Computer-Aided Design and Synthesis of 5-Substituted Tryptamines and Their Pharmacology at the 5-HT_{1D} Receptor: Discovery of Compounds with Potential Anti-Migraine Properties

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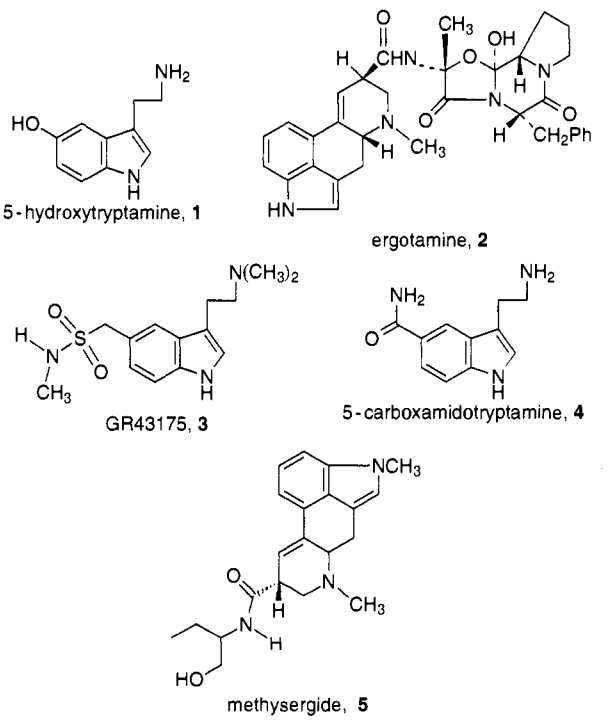
Received March 30, 1995®

The design and synthesis of a series of novel 5-substituted tryptamines with pharmacological activity at 5-HT_{1D} and other monoamine receptors is described. Structural modifications of N- and C-linked (principally hydantoin) analogues at the 5-position were synthesized and their pharmacological activities were utilized to deduce significant steric and electrostatic requirements of the 5-HT_{1D} and 5-HT_{2A} receptor subtypes. Conformations of the active molecules were computed which, when overlaid, suggested a pharmacophore hypothesis which was consistent with the affinity and selectivity measured at 5-HT_{1D} and 5-HT_{2A} receptors. This pharmacophore is composed of a protonated amine site, an aromatic site, a hydrophobic pocket, and two hydrogen-bonding sites. A "selectivity site" was also identified which, if occupied, induced selectivity for 5-HT_{1D} over 5-HT_{2A} in this series of molecules. The development and use of the pharmacophore models in compound design is described. In addition, the physicochemical constraints of molecular size and hydrophobicity required for efficient oral absorption are discussed. Utilizing the pharmacophore model in conjunction with the physicochemical constraints of molecular size and log $D_{pH7.4}$ led to the discovery of 311C90 (**6**), a new selective 5-HT_{1D} agonist with good oral absorption and potential use in the treatment of migraine.

Introduction

The precise mechanisms underlying the cause of migraine are unclear, and both vascular[1] and neurogenic theories[2,3] have been described to account for the pathophysiology of migraine. There is evidence to implicate the vaso-active hormone serotonin (5-hydroxytryptamine, **1**, 5-HT, (Chart 1) in this disorder,[4,5] and a number of drugs useful in the treatment of migraine have long been recognized to elicit constriction of cranial blood vessels and a redistribution of blood flow in the cranial circulation of animals. Serotonin receptors display a wide range of subtypes.[6-11] Recent evidence implicates 5-HT_1-like receptors which have emerged as important therapeutic targets for the treatment of migraine.[12,13] Clinical studies in migraineurs suggest that 5-HT_{1D} agonists constrict the large cerebral arteries both during and between attacks, resulting in an increased flow in these vessels.[14,15] Diverse series of molecules show pharmacological effects at these and related receptors, and indeed, some are used for the treatment or prophylaxis of migraine. Unfortunately, many of these active molecules, e.g., the ergot alkaloids, show undesirable side effects due to their poor pharmacological selectivity.[16] Ergotamine (**2**), a potent vasoconstrictor, has been in clinical use for many years, and its use in migraine treatment is limited by variable efficacy and a number of adverse reactions including vomiting, nausea, and peripheral vasoconstriction.[17] Recent interest in the search for novel therapeutic agents for migraine has increased[18,19] due to the demonstrated clinical efficacy and reduced side-effect profile

Chart 1



of selective 5-HT_{1D} agonists such as sumatriptan (GR43175)[17,20] (**3**).

We have followed a program of research aimed at developing highly selective 5-HT_{1D} agonists with the objectives of obtaining novel compounds with excellent potency, high oral bioavailability, a plasma half-life of greater than 2 h, and low central nervous system penetration.

It is evident that affinity for 5-HT_{1D} receptors may be obtained by utilizing the ethylamine and indole

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® Abstract published in *Advance ACS Abstracts*, July 15, 1995.

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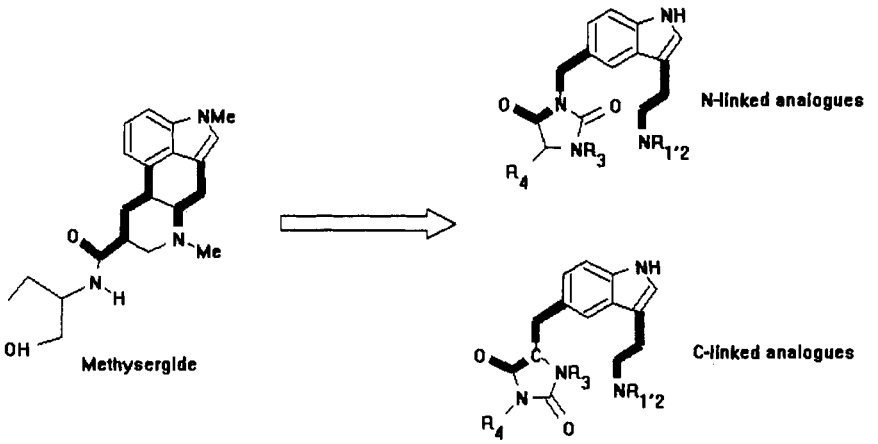
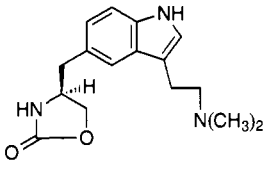


Figure 1. Rationale in the design of C- and N-linked hydantoin analogues. The indole and those regions of structure highlighted were presumed important for affinity and efficacy at 5-HT_{1D}.

Chart 2. (*S*)-4-[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone (**6**)



6

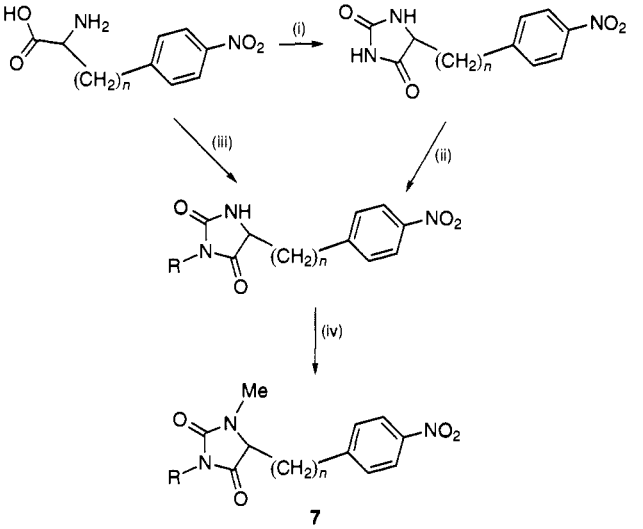
groups (tryptamine (**56**) p[A_{50}] 5-HT_{1D} = 6.85). The addition of the 5-hydroxy group gives 5-HT itself (which has increased affinity (p[A_{50}] 5-HT_{1D} = 8.0)), and replacement of the hydroxy group by an amido group (5-carboxamidotryptamine, 4, p[A_{50}] 5-HT_{1D} = 8.1) results in similar affinity. It seemed probable that maintenance of the ethylamine, indole, and the hydrogen-bond acceptor qualities of substituents in the 5-position should conserve affinity.

Thus, starting from known ligands such as 5-carboxamidotryptamine (4) and methysergide (**5**), a series of model systems was constructed in order to probe 5-HT receptors.

These analogues include the indole heterocycle and substituted ethylamine side chain (preserving the amine which would be protonated at physiological pH) with the introduction at the indole 5-position of novel structural features exemplified by a series of C-linked and N-linked heterocycles. In Figure 1, highlighted regions imply similarities between the predisposition of functional groups in methysergide, 5-carboxamidotryptamine (principally the carbonyl and ethylamine), and the novel series, indicating the rationale for their design. These receptor probes were intended to allow access to synthetic modifications with the particular aim of expanding our knowledge of the electronic and structural factors necessary for affinity and selectivity at 5-HT receptors. In particular, it was hoped that a pharmacophore model of the active site could be deduced which would aid in the design of analogues with molecular properties tailored to the clinical requirements.

We report here the development of a series of novel 5-HT_{1D} selective agonists, their synthesis, and pharmacological profile and describe the structure–activity relationships which led to the discovery of (*S*)-4-((3-(2-(dimethylamino)ethyl)-1*H*-indol-5-yl)methyl)-2-oxazolidinone (**6**, Chart 2), a new compound which satisfies our original objectives and which has potential uses in the treatment of migraine.

Scheme 1. Synthesis of C-Linked Imidazolidine-2,5-dione Intermediates[a]



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[a] Reagents: (i) KNCO/H_2O; (ii) R″X/K_2CO_3/DMF; (iii) RNCO/KOH/H_2O; (iv) K_2CO_3/ MeI.

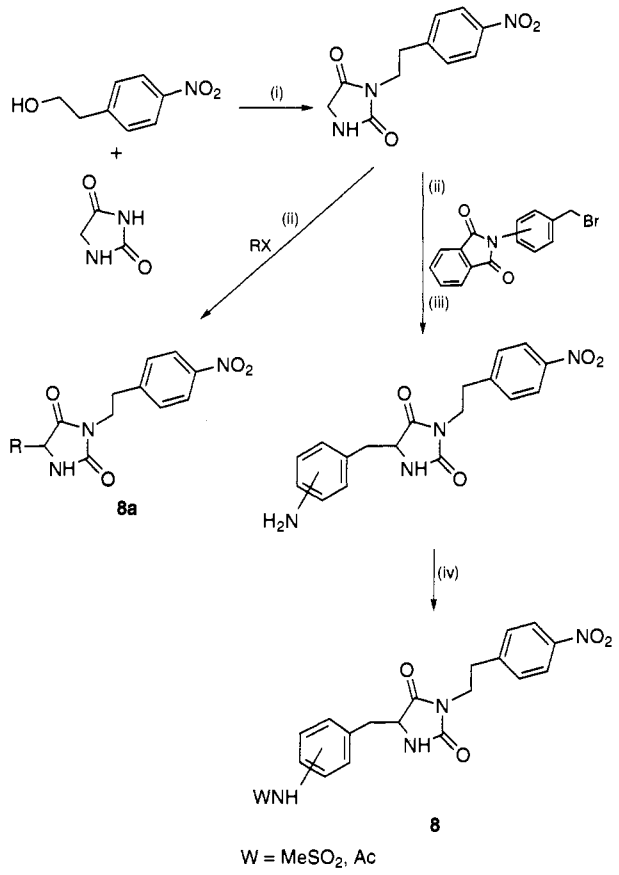
Results and Discussion

Chemistry. The Fischer indole synthesis was employed for all the analogues. In general, applications of standard methods were used for the syntheses of the C-linked (**7**) and N-linked (**8**, **8a**) imidazolidinedione analogues (Schemes 1 and 2). The substituted nitrophenols (**9**) were converted into the ethylamines (**10**) by the general sequence shown in Scheme 3, *via* reduction to the aniline, conversion to the hydrazine, and finally Fischer reaction utilizing 4-chlorobutanal diethyl acetal. Mono- (**11**) or dimethylation (**12**) was effected by the judicious use of sodium cyanoborohydride reductions and protection strategies.

The synthesis of the imidazolidinones (**13**, Scheme 4) was more involved and required laborious reduction methodology utilizing several equivalents of sodium borohydride in order to effect the initial reduction of the imidazolidinedione.

The synthesis of **6** utilized well-established methodology for production of the oxazolidinone moiety[56] from 4-nitro-L-phenylalanine (**14**) (Scheme 5). Conversion of the nitro compound **15** was achieved without incident to furnish the desired product. The *R*-enantiomer was synthesized in the same fashion using 4-nitro-D-phenylalanine.

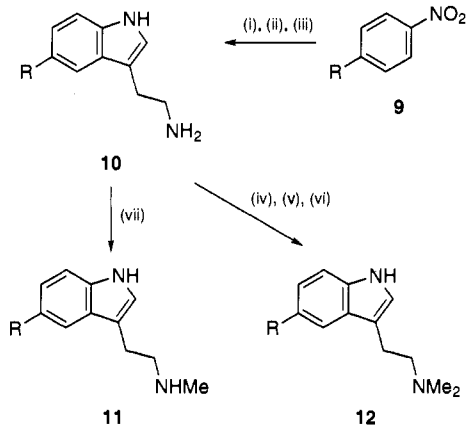
Scheme 2. Synthesis of N-Linked Imidazolidine-2,5-dione Analogues[a]



W = $MeSO_2$, Ac

[a] Reagents: (i) DEAD/PPh_3; (ii) $MeMgCO_3$/DMF; (iii) H_2NNH_2/EtOH, (iv) Ac_2O or $MeSO_2Cl$/pyridine.

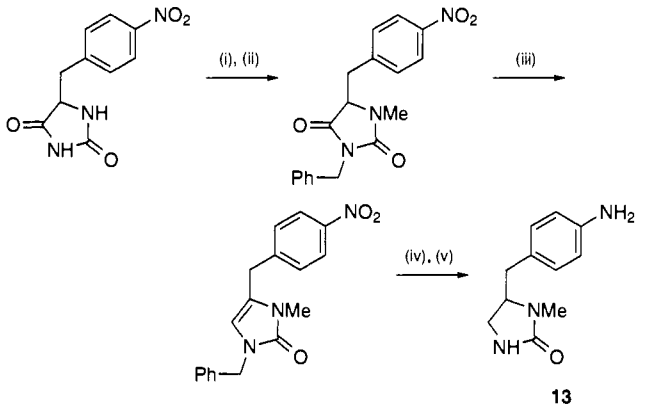
Scheme 3. General Route to 5-Substituted Indole Analogues[a]



[a] Reagents: (i) H_2/Pd/C; (ii) $NaNO_2/SnCl_2$/HCl; (iii) $Cl(CH_2)_3CH(OEt)_2$/EtOH, (iv) PhCHO/$NaCNBH_3$, (v) Me_2SO_4/K_2CO_3; (vi) H_2/Pd/C; (vii) $NaCNBH_3$/HCHO.

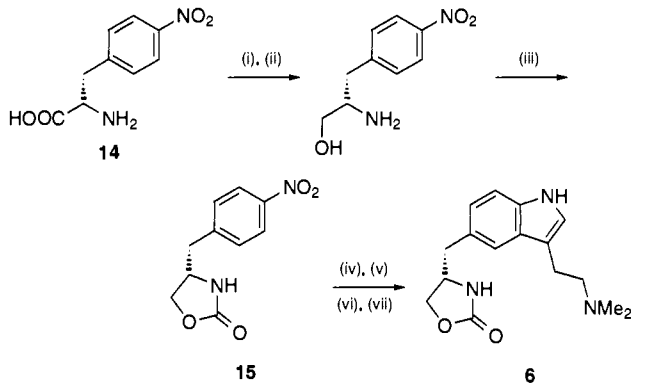
Pharmacology. The receptor activity of selected compounds was assessed using ring preparations of rabbit saphenous vein or rabbit aorta. In the former vessel, agonist contractions are mediated by a population of 5-HT_{1D}-like receptors, while in the latter, contractions are mediated by 5-HT_{2A} receptors. In both cases, agonist *potency* ($p[A_{50}]$) was estimated as the concentration of drug ($-\log_{10} M$) producing half of the maximum response. Agonist *intrinsic activity* (α) refers to the drug maximum effect expressed as a fraction of the maximum response obtained with 5-HT in the same tissue. Since, in these tissues, tryptamine agonists tend to behave as partial agonists, $p[A_{50}]$ is a reasonable approximation of the drug–receptor dissociation equilibrium constant.

Scheme 4. Synthesis of Imidazolidin-2-one Intermediates[a]



[a] Reagents: (i) NaH/$PhCH_2Br$/DMF; (ii) K_2CO_3/MeI/DMF; (iii) $NaBH_4$/AcOH; (iv) PtO_2/ H_2; (v) 45% aqueous HBr reflux.

Scheme 5. Synthesis of **6**[a]



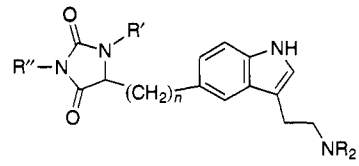
[a] Reagents: (i) $SOCl_2$/MeOH; (ii) $NaBH_4$/EtOH; (iii) $COCl_2$/KOH/H_2O; (iv) H_2/Pd/C; (v) $NaNO_2$/cHCl/$SnCl_2$; (vi) $Cl(CH_2)_3CHOMe_2$/EtOH/H_2O; (vii) $NaCNBH_3$/HCHO.

Analysis of the Activity of Tryptamine Analogues for Vascular 5-HT_{1D} and 5-HT_{2A} Receptors. As an important step in establishing the factors involved in molecular recognition at 5-HT_{1D} receptors, we synthesized new molecules and utilized information from both conformational analysis and pharmacological data (Tables 1–4) to construct a pharmacophore hypothesis. This is desirable as the precise three-dimensional structure of 5-HT_{1D} receptors is at present unknown. It was hoped that the relative three-dimensional topology of analogues binding to the 5-HT_{1D} receptor could be deduced. This exercise could identify the relative positions of important binding groups and would thus enable the construction of novel analogues whose physicochemical properties could be varied while maintaining affinity for 5-HT_{1D}.

Ligand receptor interactions were measured as $p[A_{50}]$ and intrinsic activity (α) relative to 5-hydroxytryptamine which approximate affinity and relative efficacy, respectively.

The initial results on synthesizing N-linked hydantoins were very promising. In these compounds, the hydantoin substructure is linked to the indole *via* an ethylene group which affords some flexibility to the side chain. The simplest compounds, e.g., **45** ($p[A_{50}]$ 5-HT_{1D}

Table 1. Affinity and Intrinsic Efficacy at 5-HT_{1D} and Affinity at 5-HT_{2A} for Analogues C-Linked to the Indole



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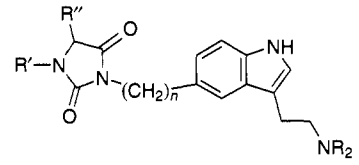
compd	R	R′	R″	X	*n*	5-HT_{1D} p[A_{50}]/α	5-HT_{2A} p[A_{50}]
16	H	H	CH_2Ph		2	6.7/0.9	<4.5
17	H	H	$(CH_2)_3Ph$		1	6.6/0.93	<4.5
18	H	H	CH_2Ph		1	6.1/0.72	4.0
19	H	H	$(CH_2)_2Ph$		1	6.7/0.67	4.5
20	Me	H	CH_2Ph-4-OPh		1	7.4/0.79	4.7
21	H	Me	CH_2Ph		1	6.0/1.0	<4.5
22	H	H	Me		1	4.8/–	4.00
23	H	H	CH_2Ph-3-OPh		1	7.4/0.79	4.7
24	H	H	CH_2Ph-3-NHCOPh		1	7.3/0.85	4.6
25	Me	H	CH_2Ph		2	6.3/0.20	5.9
26	Me	H	CH_2Ph-3-NHCOPh		1	6.3/0.55	5.0
27	H	H	CH_2Ph-3-CONHPh		1	6.6/0.53	3.9
28	H	H	CH_2Ph-3-CONHPr		1	6.8/0.99	4.5
29	H	H	CH_2Ph-4-NHAc		1	5.8/0.81	
30	H	H	CH_2Ph-3-CONHMe		1	5.8/0.71	4.3
31	Me	H	$(CH_2)_2Ph$		1	6.0/0.39	
32	H	H	CH_2Ph-4-CONHPh		1	5.9/0.7	4.5
33	H	H	CH_2Ph-4-Ph		1	6.7/0.6	
34	Me	H	CH_{2Ph}		1	5.6/-	<4.5
35	Me	Me		NH		7.0/1.0	<4.5
36	H	Me		NH		6.9/0.88	5.0
6	Me	H		O		6.8/0.77	6.6

Table 2. Affinity and Intrinsic Efficacy at 5-HT_{1D} and Affinity at 5-HT_{2A} for Analogues N-Linked to the Indole



compd	R	R′	R″	*n*	5-HT_{1D} p[A_{50}]/α	5-HT_{2A} p[A_{50}]
37	H	H	CH_2Ph-4-$NHSO_2Me$	2	7.4/0.8	5.2
38	H	H	CH_2Ph-4-COOMe	2	7.3/0.7	<4.5
39	H	H	CH_2Ph-3-$NHSO_2Me$	2	7.2/0.8	<4.5
40	H	H	(R)CH_2Ph-4-$NHSO_2Me$	2	7.1/0.7	5.3
41	H	H	CH_2Ph-3-NHAc	2	7.0/0.7	<4.5
42	Me	H	CH_2Ph-3-NHAc	2	7.2/0.6	<4.5
43	Me, H	H	CH_2Ph-3-NHAc	2	6.9/0.6	<4.5
44	Me	H	CH_2Ph-4-NO_2	2	6.8/0.6	<4.5
45	Me, H	H	H	2	6.7/0.7	<4.5
46	Me	H	(S)CH_2-Ph-4-$NHSO_2Me$	2	7.4/0.6	<4.5
47	Me	H	H	2	6.1/0.5	<4.5
48	Me	H	CH_2Ph-4-$NHSO_2Me$	2	7.4/0.6	<4.5

= 6.7, 5-HT_{2A} = <4.5) and **47** (p[A_{50}] 5-HT_{1D} = 6.1, 5-HT_{2A} = <4.5), having only the hydantoin substitution show good affinity for 5-HT_{1D}. These affinities are lower than 5-HT or 5-carboxamidotryptamine, but these compounds offer scope for chemical manipulation of other molecular properties, and importantly, unlike 5-HT itself, it is apparent from the affinity data that they are selective for 5-HT_{1D} over 5-HT_{2A}.

In the C-linked series, **22** showed low affinity (p[A_{50}] 5-HT_{1D} = 4.8); however, the introduction of a phenyl ring to give **21** showed increased affinity (p[A_{50}] 5-HT_{1D} = 6.0, 5-HT_{2A} = <4.5), possibly implying the presence of a hydrophobic receptor site. Again, selectivity is seen

Table 3. Affinity and Intrinsic Efficacy at 5-HT_{1D} and Affinity at 5-HT_{2A} of Nonselective (5-HT_{1D}) Analogues

compd	name	5-HT_{1D} p[A_{50}]/α	5-HT_{2A} p[A_{50}]
5	methysergide	6.70/0.64	8.3
49	spiroxatrine	5.1/–	6.2
50	spiperone	5.8/–	9.7
51	buspirone	4.5/–	6.1
52	ipsapirone	4.9/–	5.1
53	ketanserin	6.0/–	9.1
54	5-methyltryptamine	6.1/1.0	6.2

Table 4. Additional Analogues with Affinity at 5-HT_{1D}

compd	name	5-HT_{1D} p[A50]/α	5-HT_{2A} p[A_{50}]
55	RU24969	7.1/0.89	5.2
56	tryptamine	6.9/0.86	6.1
3	GR43175	6.6/0.83	6.2
4	5-carboxamidotryptamine	8.1/0.84	5.9
57	bufotenine	7.3/0.92	6.8
58	ergometrine	9.0/0.9	
59	see Chart 4	7.1/0.95	6.3
60	see Chart 4	7.5/–	5.0

for 5-HT_{1D} over 5-HT_{2A}. Omission of the *N*-methyl substituent on the hydantoin ring gave **18** (p[A_{50}] 5-HT_{1D} = 6.1, 5-HT_{2A} 4.0). The lower affinity of these C-linked analogues compared to their N-linked counterparts could be attributed to the different geometry of the exocyclic ring bond or the reduced flexibility of the methylene linker compared to the ethylene linker (compare **16** and **18**). This may suggest that the precise position and orientation of a hydrogen-bond acceptor group (here, a carbonyl in the hydantoin ring) relative to the rest of the molecule is important for affinity.

In deriving the relative positions of the functional groups in this series of molecules, several approaches are possible. These molecules (e.g., **47** and **18**) display torsional flexibility in both the ethylamine and the 5-substituent connecting groups. Molecular mechanics[22] using MOPAC-AM1-derived Mullikan charges[23] or semiempirical quantum mechanics calculations (MOPAC-AM1 geometry optimization[23]) in the gas phase gives the expected result. The energy-minimized conformation was found when the torsional angles about the protonated amine and hydantoin rotate to give a strong hydrogen-bond between the protonated amine and a carbonyl of the hydantoin. These calculations utilized a dielectric constant of $\epsilon = 1.0$ which may not be relevant to physiological conditions. When the dielectric is increased to $\epsilon = 78.5$ (in molecular mechanics calculations) which is the dielectric constant of water at 25 °C, the strength of this electrostatic interaction decreases. This can be simulated using molecular dynamics calculations. A 500 ps simulation (NTV ensemble, $T = 298$ °C, 1 fs steps,[24] using a dielectric of $\epsilon = 1.0$, MOPAC-AM1 derived Mullikan charges[23]) implies that the protonated nitrogen to carbonyl distance may be constrained by the electrostatic interaction to within hydrogen-bonding range 2.3–2.7 Å. With $\epsilon = 78.5$, the molecule adopts an extended conformation with the protonated nitrogen to carbonyl distance in the range 9–13 Å.

A search for phenylhydantoin analogues (a model for the indole hydantoin conformational preferences) in the Cambridge Crystallographic Database (CSDS)[25] based on the substructural fragments in Chart 3 retrieved a number of structures (Table 5).

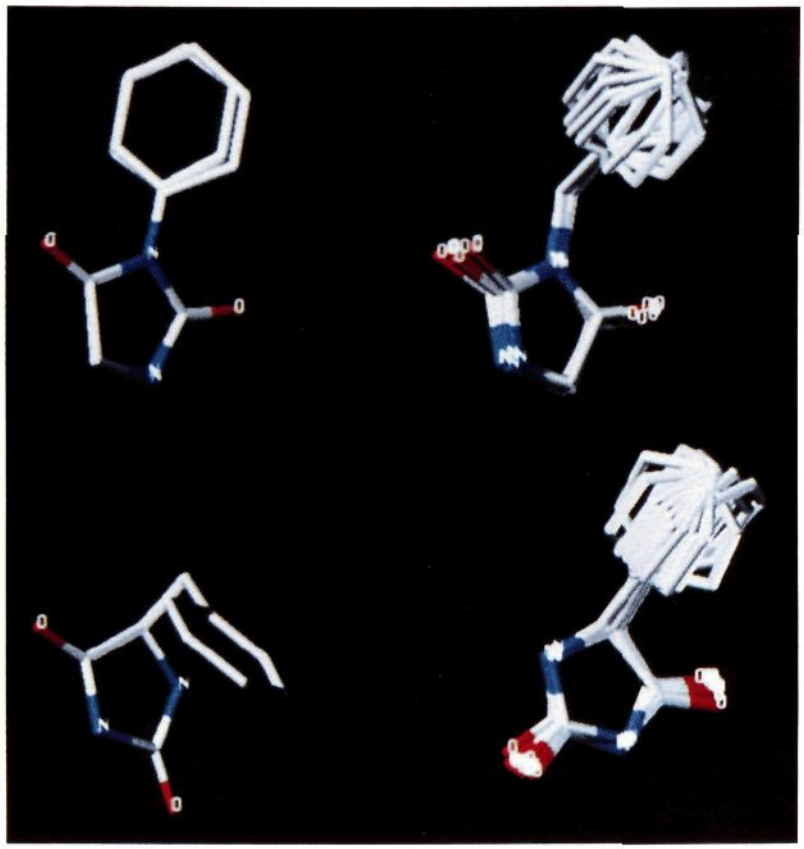
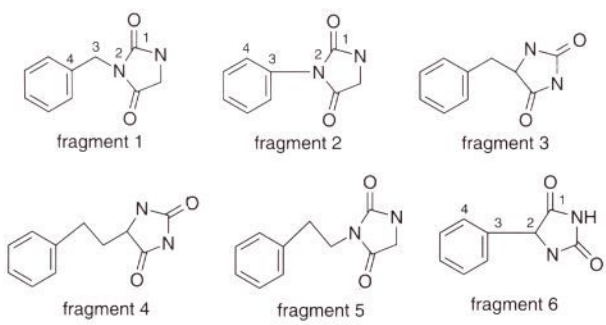


Figure 2. Conformations of the fragments retrieved from the Cambridge Structural Database. These are overlaid to show the relative conformational flexibilities of each structural type.

Chart 3. Substructures Searched for in the Cambridge Crystallographic Database



There are six different connecting motifs between the phenyl and hydantoin substructures in this set. The connecting group may be N- or C-linked and contain up to two linking atoms. Structures were retrieved for fragments 1−3 and 6. Fragments retrieved for fragment 4 were constrained by additional ring systems and were therefore not representative of available conformers. No examples of fragment 5 were found.

There are reports of a weak nonbonded interaction between a suitably oriented phenyl hydrogen and the electron-rich hydantoin ring system[26,27] which would imply preferential conformations between the phenyl and hydantoin fragments. Also, preferential conformations could be favorable due to an aromatic ring−amide dipole interaction. An overlay of the retrieved substructures for each fragment type are shown in Figure 2.

The N-linked benzyl fragments (fragment 1) show a clear preference for the torsional angle (1−2−3−4) to be ca. 90°. In fragment 2 which is *N*-phenyl linked, the preferred torsional angle (1−2−3−4) is ca. 55°. There is only one example of fragment 3 (so it is not safe to assume this is a preferred conformer), and this one has the plane of the phenyl ring parallel to the plane of the hydantoin ring. In fragment 6, the preferred torsional angle (1−2−3−4) is ca. 90°. Therefore, there appears to be some preference for the plane of the phenyl ring to lie at right angles to the plane of the hydantoin ring (which minimises steric strain) with fairly free rotation of the phenyl ring itself.

Table 5. Fragments Retrieved from the CSDS Designated by their six-letter code

Fragment1	DECZUG,[50] DEFFID,[51] DUDFAJ,[52] FAHXIV,[53] FUHNEB,[54] JOPVAL,[55] VIPGAC,[56] VIPHOR[57]
Fragment2	OXAZLB,[58] SAGCEI[59]
Fragment3	BAGXOW,[60] FUHNEB[61]
Fragment4	CEMBAX,[62] JUHGOI[63]
Fragment5	none
Fragment6	DAFFIZ01,[52] DPHEAD20,[64] DPHPZL,[65] DUDFAJ,[56] FUHNEB,[61] JOPPAF,[66] LABTIR,[67] MTHOIN01,[68] PHYDAN,[69] SAGCEI,[59] VAPZUH,[70] VARBAR[70]

[a] The six-letter code uniquely identifies the structure in the CSDS.

In an effort to gain some insight into the conformational freedom of these molecules in solution, nuclear magnetic resonance (*NMR*) analysis (*360MHz*) of the free base of **34** in $CDCl_3$ at variable temperature was performed. The ^1H NMR was broadened with a decrease in temperature over the range from 303 to 200 K. If the molecule was in one conformation, no broadening of signal would be observed. If conformations occupied had high enough barriers to prevent interconversion, signal broadening would have been followed by signal splitting and narrowing. The results suggested that over this temperature range the molecule exists

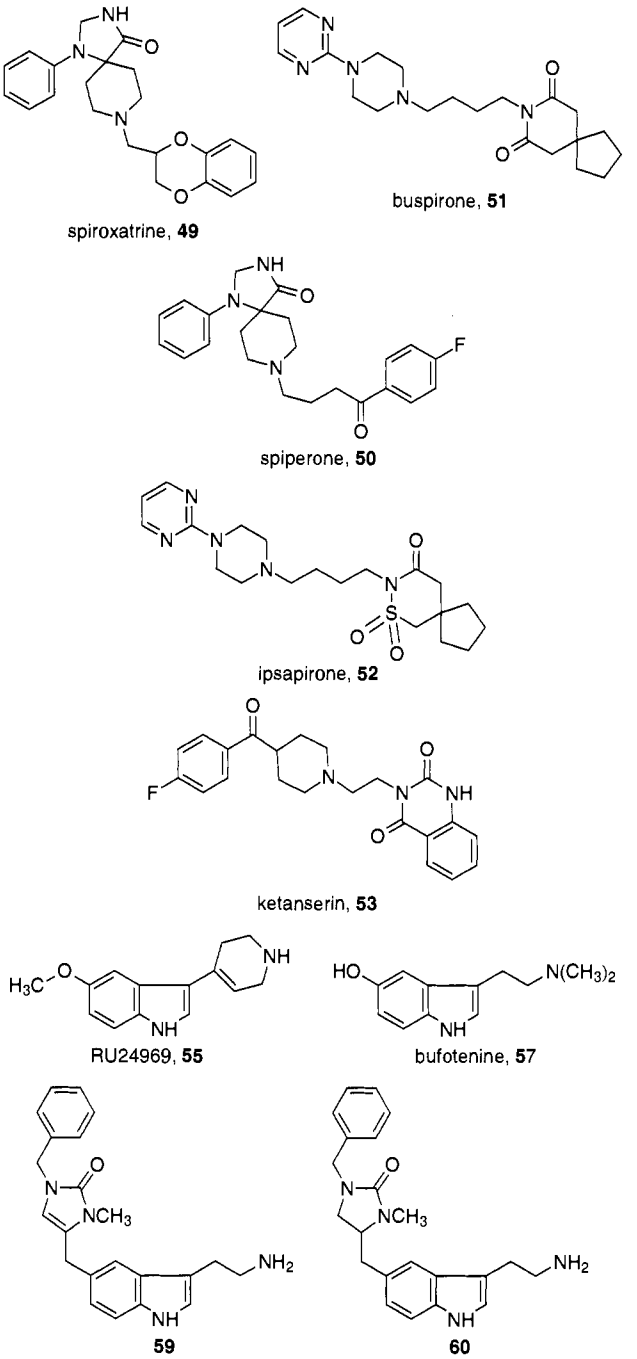
as a complex mixture of conformations with low-energy barriers to interconversion.

From these data, it was deduced that the flexibility of these molecules was such that the receptor could significantly alter their conformational preferences in the process of binding. Therefore, it was unlikely that the receptor-bound conformation (the conformations which would be most relevant when assessing compound affinity) would be obtained from such analyses in solution, in the crystal form, or by conformational energy calculations in the gas or solution phase. In the absence of the structure of the receptor or consistent experimental conformational data, the active analogue approach was adopted.[28] In this approach, constrained analogues are used to deduce the relative positions of important functional groups. The interfunctional group distances are computed and used to limit the available conformational space of more flexible molecules using a Venn diagram approach. The goal is to obtain an overlay of a series of diverse molecules with consistent orientations and conformations which satisfies the calculated distance ranges. If there is sufficient conformational constraint, then only one set of tight distance ranges will satisfy all the molecules (of good affinity) examined.

The flexibility of the ethylamine group, common to these new series, means that a large number of possible conformations and hence orientations of the protonated amine relative to the indole ring are possible. It was decided to assume a compromise conformation for the ethylamine between the ring-constrained conformations displayed by two active compounds, methysergide (**5**) and RU24969[29] (**55**) (Chart 4). This corresponds to an extended conformation[17,30] with the side chain approximately following the ethylamine portion of methysergide. The ethylamine position and conformation was obtained by constrained minimization[24] of the ethylamine and indole portions of methysergide, RU24969, and 5-HT. The indole nitrogen, phenyl ring centroid, and (protonated) amine nitrogen positions were assigned a constraint weight of 100 kcal/mol/Å^2 and used to overlay these portions of the molecules. The ethylamine conformation obtained for 5-HT was applied to the other ethylamine analogues (Figure 3).

Recent analyses using other rigid analogues have suggested an alternative extended conformation[31] for the ethylamine. There is, however, no definitive conformation which accommodates all the structural types with affinity at 5-HT$_{1D}$. To allow for this (since different structural types with different ethylamine conformations and indole to protonated amine distances bind and elicit agonism), some relative movement of molecules in the receptor must be allowed. In fact, it seems reasonable that a number of alternative conformations can coexist at the receptor particularly if the ligands are conformationally flexible and have the ability to bind in different modes. This is problematic in analysing the comparative binding of different structural types since "exact" fits overlaying functional groups are not possible. Limited conformational flexibility and multiple binding behavior of this type has been recognized for some time[32] and is much more common than is perhaps recognized.[32-38] Here, since the protonated amine probably interacts with an aspartic acid (ASP-118 in the human 5-HT$_{1D}$ sequence,[39] which is possibly equivalent to ASP-116 in the 5-HT$_{1A}$ receptor sequence[40,41]), there

Chart 4



is probably a range of interacting geometries allowed due to flexibility of the aspartic acid side chain, selection of the precise hydrogen-bonding interaction geometry with either of the carboxylic acid oxygens (or both), and flexibility of both the receptor and the ligand. This adds greatly to the complexity of the problem and explains the adopted compromise side chain conformation for the ethylamine. In fitting molecules together, those functional groups believed to contribute to affinity were fitted using a least squares procedure.[24] In the case of the novel C-linked and N-linked molecules, this would correspond to the protonated amine, a hydrogen-bond acceptor in the 5-substituent, and the centroid of the phenyl ring of the indole. The indole ring (or aromatic ring if no indole fragment is present) is maintained in a coplanar conformation with indole rings in the other molecules compared.

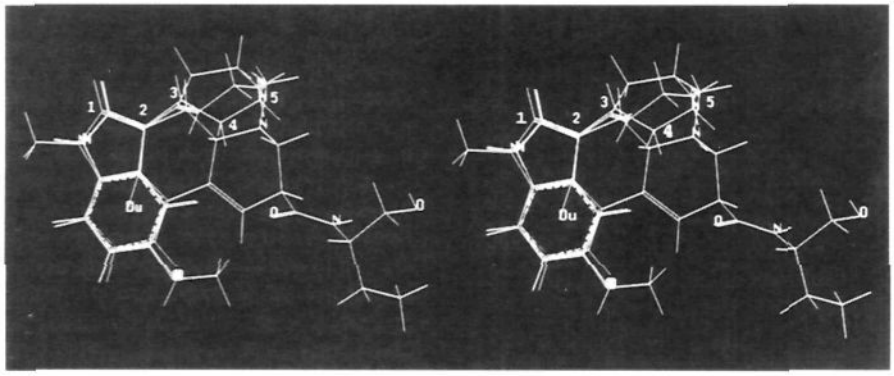


Figure 3. An overlay of 5-HT, methysergide, and RU24969 showing the ethylamine side-chain conformation adopted in subsequent conformational analyses. Torsional angle (1−2−3−4) = 175°, (2−3−4−5) = 172°.

Table 6. Distance Ranges (Å) Computed for Conformationally Restricted Methysergide, **18**, and **21** Using Systematic Search[a]

compd	name	C1−N4	C1−O	N4−O
5	methysergide	5.2	5.8−7.2	4.2−4.7
18		4.3−6.5	4.6−7.3u	3.0−12.7u
			3.6−5.9a	3.3−11.3a
21		4.3−6.5	5.1−7.1u	2.9−11.9u
			3.5−5.8a	4.2−10.1a

[a] a = hydantoin amide carbonyl, u = hydantoin urea carbonyl, C1 = centroid of the indole phenyl ring, N4 = protonated amine nitrogen, O = carbonyl oxygen (10° increments, amide bonds set to trans, van der Waals scale factors: general, 0.95; 1−4, 0.87; H-bonding, 0.65).

Systematic search[28] was used to deduce the available distance ranges between functional groups. Only those conformations which did not include van der Waals interactions were allowed. Methysergide (p[A_{50}] 5-HT_1 = 6.7), an analogue with only limited conformational freedom, was used to generate the initial set of constraints. These were between the centroid of the phenyl portion of the indole, the carbonyl oxygen, and the protonated amine. Methysergide was geometry optimized using molecular mechanics[22] prior to calculation. The computed ranges are in Table 6. The additional degree of freedom in this molecule, a small degree of ring puckering, does not effect the distance ranges calculated.

Inspection of the distance ranges in Table 6 shows that the relative position of the carbonyl functional group in methysergide has only limited movement relative to the indole and protonated amine (using the assumed ethylamine conformer). Since the hydantoin analogues have two different putative hydrogen-bonding carbonyl groups (a urea carbonyl and an amide carbonyl), it was desirable to deduce which was the more likely hydrogen-bond acceptor. Comparison with **18** (*S*-enantiomer) a C-linked analogue showed that the C1−Ou (Ou is the urea oxygen) distance range overlapped that found in methysergide while the C1−Oa (Oa is the amide oxygen) distance range barely fitted. To further constrict this series, the N-methylated analogue **21** was synthesized and was found to maintain affinity. This reduced the conformational flexibility of the hydantoin linking groups and is therefore a useful tool in understanding the recognition of the putative hydrogen-bond acceptor by the receptor. In this case, the amide oxygen is just outside the distance range while the urea oxygen fits. This implies that the urea oxygen of the hydantoin and the carbonyl of methysergide may have a receptor interaction in common. Using these distance constraints applied to methysergide and **21** (a distance map[28]), a single cluster of common conformations was defined with the protonated amine, the indole, and the carbonyl lone-pair appearing to interact with their respective common regions of the receptor. The *S*-enantiomer of **21** fits best as the carbonyl oxygen lone pair appear parallel to those of the methysergide carbonyl lone pair. The active N-linked analogues also fit into this common orientation and conformation. This procedure helps to quantify the distance ranges between important affinity regions of the receptor; however, the precise fit of molecules to these distance constraints is often ambiguous and is subjective, e.g., in racemic mixtures (as is **18**), each enantiomer fits in a slightly different way. It is likely that their degree of fit correlates with affinity and this is discussed later.

The conformation of the rest of the methysergide side chain and the phenyl substituents in **18** and **21** had still to be deduced. Ramachandran maps about the methylene linker between the hydantoin and the attached phenyl group and of the methysergide side chain indicated a number of accessible conformations; however, based solely on this information, one specific conformer could not be deduced. It was decided to synthesize a set of analogues containing additional hydrogen-bonding groups to probe the receptor in this region.

Three analogues were initially useful: **32** (p[A_{50}] 5-HT_1 = 5.9), **24** (p[A_{50}] 5-HT_1 = 7.3), and **23** (p[A_{50}] 5-HT_1 = 7.4). There is one lower affinity analogue and two of higher affinity. It was suspected that the two compounds of higher affinity may be utilizing an additional hydrogen-bonding site, as could the hydroxy group of methysergide. These analogues have the additional substitution of a hydrogen-bonding group (an amide or ether) and a phenyl group.

Systematic search was performed on this set by constraining those regions of the structure (the ethylamine, indole, and hydantoin) to overlay the conformation found for **21** (Table 7).

The indole, ethylamine, and hydrogen-bonding carbonyl of methysergide were frozen in the previous conformation. The additional single bonds were allowed to rotate (with the exception of the amide bonds which were set to the *trans* conformation). Two distance ranges were measured: the protonated amine to the hydroxy oxygen and the carbonyl oxygen to the hydroxy oxygen (see Table 7). The distance ranges calculated for methysergide were then used to constrain the

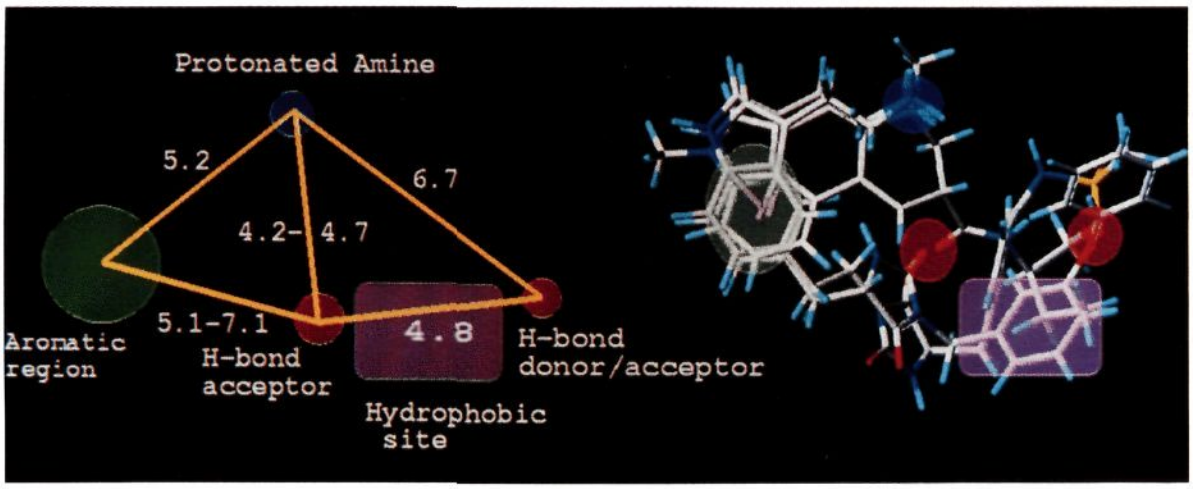


Figure 4. C-Linked and an N-linked analogues (**23** and **37**) overlaid on the pharmacophore model.

Table 7. Distance Ranges from a Systematic Search on the Second Hydrogen-Bonding Group[a]

compd	name	N4···O3	O2···O3
5	methysergide	5.4–8.2	2.6–5.3
23		6.3–8.1	4.8–5.3
24		6.7	4.8
32		6.4–14.1	5.4–8.9

[a] 10° increments, amide bonds set to trans, van der Waals scale factors: general, 0.95; 1–4, 0.87; H-bonding, 0.65).

systematic search on **23**. From the calculated distance ranges, it appears that the ether oxygen occupies a subset of these distance ranges, which narrows down the common volume occupied by the oxygens. This smaller distance range was similarly applied to **24** to determine the position of the amide carbonyl oxygen. There was one family of conformers which overlaid the oxygens as well as satisfying the distance ranges. This occurred at the distances given for **24** in Table 7.

Systematic search about the putative hydrogen-bonding oxygen in **32** (a low-affinity analogue) indicates it cannot approach within 0.8 Å of this site without incurring van der Waals interactions, which is consistent with the lowered activity. These results may imply the existence of a hydrogen-bonding group in this vicinity; however, in the absence of a larger set of restricted analogues of known affinity, this could not be determined accurately.

This exercise resulted in a pharmacophore model which appeared to define the relative positions of groups important for affinity and provided a "scaffold" on which to fit diverse series of molecules. An efficient way to fit new analogues to the model involved an initial screen of the conformational space, using the defined distance constraints (systematic search), followed by constrained minimization (again using the same pharmacophore points) followed by relaxation of the structure for 20 simplex cycles of molecular mechanics.[28] The principal regions responsible for affinity are overlaid in Figure 4 using a C-linked analogue (**23**), an N-linked analogue (**37**), and methysergide.

This model is, of course, qualitative; however, it is relatively simple using molecular graphics to gauge the "fit" of novel analogues to the principle receptor sites. Indeed, all the analogues reported in Tables 1–4 may be successfully fitted to the pharmacophore. A quantitative model has also been developed and will be reported elsewhere.

The true three-dimensional topology of the interactions proposed with the 5-HT_{1D} receptor is presently conjectural, and the precise geometry of the model so far determined may be refined as more conformationally restricted analogues appear. The pharmacophore is "real" only insofar as it is useful and predictive.

Selectivity for 5-HT_{1D} over 5-HT_{2A} Receptors. 5-HT_{1D} receptors have a high density in the cranial circulation, the current target region for an anti-migraine drug, while 5-HT_{2A} receptors are distributed throughout the vasculature. Unfortunately, agonists with affinity at 5-HT_{2A} induce undesirable vasoconstrictor effects causing changes in blood pressure. It was therefore desirable to understand how to eliminate 5-HT_{2A} effects while maintaining high affinity and efficacy at 5-HT_{1D}.

The C-linked and N-linked series of hydantoin analogues show selectivity for 5-HT_{1D} over 5-HT_{2A} (e.g., **18** (p[A_{50}] 5-HT_{1D} = 6.1, p[A_{50}] 5-HT_{2A} = <4.0). We hypothesized that this specificity is probably the result of an interaction these compounds have with one of the 5-HT receptor subclasses not seen in less specific analogues. The simplest way to determine the major structural differences between selective and nonselective analogues is to fit a series of compounds (some selective, some nonselective) to the pharmacophore model for affinity and look for differences in occupied volume. To do this, a series of structurally diverse analogues was selected which displayed affinity for both 5-HT_{1D} and 5-HT_{2A}. That such diverse molecules can be accommodated by the pharmacophore model indicates its general applicability to different structural classes of 5-HT_{1D} ligands.

The compounds in Table 3 were overlaid by fitting a phenyl group, a protonated amine and hydrogen-bond acceptors to the model. These included a selective representative of the new C-linked (**18**) hydantoin series. The volume occupied by the nonselective analogues was computed and subtracted from the volume occupied by the selective analogue. It seemed reasonable to deduce that the volume remaining, occupied by a portion of the hydantoin, was determined to be responsible for selectivity in these series. Figure 5 shows the nonselective and a selective analogues (C-

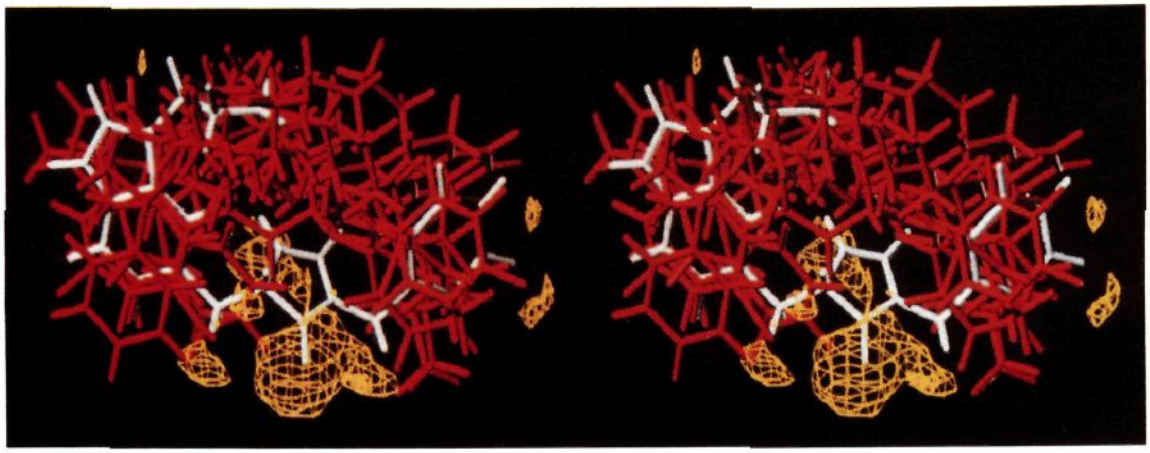


Figure 5. Nonselective and selective analogues overlaid on the pharmacophore model and the selectivity volume (relaxed-eye stereo).

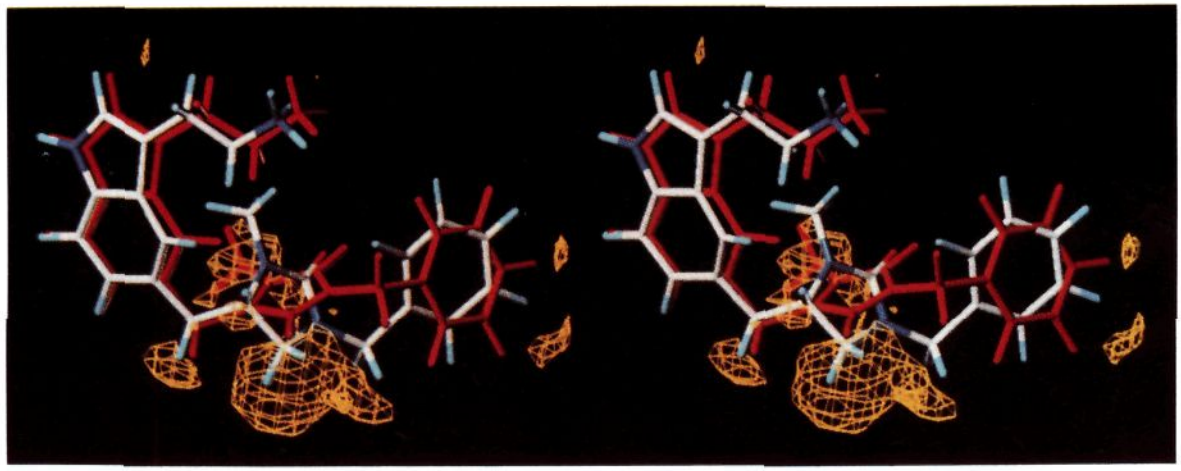


Figure 6. **59** (nonselective, red) and **60** (selective) overlaid on the pharmacophore model including the selectivity volume in yellow (relaxed-eye stereo).

linked) overlaid using the pharmacophore model with a plot of the computed "selectivity volume".

The implication in structural terms may be that the 5-HT_{2A} receptor essential volume[28] is more restricted in this region than the 5-HT_{1D} receptor essential volume. Thus, analogues with parts of their structure occupying this region lose activity for 5-HT_{2A} to a much greater extent than is seen in 5-HT_{1D}. Interestingly, bufotenine (**57**), which shows some selectivity for 5-HT_{1D} (p[A_{50}] 5-HT_{1D} = 7.3/0.92, p[A_{50}] 5-HT_{2A} = 6.8) when fitted to the pharmacophore model is seen to penetrate the selectivity volume only marginally. In order to give substance to this hypothesis, a molecule was synthesized which was in most respects similar to **18** but which did not possess the carbonyl oxygen present in the selectivity volume. This compound, **59**, had only a small part of its structure predicted to be in the selectivity volume. Its affinity at 5-HT_{1D} was p[A_{50}] = 7.08 and at 5-HT_{2A} p[A_{50}] = 6.31. Therefore, as expected, the 5-HT_{2A} affinity had relatively increased.

In addition a new analogue was designed by the simple modification of removal of the double bond from the 5-substituent in **59**. Upon fitting to the pharmacophore model, this compound appeared to significantly penetrate the selectivity volume. This analogue, **60**, has 5-HT_{1D} p[A_{50}] = 7.53, 5-HT_{2A} p[A_{50}] = 5.00. The hydrogenation of the double bond converts the trigonal carbon at the ring junction to tetrahedral geometry which results in occupation of the selectivity volume (Figure 6).

Interestingly, the replacement of the carbonyl group by a methylene in the occupation of the selectivity volume may be partly responsible for a relative increase in affinity for 5-HT_{1D}. Comparison of **18** (carbonyl occupancy) to **60** (methylene occupancy) gives 5-HT_{1D} p[A_{50}] = 6.1−7.5. This may imply the presence of a hydrophobic site in the region of the selectivity volume in 5-HT_{1D} receptors or, alternatively, indicate some degree of steric restriction in 5-HT_{2A}.

From these results, it appears that selectivity for 5-HT_{1D} over 5-HT_{2A} is easily achievable in this series simply by fitting a proposed molecule to the pharmacophore model and then determining whether or not the selectivity volume is occupied.

Realization of the Design Criteria: Discovery of 6. It appeared that analogues which were partial agonists of high affinity and selective for 5-HT_{1D} had been discovered, e.g., **37** (5-HT_{1D} p[A_{50}] = 7.4, α = 0.8, 5-HT_{2A} p[A_{50}] = 5.2) and **48** (5-HT_{1D} p[A_{50}] = 7.4, α = 0.6, 5-HT_{2A} p[A_{50}] < 4.5). However, data obtained after oral and intravenous administration to rats and cynomolgous monkeys revealed that the oral bioavailability of **48** was low: less than 5%.[42] Preliminary experiments indicated that poor oral absorption, rather than exten-

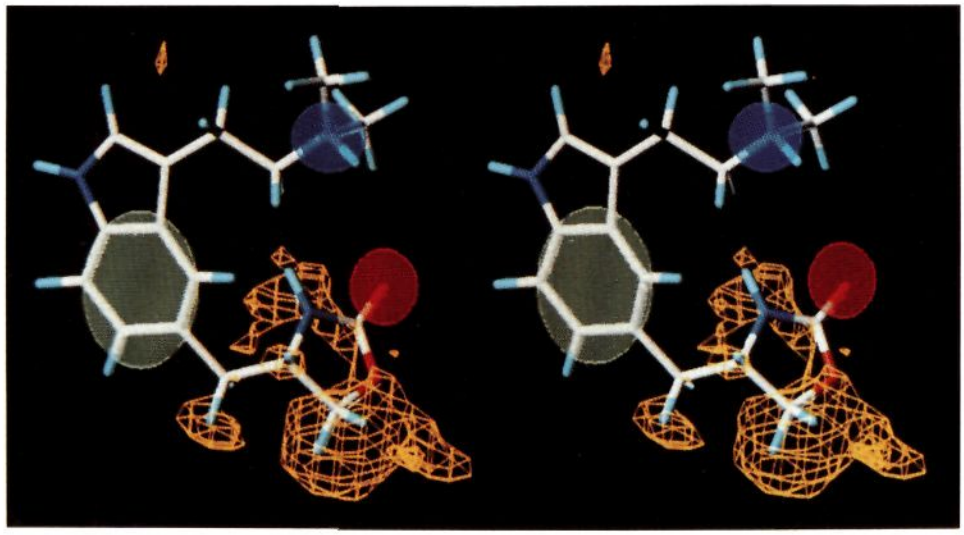


Figure 7. **6** overlaid on part of the pharmacophore model and the selectivity site.

sive first-pass metabolism, was the cause of the low oral bioavailability. A theoretical excercise was undertaken, to seek a physicochemical explanation for poor GI absorption. Inspection of the calculated physicochemical properties (log $D_{pH7.4}$ and MR[43]) for the $5HT_{1D}$ agonists in this series suggested that they lay in a region of the parameter space for which there was little precedent for oral absorption. On the basis of this observation, it was hypothesized[44] that the 5-HT_{1D} agonists were too hydrophilic to be effectively absorbed by a trans-cellular route yet too large to take advantage of aqueous pores, the para-cellular route. Subsequently, in a quantitative pharmacokinetic study, the plasma concentrations achieved after oral administration of 38 tryptamine analogues were correlated with their physicochemical properties: CMR and log $D_{pH7.4}$ (the distribution coefficient at pH 7.4[43]).[44] These experiments were expected to guide compound selection and not to give precise bioavailability data or plasma concentration−time profiles. Despite the possibility of factors other than the efficiency of absorption influencing the plasma concentrations (e.g., first-pass metabolism or differences in extent of distribution), these results demonstrated that there was a molecular size (CMR ca. 9.5) below which hydrophilic compounds were effectively absorbed. This supported the theoretical model for absorbtion and encouraged the exploitation of these physicochemical criteria as part of the overall chemical strategy. Lipophilic compounds (high log $D_{pH7.4}$), which could be well absorbed through cell membranes (transcellularly), were undesirable due to the possibility of substantial penetration into the central nervous system and subsequent activation of central 5-HT_{1A} receptors. The design criteria for molecular size were particularly stringent, especially since high affinity for 5-HT_{1D} in this series had required the incorporation of relatively large 5-substituents incorporating hydrophobic and hydrogen-bonding fragments. It is thus only possible to optimize the required features in more compact structures at the expense of affinity. Compounds such as **35**, although having the desired receptor profile, were not predicted to have the optimum oral absorbsion. Returning to the receptor model led to the possibility that an oxazolidinone side chain in the indole 5-position would satisfy the criteria for affinity. The carbonyl oxygen fits into the hydrogen-bond acceptor region while the adjacent oxygen augments the hydrogen-bonding acceptor abilities. The methylene group partly occupies the selectivity volume and, as previously discussed, is beneficial for affinity at 5-HT_{1D}. Dimethylation of the ethylamine nitrogen led to **6** which has the desired ClogD and CMR range (CMR = 8.27, log $D_{pH7.4} = -1.0$). In Figure 7, **6** is overlaid on the receptor model and the selectivity volume.

6 has a chiral center, and the expectation from the modeling studies (since chiral molecules like methysergide were included in the construction of the pharmacophore, it is of course chiral) was that the *S*-enantiomer would have higher affinity for 5-HT_{1D}. The synthesis from the *p*-nitro-L-phenylalanine leads naturally to the desired enantiomer (Scheme 5). The *R*-enantiomer, when synthesized and tested, gave the expected lower affinity and similar intrinsic efficacy at 5-HT_{1D} (p[A_{50}] 5-HT_{1D} = 6.28/0.61). In this study, only the affinity of compounds has been analyzed. The intrinsic efficacy of compounds acting at the 5-HT_{1D} receptor has also been extensively analyzed and will be reported elsewhere.

The receptor pharmacology of **6** was assessed using appropriate functional and radioligand binding assays (Table 8). The compound is a potent partial agonist at the 5-HT_{1D} receptor in the rabbit saphenous vein (RbSV) (p[A_{50}] = 6.8; intrinsic activity = 0.77, cf. 5-HT) and shows high affinity at the 5-HT_{1D} binding sites in homogenates of calf caudate nucleus. **6** demonstrates at least 30-fold selectivity over other monoamine receptors and binding sites including 5-HT receptor subtypes.

The compound is basic with a measured pK_a for the amine of 9.64. The free base is stable, nonhygroscopic, and soluble in aqueous solution at a neutral pH of >20 mg/mL. **6** is currently undergoing clinical evaluation for the treatment of migraine.

Conclusions

The active analogue approach has been used to elucidate a pharmacophore model describing key steric and electrostatic requirements of drugs acting at the 5-HT_{1D} and 5-HT_{2A} receptor subtypes. The construction of the pharmacophore was based on the pharmacological

Table 8. Affinity and Intrinsic Efficacy of **6** at Monoamine Receptors[a]

5-HT_1(RbSV) 6.8(0.1)/0.77(0.04), $N = 15$	5-HT_1(RbJV+E) <4.5/−, $N = 15$	5-HT_1(RbJV-E) 5.3(0.1)/−, $N = 15$	5-HT_{1A} 6.45(0.11), $N = 5$	5-HT_{1C} <4.0, $N = 3$
5-HT_{1D} 8.7(0.1), $N = 10$	5-$HT_{1D\alpha}$ 9.16(0.12), $N = 5$	5-$HT_{1D\beta}$ 8.32(0.09), $N = 5$	5-HT_{2A} <4.5, $N = 5$	5-HT_3 <4.5
5-HT_4 <4.5	α_1 <4.0	α_2 4.1(0.1)	b <4.0	D_1 <4.0
D_2 <4.0	H_1 5.5 (0.1)/−	H_2 <4.5/−	M_2 <4.5/-	M_3 <4.5/−

[a] RbSV, rabbit saphenous vein assay; RbJV, rabbit jugular vein assay with (+E) and without (−E) endothelium. Errors, where quoted, are in parentheses. N ≥ 3 unless otherwise stated.

activities of a series of novel C- and N-linked hydantoin analogues. The model may be used as a framework for the design of a diverse series of analogues with good affinity and selectivity for 5-HT_{1D}. In tandem with the constraints required for good oral absorption, potent selective 5-HT_{1D} agonists, exemplified by **6**, have been discovered with potential use in the treatment of migraine.

Experimental Section

(a) **Chemical Methods.** Melting points are uncorrected. Flash chromatography was carried out by the method of Still[45] except that the columns were slurry packed, Merck cat. no. 1.09385.1000, silica gel-60 230−400 mesh aspm. Thin-layer chromatography and preparative chromatography used Merck silica (cat. no. 1.05719). ^{1}H NMR spectra were run on a Bruker AC200 or AMX360 spectrometer unless otherwise indicated. Chemical shifts are in δ ppm relative to TMS. Mass spectra were obtained on a Kratos Concept IS (EIMS) or a Kratos MS50 (FAB) mass spectrometer. Products, where applicable, were dried over sodium sulfate and evaporated using a Buchi rotary evaporator at reduced pressure. Infrared spectra were run in KBr disks on a Bruker IFS66 FTIR spectrometer. Partition coefficients (log P, log D) were obtained using the filter chamber method.[46]

The following starting materials were synthesized by literature procedures: 3-phthalamidobenzyl bromide,[47] 4-phthalamidobenzyl bromide,[48] 4-chlorobutanal diethyl acetal.[49]

General Methods for the Synthesis of C-Linked Imidazolidine-2,5-diones Illustrated by the Preparation of *N*-Methyl-3-[[4-(4-nitrophenylmethyl)-2,5-dioxoimidazolidin-1-yl]methyl]benzamide. (a) 4-[(4-Nitrophenyl)methyl]imidazolidine-2,5-dione. A solution of 4-nitrophenylalanine (4.2 g, 18.4 mmol) and potassium cyanate (1.62 g, 20 mmol) in water (6 mL) was refluxed for 1 h. Concentrated hydrochloric acid (3 mL) was added and the mixture refluxed for a further 10 min, then cooled, diluted with water, and filtered. The solid was dried to give the desired product as a straw-colored solid (3.85 g, 16.4 mmol, 89%).

(b) 3-(Chloromethyl)-*N*-methylbenzamide (Preparation of Amides). A solution of 3-(chloromethyl)benzoyl chloride (7.4 g, 39.1 mmol) in dichloromethane (35 mL) was added dropwise at 0 °C over 30 min to a stirred mixture of 30% aqueous methylamine (4.5 mL, ~46 mmol) and triethylamine (3.6 g, 35.6 mmol) in dichloromethane (50 mL). The reaction mixture was allowed to warm to room temperature over 1 h. Further methylamine (0.5 mL) was added and the mixture stirred for a further 10 min. The reaction mixture was washed with water, 1 N aqueous sodium hydroxide, and brine and dried ($MgSO_4$). The solvents were evaporated to give the desired product as a colorless oil which solidified to a white solid on standing (3.3 g, 17.9 mmol, 45%).

(c) *N*-Methyl-3-[[4-[(4-nitrophenyl)methyl]-2,5-dioxoimidazolidin-1-yl]methyl]benzamide (General Method for Alkylation of Imidazolidine-2,5-diones). The product from step a (4.0 g, 17.0 mmol), the product from step b (3.3 g, 18.0 mmol), and potassium carbonate (2.55 g, 18.5 mmol) were stirred in dimethylformamide (25 mL) for 60 h at room temperature. The mixture was poured into ice water (175 mL) to give an oily precipitate. Ethyl acetate was added, and stirring continued for 1 h to solidify the precipitate. The latter was filtered off, washed with water, ethyl acetate, and ether, and dried to give the product as a peach-colored solid (4.5 g, 11.8 mmol, 65%).

General Methods for the Synthesis of N-Linked Imidazolidine-2,5-diones. (a) **1-[2-(4-Nitrophenyl)ethyl]imidazolidine-2,5-dione.** Imidazolidine-2,5-dione (20 g, 0.2 mol), 4-nitrophenethyl alcohol (34 g, 0.2 mol), and triphenylphosphine (52.4 g, 0.2 mol) were mixed in dimethylformamide (50 mL) and cooled to 0 °C. Diethyl azidodicarboxylate (34.8 g, 0.2 mol) in dimethylformamide (50 mL) was added dropwise over 45 min and the reaction mixture allowed to warm to room temperature for 1 h. The reaction mixture was poured into water and stirred for 30 min. The resultant pale orange precipitate was filtered, washed with water and ether, and dried *in vacuo*. The crude product was crystallized from methylated spirit to give pale orange crystals (29.66 g, 0.12 mol, 59%).

(c) 4-[(4-*N*-Phthalamidophenyl)methyl]-1-[2-(4-nitrophenyl)ethyl]imidazolidine-2,5-dione. A solution of methylmagnesium carbonate (20 mL of a 2 M solution in dimethylformamide) was saturated with a slow stream of CO_2 gas for 1 h at 80 °C. The CO_2 stream was replaced by nitrogen, and the imidazolidine-2,5-dione (5.0 g, 20 mmol) from step a was added. After 1.5 h the 4-phthalamidobenzyl bromide (6.96 g, 20 mmol) was added in dimethylformamide (8 mL). The mixture was stirred at 110 °C for 3 h. The reaction mixture was allowed to cool and poured onto concentrated hydrochloric acid (10 mL) in ice (40 mL). The reaction mixture was extracted with ethyl acetate, and the combined extracts were washed with water and brine. The extracts were dried ($MgSO_4$) and evaporated to give the crude product (8.2 g, 16.9 mmol, 84%).

(d) 4-[(4-aminophenyl)methyl]-1-[2-(4-nitrophenyl)ethyl]imidazolidine-2,5-dione. The product from step c (8.21 g, 17mmol) and hydrazine hydrate (6.75 mL) were heated to reflux in ethanol (200 mL) for 3 h. The reaction mixture was evaporated to dryness and the residue suspended in water and made basic with 2 N NaOH. The mixture was stirred, and the resulting yellow precipitate was filtered off, washed with water, and dried *in vacuo* (5.09 g, 10.5 mmol, 62%).

(e) 4-[[4-(Methylsulfonamido)phenyl]methyl]-1-[2-(4-nitrophenyl)ethyl]imidazolidine-2,5-dione. The product from step d (5.09 g, 14.6 mmol) was dissolved in pyridine (120 mL) and cooled to 0 °C, methanesulfonyl chloride (1.84 g, 16.6 mmol, 1.1 equiv) was added dropwise over 5 min, and the mixture was stirred for 2 h. The reaction mixture was poured onto cold (0 °C) 2 N hydrochloric acid (800 mL) and extracted with ethyl acetate. The extracts were washed with water, dried ($MgSO_4$), and evaporated to give crude product which was crystallized from ethanol. The product was obtained as a pale orange solid (4.64 g, 10.7 mmol, 73%).

Preparation of N3-Methylated Imidazolidine-2,5-diones. (a) 1-Benzyl-4-[(4-nitrophenyl)methyl]imidazolidine-2,5-dione. 4-Nitrophenylalanine (4.2 g, 20 mmol) and potassium hydroxide (1.34 g, 24 mmol) were stirred in water (40 mL) and cooled to 0 °C. Benzyl isocyanate (3.2 g, 24 mmol) was added dropwise over 20 min, and the reaction mixture was then heated to 60−70 °C for 2 h. The reaction was allowed to cool and then filtered and the filtrate acidified with concentrated hydrochloric acid. The resultant solid was filtered off, then treated with concentrated hydrochloric acid

(20 mL) and water (20 mL), and refluxed for 2 h. The reaction was allowed to cool and was diluted with water (200 mL), and the resultant solid was filtered off washed with water and dried *in vacuo* (5.7 g, 17.5 mmol, 87%).

(b) 1-Benzyl-3-methyl-4-[(4-nitrophenyl)methyl]imidazolidine-2,5-dione. To a stirred suspension of potassium carbonate (2.25 g, 16.2 mmol) in dimethylformamide (25 mL) at 0 °C was added the product of step a (4.88 g, 15 mmol) followed by methyl iodide (4.2 g, 29.6 mmol), and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured onto water and extracted with ethyl acetate. The extracts were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated to give a yellow oil which was purified by chromatography ($CHCl_3$) to give the product (4.24 g, 12.5 mmol, 83%).

General Methods for the Preparation of *N*-Methylindoleethylamines from the Nitroaryl Intermediates Illustrated by the Preparation of 4-[(3-Acetamidophenyl)methyl]-1-[2-[[3-[2-(methylamino)ethyl]indol-5-yl]ethyl]]imidazolidine-2,5-dione. (a) 4-[(3-Acetamidophenyl)methyl]-1-[2-[3-[2-(benzylamino)ethyl]indol-5-yl]ethyl]imidazolidine-2,5-dione. To the indoleethylamine (367.5 mg, 0.85 mmol) prepared by methods described above in ethanol (3 mL) was added freshly distilled benzaldehyde (89 mg, 0.82 mmol), and the reaction mixture was stirred at room temperature for 30 h. Sodium borohydride (32.1 mg, 0.85 mmol) was added portionwise over 10 min and the reaction mixture stirred for 1 h. The reaction mixture was poured onto 2 N hydrochloric acid, stirred for a few minutes, and then made basic with potassium carbonate. The resultant solid was filtered off, washed with a little water, and dried in vacuo (440 mg, 0.84 mmol, 99%).

(b) 4-[(3-Acetamidophenyl)methyl]-1-[2-[3-[2-(*N*-benzyl-*N*-methylamino)ethyl]indol-5-yl]ethyl]imidazolidine-2,5-dione. To the product of step a (435 mg, 0.82 mmol) and potassium carbonate (278 mg, 2.02 mmol) in dimethylformamide (16.5 mL) was added dimethyl sulfate (110.6 mg, 83 mL, 0.87 mmol) and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was poured onto water and extracted with ethyl acetate. The extracts were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated to give an oil (360 mg, 0.66 mmol, 81%).

(c) 4-[(3-Acetamidophenyl)methyl]-1-[2-[3-[2-(methylamino)ethyl]indol-5-yl]ethyl]imidazolidine-2,5-dione. To the product of step b (355 mg, 0.66 mmol) in ethanol (22 mL) was added 10% palladium on carbon (150 mg) and the reaction hydrogenated under 1 atm of hydrogen. When hydrogen uptake ceased, the catalyst was filtered off and the solvent evaporated. The residue was purified by chromatography (20:8:1 CH_2Cl_2:EtOH:NH_3). The purified free base was converted to the maleate salt, and the salt was freeze-dried twice (75.8 mg, 0.124 mmol, 19%).

General methods for the preparation of indoleethylamines are illustrated by steps e and f below.

Preparation of (*S*)-2-[5-[(2-Oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indol-3-yl]ethylamine. (a) (*S*)-Methyl 4-Nitrophenylalanate Hydrochloride. Methanol (110 mL) was treated dropwise with thionyl chloride (26.3 g, 0.22 mol) at −10 °C and L-4-nitrophenylalanine (Fluka, 21.7 g, 0.095 mol) added to the resulting solution as a solid. The mixture was stirred overnight at room temperature and the methanol removed *in vacuo* to give the desired product as a pale yellow solid (21.2 g, 0.0946 mol, 99%).

(b) (*S*)-2-Amino-3-(4-nitrophenyl)propanol. The product from step a (21.2 g, 0.094 mol) was dissolved in ethanol/water (190 mL, 100/90 v/v) and the solution added dropwise at 0 °C to a stirred solution of sodium borohydride (13.0 g, 0.34 mol) in ethanol/water (190 mL, 100/90 v/v). The resulting mixture was refluxed for 2.5 h and cooled and the precipitate filtered off. The ethanol was partially removed from the filtrate *in vacuo*, and the resulting precipitate was filtered off and dried to give the desired product as a pale yellow solid (7.5 g, 0.043 mol, 46%).

(c) (*S*)-4-(4-Nitrobenzyl)-1,3-oxazolidin-2-one. The product from step b (4.9 g, 28.4 mmol) was suspended in toluene, the suspension cooled to 0 °C, and a solution of potassium hydroxide (7.0 g, 125 mmol) in water (56 mL) added dropwise. A solution of phosgene (62.5 mL of a 12% w/v solution in toluene, 76 mmol) was added dropwise to the resulting solution over 30 min, and stirring continued for 1 h. The mixture was extracted with ethyl acetate, and the extracts were washed with brine, dried, and evaporated *in vacuo* to give a yellow oil. Crystallization from ethyl acetate gave the desired product as pale yellow crystals (2.3 g, 10.36 mmol, 36%).

(d) (*S*)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one Hydrochloride. A suspension of the product from step c (0.79 g, 3.56 mmol) and 10% palladium on carbon (0.26 g) in a mixture of ethanol (15 mL), water (11 mL), ethyl acetate (2.0 mL), and aqueous 2 N hydrochloric acid (2.3 mL) was stirred under 1 atm of hydrogen until uptake ceased. The mixture was filtered through Hyflo and the filtrate evaporated *in vacuo* to give the desired product as a pale yellow foam (0.79 g, 3.45 mmol, 97%).

(e) (*S*)-4-(4-Hydrazinobenzyl)-1,3-oxazolidin-2-one Hydrochloride. The product from step d (0.79 g, 3.45 mmol) was suspended in water (4.8 mL) and concentrated hydrochloric acid (8.1 mL) added dropwise. The resulting mixture was cooled to −5 °C and a solution of sodium nitrite (0.24 g, 3.48 mmol) in water (2.4 mL) added dropwise to the stirred mixture over 15 min followed by 30 min of stirring at −5 to 0 °C. The solution was then added at 0 °C over 15 min to a stirred solution of tin(II) chloride (3.8 g) in concentrated hydrochloric acid (6.9 mL), followed by 3 h of stirring at room temperature. The solution was evaporated *in vacuo* and the residue triturated with ether to give the desired product as a pale yellow solid (0.96 g) which was used directly for the next stage.

(f) (*S*)-2-[5-[(2-Oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indol-3-yl]ethylamine. The product from step e was dissolved in ethanol:water (125 mL, 5:1) and the solution treated with 4-chlorobutanal diethyl acetal (0.52 g, 3.41 mmol). The mixture was refluxed for 2 h, the solvent removed *in vacuo*, and the residue purified by chromatography using CH_2Cl_2:EtOH:NH_4OH (30:8:1) as eluant. The desired product was obtained as a colorless oil (0.21 g, 0.79 mmol).

Maleate Salt. Ethanolic maleic acid (1.0 equiv) was added dropwise to the free base (0.21 g, 0.79 mmol) and the ethanol evaporated *in vacuo*. The resulting gum was freeze-dried from water to give the desired product as a white lyopholate (0.22 g): $[\alpha]^{21}_D$ −5.92° (c = 0.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.7−3.5 (6H, m, CH_2), 3.35 (2H, s, NH_2) 4.05 (2H, m, CH_2), 4.25 (1H, m, CH), 6.05 (2H, s, maleic acid), 6.98 (1H, d, Ar) 7.2 (1H, s, Ar), 7.3 (1H, d, Ar) 7.4 (1H, s, Ar), 7.75 (1H, s, NH), and 10.9 (1H, s, NH).

The general method for dimethylation of indoleethylamines is illustrated below for (*S*)-*N*,*N*-dimethyl-2-[5-[(2-oxo-1,3-oxazolidin-4-yl)methyl)-1*H*-indol-3-yl]ethylamine 0.5 2-propanolate 0.31 hydrate.

A solution of formaldehyde (0.03 g, 1 mmol) in methanol (1.8 mL) was added to a solution of the free base from step f (0.12 g, 0.45 mmol) and sodium cyanoborohydride (0.04 g, 0.64 mmol) in a mixture of methanol (5.5 mL) and glacial acetic acid (0.14 g) and the resulting mixture stirred overnight at room temperature. The pH was adjusted to 8.0 using aqueous K_2CO_3 and the mixture extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a colorless oil (0.14 g) which crystallized from 2-propanol to give the desired product as a white crystalline solid (0.10 g, 0.31 mmol, 31%): mp 139−141 °C. ^{1}H NMR (DMSO-d_6) δ 2.2 (6H, s, NMe_2), 2.5 (2H, M, CH_2 Ar), 2.7−3.0 (4H, m, CH_2), 4.1 (2H, m, CH_2O), 4.3 (1H, m, CH), 6.9 (1H, d, Ar), 7.1 (1H, s, Ar), 7.3 (1H, d, Ar) 7.4 (1H, s, Ar) 7.7 (1H, s, NHCO), and 10.7 (1H, s, NH); $[\alpha]^{22}_D$ −5.79° (c = 0.5, MeOH).

Preparation of (±)-2-[5-[(3-Methyl-2-oxo-1,3-imidazolidin-4-yl)methyl]-1*H*-indol-3-yl]ethylamine and (±)-*N*,*N*-Dimethyl-2-[5-[(3-methyl-2-oxo-1,3-imidazolidin-4-yl)methyl]-1*H*-indol-3-yl]ethylamine. (a) 3-Methyl-[(4-nitrophenyl)methyl]-1-phenyl-2-oxo-1,2-dihydroimidazole. To 3-methyl-1-benzyl-4-[(4-nitrophenyl)methyl]imidazolidine-2,4-dione (10.9 g, 32.2 mmol) prepared from the unsubstituted imidazolidinone using the alkylation methods described above) in propan-2-ol (100 mL) were added sodium borohydride (6.11 g, 0.16 mol) and a solution of glacial acetic

Table 9 : Radioligand Binding Assays Used in Determining the Receptor Specificity of 6

receptor	radiolabel	K_D (nM)	receptor source
5-HT_{1A}	[^{3}H]5-HT (1.8 nM)	1.8	human recombinant receptor, CHO cells
5-$HT_{1D\alpha}$	[^{3}H]5-HT (1.5 nM)	1.5	human recombinant receptor, CHO cells
5-$HT_{1D\beta}$	[^{3}H]5-HT (1.5 nM)	1.5	human recombinant receptor, CHO cells
α_2-adrenoceptor	[^{3}H]idazoxan (7 nM)	7	rat cortex
dopamine D_1	[^{3}H]SCH23390 (0.3 nM)	0.3	rat striatum
dopamine D_2	[^{3}H]spiperone (0.2 nM)	0.04	rat striatum

acid in propan-2-ol (9.2 mL of AcOH in 40 mL of iPrOH). The reaction was heated to reflux for 4 h, then a further equivalent of sodium borohydride and acetic acid in propan-2-ol were added, and the reflux was continued for a further 4 h. This sequence was repeated twice more (i.e., 4 additions of sodium borohydride). The reaction mixture was evaporated to remove most of the solvents then poured onto 2 N aqueous hydrochloric acid (500mL) and extracted with ether. The ether extracts were washed with brine and dried ($MgSO_4$). The product was separated from the remaining starting material by chromatography ($CHCl_3$). This gave product (6.14 g, 19.13 mmol, 59%) and recovered starting material (2.9 g). The yield was 81% based on recovered starting material.

(b) 4-[(4-Aminophenyl)methyl]-1-benzyl-3-methylimidazolidin-2-one. To the product of step a (6.1 g, 19 mmol) in methanol (250 mL) was added platinum oxide (1.5 g) and the mixture hydrogenated under 79–86 atm of hydrogen at room temperature for 24 h. The catalyst was filtered off and the solvent evaporated to give the product as a brown oil (5.94 g, theoretical yield) which was used for the next step without further purification.

(c) 5-[(4-Aminophenyl)methyl]-3-methyl-1,3-imidazolidin-2-one. To the product of step b (9.13 g, 27.54 mmol) was added 45% aqueous hydrobromic acid (290 mL) and the reaction heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* on a rotary evaporator, ethanol was added, and the process was repeated. The azeotroping was repeated once more with toluene and the resulting crude product purified by chromatography (CH_2Cl_2:EtOH 10:1) to give a yellow foam (4.1 g, 20 mmol, 72%).

The product of step c was then carried through the hydrazine formation and Fischer indole synthesis using the general methods described to give the title compounds.

(b) Pharmacological Methods. Rabbit Saphenous and Aortic Ring Preparations. Vessels were removed from male New Zealand White rabbits killed by injecting pentobarbitone (80 mg/kg, iv) followed by exsanguination. After removing adhering connective tissue, ring segments of each vessel were prepared (saphenous vein, 4–5 mm; aorta, 3 mm) and mounted between parallel tungsten wires. Vascular rings were suspended in 20 mL organ baths containing Krebs–Henseleit buffer at 37 °C, pH 7.4, and constantly gassed with 95% O_2: 5% CO_2. After application of a passive force (vein, 2 g; aorta, 3 g), tissues were exposed to pargyline (500 μM) to inactivate monoamine oxidase. In order to prevent the direct or indirect activation of α-adrenoceptors, saphenous veins were simultaneously exposed to phenoxybenzamine (0.3 μM), while aortae were treated with benextramine tetrahydrochloride (100 μM). After 30 min, excess inhibitors were removed by several exchanges of the organ bath buffer and the tissues challenged with 5-HT (vein, 1 μM; aorta, 10 μM) to determine viability. In the saphenous vein, a cumulative concentration–effect (E/[A]) curve to 5-HT was constructed followed, after 60 min recovery, by a second curve to the test agonist. In the aorta, test drugs rarely produced agonism; hence cumulative additions were made to a maximum of $-\log_{10}$ 4.5M and a cumulative E/[A] curve to 5-HT constructed in the presence of the test. When the test produced vascular contraction, potency estimates were determined as p[A_{50}] and intrinsic activity (α) values determined from the ratio Test maximum response/5-HT maximum. When the test failed to produce agonism, it was evaluated as a 5-HT antagonist, potency being determined as an apparent pK_B. The figures quoted are the average of a number of independant determinations for $n \geq 3$ and are within ±10% of the mean.

Receptor Binding Assays. Competition binding assays were performed to determine drug affinity (pK_i or pIC_{50}) at the receptors shown in Table 9. Briefly, the appropriate radioligand ($\sim K_D$) and a wide range of test drug concentrations (in duplicate) were incubated with the relevant receptor preparation (brain homogenate or cell membranes) for 30 min at 27 °C—conditions determined previously to satisfy mass-action conditions. The assay buffer comprised 50 mM Tris-HCl, 5 mM $CaCl_2$, 0.1% w/v ascorbate, and 10 mM pargyline. Nonspecific binding was defined using an excess of cold 5-HT. Incubations were terminated by rapid filtration and washing with ice-cold buffer. Specifically bound radiolabel was measured by liquid scintillation spectroscopy. The figures quoted are the average of a number of independant determinations for $n \geq 3$ and are within ±10% of the mean.

Pharmacokinetic Methods. Pharmacokinetic experiments were performed in Wistar rats and cynomolgous monkeys.[42] [^{14}C]-**48** (labeled in the dimethylethylamine group) was administered to two cynomolgous monkeys in 0.9% saline, either intravenously *via* the saphenous vein or orally following an overnight fast (2 and 5 mg/kg, respectively). In rats [^{14}C]-**48** and unlabeled **48** were administered either intravenously, *via* the tail vein, or orally following an overnight fast (5 and 10 mg/kg, respectively). Blood was collected into heparin coated tubes by venepuncture (monkeys) or by cardiac puncture (rats) at regular intervals after dosing (3 rats per time point). The 38 tryptamine analogues were administered (10 mg/kg) to rats by the oral route only, and blood samples were obtained at 30 min and 2 h after dosing. Plasma was prepared by centrifugation and was stored at −20 °C until assay. Urine was also collected from rats and monkeys for up to 24 h after dosing; the volume of the samples was recorded prior to storing at −20 °C. The concentration of administered compounds in plasma and urine samples was determined by HPLC assay. Appropriate internal standards were added to plasma samples (0.5 mL), and ice-cold acetone (1.2 mL) was then added. Precipitated plasma proteins were removed by centrifugation. Saturated sodium chloride solution (200 mL) and Clarke's and Lub's buffer (pH 9.8, 0.25 M, 400 mL) were added to the supernatants, and the compounds of interest were extracted with chloroform (1.5 mL). After centrifuging, the upper aqueous phases were aspirated to waste and the organic fractions evaporated to dryness at 40 °C using a stream of nitrogen. The residues were reconstituted in a mixture of acetonitrile:water (1:1) prior to HPLC assay. Urine was analysed after appropriate dilution. Reversed phase HPLC analysis was carried out by injection onto a Spherisorb nitrile (CN) 5 mM cartridge column (250 × 4.0 mm; HPLC Technology) which was maintained at 40 °C. Compounds were eluted with a mobile phase consisting of acetonitrile:aqueous ammonium acetate (0.01 M) (70:30 v:v) at 1 mL/min and were detected either by UV absorbance (220 nm), fluorescence, "in-line" radioactive monitoring, or electrochemical detection. Calibration curves were generated by processing control (pretreatment) samples, "spiked" with known concentrations of analyte. Concentrations of compounds in the test samples were determined by comparison of their responses with those of the calibration curves. Alternatively, radioactivity was determined in the samples by scintillation counting after addition of Optiphase "X" scintillation fluid. Oral bioavailability was determined by comparison of the AUCs of the plasma concentration-time profiles for **48** and [^{14}C]-**48** after oral and intravenous administration and by estimation of the dose excreted unchanged in the urine. Plasma concentrations of the 38 tryptamine analogues, obtained by averaging the

concentrations measured at 30 min and 2 h, were correlated with their CMR and log $D_{pH7.4}$ values[32,64] (standard errors were below 10% for most determinations).

(c) **Computational Methods.** Initial model development was performed on a VAX 11/750 with an Evans and Sutherland PS300 for visualization. These calculations and molecular graphics have been repeated on a Silicon Graphics R4400 workstation (the data reported here). Molecular modeling, visualization, and computational chemistry was performed using SYBYL.[29] CLogP calculations used the Pomona89 Physico-Chemical Database & Medchem Software.[55]

Acknowledgment. We would like to thank Janet Williams for NMR support, Yih S. Pang for chemical support, and, in particular, David Selwood for helpful discussions and assistance in manuscript preparation.

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JM950232M