in terms of its physicochemical properties, being significantly more lipophilic with a higher CMR. The calculated log *D* is higher than the reported value[22] (~1.17 versus −0.5), the reason for this is not readily apparent. This molecule would be expected to be absorbed by a transcellular route from our model. Clearly the proposed molecules fit into our model (with the possible exception of eletriptan) and have reasonable predicted absorption properties. CNS penetration is expected to be low with such hydrophilic molecules again with the exception of eletriptan. Some increased CNS penetration has been reported for zolmitriptan, however, and is proposed to be beneficial for its antimigraine action.[7]

(iii) We utilized our model of the 5HT receptor[23] and a novel multidimensional chemometric approach for predicting agonism as described below.

Computer Modeling. We utilized a theoretical pharmacophore model (Figure 2) for the $5HT_{1D}$ receptor vasoconstrictor receptor[23] and extended the model to enable a quantitative assessment of intrinsic activity to be made. The receptor model utilizes distance constraints between the protonated amine, an aromatic center (usually the indole), a hydrophobic volume, and hydrogen-bonding sites to predict whether novel ligands will have significant affinity. Given the spatial distribution of the common pharmacophore points, it is possible to perform conformational analysis and least-squares fitting of novel compounds to the desired pharmacophoric points and hence suggest a binding mode for new compounds. The relative ease with which these pharmacophore points are accommodated within the volume of existing ligands gives a qualitative measure of their predicted affinity. The principal binding points were deduced to be the protonated amine and the hydrogen-bonding acceptor (e.g., the ketone group in the oxazolidinone ring). In some cases, due to the conformational and geometric constraints present in some molecular structures, this mode of least-squares fitting results in a displacement of the aromatic center of the indole (if present) from the aromatic site occupied by, for example, 5HT. It was observed that in such cases the affinity of a compound could be high while its intrinsic activity was greatly reduced.[18,24] This suggested to us a hypothesis that the region of the molecule that could be necessary for agonism in this series of compounds was contained within the double-bond region of the indole fragment (which, in antagonist structures that were fitted to the pharmacophore model, was displaced from its usual

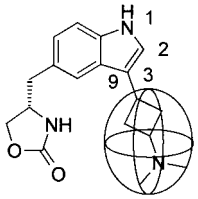


Figure 3. Ellipsoid axis and indole atom-numbering system.

position). To attempt to quantify these effects, an analysis of the molecular properties of molecules having a range of intrinsic activities (including silent compounds) was undertaken (15 agonists, 14 antagonists, and 10 test compounds were used to generate and test the model).[25] From these it was found that the molecular shape of the 3-substituent, determined by the ellipsoid axes (Figure 3), within which this substituent could be contained, and the electrophilic superdelocalizability[26] (computed from the AMI wave function, a measure of the electron density available for interactions) of the atoms in the 1-, 2-, 3-, and 9-positions of the indole ring (Figure 3) could be incorporated into a QSAR model (a hyperplane calculation constructed from these seven parameters separated agonists and antagonists). An extensive quantitative investigation using these parameters to separate agonists, partial agonists, and antagonists[27] generated a quantitative model which would predict the intrinsic acitivity of compounds closely related to the training set. To validate the model 10 randomly selected agonists and antagonists were omitted from the model generation and the model tested by incorporating their computed parameters into the generated equation. All 10 were predicted correctly. Using this model, we generated many new test structures and quantitatively predicted their intrinsic activity. The incorporation of a cyclobutane fragment replacing the ethyl fragment of the side chain (as found in zolmitriptan) resulted in a compound predicted (from the hyperplane calculation) to have very low intrinsic activity. Subsequent investigations narrowed the region which appears to be responsible for intrinsic activity down to the double bond (π-electron density) region of the indole and the steric parameters associated with the 3-substituent.

If suitable modifications are made to the remainder of the molecule such that it can still accommodate the principal pharmacophoric binding points in order to maintain affinity, then an antagonist may be obtained which has high affinity for 5HT$_{1B/1D}$. In addition, occupation of the selectivity volume promotes selectivity for the 5HT$_{1B/1D}$ receptor over the 5HT$_{2A}$ receptor.

Compounds **31** and **35** were predicted from the pharmacophore model to have difficulty in accommodating the pharmacophoric binding points necessary for high affinity. Compounds **23** and **1** were predicted to better fit the pharmacophoric model and hence have higher affinity. In addition, examination of their properties as antagonists using the 7-parameter model suggested that **1** should be of very low intrinsic activity or an antagonist. The values for the ellipsoid axes in **1** are 8.072, 6.145, and 5.490 Å and the values for the electrophilic superdelocalizabilities are −0.2369, −0.2812, −0.2215, and −0.2401 electrons. These values are autoscaled using the mean and standard deviations according to Fukui,[26] which are shown in Table 1. The

Table 1. Calculated Molecular Properties for Compound **1**

	property	mean	SEM	discrim. vector	sum
ESDL_1	−0.2369	−0.3114	0.04293	−0.23064	−0.16556
ESDL_2	−0.2812	−0.2502	0.01654	0.25885	0.28664
ESDL_3	−0.2215	−0.2652	0.01345	0.050932	0.041854
ESDL_9	−0.2401	−0.2549	0.005488	−0.03237	−0.03031
PE_*X*	9.072	8.447	0.8981	0.13866	0.024389
PE_*Y*	5.145	6.088	0.9872	0.08989	−0.01277
PE_*Z*	5.49	4.821	0.4312	−0.11227	−0.07944
constant				0.0200	result = 0.06

subsequent values are then inserted into the equation for the discrimination vector:[26] $P = -0.23064(\text{ESDL\_1}) + 0.25885(\text{ESDL\_2}) + 0.50932(\text{ESDL\_3}) - 0.03237(\text{ESDL\_9}) + 0.13866(\text{PE\_1}) + 0.089895(\text{PE\_2}) - 0.11227(\text{PE\_3}) + 0.020071$, which then yields the prediction of agonist or antagonist and distance from the zero hyperplane. It was seen that compounds near to the zero hyperplane were very partial agonists, as **1** (0.04) was predicted to be.

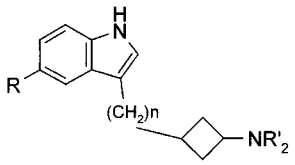
Results

Binding and Vascular Activity. Compounds were evaluated for their binding in CHO-K1 cells[28] stably transfected with human recombinant 5HT$_{1B}$ and 5HT$_{1D}$ receptors. Functional activity was assessed in rings of rabbit saphenous vein[29] and their intrinsic activity expressed relative to 5HT (1.0). The results are presented in Table 2.

A highly focused group of analogues were synthesized restricting the substitution at the 5-position to generally small heterocyclic substituents. Many of the compounds were seen to be antagonists in the rabbit saphenous vein (marked *). These included all the ethylene-linked compounds such as **25**−**28**. Not all the analogues displayed low intrinsic activity; methylation of the (*S*)-oxazolidinone as in **30** resulted in a molecule displaying an intrinsic activity, i.e., maximum effect, of 0.48 (relative to 5HT). The (*R*)-oxazolidinones **31** and **34** also displayed high intrinsic activity as did the methylene sulfonamide **29**. The heteroaryl, amide, and phenoxy analogues were all antagonists in the rabbit saphenous vein with the exception of the primary amide **14** which had an intrinsic activity value of 0.52. Thus some structural features which tend to full agonism in ethylamine indole 5HT ligands, e.g., 5-carboxamidotryptamine, can overcome the tendency to lower intrinsic activity in the 3-(3-aminocyclobutyl)indoles. Only the *trans* analogues displayed good activity with *cis* examples **24** and **35** showing reduced affinity. Extension of the 3-(3-aminocyclobutyl) side chain with a methylene spacer, i.e., in **12**, broadly retained affinity but the compound was an antagonist. In general the binding data on the human 5HT$_{1B}$ and 5HT$_{1D}$ receptors paralleled the data gathered in the rabbit saphenous vein. Few of the molecules demonstrated any selectivity between the receptors, though **1** did show 7-fold selectivity for 5HT$_{1D}$.

Alone among this group of molecules **1** demonstrated very low intrinsic activity in the rabbit saphenous vein, together with reasonable binding affinity. Evaluation against other 5HT receptors is shown in Table 3; clearly the molecule has significant activity against the related calf caudate 5HT$_{1D}$ and against human 5HT$_{1F}$ stably expressed in CHO-K1 cells but less potent activity

Table 2. $5HT_{1D}$, $5HT_{1B}$, and Rabbit Saphenous Vein Binding Data†



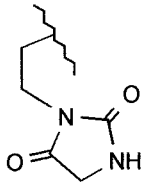
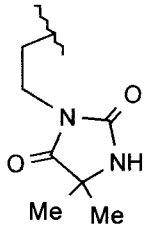
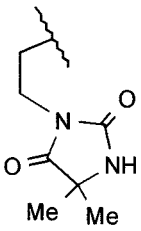
Compound	R	R'	Stereo-chemistry	$5HT_{1B}$ binding[a] pIC_{50}	$5HT_{1D}$ binding pIC_{50}	RbSv pA_{50} (α)[b] or pA_2*
sumatriptan				9.30± 1.0	8.53± 0.54	6.6 (0.83)[c]
zolmitriptan				8.21± 0.11	8.55± 0.19	6.80 (0.77)[c]
5 (CP122,288)				7.84	8.14	6.33 (0.85)
23	ox[d]	H	(S)-trans	7.74±0.06[e]	8.44±0.08	6.42± 0.06 (0.78±0.13)
24	ox	H	(S)-cis	NT	NT	5.8± 0.16 (0.76±0.07)
25		Me	trans	NT	NT	5.72*±0.16
1	ox	Me	(S)-trans	6.95±0.08	7.80±0.06	5.72(0.09)
26		Me	trans	5.92±0.18	5.83	6.05*±0.08
27		H	trans	5.95±0.07	6.3±0.07	5.57*

Table 2 (Continued)

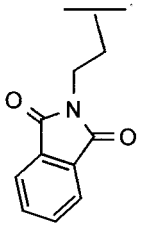
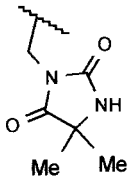
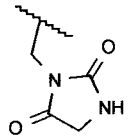
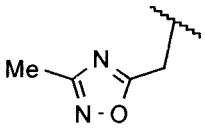
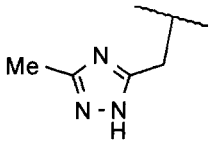
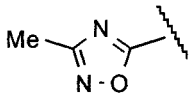
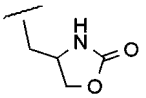
Compound	R	R'	Stereo-chemistry	5HT$_{1B}$ binding[a] pIC$_{50}$	5HT$_{1D}$ binding pIC$_{50}$	RbSv pA$_{50}$ (α)[b] or pA$_2$*
28		Me	trans	6.69	6.71	6.77*
29	CH_2SO_2NHMe	Me	trans	6.56±0.06	6.72±0.12	5.25(0.51)
30	NMe-ox	Me	(S)-trans	6.69±0.07	7.00±0.05	5.21(0.48)
31	ox	Me	(R)-trans	6.25±0.06	6.77±0.07	4.95± 0.14 (0.20±0.11)
32		Me	trans	5.42	5.51	6.23*±0.08
33		Me	trans	5.20±0.04	5.61	5.03*
12[b]	ox	Me	(S)-trans	6.85±0.09	7.54±0.15	5.73*±0.13
13	ox	Me, H	(S)-trans	7.49±0.05	8.15±0.16	6.18± 0.14 (0.72±0.06)
34	NMe-ox	Me	(R)-trans	7.01±0.15	7.24±0.16	4.85± 0.19 (0.38±0.14)
22	CH_2CONH_2	Me	trans	5.87	6.14	4.78*±0.07
14	$CONH_2$	Me	trans	7.35±0.03	7.83±0.11	6.25±0.09 (0.52±0.12)
35	ox	Me	(S)-cis	6.79±0.09	7.00±0.08	5.15(0.29)
36	OPh	H	trans	8.02	7.84	<6.5

Table 2 (Continued)

Compound	R	R'	Stereo-chemistry	$5HT_{1B}$ binding[a] pIC_{50}	$5HT_{1D}$ binding pIC_{50}	RbSv pA_{50} (α)[b] or pA_2*
37	OPh	Me	trans	7.01	7.19	6.62*±0.13
21	$CH_2CONHBn$	Me	trans	6.58	6.47	5.41*±0.15
15	CONHBn	Me	trans	6.5	6.85	5.90*±0.21
19		Me	trans	5.82	6.03	5.12*±0.09
20		Me	trans	5.41	5.69	5.18*±0.01
38		Me	trans	6.08	6.25	6.02*±0.13

[†] For the general structure $n = 0$, except **12** where $n = 1$. [a] Human receptors expressed in CHO cell lines. [b] Figures in parentheses for RbSv are intrinsic activity, where 1.0 is the value for 5HT. [c] Data from ref 20. [d] Ox = 

[e] Values are means ± SEM, $n = 3$ or more. Other values are means of duplicates.

Table 3. Binding Data for **1** against 5HT Receptors

	5HT receptor						
	$h5HT_{1B}$	$h5HT_{1D}$	$h5HT_{1A}$	$h5HT_{1F}$	$5HT_{1D}$[a]	$5HT_{2A}$[b]	$5HT_{2C}$[c]
pIC_{50}	6.95	7.80	5.45	6.44	7.05	>10 μM	>10 μM

[a] Binding to calf caudate receptors. [b] Binding in rabbit aorta, no functional activity was noted. [c] Binding to guinea pig cortex in the presence of [^{3}H]mesulergine.

against other 5HT receptors such as $5HT_{2A}$ (rabbit aorta) and $5HT_{2C}$ (guinea pig cortex). The compound was functionally silent at the $5HT_{2A}$ receptor. Compound **1** was therefore selected for evaluation in relevant animal models of migraine.

Activity against Electrically Evoked Plasma Protein Extravasation (PPE) in Guinea Pig Dura. Figure 4 illustrates the activity of **1** against PPE in guinea pigs. The compound was exceptionally potent with an ED_{50} of approximately 10 ng/kg when given iv. The ability of the compound to affect blood flow in the guinea pig ear was also assessed by laser doppler and gives a demonstration of the separation of the vasoconstrictor effects of **1** versus the PPE inhibition. The data for zolmitriptan is included in the figure for comparison. The separation is at least 4 orders of magnitude. Table 4 illustrates data for some other 5HT agonists such as sumatriptan and CP-122,288. Suprisingly **1** is even more potent than CP-122,288 in this assay, as in our hands CP-122,288 had an ED_{50} of 100 ng/kg. Sumatriptan, in common with most other triptans, had an ED_{50} of approximately 10 μg/kg.

Pharmacokinetics. The qualitative model for oral absorption had predicted that **1** would show similar properties to other bioavailable triptans. Indeed when the compound was evaluated in rats, it was shown to have an oral bioavailability comparable to that of zolmitriptan; see Figure 1. The detailed pharmaco-

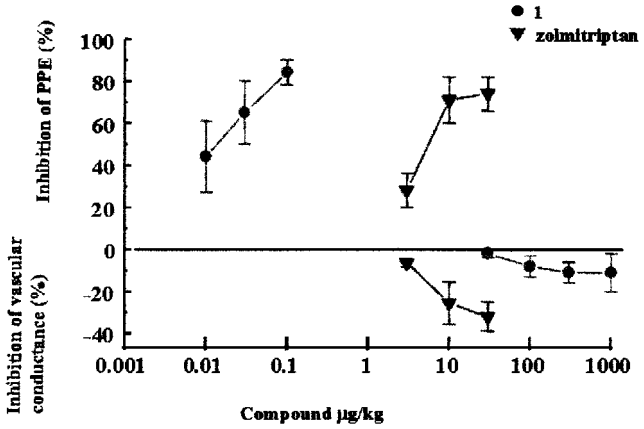


Figure 4. Effect of **1** on [^{125}I]albumin extravasation into dura following electrical stimulation of trigeminal ganglion (EC_{50}) and vascular (ear) conductance in the guinea pig (mean ± SEM).

Table 4. Inhibition of [^{125}I]Albumin Extravasation into Dura following Electrical Stimulation of Trigeminal Ganglion

compd	ED_{50}, guinea pig	RbSv[a]
1	~10 ng/kg	5.71 (0.1)
5 (CP-122,288)	~100 ng/kg	6.33 (0.85)
zolmitriptan	~12 μg/kg	6.8 (0.77)
sumatriptan	~10 μg/kg	6.6 (0.83)

[a] pA_{50}, figures in parentheses are intrinsic activity relative to 5HT.

Table 5. Pharmacokinetic Parameters for **1** in Rats

compd	β-phase half-life (h)	vol of distrib (L/kg)	plasma clearance (mL/min/kg)	oral bioavail (%)
1	1.4	2.6	40	35

kinetic parameters are shown in Table 5. The half-life of 1.5 h and oral bioavailability of 35% show that our qualitative model was predictive, at least for the tryptamine series. In humans **1** showed oral bioavailability of 41%[30] compared to the structurally related zolmitriptan at 40−49% and sumatriptan at 14%.[31] Although **1** was metabolized to the desmethyl metabolite (compound **13** in Table 2) at 20−30% of the level of **1**, no cleavage to an indole acetic acid metabolite such as that observed for zolmitriptan was reported. Thus the cyclobutylamino moiety was found to be resistant to obvious metabolic degradation.

Discussion

The most pleasing aspect of this project was the success of the design process. This built on the knowledge base in this area from previous studies.[23] In particular the hyperplane model for agonism suggested that a novel ethylamine isostere might exhibit low partial agonism against the vasoconstrictor $5HT_1$ receptors. Consideration of the physicochemical parameters necessary for good oral absorption predicted that small substituents at the 5-position might maintain the oral bioavailability of sumatriptan. Detailed investigation of potential synthetic routes eventually provided a workable synthesis to the desired 3-(3-dimethylaminocyclobutyl)indoles.

The finding of potent PPE inhibitory activity similar to that of CP-122,288 was intriguing, though PPE activity of itself has not been shown to be predictive of an antimigraine effect in humans. Other studies have shown that **1** does not affect CGRP release in the cat at non-$5HT_{1B/1D}$ receptor levels[32] and also that only $5HT_{1B/1D}$ receptor doses inhibit trigeminocervical neurons.[33] The mechanism for the potent inhibition of PPE in rodents remains unclear. It does seem however, as in the case of CP-122,288, that the potent effects may not be mediated by $5HT_{1B/1D}$ receptors. In a multicenter, randomized double-blind, placebo-controlled study, clinical studies[34] with **1** have shown that low doses of the compound (0.125 and 2.5 mg/kg/iv) carefully designed to be below the threshold for $5HT_{1B/1D}$ receptor effects were not effective in reducing the traditional 2-h acute migraine headache. In these studies 117 patients were randomized (placebo = 42; 0.125 mg of **1** = 40; 2.5 mg of **1** = 35). Traditional 2-h response rates (moderate or severe to mild or none) were 45%, 50%, and 46% in the placebo, 0.125 mg of **1**, and 2.5 mg of **1** treatment groups, respectively. For patients treating "early" (0−2 h), response rates were 53%, 42%, and 71%. Fewer patients in the groups receiving **1** had severe headache pain at 2 h (33%, 23%, and 14%). Recurrent headache occurred in 53%, 58%, and 13% of the patients with a median time to recurrence of 6.7, 7.8, and 11.9 h. The compound was well-tolerated. There were no treatment effects on blood pressure, ECGs, or clinical laboratory assessments. Therefore although **1** was not effective in the traditional 2-h HA response, the data regarding early treatment and recurrence suggest that it may modulate certain aspects of the migraine process at doses which reflect the PPE activity. The profile of **1** would seem to make it well-suited among the triptan family to be of use in the prophylaxis of migraine. The arrival of generic sumatriptan to the market is likely to have a big impact on the progression of second-generation triptan molecules.

Experimental Section

Chemistry. Melting points are uncorrected. Flash chromatography was carried out by the method of Still[35] except that the columns were slurry packed. Merck silica art. no. 9385 was used. NMR spectra were run at 200 MHz unless otherwise indicated. Chemical shifts are in ppm relative to TMS. Coupling constants are in Hz.

***trans*-*N*-(Benzyloxycarbonyl)cyclobutanamine-3-acetaldehyde (7).** *trans*-*N*-(Benzyloxycarbonyl)-3-methylenecyclobutanamine (24.27 g, 112 mmol) (prepared as described in EP-A-0366059) and tris(triphenylphosphine)rhodium chloride (400 mg 0.43 mmol) were heated to 70 °C in toluene (250 mL) under 100 atm of CO:H_2, 1:1 mixture, for 18 h. The solvent was evaporated under reduced pressure and the residue chromatographed on silica eluting with 25% EtOAc in cyclohexane. First product eluted as a mixture of *cis* and *trans* branched chain aldehydes (7.01 g, 28.4 mmol). Second product eluted as a mixture of *cis* and *trans* straight chain aldehydes (18.65 g, 75.5 mmol). The *trans* straight chain isomer was crystallized from ether (100 mL) as white needles (5.4 g, 22.0 mmol, 19.5%): mp 66−67 °C; MS (FAB) 248 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$) δ 9.71 (t, 1H, J = 1.3 Hz), 7.44−7.28 (m, 5H), 5.08 (s, 2H), 5.01 (broad d, J = 6.2, 1H), 4.25 (m, 1H), 2.65 (m, 3H), 2.13 (m, 4H). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

General Method A: Fischer Indole Synthesis and CBz Deprotection. Example: 4-[3-(*trans*-3-Aminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (23). The appropriate hydrazine (6.3 g, 30 mmol) and *trans*-*N*-(benzyloxycarbonyl)cyclobutanamine-3-acetaldehyde (6.3 g, 25.5 mmol) were heated to 80 °C for 7 h in 1% aqueous sulfuric acid (100 mL) and EtOH (150 mL). The reaction mixture was evaporated

in vacuo and brine added. Extraction with EtOAc gave the crude CBz product 10.5 g (83%). The product was refluxed in 10% formic acid−MeOH with $Pd(OH)_2$ on carbon (1 g) for 7 h. The solvent was removed in vacuo and brine added. The solution was then washed with EtOAc and then made basic (pH 10−12) with dilute ammonium hydroxide solution. Extraction with THF gave the crude product 2.0 g (28%) which was purified by flash chromatography (2:14:84 NH_3:EtOH:$CHCl_3$) to give the product **23**. The compound was obtained as a foam: ^{1}H NMR (DMSO-d_6) δ 10.71 (bs, 1H), 7.72 (bs, 1H), 7.27 (s, 1H), 7.25 (d, J = 8.2, 1H),7.16 (dd, J = 1.2, 0.5, 1H), 6.93 (dd, J = 8.2, 1.2, 1H), 4.22 (m, 1H), 4.04 (m, 1H), 4.00 (m, 1H), 3.8 (partly obscured m, 2H), 2.88 (dd, J = 13.5, 4.6, 1H), 2.77 (dd, J = 13.5, 6.9, 1H) 2.40 (bm, 2H), 2.24 (bm, 2H); MS (FAB) m/z 286 (M + 1). Anal. ($C_{16}H_{19}N_3O_2$·1.26H_2O·0.23C_2H_6O) C, H, N.

Compounds prepared using general method A:

***trans*-3-{2-[3-(3-Aminocyclobutyl)-1*H*-indol-5-yl]ethyl}-5,5-dimethylimidazolidine-2,4-dione (27):** mp 85−87 °C; ^{1}H NMR (DMSO-d_6) δ 10.63 (bs, 1H), 8.11 (bs, 1H), 7.22 (dd, J = 8.2, 0.7, 1H), 7.14 (m, 1H), 7.12 (dd, J = 2.2, 1.0, 1H), 6.87 (dd, J = 8.4, 1.6, 1H), 3.57 (ct, J = 7.5, 2H), 3.5 (m, 1H), 2.90 (m, 1H), 2.88 (bt, J = 7.5, 2H), 2.31 (m, 2H), 2.10 (m, 2H), 1.16 (s, 6H); MS (EI) m/z 297, 181, 169. Anal. ($C_{19}H_{24}N_4O_2$·0.09$CHCl_3$) C, H, N.

5-Phenoxy-3-(*trans*-3-aminocyclobutyl)-1*H*-indole (35): mp 164−166 °C; ^{1}H NMR (DMSO-d_6) δ 10.90 (bs, 1H), 7.38 (dd, J = 8.6, 0.4, 1H), 7.31 (m, 1H), 7.30 (m, 1H), 7.09 (d, J = 2.3, 1H), 7.02 (tt, J = 7.3, 1.0, 1H), 6.90 (m, 1H), 6.83 (dd, J = 8.6, 2.3, 1H), 3.74 (m, 2H), 2.42 (m, 4H); MS (EI) m/z 278, 235, 158. Anal. ($C_{18}H_{18}N_2O$·$C_6H_6O_4$) C, H, N.

General Method B: Reductive Amination. Example: *trans*-4-[3-(3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-1,3-oxazolidin-2-one (1). Formaldehyde (0.18 mL, 2.22 mmol) in MeOH (5 mL) was added to the product method A (250 mg, 0.88 mmol), AcOH (0.26 mL, 4.55 mmol) and sodium cyanoborohydride (70 mg, 1.17 mmol) in MeOH (15 mL) and stirred at room temperature under a nitrogen atmosphere overnight. Water was added and the mixture washed with EtOAc. The aqueous phase was then adjusted to pH 10 with K_2CO_3 and saturated with NaCl. Extraction with EtOAc gave a sticky gum which was purified by flash chromatography (1:9:90 NH_3:MeOH:$CHCl_3$) to give the product **1** as an off white powder 137 mg (44%): mp 159−160 °C; ^{1}H NMR (DMSO-d_6) δ 10.69 (bs, 1H), 7.73 (bs, 1H), 7.27 (partly obscured m, 1H), 7.25 (d, J = 8.2, 1H), 7.17 (dd, J = 2.1, 0.8, 1H), 6.93 (dd, J = 8.3, 1.4, 1H), 4.22 (m, 1H), 4.04 (m, 1H), 3.99 (m, 1H), 3.51 (m, 1H), 2.88 (m, 1H), 2.78 (m, 1H), 2.76 (m, 1H), 2.29 (m, 2H), 2.19 (m, 2H), 2.06 (s, 1H); MS (FAB) m/z 314 (M + 1). Anal. ($C_{18}H_{23}N_3O_2$) C, H, N.

Compounds prepared using general methods A and B:

5-Carboxamido-3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indole (14): mp 93−95 °C; ^{1}H NMR (DMSO-d_6) δ 11.00 (bs, 1H), 8.07 (dt, J = 1.6, 0.6, 1H), 7.80 (bs, 1H), 7.65 (dd, J = 8.5, 1.6, 1H), 7.33 (dd, J = 8.6, 0.6, 1H), 7.28 (dd, J = 2.2, 1.1, 1H), 7.02 (bs, 1H), 3.57 (ttt, J = 9.0, 4.4, 1.1, 1H), 2.81 (pd, J = 7.0, 0.7, 1H), 2.35 (m, 2H), 2.21 (m, 2H), 2.07 (s, 6H); MS (FAB) m/z 258 (M + 1). Anal. ($C_{15}H_{19}N_3O$·0.34H_2O·0.1AcOEt) C, H, N.

***trans*-3-{2-[3-(3-Dimethylaminocyclobutyl)-1*H*-indol-5-yl]ethyl}imidazolidine-2,4-dione (25):** mp 197−199 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (bs, 1H), 7.37 (dt, J = 1.5, 0.6, 1H), 7.29 (dd, J = 8.3, 0.6, 1H), 7.10 (dd, J = 8.5, 1.6, 1H), 7.04 (dd, J = 2.2, 1.2, 1H), 5.51 (bs, 1H), 3.92 (d, J = 17.7, 1H), 3.85 (d, J = 17.7, 1H), 3.79 (ct, J = 8.0, 6.0, 2H), 3.62 (ttt, J = 9.2, 4.0, 1.2, 1H), 3.02 (ct, J = 8.2, 6.1, 2H), 2.89 (pd, J = 7.2, 1.1, 1H) 2.44 (m, 2H), 2.30 (m, 2H), 2.18 (s, 6H); MS (FAB) m/z 341 (M + 1). Anal. ($C_{19}H_{24}N_4O_2$·0.22H_2O) C, H, N.

5,5-Dimethyl-3-{2-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-yl]ethyl}imidazolidine-2,4-dione (26): mp 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (bs, 1H), 7.35 (s, 1H), 7.32 (d, J = 8.3, 1H), 7.09 (dd, J = 8.3, 1.7, 1H), 7.03 (dd, J = 1.7, 1.3, 1H), 5.13 (bs, 1H), 3.78 (t, J = 7.6, 2H), 3.62 (m, 3H), 2.90 (q, J = 7.6, 1H), 2.46 (m, 2H), 2.31 (m, 2H), 2.20 (s, 6H), 1.32 (s, 6H); MS (EI) m/z 368, 297, 194, 156, 143; HRMS for $C_{21}H_{28}N_4O_2$ calcd 368.22123, found 368.22119.

2-{2-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-yl]ethyl}isoindole-1,3-dione (28): mp 52−53 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (bs, 1H), 7.82 (m, 2H), 7.68 (m, 2H), 7.34 (dt, J = 1.5, 0.5, 1H), 7.29 (dd, J = 8.3, 0.5, 1H), 7.13 (dd, J = 8.3, 1.5, 1H), 7.01 (dd, J = 2.1, 1.3, 1H), 3.96 (ct, J = 7.7, 5.8, 2H), 3.56 (ttt, J = 9.1, 4.6, 1.2, 1H), 3.08 (ct, J = 7.9, 5.9, 2H), 2.86 (pd, J = 7.2, 0.9, 1H), 2.39 (m, 2H), 2.22 (m, 2H), 2.17 (s, 6H); MS (FAB) m/z 388 (M + 1). Anal. ($C_{24}H_{25}N_3O_2$·0.4H_2O·0.3$CHCl_3$) C, H, N.

***N*-Methyl-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-yl]methanesulfonamide (29):** using the hydrazine prepared as reported;[36] mp 220−222 °C; ^{1}H NMR (DMSO-d_6) δ 10.82 (bs, 1H), 7.44 (m, 1H), 7.31 (d, J = 8.1, 1H), 7.22 (dd, J = 1.9, 0.9, 1H), 7.08 (dd, J = 8.2, 1.5, 1H), 6.73 (q, J = 4.9, 1H), 4.32 (s, 2H), 3.51 (ttt, J = 9.0, 4.5, 1.0, 1H), 2.81 (pd, J = 6.8, 0.6, 1H), 2.53 (d, J = 4.9, 1H), 2.30 (m, 2H), 2.21 (m, 2H), 2.06 (s, 6H); MS (FAB) m/z 322 (M + 1). Anal. ($C_{16}H_{22}N_3O_2S$·0.089$CHCl_3$) C, H, N.

4-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-3-methyl-(4*S*)-oxazolidin-2-one (30): mp 46−47 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (bs, 1H), 7.40 (m, 1H), 7.32 (dd, J = 7.2, 0.7, 1H), 7.08 (dd, J = 2.3, 1.2, 1 H), 6.97 (dd, J = 7.2, 1.5, 1H), 4.17 (t, J = 8.1, 1H), 4.05 (m, 1H), 3.94 (m, 1H), 3.64 (ttt, J = 9.2, 4.1, 1.0, 1H), 3.24 (dd, J = 13.6, 4.6, 1H), 2.92 (s, 3H), 2.91 (m, 1H), 2.77 (dd, J = 13.6, 8.6, 1H), 2.47 (m, 2H), 2.30 (m, 2H), 2.19 (s, 6H); MS (FAB) m/z 328 (M + 1). Anal. ($C_{19}H_{25}N_3O_2$·0.13$CHCl_3$) C, H, N.

4-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*R*)-oxazolidin-2-one (31): mp 163−165 °C; ^{1}H NMR (DMSO-d_6) δ 10.69 (bs, 1H), 7.72 (bs, 1H), 7.27(m, 1H), 7.25 (d, J = 8.2, 1H), 7.17 (dd, J = 1.6, 0.6, 1H), 6.93 (dd, J = 8.3, 1.2, 1H), 4.22 (m, 1H), 4.03 (m, 1H), 3.99 (m, 1H), 3.51 (ttt, J = 9.2, 4.4, 1.0, 1H), 2.88 (m, 1H), 2.78 (m, 1H), 2.75 (m, 1H), 2.31 (m, 2H), 2.19 (m, 2H), 2.06 (s, 6H); MS (FAB) m/z 314 (M + 1). Anal. ($C_{18}H_{23}N_3O_2$·0.66H_2O·0.33$C_4H_8O_2$) C, H, N.

3-{2-[3-(*trans*-3-Aminocyclobutyl)-1*H*-indol-5-yl]methyl}-5,5-dimethylimidazolidine-2,4-dione (32): mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (bs, 1H), 7.55 (dt, J = 1.5, 0.8, 1H), 7.29 (dd, J = 8.3, 0.8, 1H), 7.24 (dd, J = 8.3, 1.5, 1H), 7.05 (dd, J = 2.4, 1.2, 1H), 5.2 (bs, 1H), 4.75 (s, 1H), 3.63 (ttt, J = 9.4, 4.5, 1.2, 1H), 2.90 (pd, J = 7.4, 1.0, 1H), 2.30 (m, 2H), 2.44 (m, 2H), 2.18 (s, 6H), 1.41 (s, 6H); MS (FAB) m/z 355 (M + 1). Anal. ($C_{20}H_{26}N_4O_2$·0.1H_2O·0.2$CHCl_3$) C, H, N.

3-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]imidazolidine-2,4-dione (33): mp 106−109 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.76 (bs, 1H), 8.02 (bs, 1H), 7.37 (dt, J = 1.6, 0.6, 1H), 7.27 (dd, J = 8.3, 0.6, 1H), 7.20 (dd, J = 2.2, 1.1, 1H), 7.02 (dd, J = 8.2, 1.6, 1H), 4.56 (s, 2H) 3.93 (s, 2H), 3.49 (ttt, J = 9.5, 4.4, 1.1, 1H), 2.80 (pd, J = 7.1, 1.0, 1H), 2.29 (m, 2H), 2.17 (m, 2H), 2.06 (s, 6H); MS (EI) m/z 326, 295, 226, 211; HRMS for $C_{18}H_{22}N_2O_2$ calcd 326.17428, found 326.17371.

4-[3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-3-methyl-(4*R*)-oxazolidin-2-one (34): obtained as a foam; ^{1}H NMR (DMSO-d_6) δ 10.72 (bs, 1H), 7.29 (m, 1H), 7.27 (dd, J = 8.2, 0.5, 1H), 7.18 (dd, J = 2.3, 1.0, 1H), 6.94 (dd, J = 8.2, 1.6, 1H), 4.14 (m, 1H), 4.00 (m, 1H), 3.96 (m, 1H), 3.51 (ttt, J = 9.0, 1.1, 4.4, 1H), 3.17 (dd, J = 13.5, 3.7, 1H), 3.05 (m, 1H), 2.80 (s, 3H), 2.77 (m, 1H), 2.30 (m, 2H), 2.18 (m, 2H), 2.06 (s, 6H); MS (EI) m/z 327, 312, 283, 256, 100. Anal. ($C_{19}H_{25}N_3O_2$·0.75H_2O) C, H, N.

5-Phenoxy-3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indole (36): prepared from **35** above; mp 189−190 °C; ^{1}H NMR (DMSO-d_6) δ 11.06 (d, J = 1.6, 1H), 7.41 (m, 2H), 7.31 (m, 1H), 7.13 (d, J = 2.2, 1H), 7.02 (tt, J = 7.3, 1.1, 1H), 6.89 (m, 1H), 6.85 (dd, J = 8.6, 2.2, 1H), 3.86 (pd, J = 1.0, 8.0, 1H), 3.59 (m, 1H), 2.69 (s, 6H), 2.67 (m, 2H), 2.40 (m, 2H); MS (EI) m/z 306, 291,262, 235, 158. Anal. ($C_{20}H_{22}N_2O$·HBr·0.1C_3H_8O·0.1H_2O) C, H, N.

General Method C: For Synthesis of the *cis*-Aminocyclobutyl Analogues. The mixture of *cis*- and *trans*-CBz

aldehydes produced in the preparation of **7** was utilized as in methods A and B above. The *cis* dimethylated products were separated by HPLC using SiO_2, 2:8:90 880 NH_3:MeOH:$CHCl_3$.

Prepared using method C were:

***cis*-4-[3-(3-Aminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one acetate (24)**: mp 180−181 °C; ^{1}H NMR (DMSO-d_6) δ 10.70 (bs, 1H), 7.79 (bs, 1H), 7.41 (s, 1H), 7.24 (d, J = 8.2, 1H), 7.08 (dd, J = 1.5, 0.7, 1H), 6.92 (dd, J = 8.2, 1.5, 1H), 4.23 (tm, 1H), 4.04 (m, 3H), 3.19 (bm, 1H), 2.89 (dd, J = 13.5, 4.5, 1H), 2.78 (dd, J = 6.8, 13.5, 1H), 2.61 (bm, 2H), 1.97 (bm, 2H); MS (FAB) m/z 286 (M + 1); HRMS m/z calcd for $C_{16}H_{19}N_3O_2$ 285.1488, found 285.1477.

4-[3-(*cis*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (35): obtained as a hygroscopic solid; ^{1}H NMR ($CDCl_3$) δ 8.27 (bs, 1H), 7.44 (dt, J = 1.7, 0.7, 1H), 7.29 (dd, J = 8.3, 0.6, 1H), 7.03 (dd, J = 2.4, 0.7, 1H), 6.95 (dd, J = 8.3, 1.6, 1H), 5.28 (bs, 1H), 4.47 (m, 1H), 4.18 (m, 1H), 4.14 (om, 1H), 3.31 (tdd, J = 10.2, 7.5, 1.0, 1H), 3.00 (dd, J = 13.5, 5.7, 1H), 2.90 (dd, J = 13.5, 7.8, 1H), 2.75 (m, 1H), 2.62 (m, 2H), 2.25 (s, 6H), 2.13 (m, 2H); MS (FAB) m/z 314 (M + 1); HRMS $C_{18}H_{23}N_3O_2$ calcd 313.17903, found 313.17683.

4-[3-(*trans*-3-Dimethylaminocyclobut-1-ylmethyl)-1*H*-indol-5-ylmethyl]-(4S)-oxazolidin-2-one (12): mp 64−65 °C; ^{1}H NMR (DMSO-d_6) δ 10.66 (bs, 1H), 7.73 (bs 1H), 7.34 (dt, J = 1.6, 0.7, 1H), 7.24 (dd, J = 8.3, 0.5, 1H), 7.05 (d, J = 2.3, 1H), 6.92 (dd, J = 8.3, 1.5, 1H), 4.22 (m, 1H), 4.04 (m, 1H), 4.00 (m, 1H), 2.89 (dd, J = 13.7, 4.5, 1H), 2.80 (d, J = 8.0, 2H), 2.77 (dd, J = 13.7, 6.8, 1H), 2.75 (m, 1H), 2.42 (m, 1H), 2.00 (s, 6H), 1.91 (m, 2H), 1.78 (m, 2H); MS (EI) m/z 325, 312, 299, 241, 212. Anal. ($C_{19}H_{25}N_3O_2$·0.42H_2)O C, H, N.

4-[3-(*trans*-3-Methylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-(4*S*)-oxazolidin-2-one (13). The aldehyde **7** (1 g, 4 mmol), triethyl orthoformate (1.35 mL, 8 mmol) and pTsOH (100 mg) were refluxed in EtOH for 3 h. The reaction mixture was evaporated in vacuo and purified by flash chromatography (10:90 EtOAc/cyclohexanone) to give a colorless oil (1.2 g, 94%), which was used crude for the next stage. The *trans*-*N*-(benzyloxycarbonyl)cyclobutanamine-3-acetaldehyde diethyl acetal (1.2 g, 3.7 mmol) in dry DMF (10 mL) was added dropwise to a cold suspension of sodium hydride (60% in oil) (165 mg, 4.1 mmol) in dry DMF (10 mL). After the addition was complete the mixture was allowed to stirred at 10 °C for 30 min, MeI (0.23 mL, 3.7 mmol) in dry DMF (5 mL) was then added dropwise. The mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was then poured onto ice and extracted with ether. Flash chromatography (10:90 EtOAc:cyclohexane) gave the product as a colorless oil (1 g, 83%). The product of this step was then treated by the general methods A and B above to provide **13** as a foam: ^{1}H NMR ($CDCl_3$) δ 8.11 (bs, 1H), 7.32 (dt, J = 1.5, 0.7, 1H), 7.31 (dd, J = 8.3, 0.6, 1H), 7.07 (dd, J = 2.0, 1.0, 1H), 6.98 (dd, J = 8.3, 1.6, 1H), 5.16 (bs, 1H), 4.47 (t, J = 8.0, 1H), 4.19 (dd, J = 8.0, 5.6, 1H), 4.12 (td, J = 8.0, 5.6, 1H), 3.73 (ttt, J = 9.0, 4.0, 1.2, 1H), 3.48 (s, 1H), 3.42 (m, 1H), 2.98 (m, 1H), 2.91 (m, 1H), 2.43 (m, 2H), 2.40 (s, 3H), 2.28 (m, 2H); MS (EI) m/z 325, 312, 299, 241, 212. Anal. ($C_{19}H_{25}N_3O_2$·0.42H_2O) C, H, N.

5-*N*-Benzylcarboxamido-3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indole (15). 5-Carboxamido-3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indole (**14**; 0.4 g, 1.6 mmol), prepared using the methods described above, was refluxed in 10 M NaOH solution (15 mL) and MeOH (10 mL) for 7 h. The resulting solution was cooled in ice and neutralized with dil HCl. This was then evaporated to dryness in vacuo and MeOH added. The NaCl was filtered off and the solution evaporated to give the crude product. The crude 3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indole-5-carboxylic acid (0.4 g, 1.6 mmol), *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*^{1},*N*^{1}-tetramethyluronium tetrafluoroborate (TBTU) (0.57 g, 1.8 mmol), benzylamine (0.18 mL, 1.6 mmol) and Et_3N (0.25, 1.8 mmol) were stirred at room temperature in dry DMF (15 mL) for 5 h. The reaction was quenched with water and extracted with EtOAc. This was dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography (1:10:89 0.88 NH_3:MeOH:$CHCl_3$) (175 mg, 32%). The crude material was treated by the methods described above to give **15** as a foam: ^{1}H NMR (DMSO-d_6) δ 10.96 (bs, 1H), 8.78 (t, J = 6.0, 1H), 8.09 (m, 1H), 7.67 (dd, J = 8.5, 1.7, 1H), 7.35 (m, 1H), 7.32 (m, 2H), 7.28 (dd, J = 2.2, 1.0, 1H), 7.22 (tt, J = 6.2, 3.2,), 4.5 (d, J = 6.0, 2H), 3.58 (ttt, J = 9.3, 4.5, 1.0, 1H), 2.84 (pd, J = 7.3, 1.0, 1H), 2.34 (m, 2H), 2.20 (m, 2H), 2.08 (s, 6H); MS (FAB) m/z 348 (M + 1). Anal. ($C_{22}H_{25}N_3O$·0.71H_2O) C, H, N.

3-(*trans*-3-Dimethylaminocyclobutyl)-1*H*-indol-5-ylacetamide (22). To 4-hydrazinophenylacetic HCl in 1% aqueous sulfuric acid (75 mL) was added *trans*-*N*-(benzyloxycarbonyl)cyclobutanamine-3-acetaldehyde (5 g, 20 mmol). The mixture was heated to 90 °C for 7 h. The semisolid formed was filtered and washed with 1% H_2SO_4 and water. The solid was then taken up into EtOAc and washed with water. The organic phase was dried ($MgSO_4$). The product was obtained as a sticky solid: yield 6.5 g (74%).

To a solution of the crude 3-[*trans*-*N*-(benzyloxycarbonyl)-cyclobutanamine]-1*H*-indol-5-ylacetic acid (0.5 g, 1.38 mmol) in DMF (5 mL) was added TBTU (0.44 g, 1.38 mmol) and Et_3N (0.21 mL, 1.52 mmol). Anhydrous ammonia was then bubbled through the solution for 1 h at room temperature with cooling in ice as necessary. The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum. The residue was chromatographed on silica using 1:10:89 880 NH_3:MeOH:$CHCl_3$. Yield: 0.28 g (56%). This was treated by the general method B outlined above to give **22**: mp 57−59 °C; ^{1}H NMR (DMSO-d_6) δ 10.76 (bs, 1H), 7.30 (dt, J = 1.5, 0.9, 1H), 7.29 (bs, 1H), 7.24 (dd, J = 8.1, 0.5, 1H), 7.17 (dd, J = 2.5, 1.2, 1H), 6.98 (dd, J = 8.3, 1.6, 1H), 6.74 (bs, 1H), 3.50 (ttt, J = 8.8, 4.4, 1.1, 1H), 3.39 (s, 2H), 2.81 (pd, J = 7.0, 0.8, 1H), 2.30 (m, 2H), 2.19 (m, 2H), 2.07 (s, 6H); MS (FAB) m/z 272 (M + 1); HRMS for $C_{16}H_{21}N_3O$ calcd 271.16846, found 271.16713.

***N*-Benzyl-3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-ylacetamide (21).** To a solution of 3-[*trans*-*N*-(benzyloxycarbonyl)-3-aminocyclobutyl]indol-5-ylacetic acid (1 g, 2.76 mmol) in DMF (5 mL) was added TBTU (0.97 g 3.04 mmol), Et_3N (0.42 mL 3.04 mmol) and benzylamine (0.33 mL 3.04 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum and the residue purified by flash chromatography (1:5:94 NH_3:MeOH:$CHCl_3$) to give a pale yellow oil 0.81 g (80%). The crude product of this step was then treated by the general methods A and B outlined above to provide **21** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.08 (bs, 1H), 7.40 (dt, J = 1.5, 0.6, 1H), 7.32 (dd, J = 8.3, 0.5, 1H), 7.25 (m, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 7.06 (m, 2H), 5.79 (bt, J = 5.6, 1H), 4.39 (d, J = 5.8, 2H), 4.32 (s, 2H), 3.63 (ttt, J = 9.2, 4.0, 1.1, 1H), 2.92 (pd, J = 7.3, 1.1, 1H), 2.44 (m, 2H), 2.28 (m, 2H), 2.19 (s, 6H); MS (FAB) m/z 362 (M + 1); HRMS for $C_{23}H_{27}N_3O$ calcd 361.21541, found 361.2154.

3-Methyl-5-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-1,2,4-oxadiazole (38). To a solution containing 3-(*trans*-*N*-benzyloxycarbonyl-3-aminocyclobutyl)indol-5-ylacetamide (4.68 g 13 mmol) in toluene (10 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (40 mL). The mixture was then heated at 120 °C for 2 h under Dean & Stark conditions. The solution became very dark. The solvent was evaporated under vacuum to give *N*-[(dimethylamino)ethanylidene]-3-[*trans*-3-(benzyloxycarbonylamino)cyclobutyl]-1*H*-indol-5-ylacetamide (5.7 g crude), which was used directly for subsequent operations.

To a mixture containing hydroxylamine HCl (10 mg 1.6 mmol), 5 N NaOH (0.2 mL), *p*-dioxane (3 mL) and 70% AcOH (10 mL) was added the amidine (500 mg 1.6 mmol) and the mixture heated to 120 °C for 1.5 h. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (40:60 EtOAc:cyclohexane) to give the product, 150 mg (31%), as a foam. The product of this step was then treated by the general methods A and B above to provide **38** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.97 (bs, 1H), 7.42 (dt, J = 1.6, 0.7, 1H), 7.28 (dd, J = 8.3, 0.7, 1H), 7.11 (dd, J = 8.3, 1.7, 1H),

7.03 (dd, J = 2.2, 1.1, 1H), 3.71 (s, 2H), 3.68 (s, 3H), 3.63 (ttt, J = 9.3, 4.0, 1.2, 1H), 2.89 (pd, 1.2, 7.3, 1H), 2.44 (m, 2H), 2.29 (m, 2H), 2.17 (s, 6H); MS (FAB) *m/z* 310 (M + 1).

3-Methyl-5-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-ylmethyl]-1,2,4-triazole (20). To a solution of the amidine, prepared as above (3 g, 6.99 mmol) in 70% aqueous AcOH (100 mL), was added hydrazine hydrate (10.9 mL, 8.39 mmol). The mixture was stirred at 90 °C for 5 h. The mixture was concentrated under reduced pressure and diluted with water (100 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed using 1:10:89 NH_3:MeOH:$CHCl_3$ to give an oil, 200 mg. The product of this step was then treated by general methods A and B to provide the product **20** as a foam: ^{1}H NMR (DMSO-d_6) δ 13.12 (bs, 1H), 10.59 (bs, 1H), 7.31 (m, 1H), 7.23 (dd, J = 7.9, 05, 1H), 7.15 (dd, J = 2.0, 0.7, 1H), 6.96 (dd, J = 8.2, 1.6, 1H), 3.97 (m, 2H), 3.49 (ttt, J = 9.0, 4.6, 1.0, 1H), 2.82 (pd, J = 1.0, 7.2, 1H), 2.30 (m, 2H), 2.17 (m, 2H), 2.07 (s, 6H); MS (FAB) 310 (M + 1). Anal. ($C_{18}H_{23}N_5 \cdot 1.0H_2O$) C, H, N.

3-Methyl-5-[3-(*trans*-3-dimethylaminocyclobutyl)-1*H*-indol-5-yl]-1,2,4-oxadiazole (19). The primary amide **14**, was treated as for **38** above to give **19** as a foam. The product of this step was then treated by the general methods A and B above to provide **19** as a foam: ^{1}H NMR (DMSO-d_6) δ 11.26 (bs, 1H), 8.20 (dd, J = 1.5, 0.5, 1H), 7.79 (dd, J = 8.4, 1.6, 1H), 7.53 (dd, J = 8.5, 0.5, 1H), 7.39 (dd, J = 2.2, 1.2, 1H), 3.61 (ttt, J = 9.3, 4.3, 0.9, 1H), 2.87 (pd, J = 0.9, 8.0, 1H), 2.39 (s, 3H), 2.38 (m, 2H), 2.22 (m, 2H), 2.10 (s, 6H); MS (EI) *m/z* 296, 252, 225, 170. Anal. ($C_{17}H_{20}N_4O \cdot 0.57H_2O \cdot 0.04C_4H_8O_2$) C, H, N. ^{1}H NMR ($CDCl_3$) δ 7.97 (bs, 1H), 7.42 (dt, J = 1.6, 0.7, 1H), 7.28 (dd, J = 8.3, 0.7, 1H), 7.11 (dd, J = 8.3, 1.7, 1H), 7.03 (dd, J = 2.2, 1.1, 1H), 3.71 (s, 2H), 3.68 (s, 3H), 3.63 (ttt, J = 9.3, 4.0, 1.2, 1H), 2.89 (pd, 1.2, 7.3, 1H), 2.44 (m, 2H), 2.29 (m, 2H), 2.17 (s, 6H); MS (FAB) *m/z* 310 (M + 1).

Biological Assays. Compound binding in CHO-K1 cells stably transfected with human recombinant $5HT_{1B}$, $5HT_{1D}$, $5HT_{1A}$ and $5HT_{1F}$ receptors and also the $5HT_{2C}$ receptor in guinea pig cortex was performed as described by Martin.[28] Rabbit saphenous vein functional assays and the $5HT_{2A}$ assays in rabbit aorta were as detailed by Martin.[29]

Protocol for Binding Assay Using Calf Caudate Membranes. Membranes were prepared from homogenates of calf caudate nucleus. Competition binding studies were performed with 3.5 nM [^{3}H]5HT (ca. 25 Ci/mL) in the presence of 15 μM mesulergine and 15 μM 8-OH-DPAT, using 5 mg wet weight/mL of membranes in a total volume of 1 mL/tube. Binding data was fitted to a four-parameter logistic function to obtain estimates of pIC_{50}. These were converted to pK_i values using the Cheng−Prussof equation.

Protocols for in Vivo Studies. 1. Surgical Preparation. Male Dunkin Hartley guinea pigs (200−250 g; David Hall Supplies) were housed under diurnal lighting conditions and allowed food and water ad libitum. Each animal was anesthetized using pentabarbitone (50 mg/kg ip) and the rectal temperature was maintained at 37 °C with a homeothermic blanket control unit (Harvard model 50-7061, Harvard Apparatus Ltd.). The trachea was cannulated and the animals were artificially ventilated with room air throughout the experiment using a mechanical respirator (Harvard model 50-1718, Harvard Apparatus Ltd.). A tidal volume of 10 mL/kg and a frequency of 80 breaths/min was used. A 2FG polythene cannula (Portex Ltd.) was inserted into the right external jugular vein. In the animals used for flow studies a 3FG polythene cannula (Portex Ltd.) was inserted into the right carotid artery to monitor blood pressure via a Statham P23 pressure transducer attached to a model 7D Polygraph (Grass Instruments).

2. Electrical Trigeminal Ganglion Stimulation and Plasma Protein Extravasation Measurement. Animals were placed in a stereotaxic frame (model 900, Kopf Instruments, Tujunga, CA), with the incisor bar set at −4 mm from the horizontal, and the skull exposed by a midline incision. Symmetrical burr holes (1−2 mm diameter) were drilled 3.2 mm laterally and 2.0 mm posteriorly to bregma for electrode placement. Each animal then received a single bolus dose of **1** (0.01, 0.03 or 0.1 μg/kg) or vehicle (0.9% w/v saline) via the right jugular vein and, after 5 min, 50 μCi/kg [^{125}I]bovine serum albumin (BSA) (50 μCi/mL saline) was administered via the same cannula. Subsequently, paired nonconcentric bipolar electrodes (Rhodes NE-200, Clark Electromedical Instruments, U.K.) were lowered into the trigeminal ganglia, under stereotactic control, to a depth of 10.5 mm from the dura mater. The left or right side was arbitrarily designated for stimulation. Five minutes after the administration of [^{125}I]BSA the test side was electrically stimulated consecutively for a further 5 min using paired rectangular pulses of opposite polarity with 5 pulses/s of 5-ms duration at an intensity of 1.2 mA (Stimulator, model S88; Stimulus Isolation Unit, model SIU5A; Constant Current Unit, model CCU1A; Grass Instruments). Ipsilateral contraction of the muscles of mastication during stimulation was assumed to indicate correct placement of the electrodes. Immediately following the stimulation period the thorax was opened, the descending aorta clamped and the right atrium incised for drainage. Saline was perfused via the left ventricle at a pressure of 100 mm Hg for 3 min in order to flush all blood from the intravascular compartment. The skull was removed and the dura mater both overlying and underlying the brain was carefully dissected from both the stimulated and nonstimulated sides. The large dural sinuses, the region of dura through which the electrodes penetrated and the dura covering the trigeminal ganglia were excluded from analysis. In some experiments a mantle of frontoparietal cortex from each side of the brain was also dissected. After rinsing in saline, the samples were dried on tissue paper, weighed and counted for [^{125}I] for 20 min in a Wallac Gamma Counter (Wizard 1470, Wallac). Extravasation of [^{125}I]albumin into the dura was calculated as cpm/mg wet weight for both the stimulated and the unstimulated sides from each animal and the data (mean ± SEM) are expressed as the ratio between each side.

At least one animal was treated with vehicle (0.9% w/v saline) on each day of experimentation to control for variability in albumin leakage noted in the perfused tissues from week to week.

3. Ear Blood Flow/Conductance Measurement. In a separate group of guinea pigs the effect of **1** on vascular conductance in the ear was determined. Animals were anesthetized and surgically prepared as described above. Blood flow was continuously measured in the right ear using a single laser Doppler flow probe attached to an MBF3 laser Doppler blood flow monitor (Moor Instruments, U.K.). The flow probe and flow monitor were set to operate at a frequency of 10 Hz and a time constant of 1 s. Data were output to an IBM PC and displayed and analyzed using Moorsoft 4.1 software. Blood flow was recorded as red blood cell flux (the product of mean velocity and concentration of moving red blood cells) determined as a percentage of a standardized signal obtained in a particulate control medium. Effects on vascular conductance were calculated by dividing blood flow by blood pressure changes in each animal studied. Both measurements were made at the time that maximum changes in flow were observed.

Supporting Information Available: Complete NMR assignments for the target compounds; table of combustion analyses; and data used to construct the pharmacokinetic absorption model, i.e., the tryptamine structures, calculated log *D* values, and measured plasma levels. This information is available free of charge via the Internet at http://pubs.acs.org.

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