3-[3-(Piperidin-1-yl)propyl]indoles as Highly Selective h5-HT$_{1D}$ Receptor Agonists

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Several 5-HT$_{1D/1B}$ receptor agonists are now entering the marketplace as treatments for migraine. This paper describes the development of selective h5-HT$_{1D}$ receptor agonists as potential antimigraine agents which may produce fewer side effects. A series of 3-[3-(piperidin-1-yl)propyl]indoles has been synthesized which has led to the identification of **80** (L-772,405), a high-affinity h5-HT$_{1D}$ receptor full agonist having 170-fold selectivity for h5-HT$_{1D}$ receptors over h5-HT$_{1B}$ receptors. L-772,405 also shows very good selectivity over a range of other serotonin and nonserotonin receptors and has excellent bioavailability following subcutaneous administration in rats. It therefore constitutes a valuable tool to delineate the role of h5-HT$_{1D}$ receptors in migraine. Molecular modeling and physical properties have been utilized to postulate the binding conformation of these compounds in the receptor cavity.

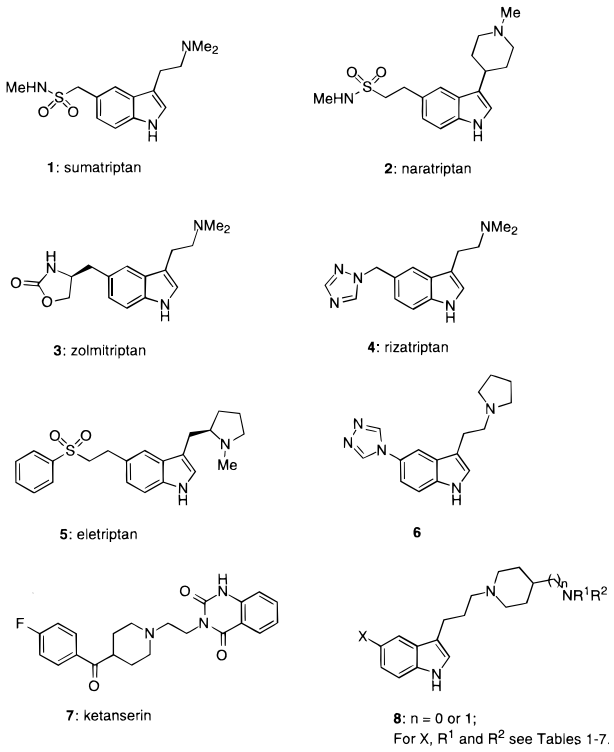
Introduction

Since the discovery of sumatriptan (**1**, Chart 1),[1] a 5-HT$_{1B/1D}$ receptor agonist, as an effective treatment for migraine headache, intensive research in this area[2−4] has led to several related compounds such as naratriptan (**2**),[5] zolmitriptan (**3**),[6] rizatriptan (**4**),[7] and eletriptan (**5**)[8] entering the marketplace and late phase clinical trials. Their mechanism of action is still a matter of some debate,[9] and both a direct vasoconstrictor effect on excessively dilated intracranial, extracerebral arteries and an inhibition of vasoactive neuropeptide release from perivascular trigeminal sensory neurons, preventing neurogenic dural vasodilation, have been proposed. It has also been suggested that some of the newer, more lipophilic agents may have a centrally mediated component to their antimigraine effects.[10]

Consistent with the neurogenic hypothesis is the fact that levels of calcitonin gene-related peptide (CGRP) increase during migraine attacks, and these levels are normalized by administration of sumatriptan with concomitant relief of the headache.[11] Recent studies, using intravital microscopy, have shown that rizatriptan reduced electrically stimulated dural vasodilation in anaesthetized rats but had no effect on increases in dural vessel diameter produced by exogenous substance P or CGRP.[12] Since it has been shown that electrically stimulated dural vasodilation is mediated predominantly by CGRP,[13] then this suggests that rizatriptan inhibits the release of CGRP via activation of prejunctional receptors located on the terminals of trigeminal sensory nerves, thus preventing neurogenic vasodilation.

Receptor mapping studies using polymerase chain reaction (PCR) amplification have shown that in the human trigeminal ganglia mRNA's encoding for both h5-HT$_{1D}$ and h5-HT$_{1B}$ receptor subtypes (previously termed 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$, respectively[14]) appear to be present, whereas in human cerebral blood vessels there is a preponderance of mRNA encoding for the h5-HT$_{1B}$ subtype only.[15−17] Moreover, studies using h5-HT$_{1D}$ and h5-HT$_{1B}$ receptor-specific antibodies showed that only h5-HT$_{1B}$ receptor protein was found on dural arteries, whereas only h5-HT$_{1D}$ receptor protein was found on trigeminal sensory neurons both on the peripheral projections to dural blood vessels and on the central projections that terminate behind the blood-brain barrier where they synapse with neurons that convey pain impulses to higher brain centers.[18] This suggests that 5-HT$_{1D}$ receptors are responsible for

Chart 1



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blocking the release of CGRP in the peripheral meningeal arteries and also for inhibiting neurotransmitter release within the brainstem and interrupting central pain transmission, whereas 5-HT_{1B} receptors are involved in direct vasoconstriction.

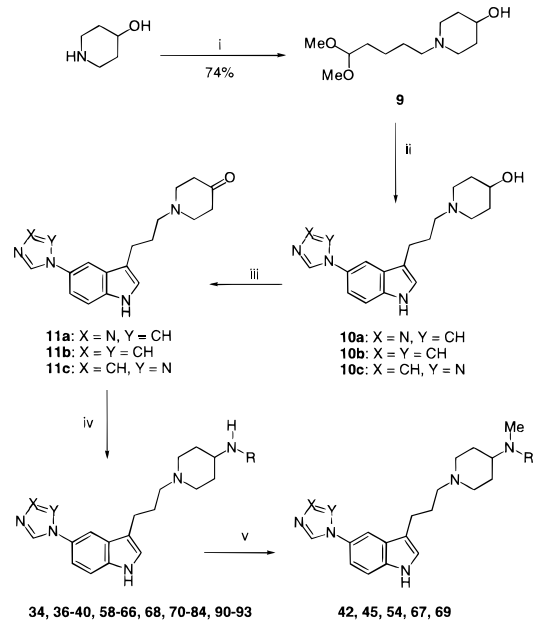
Although the safety profile of the "triptans" is extremely good, there exists the potential for rare cardiovascular adverse events[19] that precludes their use in patients with known heart disease. Although coronary vasoconstriction appears to be mediated mainly through 5-HT_{2A} receptors, the triptans show good selectivity over the 5-HT_{2A} subtype, so it is a possibility that the cardiovascular adverse events may be due to their action on h5-HT_{1B} receptors. None of the agents mentioned above have significant selectivity between the h5-HT_{1D} and h5-HT_{1B} receptor subtypes. If inhibition of peptide release is involved in the therapeutic action, it might be expected that a selective 5-HT_{1D} receptor agonist would have the clinical advantage of reduced vasoconstrictor liability yet still produce pain relief. This prompted us to seek to identify a selective h5-HT_{1D} receptor agonist in order to confirm the target tissue for antimigraine drugs and develop an antimigraine agent with a potentially lower side effect liability.

The Merck sample collection of 5-substituted tryptamines, synthesized during the discovery of rizatriptan, was screened but found generally to have minimal selectivity for h5-HT_{1D} over h5-HT_{1B} receptors. However, the pyrrolidine analogue (**6**) did show a modest 9-fold selectivity in favor of h5-HT_{1D}, and it was also known that ketanserin (**7**) was >37-fold selective for h5-HT_{1D} over h5-HT_{1B} receptors, albeit not particularly potent. As the amine functionality of both compounds is anticipated to interact with Asp 118 on transmembrane helix 3 of the h5-HT_{1D} receptor, it was speculated that incorporation of a more elaborate amine side chain into **6** could lead to improvements in selectivity. This paper describes the synthesis and biological evaluation of a series of 4-substituted piperidines (**8**) which avoids the introduction of a chiral center that would otherwise be present by substituting the pyrrolidine ring of **6**, thus simplifying the molecule. To achieve high binding affinity with a piperidine ring instead of a pyrrolidine, it was discovered that a lengthening of the side chain from two to three carbon atoms was required.[20] This work has led to the discovery of L-772,405 (**80**), a high-affinity h5-HT_{1D} receptor full agonist having 170-fold selectivity for h5-HT_{1D} over h5-HT_{1B} receptors.

Chemistry

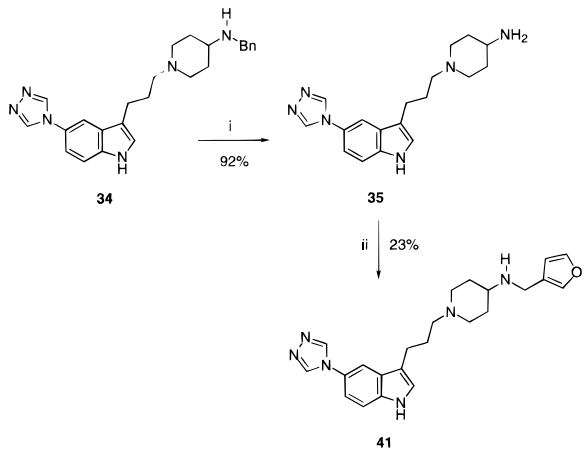
The 4-aminopiperidine analogues were prepared using three general synthetic strategies. The first route involved reductive amination of the ketones (**11a**−**c**) with the appropriate amine using sodium cyanoborohydride (Scheme 1). The ketones (**11a**−**c**) were prepared from 4-hydroxypiperidine by alkylation with 5-bromopentanal dimethyl acetal to give acetal **9**, followed by Fischer indolization with the appropriate 4-(heteroaryl)phenylhydrazine and oxidation of the intermediate 4-piperidinols (**10a**−**c**) using Parikh conditions. An alternative method was employed for the synthesis of the 3-furylmethyl derivative (**41**) in which the *N*-benzyl analogue (**34**) was debenzylated by transfer hydrogenation and the resulting primary amine (**35**) was reductively alkylated with 3-furfuraldehyde (Scheme 2). If a primary amine was employed in the reductive amination of **11**, it could be methylated by treatment with formaldehyde and sodium cyanoborohydride. Alternatively, the *N*-methyl analogues were prepared by a second approach which involved reduction of 1-benzyl-4-[*N*-(*tert*-butoxycarbonyl)amino]piperidine with lithium aluminum hydride, followed by reprotection with di-*tert*-butyl dicarbonate to afford **12** (Scheme 3). Attempted preparation of this last compound by direct methylation of the sodium salt of 1-benzyl-4-[*N*-(*tert*-butoxycarbonyl)-amino]piperidine was less efficient. Debenzylation of **12** by hydrogenation over palladium hydroxide gave amine (**13**), which was alkylated with 5-bromopentanal dimethyl acetal and subjected to a Fischer indolization to afford the versatile intermediate (**14**). This could be treated with sulfonyl chlorides to form sulfonamides, or

Scheme 1[a]



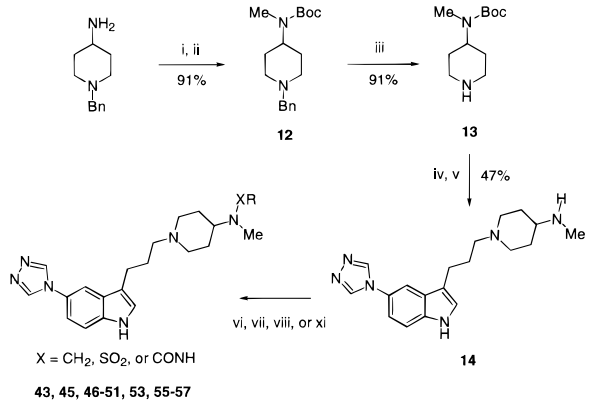
[a] Reagents: (i) $(MeO)_2CH(CH_2)_4Br$, K_2CO_3, DMF, 90 °C, 3 h; (ii) 4% H_2SO_4(aq), 4-(heteroaryl)phenylhydrazine, reflux; (iii) pyridine·SO_3, Et_3N, DMSO, rt; (iv) RNH_2, $NaCNBH_3$, AcOH, MeOH, rt (method A); (v) 38% CH_2O(aq), $NaCNBH_3$, AcOH, MeOH, rt (method B).

Scheme 2[a]



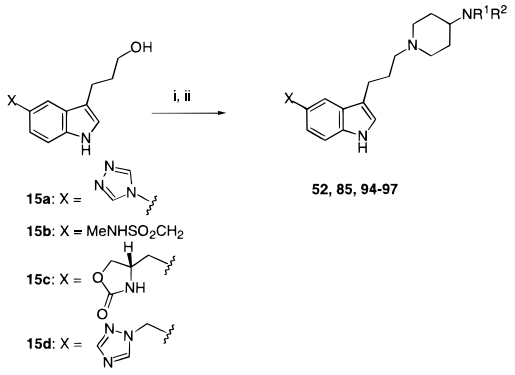
[a] Reagents: (i) Pd/C, HCO_2NH_4, MeOH, reflux, 3 h; (ii) 3-furfuraldehyde, $NaCNBH_3$, AcOH, MeOH, rt, 18 h.

Scheme 3[a]



[a] Reagents: (i) Boc_2O, CH_2Cl_2, rt, 18 h; (ii) (a) $LiAlH_4$, THF, reflux, 2.5 h; (b) Boc_2O, rt, 2 h; (iii) H_2, $Pd(OH)_2/C$, MeOH, 40−50 psi, 18 h; (iv) 5-bromopentanal dimethyl acetal, K_2CO_3, DMF, 80 °C, 19 h; (v) 4-(1,2,4-triazol-4-yl)phenylhydrazine, 4% H_2SO_4(aq), reflux, 18 h; (vi) RCHO, [Ti(O*i*-Pr)$_4$], $NaCNBH_3$, AcOH, MeOH, rt (method C); (vii) RSO_2Cl, Et_3N, DME, rt (method D); (viii) RNCO, THF, rt (method E); (ix) RCH_2Br, K_2CO_3, DMF, 60 °C (method F).

Scheme 4[a]



[a] Reagents: (i) $MeSO_2Cl$, Et_3N, THF, rt; (ii) 4-(2-keto-1-benzimidazolinyl)piperidine, **86**, **87**, **88**, or **89**, K_2CO_3, *i*-PrOH, 100 °C (method G).

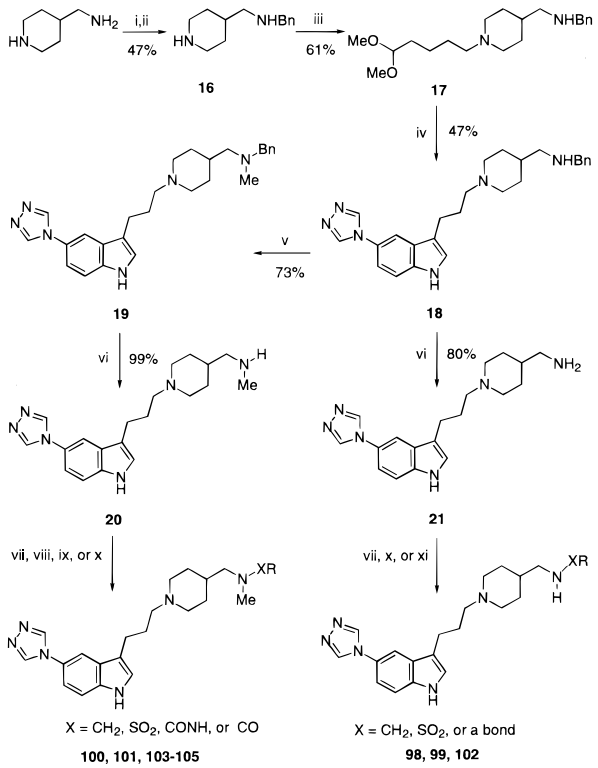
isocyanates to produce ureas, or alkylated with aldehydes and sodium cyanoborohydride or bromides and potassium carbonate.

The third route involved displacement of the crude mesylate, formed from the 3-(5-substituted-indol-3-yl)-propanols (**15a**−**d**), by the appropriate 4-substituted piperidines (**86**−**89**) (Scheme 4).

The 4-(aminomethyl)piperidine analogues were prepared by two routes. The first started with 4-(aminomethyl)piperidine, which was regioselectively N-benzylated to give **16** (Scheme 5). Alkylation of **16** with 5-bromopentanal dimethyl acetal to give **17**, followed by Fischer indolization, afforded **18**. This was N-methylated to give **19**, which was then debenzylated to the secondary amine (**20**). This could then be used to prepare further analogues in a manner similar to that described above. Alternatively, the benzyl group was removed by hydrogenation over palladium hydroxide to give the primary amine (**21**), which was then reductively alkylated with various aldehydes.

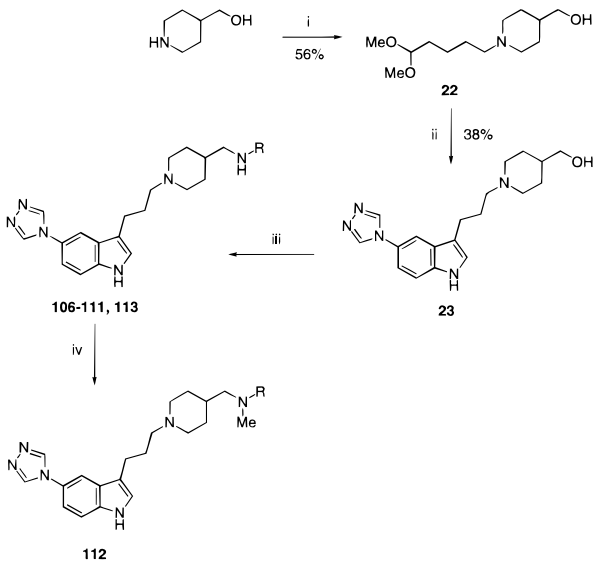
The second route proceeded by alkylation of 4-piperidinemethanol with 5-chloropentanal dimethyl acetal to produce **22**, which was then converted to the indole derivative (**23**) (Scheme 6). The hydroxyl group was

Scheme 5[a]



[a] Reagents: (i) PhCHO, toluene, Dean−Stark trap, reflux, 5 h; (ii) $NaBH_4$, EtOH, rt, 1.25 h; (iii) $(MeO)_2CH(CH_2)_4Br$, K_2CO_3, DMF, 90 °C, 4 h; (iv) 4-(1,2,4-triazol-4-yl)phenylhydrazine, 4% H_2SO_4(aq), reflux, 20 h; (v) 38% CH_2O(aq), $NaCNBH_3$, AcOH, MeOH, rt, 3 h; (vi) H_2, $Pd(OH)_2$, EtOH, 40−50 psi, 23−24 h; (vii) RCHO, $NaCNBH_3$, AcOH, MeOH, rt (method C); (viii) RSO_2Cl, Et_3N, DME or CH_2Cl_2, rt (method D); (ix) RNCO, THF, rt (method E); (x) RCO_2H, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate, Et_3N, DMF, rt (method I); (xi) R−Br, *i*-Pr_2NEt, $EtOCH_2CH_2OH$, 145 °C (method H).

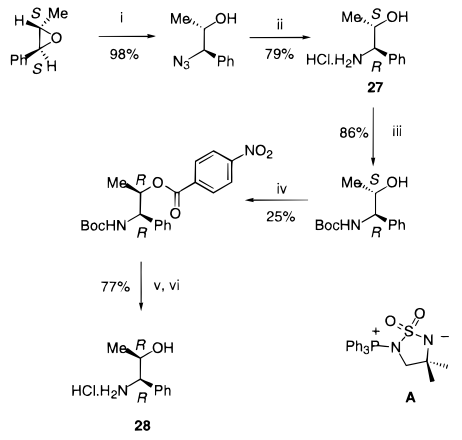
Scheme 6[a]



[a] Reagents: (i) $(MeO)_2CH(CH_2)_4Cl$, K_2CO_3, DMF, 80 °C, 20 h; (ii) 4-(1,2,4-triazol-4-yl)phenylhydrazine, 4% H_2SO_4(aq), reflux, 18 h; (iii) (a) pyridine·SO_3, Et_3N, DMSO, rt; (b) RNH_2, $NaCNBH_3$, AcOH, MeOH, rt (method J); (iv) 38% CH_2O(aq), $NaCNBH_3$, AcOH, MeOH, rt (method B).

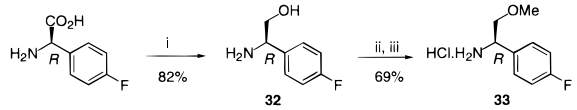
oxidized to the aldehyde using sulfur trioxide pyridine complex and triethylamine in DMSO. This aldehyde,

Scheme 7[a]



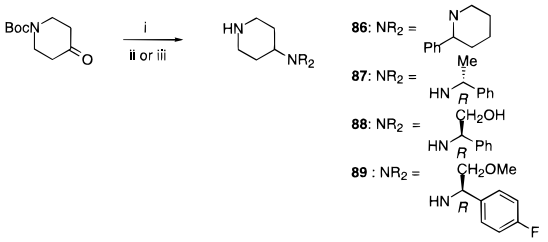
[a] Reagents: (i) NaN_3, NH_4Cl, EtOH−H_2O, reflux, 2 h; (ii) H_2, Pd−C, EtOH, 5 N HCl, 50 psi, 16 h; (iii) Boc_2O, CH_2Cl_2, Et_3N, rt, 1 h; (iv) 4-nitrobenzoic acid, **A**, toluene, rt 17 h; (v) 2 N NaOH(aq), MeOH, rt, 30 min; (vi) HCl(g), MeOH, rt, 1.5 h.

Scheme 8[a]



[a] Reagents: (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) KH, MeI, THF, rt, 2 h; (iii) HCl, Et_2O.

Scheme 9[a]



[a] Reagents: (i) HNR_2, (Ti(O*i*-Pr)$_4$), $NaCNBH_3$, MeOH, (AcOH); (ii) CF_3CO_2H, CH_2Cl_2; (iii) HCl, Et_2O.

which proved to be unstable when concentrated, was utilized crude in the final reductive amination step.

The amines utilized in the reductive aminations in Schemes 1 and 6 were generally commercially available or known in the literature. However, some compounds (**24**−**33**) were novel, or the known synthetic routes were not appropriate, and they were prepared as described in the Experimental Section and shown in Schemes 7 and 8. The 4-substituted piperidines used in Scheme 4 that were not commercially available (**86**−**89**) were prepared as shown in Scheme 9 by reductive amination of *N*-(*tert*-butoxycarbonyl)-4-piperidone by the appropriate amine.

Results and Discussion

The compounds in Tables 1−7 were evaluated for their affinity to cloned human 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in CHO cells.[21] Their intrinsic efficacy, expressed as a percentage of the maximal 5-HT response, was measured in the same cell lines using agonist-induced [^{35}S]GTPγS binding.

It can be seen from Table 1 that the direct attachment of a benzylamino functionality to the 4-position of the piperidine to give **34** led to an increase in h5-HT_{1D} receptor affinity and 1B/1D selectivity over the simple 4-amino derivative (**35**). Substitution of the phenyl ring in the para position with an acetamido group (**36**) did not improve this, and insertion of an extra methylene spacer between the phenyl ring and the nitrogen atom (**37**) led to a fall in affinity.

Replacement of phenyl by 2-, 3-, or 4-pyridyl (**38**, **39**, and **40**) was detrimental to both affinity and selectivity, although the 3-furyl analogue (**41**) had similar affinity and selectivity to **34**. However, this compound, like **34**, was only a partial agonist at the 5-HT_{1D} receptor, whereas a level of agonism similar to that of sumatriptan (≥90% efficacy) was desired.

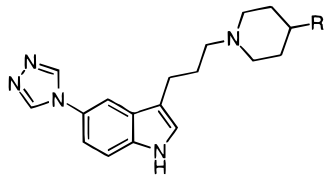
Methylation of the exocyclic nitrogen atom of **34** to give **42** resulted in an increase in selectivity and, moreover, this compound was a full agonist. Similar changes to those performed above such as substitution at the para position (**43** and **44**), insertion of an additional methylene (**45**), and replacement by a heterocycle (**46**−**49**) were generally detrimental to selectivity, although the 3-thienyl analogue (**48**) had comparable affinity to **42** and was again a full agonist.

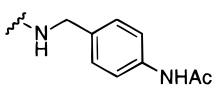
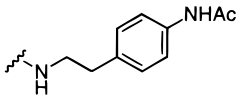
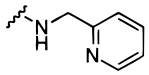
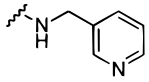
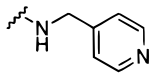
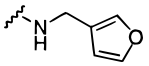
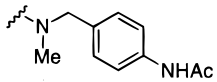
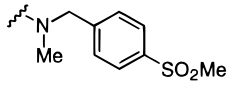
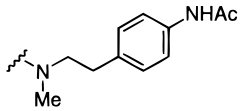
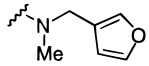
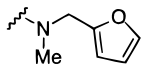
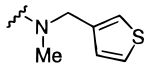
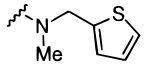
Replacing the methylene linkage between the phenyl ring and the nitrogen atom of **42** by sulfonyl (**50**) or an amide linkage (**51**) led to a loss in selectivity and, in the case of the latter compound, affinity (Table 2). The benzimidazolinyl derivative (**52**), which can be viewed as a conformationally restricted analogue of **51**, had good affinity and selectivity but was a partial agonist. Replacement of the phenyl group by cyclopropylmethyl (**53**), 2-butyn-1-yl (**54**), allyl (**55**), or 4-methyl-3-penten-1-yl (**57**) gave much reduced selectivity and, in most cases, affinity. However, the dimethylallyl group proved to be a very good phenyl bioisostere with **56** having excellent affinity and selectivity as well as being a full agonist.

Since it appeared that, in order to obtain full agonism in this series, the exocyclic nitrogen atom had to be methylated, it was speculated whether this methyl group could be transposed to the adjacent benzylic carbon atom and retain this property. When this was performed, it was found gratifyingly that both *R*- and *S*-enantiomers (**58** and **59**) had high affinity and selectivity, although only the *R*-isomer was a full agonist (Table 3). Following this discovery, modifications were once again explored such as substitution at the para position (**60** and **61**) and spacing out the phenyl ring with a methylene (**62**), a hydroxymethylene (**64** and **65**), or an amide linkage (**63**). However, with the notable exception of the racemic *p*-fluorophenyl derivative (**61**), affinity, selectivity, and efficacy suffered as a result of these changes.

Modifications of the α-methyl group of **58** by introduction of polar functionalities were then prepared (Table 4). Replacement of the methyl in **58** by a hydroxymethyl group to give the phenylglycinol derivative (**66**) resulted in a significant reduction in affinity and efficacy. (Note that **58** and **66** have the same absolute configuration, with the change from (*R*) to (*S*) in the nomenclature arising from the change in the priorities of the groups.) Interestingly, when the same modification was carried out on the opposite enantiomer (**59**) to give **68**, there was little change in the affinity and selectivity, and moreover **68** was found to be a full

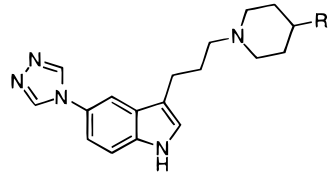
Table 1. Binding and Efficacy of 4-(Arylalkylamino)piperidines

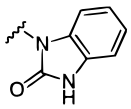
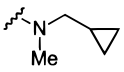
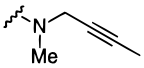
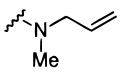
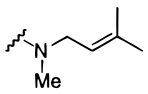
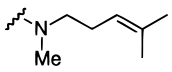


		IC$_{50}$ (nM)[a]		selectivity	EC$_{50}$ (nM)[c]	efficacy		
compound	R	h5-HT$_{1D}$	h5-HT$_{1B}$	1B/1D[b]	h5-HT$_{1D}$	(% 5-HT)[d]	Method[e]	Yield (%)
sumatriptan (**1**)		6.8 (6.2, 7.4)	10 (8.9, 12)	1.5	12 (10, 14)	100±5		
6		3.1 (2.6, 3.7)	28 (23, 34)	9.0	2.3 (1.7, 3.2)	120±13		
ketanserin (**7**)		270[f]	>10,000[f]	>37				
35	NH_2	12	63	5.3			[g]	
34	NHBn	4.6	120	26	7.6	76	A	92
36		3.0 (2.4, 3.6)	45 (30, 66)	15	5.0	75	A	65
37		12	170	14			A	64
38		14	76	5.4			A	66
39		35	140	4.0			A	66
40		24	140	5.8	13 (11, 17)	80±6	A	53
41		4.5	78	17	7.1 (6.0, 8.3)	65±6	[g]	
42	N(Me)Bn	2.1	140	67	1.5	94	B	76
43		19	100	5.3			C	37
44		18	140	7.8			C	23
45		5.7	66	12			B	57
46		8.1	200	25	8.9	87	C	60
47		9.3 (6.5, 13)	89 (79, 100)	9.6			C	49
48		1.5	35	23	4.2 (2.9, 6.0)	93±19	C	78
49		4.3	140	33	3.5	81	C	26

[a] Displacement of [^{3}H]-5-HT binding to cloned h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors stably expressed in CHO cells. The figures are the geometric mean of at least two independent determinations performed in duplicate. The values in parentheses are the upper and lower limits derived as a result of the SEM. Where these limits are not quoted, only two independent determinations were performed. In each case the radioligand concentration used was approximately at the K_D for the receptor. [b] Binding selectivity for h5-HT$_{1D}$ receptors. [c] Measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells stably transfected with h5-HT$_{1D}$ receptors. The values in parentheses are the upper and lower limits derived as a result of the SEM. Where these limits are not quoted, only two independent determinations were performed. [d] Maximum stimulation of [^{35}S]GTPγS binding expressed relative to the maximal effect produced by 5-HT. Values are the arithmetic mean ± SEM of at least two independent determinations. Where SEM is not quoted, only two independent determinations were performed. [e] See Experimental Section. [f] This value is from a single determination. [g] See Scheme 2.

Table 2. Binding and Efficacy of Alternatively Substituted 4-(Amino)piperidines



		IC_{50} (nM)[a]		selectivity	EC_{50} (nM)[c]	efficacy		
compound	R	h5-HT_{1D}	h5-HT_{1B}	1B/1D[b]	h5-HT_{1D}	(% 5-HT)[d]	Method[e]	Yield (%)
50	$N(Me)SO_2Ph$	1.5	10	6.7			D	37
51	N(Me)CONHPh	18	140	7.8			E	65
52		1.2	74	62	2.2	72	G	53
53		22	260	12			C	86
54		9.8	81	8.3			A+B	5[f]
55		20	320	16			F	30
56		0.5	41	82	1.8	115	F	26
57		2.6	24	9.2			F	29

[a–e] See corresponding footnotes in Table 1. [f] Yield for two steps.

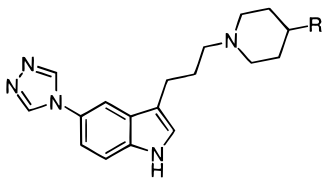
agonist. N-Methylation of both isomers to give **67** and **69** resulted in reduced selectivity for **67** and reduced efficacy for **69**. A reduction in selectivity was also observed on derivatization of the hydroxyl group of **68** to form the primary carbamate (**73**) and replacement by a methanesulfonamide moiety (**76**) or by a dimethylamino group (**77**).

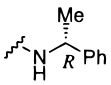
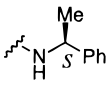
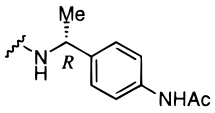
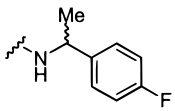
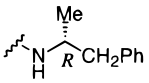
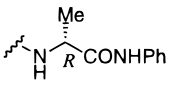
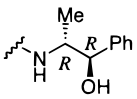
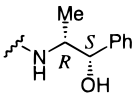
One carbon homologation of **66** to give the (*S*)-phenylalaninol derivative (**71**) retained the affinity and selectivity, although this was still a partial agonist. Surprisingly, the corresponding *R*-enantiomer (**72**) showed a reduction in both affinity and selectivity. Two of the more successful changes, in terms of retaining efficacy, were methylation of the hydroxyl group of **68** to give **74**, which retained similar properties to **68**, and one carbon homologation of the hydroxy functionality to give the hydroxyethyl analogue (**75**), which was a full agonist as the racemate but suffered a slight drop in affinity and selectivity.

Inspection of the log *D* values for the (*R*)-phenylglycinol (**68**) and its N-methylated analogue (**69**) showed that, although **68** is a secondary amine, its log *D* was +0.53. This is higher than the tertiary amine (**69**), which had a value of +0.44. In the absence of the hydroxymethyl substituent, N-methylation of a secondary amine usually results in an increase of log *D* by at least half a log unit. Thus, **34** and **42** have log *D* values of +0.79 and +1.65, respectively. Although spectroscopic support has not yet been obtained, it was hypothesized that this apparent anomalous behavior may be due to intramolecular hydrogen bonding between the exocyclic amino and the hydroxy functionalities. Thus, in the case of the secondary amine **68**, such a five-membered intramolecular H-bond would not suffer from the unfavorable 1,2-steric interactions between the *N*-methyl group and the phenyl ring that would be present in **69**. This would make the H-bond less energetically favorable in the latter compound and lead to a more solvent exposed hydroxyl group and an unusually low log *D*.

The lack or presence of this intramolecular H-bond would dictate the conformation of this part of the molecule and might influence the optimal position of the phenyl ring in the receptor cavity and lead to changes in affinity and efficacy. It was envisaged that modulation of these H-bonding characteristics could also be achieved by moving the methyl group on the nitrogen atom of **69** to the carbon atom bearing the hydroxyl group. To test this hypothesis the diastereomeric compounds **78** and **79** were prepared. It was anticipated that the former diastereomer would make the intramolecular H-bond less favorable by introducing 1,2-steric interactions between the phenyl and methyl groups, which would be absent in the latter. As anticipated, despite the introduction of the methyl group, the log *D* of **78** was only +0.46, supporting a weakening of the intramolecular H-bond, whereas the log *D* of **79** was significantly higher at +0.86.[22] It appeared that this was also important for affinity and selectivity since **79**

Table 3. Binding and Efficacy of α-Methyl Substituted 4-(Amino)piperidines



		IC$_{50}$ (nM)[a]		selectivity	EC$_{50}$ (nM)[c]	efficacy		
compound	R	h5-HT$_{1D}$	h5-HT$_{1B}$	1B/1D[b]	h5-HT$_{1D}$	(% 5-HT)[d]	Method[e]	Yield (%)
58		0.4 (0.4, 0.4)	35 (34, 37)	88	13 (8.9, 19)	90±3	A	72
59		0.6 (0.4, 0.8)	95 (78, 120)	160	12	76	A	56
60		29	350	12			A	35
61		1.9	230	120	0.5 (0.3, 0.9)	99±2	A	51
62		5.5	170	31	6.8 (5.9, 7.8)	71±5	A	47
63		7.6	85	11	15	61	A	66
64		11	200	18	15	76	A	59
65		12	210	18			A	83

[a–e] See corresponding footnotes in Table 1.

retained the properties of **68**, whereas **78** showed a 6-fold reduction in affinity and a drop in selectivity too. Unfortunately, the stabilization of an intramolecular H-bond in **79** could not be supported by molecular modeling studies.[23]

Rather than utilizing intramolecular H-bonding, another way of orientating the phenyl ring is to use covalent conformational constraints. Thus, some conformationally restricted analogues of **58** and **68** were prepared (Table 5). Although the racemic indanyl analogue (**82**) and the 1-amino-2-indanols (**83** and **84**) were found to have reduced selectivity and efficacy, the 2-phenylpiperidine (**85**) did show excellent selectivity, albeit it was not a full agonist. Molecular modeling showed a good overlay of the second-to-lowest energy conformer of **68** onto the lowest energy conformer of **85** (Figure 1) and lended some support to the existence of a H-bond, although its geometry was not that favorable.[23]

Finally, the optimal compound from this series was achieved by a simple incorporation of a fluorine atom in the para position of the phenyl ring of **68** to produce

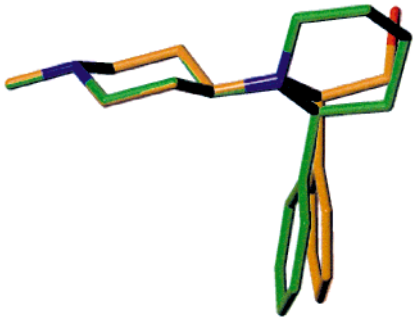
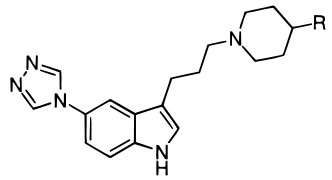


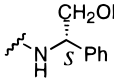
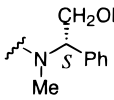
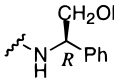
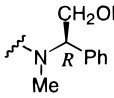
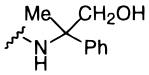
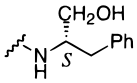
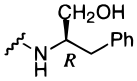
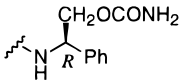
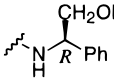
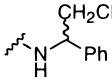
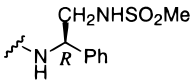
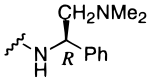
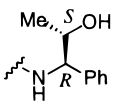
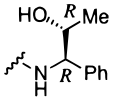
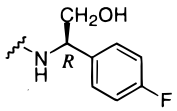
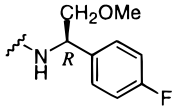
Figure 1. Overlay of low-energy conformations of **68** (brown) onto **85** (green).

a compound (**80**, L-772,405) with excellent affinity (0.9 nM), selectivity (1B/1D 170), and efficacy (102%). This compound also showed functional selectivity, having lower efficacy for the h5-HT$_{1B}$ subtype in the GTPγS assay (EC$_{50}$ 1600 ± 300 nM; 73 ± 2% 5-HT). The methoxy analogue (**81**) was not quite so selective.

To determine whether the 1,2,4-triazol-4-yl was the optimum substituent at the C-5 position of the indole ring, analogues of **58**, **68**, and **81** with other heterocycles

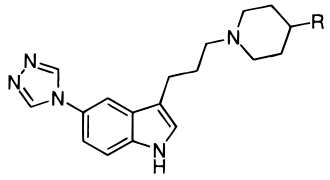
Table 4. Binding and Efficacy of Other α-Substituted 4-(Amino)piperidines

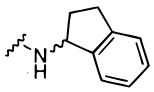
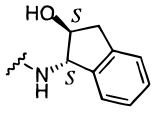
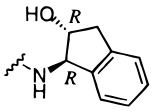
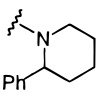


		IC_{50} (nM)[a]		selectivity	EC_{50} (nM)[c]	efficacy		
compound	R	h5-HT_{1D}	h5-HT_{1B}	1B/1D[b]	h5-HT_{1D}	(% 5-HT)[d]	Method[e]	Yield (%)
66		3.5	160	46	2.6	67	A	59
67		4.3	71	17			B	58
68		1.3 (1.1, 1.4)	110 (87, 115)	85	1.7	95	A	78
69		4.5	210	47	10	82	B	66
70		5.2	98	19	3.4	59	A	7
71		2.1	140	67	3.6	76	A	61
72		8.3	100	12	14	74	A	63
73		4.7	120	26	9.3	73	A	67
74		3.0	210	70	0.9	93	A	35
75		5.5	150	27	5.1	100	A	92
76		15	78	5.2			A	66
77		1.5	13	8.7			A	92
78		7.6	150	20	30	81	A	50
79		0.9	48	53	1.0	85	A	43
80		0.9 (0.8, 1.1)	150 (120, 190)	170	0.8 (0.7, 1.0)	102±7	A	51
81		1.4	89	64			A	42

[a–e] See corresponding footnotes in Table 1.

Table 5. Binding and Efficacy of Conformationally Restricted 4-(Benzylamino)piperidines



		IC$_{50}$ (nM)[a]		selectivity	EC$_{50}$ (nM)[c]	efficacy		
compound	R	h5-HT$_{1D}$	h5-HT$_{1B}$	1B/1D[b]	h5-HT$_{1D}$	(% 5-HT)[d]	Method[e]	Yield (%)
82		8.9 (7.1, 11)	280 (180, 420)	31	25	68	A	74
83		37	300	8.1			A	37
84		6.6	210	32	13	75	A	74
85		1.9	410	220	4.7	65	G	29

[a−e] See corresponding footnotes in Table 1.

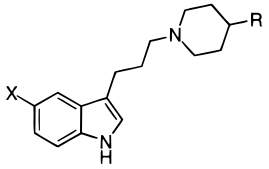
were synthesized (Table 6). The 1,2,4-triazol-1-yl derivative (**90**) and the imidazol-1-yl analogue (**92**) having the α-methylbenzyl group of **58** showed significantly reduced affinity, selectivity, and efficacy, while the corresponding analogues (**91** and **93**) having the α-(hydroxymethyl)benzyl group of **68** gave comparable affinities and selectivities but again were only partial agonists. The (1,2,4-triazol-1-yl)methyl side chain found in rizatriptan resulted in compounds (**94** and **95**) with very good selectivity, although affinity was somewhat lowered as was efficacy. The (2-oxo-1,3-oxazolidin-4-yl)-methyl side chain of zolmitriptan in **96** led to a drop in affinity and efficacy, though selectivity was maintained. Finally, the (methylaminosulfonyl)methyl substituent of sumatriptan in **97** gave a dramatic reduction in both affinity (130-fold) and selectivity (17-fold).

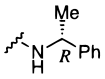
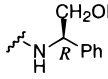
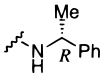
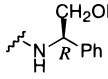
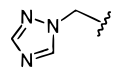
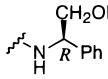
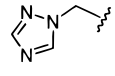
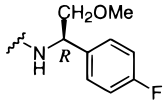
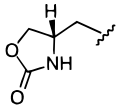
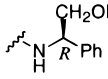
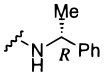
A series of compounds was also prepared in which the exocyclic nitrogen atom was moved out by one carbon atom (Table 7). The simple benzylaminomethyl derivative (**18**) had good affinity and moderate selectivity and encouragingly was a full agonist, properties that were maintained in its *N*-methyl analogue (**19**). Modifications similar to those shown in Tables 1−6 were explored in this series such as substitution on the phenyl ring (**98**, **100**, and **101**), replacement of the phenyl ring by a heterocycle (**99**), and changes of the methylene group linking the phenyl ring and the exocyclic nitrogen atom to a sulfonyl (**102** and **103**), carbonyl (**105**), or amide spacer (**104**). The best compound to emerge from this series was the *N*-methyl-4-acetamidobenzyl analogue (**100**) which had excellent affinity (0.6 nM) and efficacy (94%), but only moderate binding selectivity (1B/1D 40). Remarkably, **100** had 780-fold selectivity over 5-HT$_{1A}$ receptors (IC$_{50}$ 470 nM), a level not usually seen before with other 5-HT$_{1D}$ receptor agonists.[24] Introduction of methyl (**106**−**109**) or hydroxymethyl (**110**−**112**) substituents at the benzylic position, which had proved so successful in the aminopiperidine series, did not confer any improvement in selectivity in this series.

The selectivity of **80** (L-772,405) was tested on other cloned serotonin receptors using radioligand binding techniques (Table 8) and found to have >70-fold selectivity over h5-HT$_{1A}$ receptors, >500-fold selectivity over 5-HT$_7$ receptors, and >1000-fold selectivity over all other 5-HT receptors tested. The selectivity over h5-HT$_{1A}$ receptors was better than any other directly linked aminopiperidine tested and may be important to avoid unwanted side effects, such as hypotension, resulting from binding to these receptors in the brain. The >10000-fold selectivity over 5-HT$_{1F}$ receptors is also worthy of mention since the triptans (**1**−**5**) all have some affinity (<1 μM) for this receptor. In addition, L-772,405 had >1 μM affinity at over 100 other receptors, ion channels, and proteins tested, including 5-HT$_3$ and 5-HT$_4$.

L-772,405 exhibited low oral bioavailability in rat (F < 5%), this being a general feature of the series. It was found that the concentrations of L-772,405 in the hepatic portal vein after 0.5 and 2 h following a 3 mg/kg po dose were extremely low (<2 and 6 ± 4 ng/mL, respectively), suggesting that the poor oral bioavailability was due to poor absorption or gut wall metabolism rather than first pass metabolism alone. A major metabolizing enzyme in gut wall is cytochrome P450 3A, and therefore L-772,405 was coadministered with erythromycin, an inhibitor of cytochrome P450 3A. Much higher concentrations of L-772,405 in the hepatic portal vein (ca. 140 ng/mL) were obtained, suggesting that gut wall metabolism was at least a factor in limiting the oral bioavailability of the compound. Following subcu-

Table 6. Binding and Efficacy of Alternative 5-Substituted 4-(Benzylamino)piperidines



compound	X	R	IC_{50} (nM)[a] h5-HT_{1D}	IC_{50} (nM)[a] h5-HT_{1B}	selectivity 1B/1D[b]	EC_{50} (nM)[c] h5-HT_{1D}	efficacy (% 5-HT)[d]	Method[e]	Yield (%)
90			18	420	23	18	69	A	66
91			4.1 (3.2, 5.1)	400 (350, 460)	98	7.4	77	A	65
92			4.2	110	26	6.2 (4.3, 8.9)	65±3	A	89
93			0.7	100	140	0.8 (0.6, 1.0)	74±9	A	62
94			23	1300	57	32 (24, 44)	76±2	G	67
95			5.0	1200	240	8.9 (4.8, 17)	89±3	G	12
96			6.3	460	73	6.0	83	G	63
97	$MeNHSO_2CH_2$		43	260	6.0			G	74

[a–e] See corresponding footnotes in Table 1.

taneous dosing to rats at 3 mg/kg, L-772,405 showed excellent bioavailability (*F* 88%) and plasma concentrations (C_{max} 323 ng/mL; T_{max} 30 min) (Figure 2) and is well distributed into body tissue (V_D 7.4 L/kg), resulting in a fairly long plasma half-life ($t_{1/2}$ 7.2 h).[25] The compound was also found to significantly penetrate into the brain following both iv and sc administration, with brain/plasma ratios at 6 h greater than unity. This may be relevant in order for it to possess the centrally mediated component to its potential effectiveness as an antimigraine agent.

Conclusions

A series of novel, potent, selective h5-HT_{1D} receptor agonists have been developed which have up to 240-fold selectivity over the h5-HT_{1B} subtype. This has led to the identification of **80** (L-772,405), which also shows very good selectivity over a range of other serotonin and nonserotonin receptors. This compound, therefore, constitutes a valuable tool to delineate the role of h5-HT_{1D} receptors in migraine and other diseases.

Experimental Section

General Methods. Melting points were obtained on a Reichert Thermovar hot stage and are uncorrected. Proton and carbon NMR spectra were obtained using either a Bruker AM360 or a Bruker AC250 spectrometer. Mass spectra were recorded on a Quattro operating in an electrospray (ES) mode.

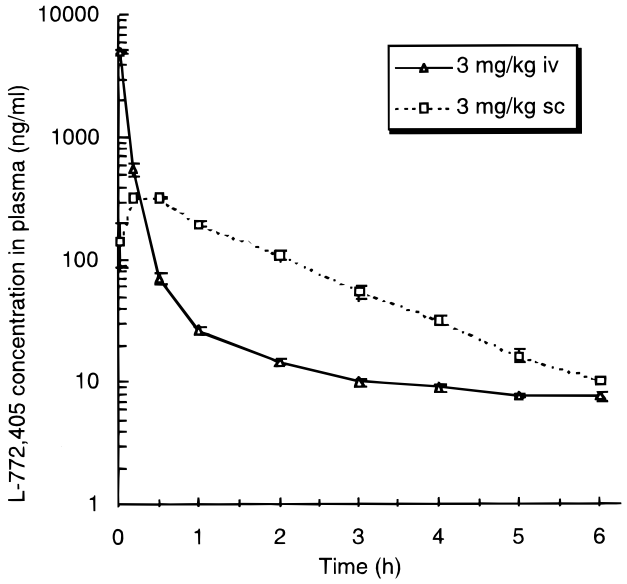
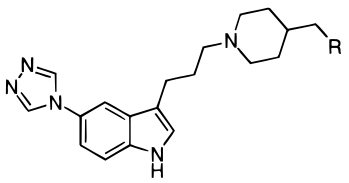
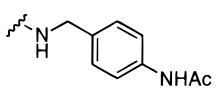
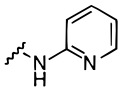
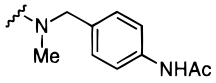
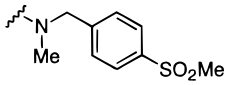
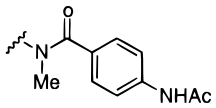
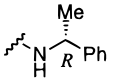
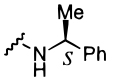
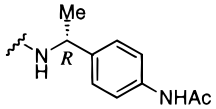
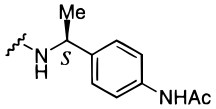
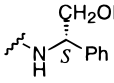
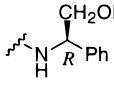
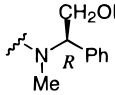
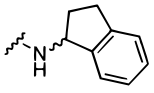


Figure 2. Concentrations of **80** (L-772,405) in plasma following iv and sc administration to male Sprague–Dawley rats.

Table 7. Binding and Efficacy of Substituted 4-(Aminomethyl)piperidines



		IC$_{50}$ (nM)[a]		selectivity	EC$_{50}$ (nM)[c]	efficacy		
compound	R	h5-HT$_{1D}$	h5-HT$_{1B}$	1B/1D[b]	h5-HT$_{1D}$	(% 5-HT)[d]	Method[e]	Yield (%)
18	NHBn	1.6	28	18	5.6	101	[f]	
98		4.2 (2.9, 6.0)	8.9 (6.3, 13)	2.1			C	41
99		1.7	3.3	1.9			H	20
19	N(Me)Bn	0.9	27	30	0.9	93	[f]	
100		0.6	24	40	2.8	94	C	70
101		8.1	66	8.1			C	44
102	NHSO$_2$Ph	6.2	60	10	12	73	D	28
103	N(Me)SO$_2$Ph	1.6	18	11			D	68
104	N(Me)CONHPh	5.9	6.2	1.1			E	89
105		17	40	2.4			I	38
106		1.4	14	10			J	13
107		4.4	58	13			J	34
108		1.5 (1.3, 1.8)	8.9 (6.8, 12)	5.9			J	5
109		0.6	9.3	16	3.0 (1.9, 4.7)	99±6	J	5
110		3.4	34	10			J	32
111		5.9	79	13			J	34
112		6.0	85	14			B	55
113		1.1	25	23	1.3	78	J	37

[a–e] See corresponding footnotes in Table 1. [f] See Scheme 5.

Table 8. In Vitro Binding Profile of 80 (L-772,405)

	IC_{50} (nM)[a]								
compd	h5-HT_{1D}	h5-HT_{1B}	h5-HT_{1A}	h5-HT_{1E}	h5-HT_{1F}	h5-HT_{2A}	h5-HT_{5A}	r5-HT_6	r5-HT_7
80	0.9 (0.8, 1.1) ($n = 5$)	150 (120, 190) ($n = 4$)	66 (54, 81) ($n = 3$)	>10000 ($n = 3$)	>10000 ($n = 3$)	1100 ($n = 2$)	>10000 ($n = 2$)	>10000 ($n = 2$)	540 ($n = 2$)

[a] See corresponding footnote in Table 1. Cloned rat receptors were used for 5-HT_6 and 5-HT_7 determinations.

(Note that only the strongest peaks from the mass spectra are reported below.) Elemental analysis for carbon, hydrogen, and nitrogen were performed by Butterworth Laboratories Ltd. High-performance liquid chromatography (HPLC) was performed on a Hewlett-Packard HP1090 instrument using a Spherisorb S5 ODS2 column, eluting with acetonitrile/water (containing 0.2% triethylamine and made to pH 3 with orthophosphoric acid). Analytical thin-layer chromatography (TLC) was conducted either on precoated silica gel 60 F_{254} plates (Merck) or on precoated aluminum oxide 60 F_{254} neutral (type E) aluminum sheets (Merck). Visualization of the plates was accomplished by using UV light and/or iodine and/or aqueous potassium permanganate solution. Chromatography was conducted either on silica gel 60, 220−440 mesh (Fluka), or aluminum oxide 90, activity II−III (Merck), under low pressure. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated. Triethylamine, *N*,*N*-diisopropylethylamine, and piperidine were distilled from calcium hydride. Petroleum ether refers to that fraction having a boiling point range of 60−80 °C.

The method of synthesis of each final compound is indicated in Tables 1−7, and only one representative example of each method is described below.

5-Bromopentanal Dimethyl Acetal. To a solution of 5-bromovaleryl chloride (50 g, 0.251 mol) in anhydrous THF (500 mL), at −78 °C, was added lithium tri-*tert*-butoxyaluminohydride (1.0 M solution in THF, 300 mL, 0.30 mol), keeping the temperature below −70 °C. The solution was stirred at −78 °C for 5 h and then quenched by the dropwise addition of 2 M aqueous HCl (350 mL). The mixture was warmed to room temperature and stirred for 16 h. Diethyl ether (500 mL) was added, the aqueous phase was separated and extracted further with ether (×2). The combined extracts were washed with saturated aqueous Na_2CO_3, water, then brine (×2), dried (Na_2SO_4), and evaporated to give 5-bromovaleraldehyde (37.5 g, 91%). A solution of 5-bromovaleraldehyde (37.5 g, 0.227 mol) in methanol (250 mL) and concentrated sulfuric acid (0.5 mL) was stirred at room temperature for 3 h. The solvent was evaporated, and to the residue were added aqueous K_2CO_3 (50 mL) and diethyl ether (500 mL). The aqueous layer was separated and re-extracted with ether (×2). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 10% Et_2O/hexane) to give 27.5 g (57%) of 5-bromopentanal dimethyl acetal: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43−1.67 (4H, m), 1.83−1.94 (2H, m), 3.38 (6H, s), 3.42 (2H, t, $J = 7$ Hz), 4.37 (1H, t, $J = 7$ Hz).

5-(4-Hydroxypiperidin-1-yl)pentanal Dimethyl Acetal (9). A mixture of 5-bromopentanal dimethyl acetal (3.34 g, 15.8 mmol), anhydrous potassium carbonate (2.218 g, 15.8 mmol), and 4-hydroxypiperidine (2.0 g, 19.8 mmol) in anhydrous DMF (50 mL) was stirred at 80−90 °C for 3 h under nitrogen. After cooling, the mixture was diluted with water (150 mL) and basified with saturated aqueous K_2CO_3, and the product was extracted with ethyl acetate (3 × 250 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) gave 2.71 g (74%) of **9** as a colorless oil: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.06−1.56 (8H, m), 1.62−1.75 (2H, m), 1.86−2.00 (2H, m), 3.20 (6H, s), 3.34−3.47 (1H, m), 4.31 (1H, t, $J = 5.7$ Hz), 4.53 (1H, d, $J = 4.2$ Hz); MS (ES^+) m/z 232 $(M + H)^+$.

1-{3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-ol (10a). A solution of **9** (2.70 g, 11.7 mmol) and 4-(1,2,4-triazol-4-yl)phenylhydrazine[26] (2.15 g, 12.3 mmol) in 4% aqueous H_2SO_4 (100 mL) was refluxed for 9 h. After cooling to room temperature, the reaction mixture was basified with saturated aqueous K_2CO_3 and extracted with ethyl acetate (3 × 250 mL) and then ethyl acetate/1-butanol (1:1, 2 × 250 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 85:15:1.5) gave 1.96 g (52%) of **10a** as a pale yellow foam. The oxalate salt was prepared and recrystallized from ethanol−diethyl ether: mp 102−105 °C; ^{1}H NMR (360 MHz, D_2O) δ 7.31 (1H, dd, $J = 8.6$ and 2.6 Hz), 7.36 (1H, d, $J = 2.6$ Hz), 7.61 (1H, d, $J = 8.6$ Hz), 7.75 (1H, s), 8.87 (2H, s) among other signals; MS (ES^+) m/z 326 $(M + H)^+$. (Found: C, 55.76; H, 5.99; N, 15.43. $C_{18}H_{23}N_5O \cdot 1.35(C_2H_2O_4)$ requires: C, 55.63; H, 5.80; N, 15.67%).

1-{3-[5-(Imidazol-1-yl)-1*H*-indol-3-yl]propyl}piperidin-4-ol (10b). To a stirred solution of imidazole (34.1 g, 0.501 mol) in anhydrous DMF (300 mL) under Ar was added portionwise, over 23 min, sodium hydride (60% dispersion in oil; 20.02 g, 0.500 mol). The mixture was then stirred at room temperature for 18 min before adding dropwise, over 40 min, a solution of 1-fluoro-4-nitrobenzene (70.62 g, 0.500 mol) in anhydrous DMF (60 mL). The mixture was then stirred at room temperature overnight. Water (600 mL) was then added, and the solid was collected by filtration, washed with water, then stirred in boiling ethyl acetate (400 mL), and allowed to cool. The resulting solid was again collected by filtration, washed with more ethyl acetate (50 mL), and then washed with petroleum ether (250 mL). The filtrate, now containing more solid, was refiltered and washed with petroleum ether. The combined solids were dried in a vacuum desiccator overnight to give 90.14 g (95%) of 4-(imidazol-1-yl)-1-nitrobenzene as a yellow solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.19 (1H, t, $J = 1.1$ Hz), 7.97−8.03 (3H, m), 8.38 (2H, d, $J = 9.2$ Hz), 8.52 (1H, t).

A mixture of 4-(imidazol-1-yl)-1-nitrobenzene (89.60 g, 0.474 mol) and 10% palladium on carbon (4.50 g) in ethanol (1200 mL) and 5 N aqueous HCl (189 mL) was hydrogenated in two batches at 40 psi for 80 min. Water (450 mL) was then added to dissolve the product, the catalyst was removed by filtration, washing with more water, and the combined filtrates were evaporated, using finally a freeze-drier, to give 105.4 g (96%) of 4-(imidazol-1-yl)aniline dihydrochloride as a cream solid: ^{1}H NMR (250 MHz, D_2O) δ 7.22 (2H, d, $J = 8.8$ Hz), 7.35 (1H, t, $J = 2.1$ Hz), 7.44 (2H, d, $J = 9.0$ Hz), 7.59 (1H, t, $J = 1.8$ Hz), 8.89 (1H, t, $J = 1.5$ Hz).

To a stirred suspension of 4-(imidazol-1-yl)aniline dihydrochloride (20 g, 86.16 mmol) in concentrated hydrochloric acid (100 mL), cooled to −15 °C, was added dropwise, over 1 h, a solution of sodium nitrite (6.25 g, 9.05 mmol) in water (40 mL). After a further 10 min of stirring at −12 °C, the mixture was quickly filtered to remove a solid, and the filtrate was added portionwise to a stirred solution of tin(II) chloride dihydrate (100 g) in concentrated hydrochloric acid (50 mL), cooled to −20 °C, at such a rate as to maintain the internal temperature below −10 °C (15 min). The mixture was allowed to warm to 5 °C over 30 min, and the solid was collected and washed with diethyl ether (4 × 100 mL). The above solid was suspended in water (200 mL) and basified with 4 N aqueous NaOH and extracted with ethyl acetate (5 × 500 mL). The combined organic solutions were dried (Na_2SO_4) and filtered. Hydrogen chloride was then bubbled through the filtrate while stirring vigorously until a deep red mixture was obtained. Stirring was continued for a further 20 min to give a cream solid which was collected by filtration and dried over phosphorus pentox-

ide−potassium hydroxide under high vacuum to leave 12.7 g (60%) of 4-(imidazol-1-yl)phenylhydrazine dihydrochloride: ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.20 (2H, d, J = 9.0 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.91 (1H, t, J = 1.5 Hz), 8.23 (1H, t, J = 1.7 Hz), 9.71 (1H, t, J = 1.3 Hz).

4-(Imidazol-1-yl)phenylhydrazine dihydrochloride was reacted with **9**, using a method similar to that described for **10a**, to give **10b** as a foamy brown solid in 34% yield: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.36 (2H, m), 1.67−1.85 (4H, m), 2.30 (2H, t, J = 6.8 Hz), 2.70 (4H, m), 4.54 (1H, d, J = 4.2 Hz), 7.08 (1H, t, J = 1.1 Hz), 7.23−7.28 (2H, m), 7.44 (1H, d, J = 8.6 Hz), 7.65 (1H, t, J = 1.2 Hz), 7.68 (1H, d, J = 2.1 Hz), 8.12 (1H, t, J = 1.1 Hz), 10.99 (1H, s); MS (ES$^+$) m/z 325 (M + H)$^+$, 210, 163, 154.

1-{3-[5-(1,2,4-Triazol-1-yl)-1*H*-indol-3-yl]propyl}piperidin-4-ol (10c). This was prepared from 4-(1,2,4-triazol-1-yl)-phenylhydrazine (prepared in a similar way to 4-(imidazol-1-yl)phenylhydrazine described above) and **9**, using a method similar to that described for **10a**, to give **10c** in 65% yield: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.28−1.46 (2H, m), 1.64−2.04 (6H, m), 1.95 (2H, m), 2.30 (2H, t, J = 6.8 Hz), 2.72 (4H, br t), 3.35−3.50 (1H, m), 4.53 (1H, d, J = 4.2 Hz), 7.25 (1H, d, J = 2.2 Hz), 7.44−7.54 (2H, m), 7.92 (1H, d, J = 1.7 Hz), 8.18 (1H, s), 9.18 (1H, s), 11.06 (1H, s); MS (ES$^+$) m/z 326 (M + H)$^+$.

1-{3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-one (11a). To a stirred solution of **10a** (105 mg, 0.322 mmol) in a mixture of anhydrous DMSO (3 mL) and anhydrous triethylamine (314 μL, 2.25 mmol) was added portionwise, under nitrogen, solid sulfur trioxide pyridine complex (185 mg, 1.16 mmol) over 7 min. The mixture was stirred at room temperature for 55 min, then diluted with water (20 mL), basified with saturated aqueous K_2CO_3 and extracted with ethyl acetate (3 × 70 mL). The organic extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) afforded 72 mg (69%) of **11a** as a waxy solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.96 (2H, qn, J = 7.3 Hz), 2.42−2.62 (6H, m), 2.72−2.90 (6H, m), 7.13−7.19 (2H, m), 7.50 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 2.0 Hz), 8.42 (1H, br s), 8.48 (2H, s). MS (ES$^+$) m/z 324 (M + H)$^+$.

1-{3-[5-(Imidazol-1-yl)-1*H*-indol-3-yl]propyl}piperidin-4-one (11b). This was prepared from **10b**, using a method similar to that described for **11a**, in 61% yield as a cream solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.96 (2H, qn, J = 7.5 Hz), 2.46 (4H, t, J = 6.1 Hz), 2.56 (2H, t, J = 7.4 Hz), 2.76 (4H, t, J = 6.1 Hz), 2.84 (2H, t, J = 7.5 Hz), 7.13 (1H, d, J = 2.2 Hz), 7.18−7.23 (2H, m), 7.30 (1H, t, J = 1.2 Hz), 7.44 (1H, d, J = 8.5 Hz), 7.58 (1H, d, J = 2.1 Hz), 7.84 (1H, t, J = 1.0 Hz), 8.41 (1H, br s); MS (ES$^+$) m/z 323 (M + H)$^+$.

1-{3-[5-(1,2,4-Triazol-1-yl)-1*H*-indol-3-yl]propyl}piperidin-4-one (11c). This was prepared from **10c**, following a procedure similar to that described for **11a**, in 74% yield as a pale yellow solid: mp 158−161 °C (EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.96 (2H, qn, J = 7.3 Hz), 2.46 (4H, t, J = 6.1 Hz), 2.55 (2H, t, J = 7.2 Hz), 2.75 (4H, t, J = 6.1 Hz), 2.86 (2H, t, J = 7.5 Hz), 7.12 (1H, d, J = 2.2 Hz), 7.40−7.48 (2H, m), 7.88 (1H, s), 8.12 (1H, s), 8.20 (1H, br s), 8.53 (1H, s); MS (ES$^+$) m/z 324 (M + H)$^+$.

1-Benzyl-4-[*N*-(*tert*-butyloxycarbonyl)methylamino]-piperidine (12). To a stirred solution of 4-amino-1-benzylpiperidine (40 g, 0.21 mol) in anhydrous dichloromethane (500 mL) was added di-*tert*-butyl dicarbonate (50.4 g, 0.23 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was removed, and the residue was triturated with diethyl ether. The solid was collected by filtration to give 60.29 g (99%) of 1-benzyl-4-[*N*-(*tert*-butyloxycarbonyl)amino]piperidine as a white solid: mp 135−138 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.53 (2H, m), 1.92 (2H, s), 2.12 (2H, m), 2.83 (2H, m), 3.51 (2H, s), 4.42 (1H, s), 7.22−7.32 (5H, m).

To a cooled (−5 °C) and stirred solution of lithium aluminum hydride (1 M solution in THF; 258 mL) in anhydrous THF (250 mL) under nitrogen was added a solution of 1-benzyl-4-[*N*-(*tert*-butyloxycarbonyl)amino]piperidine (50 g, 172 mmol) in anhydrous THF (750 mL) over 20 min. The mixture was then heated at reflux for 2.5 h, cooled to room temperature, and quenched by the successive addition of water (10 mL), 15% aqueous NaOH (15 mL), and water (30 mL). The resulting mixture was filtered to remove a granular precipitate, and the filtrate was cooled to 0 °C before di-*tert*-butyl dicarbonate (41.3 g) was added. After 2 h at room temperature, the solvent was evaporated and the residue was partitioned between 2 N aqueous NaOH and dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 89:10:1) gave 47.7 g (91%) of **12** as a colorless oil: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.38 (9H, s), 1.49 (2H, m), 1.64 (2H, m), 1.94 (2H, m), 2.66 (3H, s), 2.84 (2H, m), 3.44 (2H, s), 3.70 (1H, m), 7.20−7.35 (5H, m).

4-[*N*-(*tert*-Butyloxycarbonyl)methylamino]piperidine (13). A solution of **12** (42.7 g, 140 mmol) in methanol (500 mL) was shaken under hydrogen over palladium hydroxide on carbon (5 g) at 50 psi for 4 h. More catalyst (5 g) was added, and the mixture was shaken under hydrogen at 40 psi overnight. The catalyst was filtered off, and the filtrate was evaporated to give 27.38 g (91%) of **13** as a colorless solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.39 (9H, s), 1.47−1.60 (4H, m), 2.50 (2H, m), 2.65 (3H, s), 3.00 (2H, m), 3.82 (1H, m).

4-Methylamino-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (14). This was prepared from **13**, using a method similar to that described for **9** and **10a**, to afford **14** as a brown solid in 47% yield over two steps: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.16−1.24 (3H, m), 1.73−1.90 (6H, m), 2.25 (6H, m), 2.70 (2H, t), 2.78 (2H, m), 7.28 (2H, m), 7.46 (1H, d), 7.77 (1H, d), 9.01 (2H, s), 11.08 (1H, s); MS (ES$^+$) m/z 677 (2M + H)$^+$, 339 (M + H)$^+$, 201, 170, 114.

3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol (15a) and **3-(3-hydroxypropyl)-1*H*-indol-5-yl-*N*-methylmethanesulfonamide (15b)** were synthesized by literature procedures.[27,28]

(*S*)-4-[3-(3-Hydroxyproyl)-1*H*-indol-5-ylmethyl]-1,3-oxazolidin-2-one (15c). A mixture of (*S*)-4-(3-iodo-4-aminobenzyl)-1,3-oxazolidin-2-one[26] (800 mg, 2.51 mmol), 1,5-bis-(triethylsilyl)pent-4-yn-1-ol (1.169 g, 3.77 mmol), lithium chloride (107 mg, 2.51 mmol), sodium carbonate (1.33 g, 12.6 mmol), and triphenylphosphine (0.1573 g, 0.60 mmol) in anhydrous DMF (30 mL) was degassed by bubbling through nitrogen for 30 min. Palladium acetate (67.3 mg, 0.30 mmol) was then added, and the mixture was heated at 100 °C, under nitrogen, for 16.5 h. The solvent was evaporated, and the residue was partitioned between water (75 mL) and ethyl acetate (125 mL). The aqueous layer was further extracted with ethyl acetate (2 × 125 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in 5 N aqueous HCl (25 mL) and ethanol (25 mL) and allowed to stand at room temperature for 30 min. The mixture was basified to pH 10 with saturated aqueous K_2CO_3, diluted with water (25 mL), and extracted with ethyl acetate (2 × 125 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 95:5:0.5) to afford 0.420 g (61%) of **15c** as a thick brown oil: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.78 (2H, q, J = 7.9 Hz), 2.69 (2H, t, J = 7.4 Hz), 2.77 (1H, dd, J = 13.5 and 7.1 Hz), 2.89 (1H, dd, J = 13.5 and 4.6 Hz), 3.46 (2H, q, J = 5.3 Hz), 3.98−4.08 (2H, m), 4.18−4.28 (1H, m), 4.42 (1H, t, J = 5.1 Hz), 6.92 (1H, dd, J = 8.3 and 1.5 Hz), 7.06 (1H, d, J = 2.1 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.35 (1H, s), 7.77 (1H, s), 10.66 (1H, s); MS (ES$^+$) m/z 275 (M + H)$^+$.

3-[5-(1,2,4-Triazol-1-ylmethyl)-1*H*-indol-3-yl]propan-1-ol (15d). This was prepared from 2-iodo-4-(1,2,4-triazol-1-ylmethyl)aniline,[29] using a procedure similar to that described for **15c**, in 56% yield as a beige solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.74−1.82 (2H, m), 2.66−2.70 (2H, m), 3.43−3.49 (2H, m), 4.41−4.44 (1H, m), 5.42 (2H, s), 7.01−7.04 (1H, m), 7.11−7.12 (1H, m), 7.28−7.30 (1H, m), 7.51 (1H, s), 7.93 (1H, s), 8.60 (1H, s), 10.79 (1H, s).

4-(Benzylaminomethyl)piperidine (16). A solution of 4-(aminomethyl)piperidine (22.8 g, 200 mmol) and benzaldehyde (21.2 g, 200 mmol) in toluene (200 mL) was refluxed for 5 h, under nitrogen, using a Dean−Stark trap. After cooling, the toluene was removed under vacuum, and the residual oil was dissolved in absolute ethanol (400 mL) and cooled to 5 °C. Sodium borohydride (6 g, 159 mmol) was added portionwise to the above solution over 40 min, under nitrogen, and the mixture was stirred for a further 1.25 h before excess borohydride was destroyed by dropwise addition of 5 N aqueous HCl (150 mL) (CAUTION: hydrogen evolution). The ethanol was evaporated, and the aqueous residue was basified and extracted with ethyl acetate (5 × 500 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated. Column chromatography (alumina, CH_2Cl_2−MeOH−NH_3(aq); 95:5:0.35) of the residue afforded 19.3 g (47%) of **16** as a pale yellow oil: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.13 (2H, dq, J = 12 and 4.0 Hz), 1.50−1.70 (1H, m), 1.78 (2H, br d, J = 11 Hz), 2.47 (2H, d, J = 6.6 Hz), 2.56 (2H, dt, J = 12 and 2.3 Hz), 3.05 (2H, br d, J = 12 Hz), 3.83 (2H, s), 7.30−7.50 (5H, m); MS (ES$^+$) m/z 205 (M + H)$^+$.

5-{4-(Benzylaminomethyl)piperidin-1-yl}pentanal Dimethyl Acetal (17). This was prepared from 5-bromopentanal dimethyl acetal and **16**, using a method similar to that described for **9**, in 61% yield as a pale yellow oil: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.26−2.14 (13H, m), 2.49 (2H, t, J = 7.0 Hz), 2.63 (2H, d, J = 6.6 Hz), 3.04−3.14 (2H, m), 3.49 (6H, s), 3.95 (2H, s), 4.61 (1H, t, J = 5.7 Hz), 7.44−7.62 (5H, m); MS (ES$^+$) m/z 335 (M + H)$^+$.

4-Benzylaminomethyl-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (18). A solution of **17** (2.70 g, 8.07 mmol) and 4-(1,2,4-triazol-4-yl)phenylhydrazine[26] (1.50 g, 8.5 mmol) in 4% H_2SO_4 (100 mL) was refluxed for 20 h. After cooling, the mixture was basified with 4 N sodium hydroxide, and products were extracted with ethyl acetate (3 × 200 mL). The combined organic solutions were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:0.9) gave 1.63 g (47%) of **18** as a thick pale yellow oil. The oxalate salt was prepared and recrystallized from ethanol−methanol: mp 215−220 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.36−1.56 (2H, m), 1.86−2.12 (5H, m), 2.70−2.94 (6H, m), 2.98−3.08 (2H, m), 3.36−3.50 (2H, m), 4.12 (2H, s), 7.30−7.54 (8H, m), 7.80(1H, s), 9.02 (2H, s), 11.95 (1H, s); MS (ES$^+$) m/z 429 (M + H)$^+$. Anal. [$C_{26}H_{32}N_6$·2.5($C_2H_2O_4$)] C, H, N.

4-(*N*-Methylbenzylaminomethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (19) (Method B). To a stirred solution of **18** (1.1 g, 2.57 mmol), formaldehyde (38% w/v solution in H_2O, 263 μL, 3.33 mmol) and glacial acetic acid (734 μL, 12.8 mmol) in anhydrous methanol (40 mL) was added sodium cyanoborohydride (194 mg, 3.08 mmol), and the mixture was stirred for 3 h. Aqueous NaOH (4 N, 15 mL) was added, and the methanol was removed under vacuum. The aqueous residue was extracted with ethyl acetate (2 × 150 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 92:8:0.7) gave 829 mg (73%) of **19**. The oxalate salt was prepared and recrystallized from ethanol: mp 131−134 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.29 (3H, s), 3.72 (2H, s), 7.40−7.24 (7H, m), 7.50 (1H, d, J = 8.6 Hz), 7.81 (1H, d, J = 1.9 Hz), 9.02 (2H, s), 11.19 (1H, s) among other signals; MS (ES$^+$) m/z 443 (M + H)$^+$. Anal. [$C_{27}H_{34}N_6$·2.56($C_2H_2O_4$)] C, H, N.

4-Methylaminomethyl-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (20). A solution of **19** (730 mg, 1.65 mmol) in absolute ethanol (60 mL) was hydrogenated over palladium hydroxide on carbon (20% Pd, 530 mg) for 24 h at 45 psi. The catalyst was removed by filtration, washed with ethanol (3 × 30 mL), and the filtrate was evaporated to leave 573 mg (99%) of **20** as a yellow foam: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.11 (2H, m), 1.33 (1H, m), 1.63 (2H, m), 1.75−1.84 (4H, m), 2.24 (3H, s), 2.26−2.32 (4H, m), 2.70 (2H, t, J = 7.5 Hz), 2.82 (2H, m), 7.26−7.31 (2H, m), 7.47 (1H, d, J = 8.5 Hz), 7.78 (1H, d, J = 2.1 Hz), 9.02 (2H, s), 11.08 (1H, s); MS (ES$^+$) m/z 353 (M + H)$^+$, 177 [M + 2H]$^{2+}$/2, 162, 118.

4-Aminomethyl-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (21). This was prepared from **18**, using a procedure similar to that described for **20**, in 80% yield as a yellow foam: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.06−1.23 (3H, m), 1.64 (2H, m), 1.74−1.83 (4H, m), 2.27 (2H, t, J = 7.7 Hz), 2.43 (2H, d, J = 6.1 Hz), 2.71 (2H, t, J = 7.5 Hz), 2.84 (2H, m), 7.27−7.31 (2H, m), 7.47 (1H, d, J = 8.6 Hz), 7.77 (1H, d, J = 2.0 Hz), 9.01 (2H, s), 11.09 (1H, s); MS (ES$^+$) m/z 339 (M + H)$^+$, 170 [M + 2H]$^{2+}$/2, 162.

5-[4-(Hydroxymethyl)piperidin-1-yl]pentanal Dimethyl Acetal (22). This was prepared from 5-chloropentanal dimethyl acetal and 4-piperidinemethanol,[30] using a method similar to that described for **8**, in 56% yield as a pale yellow oil: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.10 (2H, m), 1.28 (2H, m), 1.39 (2H, m), 1.48 (2H, m), 1.60 (2H, br d), 1.77 (2H, t), 2.20 (2H, t), 2.80 (2H, br d), 3.21 (8H, m), 4.31 (1H, t), 4.37 (1H, t).

1-{3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-ylmethanol (23). This was prepared from **22** and 4-(1,2,4-triazol-4-yl)phenylhydrazine,[26] using a method similar to that described for **10a**, in 38% yield as a yellow foam: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.11 (2H, m), 1.30 (1H, m), 1.60 (2H, d), 1.80 (4H, m), 2.29 (2H, t), 2.70 (2H, t), 2.84 (2H, d), 3.22 (2H, t), 4.40 (1H, t), 7.26−7.31 (2H, m), 7.46 (1H, d), 7.78 (1H, d), 9.02 (2H, s), 11.08 (1H, s).

(*S*)-*N*-[4-(1-Aminoethyl)phenyl]acetamide (24). To a suspension of (*S*)-1-(4-aminophenyl)ethylamine dihydrochloride[31] (2.28 g, 10.4 mmol) in 50% aqueous 1,4-dioxane (100 mL) was added 2 N aqueous NaOH (11.4 mL, 22.8 mmol) and di-*tert*-butyl dicarbonate (2.28 g, 10.4 mmol), and the mixture was stirred at room temperature overnight. The mixture was filtered, and the filtrate was extracted with dichloromethane. The extract was evaporated, and the residue was purified by flash chromatography (silica gel, 20% EtOAc/petroleum ether) to afford 0.86 g (38%) of (*S*)-[1-(4-aminophenyl)ethyl]carbamic acid *tert*-butyl ester as a brown oil:^{1}H NMR (250 MHz, DMSO-d_6) δ 1.23 (3H, d, J = 7.0 Hz), 1.35 (9H, s), 4.44 (1H, m), 4.89 (2H, s), 6.47 (2H, d, J = 8.4 Hz), 6.93 (2H, d, J = 8.4 Hz), 7.12 (1H, d, J = 8.2 Hz).

To a solution of (*S*)-[1-(4-aminophenyl)ethyl]carbamic acid *tert*-butyl ester (0.86 g, 3.9 mmol) in dichloromethane (100 mL) was added acetic anhydride (0.37 mL, 3.9 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, the residue was dissolved in 90% formic acid (5 mL), and the mixture was stirred at room temperature until the reaction was complete. The mixture was concentrated, and the residue was made basic with saturated aqueous K_2CO_3 and extracted with 1-butanol. The combined organic extracts were evaporated, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq)) to give 508 mg (73%) of **24** as a brown oil. This was crystallized from methanol−ethyl acetate to give a beige solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.32 (3H, d, J = 6.6 Hz), 2.03 (3H, s), 4.09 (1H, m), 7.31 (2H, d, J = 8.6 Hz), 7.52 (2H, d, J = 8.6 Hz), 8.44 (2H, br s), 10.02 (1H, s); MS (ES$^+$) m/z 179 (M + H)$^+$, 162 [M − NH_2]$^+$, 120 [M − NH_2 − COMe + H]$^+$; ee = 96.6% (Daicel crownpak CR (+) column eluting at 1.5 mL/min with 5% MeOH/dilute $HClO_4$ at 40 °C, detecting by UV at 210 nm).

(*R*)-*N*-[4-(1-Aminoethyl)phenyl]acetamide (25) was prepared in an analogous fashion and had an enantiomeric excess of 94.8%.

(*R*)-2-Amino-*N*-phenylpropionamide (26). To a stirred solution of *N*-(9-fluorenylmethoxycarbonyl)-D-alanine (1.0063 g, 3.23 mmol) and aniline (0.295 mL, 3.23 mmol) in anhydrous dichloromethane (20 mL) under nitrogen was added dropwise triethylamine (0.90 mL, 6.46 mmol), and then bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.823 g, 3.23 mmol) was added. The mixture was stirred at room temperature for 2.25 h, then diluted with diethyl ether (100 mL), and washed successively with 10% aqueous citric acid (100 and 25 mL), water (25 mL), dilute aqueous $NaHCO_3$ (50 mL), and water

(50 mL). To the remaining organic phase was added dichloromethane (75 mL) to dissolve some solid present, and this was then washed with saturated aqueous NaCl (25 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 2% MeOH/CH_2Cl_2) to afford 1.0957 g (88%) of (*R*)-2-[*N*-(9-fluorenylmethoxycarbonyl)amino]-*N*′-phenylpropionamide as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47 (3H, d, J = 7.0 Hz), 4.21 (1H, t, J = 6.8 Hz), 4.40 (1H, m), 4.46 (2H, d, J = 7.3 Hz), 5.38 (1H, m), 7.11 (1H, t, J = 7.4 Hz), 7.28−7.42 (6H, m), 7.50 (2H, d, J = 7.5 Hz), 7.57 (2H, d, J = 7.4 Hz), 7.76 (2H, d, J = 7.5 Hz), 8.14 (1H, br s); MS (ES$^+$) m/z 387 (M + H)$^+$, 179, 165 (M − Fmoc + 2H)$^+$.

This was dissolved in anhydrous dichloromethane (50 mL) and piperidine (1 mL) was added. The solution was stirred under nitrogen for 24 h and then evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 95:5:0.5 to 90:10:1) to give 0.4166 g (90%) of **26** as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.0 Hz), 3.63 (1H, q, J = 7.0 Hz), 7.10 (1H, m), 7.33 (2H, t, J = 7.5 Hz), 7.61 (2H, m), 9.47 (1H, br s); MS (ES$^+$) m/z 165 (M + H)$^+$.

(1*R*,2*S*)-1-Amino-1-phenylpropan-2-ol Hydrochloride (27). A mixture of (1*S*,2*S*)-(−)-1-phenylpropylene oxide (1.0 g, 7.45 mmol), sodium azide (0.96 g, 14.8 mmol), and ammonium chloride (0.80 g, 15 mmol) in 80% aqueous ethanol (20 mL) was heated at reflux for 2 h. After cooling, water (80 mL) was added, and the mixture was extracted with diethyl ether (2 × 125 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 35% Et_2O/hexane) to afford 1.29 g (98%) of (1*R*,2*S*)-1-azido-1-phenylpropan-2-ol as a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (3H, d, J = 6.2 Hz), 1.72 (1H, d, J = 4.3 Hz), 3.98 (1H, m), 4.48 (1H, d, J = 5.7 Hz), 7.32−7.45 (5H, m).

This was dissolved in ethanol (70 mL) and 5 N aqueous HCl (2.9 mL) and hydrogenated at 50 psi over 10% palladium on carbon (200 mg) for 16 h. The catalyst was removed by filtration and washed with ethanol (2 × 30 mL), and the combined filtrates were evaporated. The residue was azeotroped with ethanol (50 mL) and then crystallized from EtOH−Et_2O to give 1.069 g (79%) of **27** as a white solid: $[\alpha]_D$ −10.7° (*c* 1.0, H_2O) [lit.[32] $[\alpha]_D$ −11° (*c* 0.9, H_2O)]; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.92 (3H, d, J = 6.2 Hz), 4.10−4.17 (2H, m), 5.39 (1H, d, J = 4.5 Hz), 7.36−7.49 (5H m), 8.53 (3H, br s); MS (ES$^+$) m/z 152 (M + H)$^+$, 135; HPLC (10% MeCN/pH 3 buffer) retention time 4.23 min.

(1*R*,2*R*)-1-Amino-1-phenylpropan-2-ol Hydrochloride (28). To a stirred mixture of **27** (800 mg, 4.26 mmol) and triethylamine (0.72 mL, 5.11 mmol) in dichloromethane (30 mL) was added di-*tert*-butyl dicarbonate (1.03 g, 4.7 mmol), and the mixture was stirred at room temperature for 1 h. It was then diluted with diethyl ether (200 mL), washed with 1 N aqueous HCl (40 mL) and then brine (2 × 35 mL), dried ($MgSO_4$), and evaporated. The residue was crystallized from Et_2O−hexane to yield 920 mg (86%) of (1*R*,2*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-ol: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 6.4 Hz), 1.41 (9H, br s), 1.76 (1H, m), 4.08 (1H, m), 4.61 (1H, m), 5.36 (1H, m), 7.27−7.40 (5H, m); MS (ES$^+$) m/z 252 (M + H)$^+$, 196 [M − CMe_3 + 2H]$^+$, 178, 152, 135.

To a stirred suspension of (1*R*,2*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-ol (100 mg, 0.397 mmol) and 4-nitrobenzoic acid (99.7 mg, 0.597 mmol) in anhydrous toluene (5 mL) under nitrogen was added portionwise, over 7 min, solid triphenylphosphine-cyclic sulfamide betaine[33] (245 mg, 0.597 mmol). The mixture was stirred at room temperature for 17 h, then diluted with diethyl ether (100 mL), and washed with dilute aqueous K_2CO_3 (25 mL) and brine (25 mL). The remaining organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 35% Et_2O/hexane) to afford 40 mg (25%) of (1*R*,2*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenyl-2-propyl 4-nitrobenzoate as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.33 (12 H, s and d), 4.92 (1H, br s), 5.09 (1H, br d, J = 9.5 Hz), 5.45 (1H, quintet, J = 6.7 Hz), 7.28−7.40 (5H, m), 8.21 (2H, d, J = 8.7 Hz), 8.29 (2H, d, J = 8.7 Hz).

A solution of (1*R*,2*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenyl-2-propyl 4-nitrobenzoate (300 mg, 0.749 mmol) in methanol (10 mL) and 2 N aqueous NaOH (3 mL) was allowed to stand for 30 min at room temperature. The methanol was evaporated, and the residue was diluted with water (10 mL) and extracted with diethyl ether (2 × 75 mL). The organic phase was washed with brine (15 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 40% EtOAc/hexane) to afford 172 mg of (1*R*,2*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-ol: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 9.1 Hz), 1.43 (9H, s), 3.96−4.12 (1H, m), 4.50−4.62 (1H, m), 5.26−5.38 (1H, m), 7.22−7.40 (5H, m).

This was dissolved in saturated methanolic HCl (15 mL) and allowed to stand at room temperature for 1.5 h. The solvent was evaporated, and the residue was azeotroped with ethanol (2 × 15 mL) and then crystallized from EtOH−Et_2O to give 108 mg (77% over two steps) of **28** as a white solid: $[\alpha]_D$ −11.5° (*c* 0.99, H_2O); ^{1}H NMR (360 MHz, DMSO-d_6, 353 K) δ 0.95 (3H, d, J = 6.0 Hz), 3.90−4.04 (2H, m), 5.41 (1H, br s), 7.32−7.50 (5H, m), 8.32 (3H, br s); MS (ES$^+$) m/z 152 (M + H)$^+$; HPLC (10% MeCN/pH 3 buffer) retention time 6.07 min.

***(R)*-*N*^{2},*N*^{2}-Dimethyl-1-phenyl-1,2-ethanediamine (29).** To a stirred solution of (*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-phenylethylamine hydrochloride[34] (0.200 g, 0.73 mmol) in methanol (10 mL) was added acetic acid (0.170 mL, 2.92 mmol), followed by sodium cyanoborohydride (92 mg, 1.46 mmol), then a solution of 38% aqueous formaldehyde (0.174 mL, 2.20 mmol) in methanol (3 mL). The mixture was stirred at room temperature under nitrogen for 16 h and then saturated aqueous K_2CO_3 (5 mL) was added. The methanol was evaporated, and the residue was diluted with water (25 mL) and extracted with diethyl ether (2 × 125 mL). The organic extracts were washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated to give crude (*R*)-(2-(dimethylamino)-1-phenylethyl)carbamic acid *tert*-butyl ester as a colorless solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.90 (3H, s), 3.49 (2H, br t, J = 5.9 Hz), 4.66−4.88 (2H, m), 5.16 (1H, br d), 7.26−7.42 (5H, m); MS (ES$^+$) m/z 315 (M + H)$^+$.

This was dissolved in dichloromethane−trifluoroacetic acid (1:1; 10 mL) and allowed to stand at room temperature for 1 h. The solvents were evaporated, and the residue was azeotroped with methanol (2 × 10 mL). The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) to give 95 mg (79%) of **29** as a colorless liquid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.25 (1H, dd, J = 12.2 and 3.6 Hz), 2.29 (6H, s), 2.48 (1H, dd, J = 12.2 and 10.4 Hz), 4.07 (1H, dd, J = 10.4 and 3.6 Hz), 7.20−7.40 (5H, m); MS (ES$^+$) m/z 165 (M + H)$^+$.

***(R)*-*N*-(2-Amino-2-phenylethyl)methanesulfonamide (30).** To a stirred suspension of (*R*)-1-[*N*-(*tert*-butoxycarbonyl)-amino]-1-phenylethylamine hydrochloride[34] (0.180 g, 0.66 mmol) in anhydrous THF (10 mL) was added methanesulfonyl chloride (78 μL, 0.99 mmol), followed by anhydrous triethylamine (0.250 mL, 1.78 mmol). The mixture was stirred at room temperature under nitrogen for 5.5 h, then diluted with ethyl acetate (200 mL), washed with 1 M aqueous HCl (30 mL) and then brine (30 mL), dried ($MgSO_4$), and evaporated to leave 205 mg (99%) of (*R*)-*N*-{2-[*N*′-(*tert*-butoxycarbonyl)amino]-2-phenylethyl}methanesulfonamide. This was dissolved in dichloromethane−trifluoroacetic acid (5:2; 7 mL) and allowed to stand at room temperature for 2 h. The solvents were evaporated, and the residue was azeotroped with methanol (2 × 25 mL). The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 92:8:0.8) to give 129 mg (95%) of **30** as a waxy white solid:^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (3H, s), 3.23 (1H, dd, J = 12.9 and 7.8 Hz), 3.37 (1H, dd, J = 12.9 and 4.9 Hz), 4.14 (1H, dd, J = 7.8 and 4.9 Hz), 7.26−7.44 (5H, m).

(*R*)-2-Amino-2-phenylethyl Carbamate (31). To a stirred solution of (*R*)-*N*-(*tert*-butyloxycarbonyl)phenylglycinol[34] (500 mg, 2.1 mmol) in anhydrous dichloromethane (10 mL) was

added dropwise, under nitrogen, trichloroacetyl isocyanate (275 μL, 2.31 mmol) over 2 min. The resulting clear colorless solution was stirred at room temperature for 45 min before neutral alumina (activity III; 12 g) was added. The mixture was stirred for a further 40 min and then filtered, and the alumina was washed with dichloromethane (25 mL) and then with dichloromethane−ethyl acetate (1:1, 3 × 25 mL). The filtrate was concentrated under vacuum to leave a white solid, which was dissolved in dichloromethane−trifluoroacetic acid (3:1, 40 mL), and the solution was allowed to stand at room temperature for 35 min. The solvents were evaporated, and the residue was azeotroped with methanol (2 × 50 mL). Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) gave 333 mg (88%) of **31** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.06 (1H, dd, J = 11.8 and 9.5 Hz), 4.21−4.28 (2H, m), 4.68 (2H, br s), 7.24−7.40 (5H, m); MS (ES^+) m/z 181 $(M + H)^+$.

(*R*)-2-Amino-2-(4-fluorophenyl)ethanol (32). To a stirred 1.0 M solution of $LiAlH_4$ in THF (23.5 mL, 23.5 mmol), cooled to 0 °C, was added (−)-4-fluoro-D-α-phenylglycine (1.98 g, 11.7 mmol), portionwise, over 1.75 h. The mixture was stirred at room temperature for 16 h before adding water (0.9 mL), then 4 N aqueous NaOH (0.9 mL), and water (2.68 mL). The mixture was stirred for 0.25 h and filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) to give 1.5 g (82%) of **32** as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.52 (1H, dd, J = 8.2 and 10.7 Hz, CH), 3.71 (1H, dd, J = 4.4 and 10.7 Hz, CH), 4.06 (1H, dd, J = 4.4 and 8.1 Hz, CH), 6.99−7.08 (2H, m, Ar−H), 7.28−7.34 (2H, m, Ar−H). The enantiomeric excess was determined to be 98.8% by comparison with the similarly prepared racemate on a Beckman P/ACE MDQ capillary electrophoresis instrument using a 20-(30) cm × 50 μm capillary at −10 kV, eluting with 5% w/v HS α-cyclodextrin in 25 mM KH_2PO_4 buffer at pH 2.5 and detecting by UV at 206 nm.

(*R*)-1-(4-Fluorophenyl)-2-(methoxy)ethylamine Hydrochloride (33). A solution of **32** (600 mg, 3.87 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred suspension of potassium hydride (0.46 g, 4.01 mmol of 35 wt % dispersion in oil, washed with anhydrous pentane) in anhydrous THF (5 mL). The mixture was stirred for 2 h, treated with a solution of iodomethane (237 μL, 3.81 mmol) in THF (5 mL), and allowed to stand for 18 h. The mixture was partitioned between diethyl ether and saturated aqueous NaCl. The organic phase was dried ($MgSO_4$), evaporated, and redissolved in diethyl ether. The solution was treated with hydrogen chloride−diethyl ether (10 mL) and evaporated. Recrystallization from ethyl acetate gave 551 mg (69%) of **33** as colorless needles: ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.32 (3H, s), 3.57−3.72 (2H, m), 4.48−4.53 (1H, m), 7.24−7.32 (2H, m), 7.56−7.61 (2H, m), 8.6 (3H, br s).

(*R*)-2-Methoxy-1-phenylethylamine was prepared according to the procedure of Meyers et al.[35]

(*R*,*S*)-3-Amino-3-phenylpropan-1-ol was prepared according to the procedure of Shih et al.[36]

(*R*,*S*)-2-Amino-2-phenylpropan-1-ol was prepared from 2-amino-2-phenylpropionic acid[37] using a method similar to that described by Newman and Edwards.[38]

4-Acetamidophenethylamine was synthesized by a route similar to that used by Kornet et al.[39]

4-Acetamidobenzylamine hydrochloride can be prepared by the method of Brown et al.[40] or King et al.[41]

(1*S*,2*S*)- and (1*R*,2*R*)-1-Amino-2-hydroxyindan were prepared from (±)-*trans*-1-amino-2-hydroxyindan by a procedure similar to that described by Thompson et al.[42] for the (1*S*,2*R*) diastereomer.

4-Benzylamino-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (34) (Method A). To a stirred solution of **11a** (204 mg, 0.631 mmol) and benzylamine (68 μL, 0.623 mmol) in anhydrous methanol (4 mL) was added glacial acetic acid (140 μL, 2.45 mmol) and then sodium cyanoborohydride (40 mg, 0.637 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was evaporated, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 92:8:1) to give 241 mg (92%) of **34** as a yellow foamy solid. The oxalate salt was prepared in diethyl ether: mp 233−234 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.85−2.00 (2H, m), 2.01−2.11 (2H, m), 2.19−2.22 (2H, m), 2.73−2.90 (4H, m), 2.91−3.00 (2H, m), 3.16−3.25 (1H, m), 3.4−3.5 (2H, m), 4.14 (2H, s), 7.30−7.33 (2H, m), 7.40−7.42 (3H, m), 7.48−7.51 (3H, m), 7.80−7.81 (1H, m), 9.02 (2H, s), 11.20 (1H, s); MS (ES^+) m/z 415 $(M + H)^+$. Anal. [$C_{25}H_{30}N_6$·2($C_2H_2O_4$)·2H_2O] C, H, N.

4-Amino-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (35). A mixture of **34** (765 mg, 1.84 mmol), ammonium formate (349 mg, 5.54 mmol), and palladium on carbon (10% w/w; 300 mg) in anhydrous methanol (10 mL) was heated at reflux, under nitrogen, for 3 h. After cooling, the solids were removed by filtration, and the filtrate was evaporated. The residue was partitioned between water and 1-butanol, and the organic layer was evaporated to yield 544 mg (92%) of **35** as a white foam. The oxalate salt was prepared: mp 182−184 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.51 (2H, m), 1.82 (4H, m), 1.98 (2H, m), 2.38 (2H, m), 2.71 (2H, m), 2.89−2.94 (3H, m), 7.27−7.32 (2H, m), 7.48 (1H, d, J = 8.6 Hz), 7.77 (1H, d, J = 2.0 Hz), 9.02 (2H, s), 11.12 (1H, s); MS (ES^+) m/z 325 $(M + H)^+$. Anal. [$C_{18}H_{24}N_6$·1.2($C_2H_2O_4$)·H_2O] C, H, N.

4-(Furan-3-ylmethylamino)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (41). A solution of **35** (150 mg, 0.462 mmol), 3-furfuraldehyde (42 μL, 0.485 mmol), acetic acid (160 μL, 2.77 mmol), and sodium cyanoborohydride (30 mg, 0.485 mmol) in methanol (20 mL) was stirred at room temperature, under nitrogen, for 18 h. The solvent was evaporated, and the residue was partitioned between saturated aqueous K_2CO_3 and ethyl acetate. The aqueous phase was extracted another three times with ethyl acetate, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 95:5:0.5 to 90:10:1) gave 73 mg of the dialkylated amine and 43 mg (23%) of **41**. The oxalate salt was prepared: mp 150−152 °C (MeOH−Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6, 353 K) δ 1.60−1.70 (2H, m), 1.90−2.00 (2H, m), 2.05−2.10 (2H, m), 2.40−2.50 (2H, m), 2.70−2.80 (4H, m), 2.95−3.05 (1H, m), 3.15−3.20 (2H, m), 3.92 (2H, s), 6.58 (1H, s), 7.26−7.29 (2H, m), 7.48 (1H, d, J = 8.7 Hz), 7.63 (1H, s), 7.71 (1H, s), 7.73 (1H, s), 8.88 (2H, s), 10.95 (1H, s); MS (ES^+) m/z 405 $(M + H)^+$, 203 $(M + 2H)^{2+}/2$. Anal. [$C_{23}H_{28}N_6O$·2($C_2H_2O_4$)·1.5H_2O] C, H, N.

4-(*N*-Methylthiophen-3-ylmethylamino)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (48) (Method C). To a solution of **14** (200 mg, 0.591 mmol), acetic acid (0.344 mL, 6.00 mmol), and 3-thiophenecarboxaldehyde (58 μL, 0.622 mmol) in methanol (20 mL) was added sodium cyanoborohydride (41 mg, 0.652 mmol). The mixture was stirred under nitrogen for 18 h. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (5 mL) and concentrated. The residue was partitioned between water and 1-butanol, and the organic layer was evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq)) to afford 201 mg (78%) of **48** as a yellow solid. The oxalate salt was prepared and recrystallized from methanol−diethyl ether: mp 135−137 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.35−1.50 (2H, m), 1.64−1.72 (2H, m), 1.72−1.84 (4H, m), 2.09 (3H, s), 2.22−2.34 (3H, m), 2.68−2.72 (2H, m), 2.86−2.90 (2H, m), 3.53 (2H, s), 6.99−7.01 (1H, m), 7.24−7.30 (3H, m), 7.43−7.47 (2H, m), 7.77−7.78 (1H, m), 9.01 (2H, s), 11.05 (1H, s); MS (ES^+) m/z 435 $(M + H)^+$. Anal. [$C_{24}H_{30}N_6S$·2.25($C_2H_2O_4$)·2H_2O] C, H, N.

4-(Methanesulfonyl)benzaldehyde, used to prepare compounds **44** and **101**, was synthesized according to the method of Creary and Mehrsheikh-Mohammadi.[43]

***N*-Methyl-*N*-{1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-yl}benzenesulfonamide (50) (Method D).** To a solution of **14** (330 mg, 0.975 mmol) and triethylamine (149 μL, 1.07 mmol) in DME (10 mL), cooled under nitrogen to 0 °C, was added dropwise benzenesulfonyl chloride (137 μL,

1.07 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was then evaporated, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq)) to yield 175 mg (37%) of **50** as a yellow solid. The oxalate salt was prepared: mp 111−113 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.40 (2H, m), 1.88 (2H, m), 1.98 (2H, m), 2.67 (3H, s), 2.74 (2H, m), 2.93 (4H, m), 3.35 (2H, m), 4.01 (1H, s), 7.30−7.33 (2H, m), 7.49 (1H, d, J = 6.0 Hz), 7.62 (2H, t, J = 5.4 Hz), 7.69 (1H, t, J = 5.1 Hz), 7.79−7.83 (3H, m), 9.01 (2H, s), 11.17 (1H, s); MS (ES$^+$) m/z 479 (M + H)$^+$. Anal. [$C_{25}H_{30}N_6O_2S$·1.5($C_2H_2O_4$)·0.1$C_4H_{10}O$] C, H, N.

1-Methyl-3-phenyl-1-[1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-yl]urea (51) (Method E). To a solution of **13** (346 mg, 1.02 mmol) in anhydrous THF (25 mL) under nitrogen was added phenyl isocyanate (0.119 mL, 1.09 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was then evaporated, and the residue was purified by crystallization from methanol and flash chromatography of the mother liquors (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 95:5:1) to afford 302 mg (65%) of **51**: mp 220−222 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.49 (2H, m), 1.68 (2H, m), 1.81 (2H, m), 1.94 (2H, m), 2.33 (2H, t, J = 7.4 Hz), 2.73 (2H, t, J = 7.4 Hz), 2.80 (3H, s), 2.92 (2H, m), 4.02 (1H, s), 6.92 (1H, t, J = 7.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.28−7.31 (2H, m), 7.43−7.49 (3H, m), 7.80 (1H, d, J = 2.1 Hz), 8.18 (1H, s), 9.02 (2H, s), 11.07 (1H, s); MS (ES$^+$) m/z 458 (M + H)$^+$. Anal. [$C_{26}H_{31}N_7O$·0.23(CH_2Cl_2)] C, H, N.

4-(*N*-Methyl-3-methylbut-2-enylamino)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (56) (Method F). A solution of **13** (417 mg, 1.23 mmol), 4-bromo-2-methyl-2-butene (149 μL, 1.29 mmol) and potassium carbonate (170 mg, 1.29 mmol) in DMF (10 mL) was heated at 80 °C for 16 h. The reaction was partitioned between water and ethyl acetate. The aqueous layer was extracted three more times with ethyl acetate, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) to give 130 mg (26%) of **56** as a yellow glass. The oxalate salt was prepared and crystallized from methanol−diethyl ether: mp 128−130 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.66−1.74 (2H, m), 1.66 (3H, s), 1.74 (3H, s), 1.89−1.93 (4H, m), 2.29 (2H, m), 2.43 (3H, s), 2.62 (2H, m), 2.73 (2H, t, J = 7.4 Hz), 2.92 (1H, m), 3.17 (2H, m), 3.42 (2H, m), 5.24 (1H, m), 7.29−7.33 (2H, m), 7.49 (1H, d, J = 8.6 Hz), 7.79 (1H, d, J = 2.0 Hz), 9.03 (2H, s), 11.16 (1H, s); MS (ES$^+$) m/z 407 (M + H)$^+$. Anal. [$C_{24}H_{34}N_6$·1.25($C_2H_2O_4$)·1.5H_2O] C, H, N.

4-(2-Phenylpiperidin-1-yl)piperidine (86). A mixture of *N*-(*tert*-butyloxycarbonyl)-4-piperidone (5.0 g, 25 mmol), 2-phenylpiperidine (4.03 g, 25 mmol), and titanium(IV) isopropoxide (8.9 mL, 30 mmol) was stirred at room temperature under nitrogen for 3 h. The resulting orange solution was diluted with methanol (40 mL), treated with sodium cyanoborohydride (1.6 g, 25 mmol), and stirred for 20 h. Water (50 mL) was added to give a precipitate, which was removed by filtration through Celite. The filtrate was partitioned between water and ethyl acetate, and the organic layer was evaporated. The residue was flash chromatographed (silica gel, 20−50% EtOAc/petroleum ether), and the partially purified product was dissolved in ethyl acetate and washed with saturated aqueous citric acid. The aqueous phase was basified to pH 10 using 4 N aqueous NaOH and extracted into ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated to give 250 mg (3%) of 1-(*tert*-butyloxycarbonyl)-4-(2-phenylpiperidin-1-yl)-piperidine: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24−1.79 (10H, m), 1.42 (9H, s), 2.23 (2H, m), 2.44 (2H, m), 2.97 (1H, m), 3.40 (1H, dd, J = 10.5 and 2.9 Hz), 4.01 (2H, m), 7.16−7.40 (5H, m).

This was dissolved in dichloromethane (7 mL), and trifluoroacetic acid (0.55 mL) was added. The solution was stirred at 35 °C for 4 h, then cooled to room temperature, and poured into water (10 mL). The pH was adjusted to >10, and the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield 170 mg (98%) of **86** as a yellow solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.29−1.83 (10H, m), 2.15 (1H, td, J = 12.1 and 2.5 Hz), 2.25−2.45 (3H, m), 2.97−3.06 (3H, m), 3.41 (1H, dd, J = 10.7 and 2.9 Hz), 7.21−7.30 (5H, m).

(*R*)-4-(1-Phenylethylamino)piperidine (87). To a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-piperidone (2.0159 g, 10.1 mmol) in anhydrous methanol (100 mL) was added D-(+)-α-methylbenzylamine (1.55 mL, 12.2 mmol), followed by acetic acid (2.32 mL, 40.5 mmol), and then sodium cyanoborohydride (0.7626 g, 12.1 mmol), and the mixture was stirred at room temperature under nitrogen for 3 days. Saturated aqueous K_2CO_3 (10 mL) was added and the mixture was concentrated. The residue was diluted with more saturated aqueous K_2CO_3 (40 mL) and extracted with ethyl acetate (100 and 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification by flash chromatography (silica gel, 7% MeOH/CH_2Cl_2) yielded (*R*)-1-(*tert*-butoxycarbonyl)-4-(1-phenylethylamino)piperidine as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (2H, m), 1.36 (3H, d, J = 6.6 Hz), 1.43 (9H, s), 1.65 (2H, m), 1.92 (1H, m), 2.46 (1H, m), 2.66 (2H, m), 3.94−4.01 (3H, m), 7.23−7.37 (5H, m).

This was dissolved in anhydrous dichloromethane (15 mL) and cooled to 0 °C under nitrogen before trifluoroacetic acid (7.5 mL) was added. The solution was stirred at room temperature for 2.75 h, then anhydrous methanol (2 mL) was added, and the solvents were evaporated. The residue was azeotroped with methanol (5 mL), and the residual oil was dissolved in dichloromethane (50 mL) and washed with 2 N aqueous NaOH (30 mL). The aqueous layer was further extracted with dichloromethane (50 mL), and the combined organic extracts were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and evaporated to leave 1.9456 g (94% over two steps) of **87** as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (2H, qd, J = 12.3 and 4.0 Hz), 1.33 (3H, d, J = 6.6 Hz), 1.71 (2H, m), 1.98 (1H, m), 2.34−2.56 (3H, m), 3.04 (2H, m), 3.97 (1H q, J = 6.6 Hz), 7.20−7.37 (5H, m); MS (ES$^+$) m/z 205 (M + H)$^+$, 105.

(*R*)-2-Phenyl-2-(piperidin-4-ylamino)ethanol (88). This was prepared in 64% yield over two steps using a procedure similar to that described above for **87**, but substituting (*R*)-phenylglycinol for D-(+)-α-methylbenzylamine, giving **88** as a white solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 0.96−1.12 (2H, m), 1.52 (1H, d, J = 12.0 Hz), 1.78−2.06 (2H, br s and d, J = 12.6 Hz), 2.17−2.32 (3H, m), 2.76−2.90 (2H, m), 3.26 (1H, t, J = 8.5 Hz), 3.40 (1H, dd, J = 10.5 and 4.5 Hz), 3.83 (1H, dd, J = 8.5 and 4.5 Hz), 4.82 (1H, br s), 7.27−7.37 (5H, m); MS (ES$^+$) m/z 221 (M + H)$^+$.

(*R*)-4-[1-(4-Fluorophenyl)-2-(methoxy)ethylamino]piperidine Hydrochloride (89). This was prepared in 75% yield over two steps using a procedure similar to that described above for **87**, but substituting **33** for D-(+)-α-methylbenzylamine and using ethereal HCl instead of TFA to remove the Boc group, followed by recrystallization from methanol−ethyl acetate to give **89** as a colorless solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.08−2.44 (4H, m), 2.84−3.08 (2H, m), 3.43 (2H, br s), 3.47 (3H, s), 3.76−3.96 (2H, m), 7.15−7.22 (2H, m), 7.61−7.66 (2H, m).

(*R*)-2-Phenyl-2-[1-{3-[5-(1,2,4-triazol-1-yl)methyl-1*H*-indol-3-yl]propyl}piperidin-4-ylamino]ethanol (94) (Method G). To a solution of **15d** (209 mg, 0.81 mmol) in anhydrous THF (10 mL), cooled to −40 °C under nitrogen, was added triethylamine (146 μL, 1.05 mmol) followed by methanesulfonyl chloride (75 μL, 0.949 mmol), and the mixture was allowed to warm to room temperature over 10 min. The mixture was filtered, and the filtrate was evaporated. The residue was partitioned between water and dichloromethane, and the organic phase was dried ($MgSO_4$) and evaporated.

This crude mesylate was dissolved in anhydrous THF (20 mL), and *N*,*N*-diisopropylethylamine (310 μL, 1.78 mmol) and **88** (231 mg, 1.05 mmol) were added. The mixture was heated at 40 °C for 4 h and at 60 °C for 6 h. Sodium iodide (150 mg, 1.00 mmol) was added, and heating was continued for a further 17 h in a foil-covered reaction vessel. Saturated aqueous NaCl was added, and the organic solvent was evaporated. The aqueous residue was extracted with 1-butanol twice, and the

combined organic extracts were evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 84:15:1) to give 250 mg (67%) of **94** as a pale brown foamy solid. The oxalate salt was prepared and crystallized from ethanol−diethyl ether: mp 128−130 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.60−1.75 (2H, m), 1.85−2.10 (4H, m), 2.60−2.80 (4H, m), 2.80−2.95 (2H, m), 3.20−3.30 (2H, m), 3.50−3.60 (2H, m), 4.05−4.15 (1H, m), 5.42 (2H, s), 7.02−7.05 (1H, m), 7.16 (1H, m), 7.29−7.39 (4H, m), 7.44−7.50 (3H, m), 7.93 (1H, s), 8.60 (1H, s), 10.90 (1H, s); MS (ES$^+$) *m*/*z* 459 (M + H)$^+$. Anal. [$C_{26}H_{31}N_5O_2$·2($C_2H_2O_4$)·1.5H_2O] C, H, N.

4-(Pyridin-2-ylaminomethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (99) (Method H). A solution of **21** (165 mg, 0.488 mmol), 2-bromopyridine (1.6 mL, 16.5 mmol), and *N*,*N*-diisopropylethylamine (255 μL, 1.46 mmol) in 2-ethoxyethanol (5 mL) was heated at reflux for 2 days, adding more *N*,*N*-diisopropylethylamine (0.5 mL, 2.87 mmol) after 1 day. After cooling, the mixture was diluted with water (40 mL) and acidified to pH 4 with 2 N aqueous HCl. The aqueous phase was washed with diethyl ether (3 × 60 mL), then basified with 4 N aqueous NaOH, and extracted with ethyl acetate (2 × 70 mL). The combined extracts were washed with brine (40 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 85:15:1.1) to afford 40 mg (20%) of **99**. The oxalate salt was prepared and recrystallized from methanol−ethanol−diethyl ether: mp 105−112 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.30−1.48 (2H, m), 1.74−1.94 (3H, m), 2.00−2.12 (2H, m), 2.72−2.92 (4H, m), 3.00−3.22 (4H, m), 3.42−3.56 (2H, m), 6.43−6.52 (2H, m), 6.74 (1H, br s), 7.30−7.40 (3H, m), 7.50 (1H, d, J = 8.6 Hz), 7.80 (1H, d, J = 2.0 Hz), 7.93 (1H, m), 9.01 (2H, s), 11.19 (1H, s); MS (ES$^+$) *m*/*z* 416 (M + H)$^+$. Anal. [$C_{24}H_{29}N_7$·2($C_2H_2O_4$)] C, H, N.

4-Acetylamino-*N*-methyl-*N*-[1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidin-4-ylmethyl]benzamide (105) (Method I). To a stirred solution of **20** (0.1135 g, 0.322 mmol) in DMF (5 mL) was added 4-acetamidobenzoic acid (61.1 mg, 0.341 mmol), 1-hydroxybenzotriazole hydrate (46.5 mg, 0.344 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (65.2 mg, 0.340 mmol), and triethylamine (47.1 μL, 0.338 mmol), and the mixture was stirred for 18 h. The solvent was evaporated, and the residue was partitioned between water and ethyl acetate (80 mL). The aqueous layer was further extracted with ethyl acetate (80 mL), and the combined organic extracts were washed with 4 N aqueous NaOH (20 mL) and saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 90:10:1) to give 63.6 mg (38%) of **105** as a white solid. The oxalate salt was prepared and crystallized from ethanol−diethyl ether: mp 120−125 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.47 (2H, m), 1.83 (2H, m), 2.06 (6H, m), 2.77 (2H, m), 2.84 (2H, m), 2.92 (3H, s), 3.06 (2H, m), 3.35−3.47 (4H, m), 7.31−7.34 (4H, m), 7.50 (1H, d, J = 8.6 Hz), 7.62 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 9.02 (2H, s), 10.12 (1H, s), 11.20 (1H, s); MS (ES$^+$) *m*/*z* 514 (M + H)$^+$. Anal. [$C_{29}H_{35}N_7O_2$·1.9($C_2H_2O_4$)·H_2O·0.17$C_4H_{10}O$] C, H, N.

(*R*)-4-(1-Phenylethylaminomethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl}piperidine (106) (Method J). To a solution of **23** (0.500 g, 1.47 mmol) in anhydrous DMSO (20 mL) and anhydrous triethylamine (755 μL, 10.3 mmol) was added portionwise, under nitrogen, solid sulfur trioxide pyridine complex (844 mg, 5.30 mmol). The mixture was stirred for 3 h, basified with 2 M aqueous NaOH, and extracted with 1-butanol. The organic phase was concentrated to 3 mL under vacuum and diluted with methanol (10 mL). Acetic acid (506 μL, 8.82 mmol) and (*R*)-α-methylbenzylamine (209 μL, 1.62 mmol) were added followed, after 15 min, by sodium cyanoborohydride (102 mg, 1.62 mmol). The mixture was stirred for 18 h, then quenched with saturated aqueous K_2CO_3 (3 mL). The volatiles were evaporated, and the residue was partitioned between water and 1-butanol. The organic phase was evaporated, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq); 95:5:1 to 90:10:1) to give 85 mg (13%) of **106** as a yellow oil. The oxalate salt was prepared and crystallized from methanol−diethyl ether: mp 140 °C (softens); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.20 (2H, m), 1.39 (3H, d), 1.58 (1H, m), 1.76 (2H, brt), 1.92 (2H, m), 2.27−2.30 (3H, m), 2.69−2.72 (5H, m), 3.12−3.16 (2H, m), 3.97 (1H, d), 7.29−7.50 (8H, m), 7.78 (1H, d), 9.02 (2H, s), 11.16 (1H, s); MS (ES$^+$) *m*/*z* 443 (M + H)$^+$. Anal. [$C_{27}H_{34}N_6$·($C_2H_2O_4$)·2.6H_2O] C, H, N.

Log *D* Determination Method. Log *D* was determined experimentally using modified shake-flask methodology.[44] The procedure was conducted in a total volume of 1 mL in duplicate at two concentrations. This ensured that the phases were not saturated since identical final concentrations in one phase at two different starting concentrations would be indicative of this. Typically, compounds were dissolved in octanol (Spectroscopic grade) at ca. 1 mg/mL, then 200 μL of this solution was added to one eppendorf and 400 μL to another. Both were then made up to a total volume of 500 μL with pure octanol. To each eppendorf was added 500 μL of 100 mM KH_2PO_4 buffer, adjusted to pH 7.4 with phosphoric acid. The eppendorfs were sealed and then reciprocally shaken for 20 min to ensure complete partition without emulsion forming. Samples were then briefly centrifuged to separate layers, and 200 μL of each layer was removed to a HPLC vial. Analysis was performed by HPLC rather than spectrophotometrically to ensure that only the component of interest was quantified. Ten microliters of the octanol phase and 10−100 μL of the aqueous phase were injected onto a suitable HPLC system, and the distribution coefficient was calculated as the ratio of the peak areas of the compound in the organic to the aqueous phase. Log *D* is the $\log_{10}$ of this ratio.

Pharmacokinetic Methods. Oral Absorption Studies. The test compound (typically as a solution in water) was administered orally (3 mg/kg, 5 mL/kg dose volume) to eight male Sprague−Dawley rats (approximate weight 300 g) that had been deprived of food overnight. At either 0.5 or 2 h after dosing the rats (four per time point) they were anesthetized (isoflurane), and hepatic portal vein and cardiac blood samples were removed. Plasma separated from the blood samples by centrifugation was processed either by solid-phase or liquid−liquid extraction and then analyzed for test compound by reversed-phase HPLC employing fluorescence detection.

Pharmacokinetic Profile of 80. The tail arteries of six male Sprague−Dawley rats were surgically cannulated to allow sequential blood sampling. Each animal was given a 3 mg/kg dose of **80** (formulated from the oxalate salt as a solution in water) by either intravenous or subcutaneous injection (three rats per dose route). Serial blood samples (ca. 600 μL) were taken from each animal up to 6 h following dosing. At 6 h the rats were anesthetized (isoflurane), and the brain was also removed. Plasma separated from the blood samples was processed by solid-phase extraction and then analyzed by reversed-phase HPLC with fluorescence detection (λ_{exc} = 235 nm, λ_{emm} = 370 nm). Brain samples were homogenized in acetonitrile using an ultrasonic probe. The supernatant obtained following centrifugation of the brain homogenate was evaporated to dryness and dissolved in HPLC mobile phase and then assayed by HPLC as described for the plasma samples.

Molecular Modeling Methods. Conformations were initially generated by using the systematic search facility within Sybyl,[45] using a 10° increment for bond rotations about all rotatable bonds except methyl groups (which were treated as rigid) and the hydroxyl group C−O bond (where applicable) which was rotated using a 30° increment. Full circles were searched for all rotatable bonds except where this could be reduced by symmetry (e.g., bond to the ipso carbon of the aromatic ring, which was searched 0−179°). A line-search algorithm was then used to find candidate minima in torsional space, and all candidate minima (points in torsion space where variation of any single rotatable bond torsion could not produce a lower-lying conformer) were then subjected to minimization using the Tripos force field and minimizer with Gasteiger charges. Conformers were rejected if they were either more

than 5 kcal/mol above the global minimum found or if they showed a heavy-atom RMS fit of better than 0.1 Å. Few conformers were rejected on energy (0−12), but large numbers of duplicate conformers were found (0−160). The resulting unique conformers were then subjected to energy minimization using MOPAC with the AM1 Hamiltonian.[46] The cyclic compound **85** showed a well-defined minimum (that illustrated) which was separated from its nearest neighbor energetically by 2.7 kcal/mol, an energy difference that was maintained on optimization using the AM1/SM2.1 solvation model within AMSOL.[47] The lowest energy conformer of **85** was also the only one that produced good overlays with low-energy conformers of the acyclic species **68** (as measured by low RMS fitting error) using the aromatic ring carbons and the heavy atoms of the 4-amino-*N*-methylpiperidine group as match points. All the minima found by optimization with AM1 in the gas phase which differed from one another by more than 0.1 RMS Å (using the same match points as before) were also optimized using AMSOL with AM1/SM2.1 as the Hamiltonian to determine whether solvation effects would dramatically affect the ordering or energy difference between conformers. Although there were slight changes in the ordering of the energies of the various conformations (Spearman rank correlation coefficients in the range 0.71−0.93), the overall conclusions remain the same as for the gas phase.

All calculations were run on SG R4400 or R10000 workstations running under IRIX 6.2 to 6.4 using versions 6.2 to 6.4 of Sybyl as user interface, except AMSOL calculations which were run on a Cray J90 running under unicos 10.0.0.1.

Biochemical Methods. [^{3}H]5-HT Radioligand Binding Studies. On the day of assay, chinese hamster ovary (CHO) cells stably transfected with either the human 5-HT$_{1B}$ or 5-HT$_{1D}$ receptors were thawed, homogenized in 10−15 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.7 at room temperature) with a Kinematica polytron (setting 5, 10 s), and centrifuged at 48000*g*, 4 °C for 11 min. The resulting supernatant was discarded and the pellet resuspended in the same volume of ice-cold Tris-HCl buffer before being incubated at 37 °C for 10 min, to remove any endogenous 5-HT, and recentrifuged at 48000*g*, 4 °C for a further 11 min. The final pellet was then resuspended in 50 mM Tris assay buffer containing 0.1% ascorbate, 10 μM pargyline, and 4 mM $CaCl_2$, pH 7.7, at room temperature, to give 6 mg of wet weight tissue per assay tube. When added to the assay tubes in 500 mL volumes this resulted in approximately 180−220 μg protein per tube.

All assays were carried out in duplicate on two to five separate occasions. Test drug or buffer was incubated with 500 μL membrane and 2.0 nM [^{3}H]5-HT in a final assay volume of 1 mL, at 37 °C in a shaking water bath. 5-HT (10 μM) was used to define nonspecific binding. The incubation was started by addition of membrane suspension and was terminated, after 30 min, by rapid filtration over GF/B filters using a Brandel cell harvester. Each assay tube was washed twice with 4 mL of ice-cold Tris-HCl buffer. Filters had previously been soaked in 0.3% polyethylenimine/0.5% Triton X-100 to reduce nonspecific binding. Radioactivity was counted by liquid scintillation spectrometry (45−55% efficiency).

Binding parameters were analyzed by nonlinear, least squares regression analysis using an iterative curve fitting routine (Marquardt−Levenberg method) provided by the data manipulation software RS/1 (Software Products Corporation, Cambridge, MA). Data represent specific binding (total − nonspecific). The affinity values of competing compounds in the displacement studies are expressed as IC_{50} values (concentration of drug that inhibits specific binding by 50%). Data are expressed as mean ± SEM from at least two to five experiments

Agonist-Induced [^{35}S]GTPγS Binding. On the day of assay, CHO cells stably transfected with either the human 5-HT$_{1B}$ or 5-HT$_{1D}$ receptors were thawed. Cell membranes were prepared, and the assay was carried out essentially as described by Lazareno and Birdsall.[48] Cells were homogenized in ice-cold 20 mM Hepes buffer containing 10 mM ethylenediaminetetraacetic acid (EDTA) (pH 7.4 at room temperature) using a Kinematica polytron (setting 5, 10 s) and centrifuged at 40000*g*, 4 °C for 15 min. The pellet was resuspended in ice-cold 20 mM Hepes buffer containing 0.1 mM EDTA (pH 7.4 at room temperature) and recentrifuged at 40000*g*, 4 °C for 15 min. The final pellet was resuspended in 20 mM Hepes buffer containing 100 mM NaCl, 10 mM $MgCl_2$, 0.1% ascorbate, and 10 μM pargyline, pH 7.4, at room temperature.

All assays were carried out in duplicate on two to five separate occasions. Membranes (2.5 mg of wet weight (30−80 μg protein per tube)) were incubated with GDP (30 μM for the 5-HT$_{1B}$ receptor cell line, 100 μM for the 5-HT$_{1D}$ receptor cell line) and test drug for 20 min at 30 °C in a volume of 900 μL and then transferred to ice for 15 min. [^{35}S]GTPγS (100 pM) was added to all tubes, giving a final assay volume of 1 mL, and the tubes were incubated for a further 30 min at 30 °C. The incubation was terminated by filtering over GF/B filters using a Brandel cell harvester, and the filters were washed once with 5 mL of water. Radioactivity was counted by liquid scintillation spectrometry at an efficiency of >90%.

Dose−response curves were analyzed by nonlinear, least squares regression analysis using an iterative curve fitting routine (Marquardt−Levenberg method) provided by the data manipulation software RS/1 (Software Products Corporation, Cambridge, MA). Background filter counts, i.e., residual radioactivity bound to the filter in the absence of membrane, were subtracted from each sample count. Test results were then represented as percentage increase in binding above basal, i.e., that seen in the absence of test compound, and dose−response curves were plotted and analyzed. The maximal stimulation (E_{max}) achieved for each drug was expressed as a percentage of the maximal 5-HT response. Data are expressed as mean ± SEM from at least two to five experiments.

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References

(1) Perry, C. M.; Markham, A. Sumatriptan: An Updated Review of its Use in Migraine. *Drugs* **1998**, *55*, 889−922.
(2) Yevich, J. P.; Yocca, F. D. Second Generation Antimigraine 5-HT$_{1B/D}$ Agonists: Structure Activity Relationship and Preclinical Pharmacological Distinctions. *Curr. Med. Chem.* **1997**, *4*, 295−312.
(3) Longmore, J.; Dowson, A.; Hill, R. G. Advances in Migraine Therapy − 5-HT Receptor Subtype-specific Agonist Drugs. *Curr. Opin. CPNS Invest. Drugs* **1999**, *1*, 39−53.
(4) Russell, M. G. N. Recent Developments in 5-HT$_{1D}$ Agonists. *IDrugs* **1999**, *2*, 37−43.
(5) Connor, H. E.; Fenuik, W.; Beattie, D. T.; North, P. C.; Oxford, A. W.; Saynor, D. A.; Humphrey, P. P. A. Naratriptan: Biological Profile in Animal Models Relevant to Migraine. *Cephalagia* **1997**, *17*, 145−152.
(6) Glen, R. C.; Martin, G. R.; Hill, A. P.; Hyde, R. M.; Woollard, P. M.; Salmon, J. A.; Buckingham, J.; Robertson, A. D. 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. *J. Med. Chem.* **1995**, *38*, 3566−3580.
(7) Street, L. J.; Baker, R.; Davey, W. B.; Guiblin, A. R.; Jelley, R. A.; Reeve, A. J.; Routledge, H.; Sternfeld, F.; Watt, A. P.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Sohal, B.; Graham, M. I.; Matassa, V. G. Synthesis and Serotonergic Activity of *N*,*N*-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine and Analogues: Potent Agonists for 5-HT$_{1D}$ Receptors. *J. Med. Chem.* **1995**, *38*, 1799−1810.
(8) Ngo, J.; Rabasseda, X.; Castañer, J. Eletriptan. *Drugs Future* **1997**, *22*, 221−224.

(9) Goadsby, P. J. Serotonin 5-$HT_{1B/1D}$ Receptor Agonists in Migraine. *CNS Drugs* **1998**, *10*, 271−286.
(10) Cumberbatch, M. J.; Hill, R.; Hargreaves, R. J. Rizatriptan has Central Antinociceptive Effects Against Durally Evoked Responses. *Eur. J. Pharmacol.* **1997**, *328*, 37−40.
(11) Goadsby, P. J.; Edvinsson, L. The Trigeminovascular System and Migraine: Studies Characterizing Cerebrovascular and Neuropeptide Changes Seen in Humans and Cats. *Ann. Neurol.* **1993**, *33*, 48−56.
(12) Williamson, D. J.; Shepheard, S. L.; Hill, R. G.; Hargreaves, R. J. The Novel Antimigraine Agent Rizatriptan Inhibits Neurogenic Dural Vasodilation and Extravasation. *Eur. J. Pharmacol.* **1997**, *328*, 61−64.
(13) Williamson, D. J.; Hargreaves, R. J.; Hill, R. G.; Shepheard, S. L. Sumatriptan Inhibits Neurogenic Vasodilation of Dural Blood Vessels in the Anaesthetized Rat − Intravital Microscope Studies. *Cephalagia* **1997**, *17*, 525−531.
(14) Hartig, P. R.; Hoyer, D.; Humphrey, P. P. A.; Martin, G. R. Alignment of Receptor Nomenclature with the Human Genome: Classification of 5-HT_{1B} and 5-HT_{1D} Receptor Subtypes. *Trends Pharmacol. Sci.* **1996**, *17*, 103−105.
(15) Hamel, E.; Fan, E.; Linville, D.; Ting, V.; Villemure, J.-G.; Chia, L.-S. Expression of mRNA for the Serotonin 5-hydroxytryptamine$_{1D\beta}$ Receptor Subtype in Human and Bovine Cerebral Arteries. *Mol. Pharmacol.* **1993**, *44*, 242−246.
(16) Rebeck, G. W.; Maynard, K. I.; Hyman, B. T.; Moskowitz, M. A. Selective 5-$HT_{1D\alpha}$ Serotonin Receptor Gene Expression in Trigeminal Ganglia: Implications for Antimigraine Drug Development. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3666−3669.
(17) Bouchelet, I.; Cohen, Z.; Case, B.; Séguéla, P.; Hamel, E. Differential Expression of Sumatriptan-sensitive 5-hydroxytryptamine Receptors in Human Trigeminal Ganglia and Cerebral Blood Vessels. *Mol. Pharmacol.* **1996**, *50*, 219−223.
(18) Longmore, J.; Shaw, D.; Smith, D.; Hopkins, R.; McAllister, G.; Pickard, J. D.; Sirinathsinghji, D. R. S.; Butler, A. J.; Hill, R. Differential Distribution of $5HT_{1D}$- and $5HT_{1B}$-immunoreactivity within the Human Trigemino-cerebrovascular System: Implications for the Discovery of New Antimigraine Drugs. *Cephalagia* **1997**, *17*, 833−842.
(19) Ottervanger, J. P.; Stricker, B. H. Ch. Cardiovascular Adverse Reactions to Sumatriptan. Cause for Concern? *CNS Drugs* **1995**, *3*, 90−98.
(20) A preliminary part of this work has been communicated previously: Castro, J. L.; Street, L. J.; Guiblin, A. R.; Jelley, R. A.; Russell, M. G. N.; Sternfeld, F.; Beer, M. S.; Stanton, J. A.; Matassa, V. G. 3-[2-(Pyrrolidin-1-yl)ethyl]indoles and 3-[3-(Piperidin-1-yl)propyl]indoles: Agonists for the h5-HT_{1D} Receptor with High Selectivity over the h5-HT_{1B} Subtype. *J. Med. Chem.* **1997**, *40*, 0, 3497−3500.
(21) Veldman, S. A.; Bienkowski, M. J. Cloning and Pharmacological Characterization of a Novel Human 5-Hydroxytryptamine$_{1D}$ Receptor Subtype. *Mol. Pharmacol.* **1992**, *42*, 439−444.
(22) Interestingly, **27** was shown to have a significantly shorter retention time than **28** on reverse-phase HPLC (see Experimental Section), again lending support to the theory that stabilization of an intramolecular H-bond is occurring in the latter.
(23) Molecular modeling was performed in the gas phase (MOPAC, AM1 Hamiltonian, PRECISE convergence criteria) on analogues which, for ease of calculation, were truncated to leave a methyl group on the N atom of the piperidine ring. It showed that the low-energy conformers of **68** were such that intramolecular H-bonding was possible, and one of these conformers (the second-to-lowest in energy, being less than 0.5 kcal/mol above the global minimum and showing an RMS fit of the piperidine ring, the piperidine nitrogen substituent, the amino nitrogen, and the aromatic ring carbons of <1 Å) overlaid well onto the rigid, lowest energy conformer of **85** (Figure 1). For **79** there was insufficient energy differences between conformers that could have a H-bond and those that could not have a H-bond to say that this existed in a H-bonded conformation, whereas the low-energy conformers of **78** were such that intramolecular H-bonding was possible. Therefore, stabilization of the H-bonded conformer by the methyl substituent in **79** cannot be convincingly demonstrated on energetic grounds. Using the AM1/SM2.1 solvation model within AMSOL gave the same overall conclusions.
(24) During the preparation of this manuscript a 5-HT_{1D} agonist with >1000-fold selectivity over 5-HT_{1A} was reported: Ennis, M. D.; Ghazal, N. B.; Hoffman, R. L.; Smith, M. W.; Schlacter, S. K.; Lawson, C. F.; Im, W. B.; Pregenzer, J. F.; Svensson, K. A.; Lewis, R. A.; Hall, E. D.; Sutter, D. M.; Harris, L. T.; McCall, R. B. Isochroman-6-carboxamides as Highly Selective 5-HT_{1D} Agonists: Potential New Treatment for Migraine without Cardiovascular Side Effects. *J. Med. Chem.* **1998**, *41*, 2180−2183.
(25) The half-life was calculated from data over 3−6 h.
(26) Sternfeld, F.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Heald, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J. Synthesis and Serotonergic Activity of 3-[2-(Pyrrolidin-1-yl)ethyl]indoles: Potent Agonists for the h5-HT_{1D} Receptor with High Selectivity over the h5-HT_{1B} Receptor. *J. Med. Chem.* **1999**, *42*, 677−690.
(27) Chambers, M. S.; Street, L. J.; Goodacre, S.; Hobbs, S. C.; Hunt, P.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Sternfeld, F.; Beer, M. S.; Stanton, J. A.; Rathbone, D.; Watt, A. P.; MacLeod, A. M. 3-(Piperazinylpropyl)indoles: Selective, Orally Bioavailable h5-HT_{1D} Receptor Agonists as Potential Antimigraine Agents. *J. Med. Chem.* **1999**, *42*, 691−705.
(28) Smith, D. W.; Yocca, F. D.; Yevich, J. P.; Mattson, R. J.; Williams, A.; Ruediger, E. U.S. Patent 5,300,506, 1994. See also: Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R., Sr.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. An Efficient Fischer Indole Synthesis of Avitriptan, a Potent 5-HT_{1D} Receptor Agonist. *J. Org. Chem.* **1997**, *62*, 9192−9202.
(29) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J.; Cottrell, I. F.; Houghton, P. G. Synthesis of the 5-HT_{1D} Receptor Agonist MK-0462 via a Pd-catalysed Coupling Reaction. *Tetrahedron Lett.* **1994**, *35*, 6981−6984.
(30) Bradbury, B. J.; Baumgold, J.; Paek, R.; Kammula, U.; Zimmet, J.; Jacobson, K. A. Muscarinic Receptor Binding and Activation of Second Messengers by Substituted *N*-Methyl-*N*-[4-(1-azacycloalkyl)-2-butynyl]acetamides. *J. Med. Chem.* **1991**, *34*, 1073−1079.
(31) Il'ina, I. G.; Ivanova, E. V.; Nozdrina, V. A.; Mikhalev, O. V.; Potapov, V. M. Synthesis of Electron Acceptors of the Picryl Series and their Chiral-optical Characteristics. *Zh. Org. Khim.* **1985**, *21*, 1922−1925.
(32) Prelog, V.; Mutak, S. Stereoselectivity of 9,9′-Spirobifluorene Crown Ethers Towards α-Amino Alcohols. *Helv. Chim. Acta* **1983**, *66*, 2274−2278.
(33) Castro, J. L.; Matassa, V. G. Mitsunobu-like Processes with a Novel Triphenylphosphine-Cyclic Sulfamide Betaine. *J. Org. Chem.* **1994**, *59*, 2289−2291.
(34) O'Brien, P. M.; Sliskovic, D. R.; Blankley, C. J.; Roth, B. D.; Wilson, M. W.; Hamelehle, K. L.; Krause, B. R. Inhibitors of Acyl-CoA:Cholesterol *O*-Acyl Transferase (ACAT) as Hypocholesterolemic Agents. 8. Incorporation of Amide or Amine Functionalities into a Series of Disubstituted Ureas and Carbamates. Effects on ACAT Inhibition in Vitro and Efficacy in Vivo. *J. Med. Chem.* **1994**, *37*, 1810−1822.
(35) Meyers, A. I.; Poindexter, G. S.; Brich, Z. Asymmetric Synthesis of (+)- or (−)-2-Methyloctanal via the Metalloenamines of Chiral Alkoxy Amines. *J. Org. Chem.* **1978**, *43*, 892−898.
(36) Shih, Y.-E.; Wang, J.-S.; Chen, C.-T. Studies on Potential Antitumor Agents (III). Synthesis of 4-Arylcyclophosphamides. *Heterocycles* **1978**, *9*, 1277−1285.
(37) Owens, A. P.; Williams, B. J.; Harrison, T.; Swain, C. J.; Baker, R.; Sadowski, S.; Cascieri, M. A. Phenylglycinol-Based NK1 Receptor Antagonists − Towards the Minimum Pharmacophore. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2761−2766.
(38) Newman, M. S.; Edwards, W. M. New Reactions Involving Alkaline Treatment of 3-Nitroso-2-oxazolidones. *J. Org. Chem.* **1954**, *19*, 1840−1845.
(39) Kornet, M. J.; Crider, A. M.; Magarian, E. O. Potential Long-acting Anticonvulsants. 2. Synthesis and Activity of Succinimides Containing an Alkylating Group on Nitrogen or at the 3-Position. *J. Med. Chem.* **1977**, *20*, 1210−1213.
(40) Brown, N. C.; Gambino, J.; Wright, G. E. Inhibitors of *Bacillus subtilis* DNA Polymerase III. 6-(Arylalkylamino)uracils and 6-Anilinouracils. *J. Med. Chem.* **1977**, *20*, 1186−1189.
(41) King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. pH Optimization of Nucleophilic Reactions in Water. *J. Am. Chem. Soc.* **1992**, *114*, 3028−3033.
(42) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. Synthesis and Antiviral Activity of a Series of HIV-1 Protease Inhibitors with Functionality Tethered to the P_1 or P_1' Phenyl Substituents: X-ray Crystal Structure Assisted Design. *J. Med. Chem.* **1992**, *35*, 1685−1701.
(43) Creary, X.; Mehrsheikr-Mohammadi, M. E. Methylenecyclopropane Rearrangement as a Probe for Free Radical Substituent Effects. Effect of Sulfur in Various Oxidation States. *J. Org. Chem.* **1986**, *51*, 1110−1114.

(44) Leo, A.; Hansch, C. Linear Free-Energy Relationships between Partitioning Solvent Systems. *J. Org. Chem.* **1971**, *36*, 1539−1544.
(45) Tripos, Inc., St. Louis, Missouri.
(46) Stewart, J. J. P. QCPE Program 455.
(47) Hawkins G. D.; Lynch, G. C.; Giesen, D. J.; Rossi, I.; Storer, J. W.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. AMSOL-Version 5.4, QCPE Program 606-Version 5.4.
(48) Lazareno, S.; Birdsall, N. J. M. Pharmacological Characterization of Acetylcholine-stimulated [^{35}S]GTPγS Binding Mediated by Human Muscarinic m1-m4 Receptors: Antagonist Studies. *Br. J. Pharmacol.* **1993**, *109*, 1120−1127.

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