Fluorination of 3-(3-(Piperidin-1-yl)propyl)indoles and 3-(3-(Piperazin-1-yl)propyl)indoles Gives Selective Human 5-HT_{1D} Receptor Ligands with Improved Pharmacokinetic Profiles

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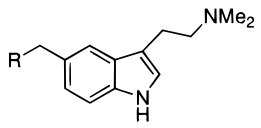
It has previously been reported that a 3-(3-(piperazin-1-yl)propyl)indole series of 5-HT_{1D} receptor ligands have pharmacokinetic advantages over the corresponding 3-(3-(piperidin-1-yl)propyl)-indole series and that the reduced pK_a of the piperazines compared to the piperidines may be one possible explanation for these differences. To investigate this proposal we have developed versatile synthetic strategies for the incorporation of fluorine into these ligands, producing novel series of 4-fluoropiperidines, 3-fluoro-4-aminopiperidines, and both piperazine and piperidine derivatives with one or two fluorines in the propyl linker. Ligands were identified which maintained high affinity and selectivity for the 5-HT_{1D} receptor and showed agonist efficacy in vitro. The incorporation of fluorine was found to significantly reduce the pK_a of the compounds, and this reduction of basicity was shown to have a dramatic, beneficial influence on oral absorption, although the effect on oral bioavailability could not always be accurately predicted.

Introduction

Since the introduction of sumatriptan[1] (**1**) as a new treatment for migraine, many migraineurs have achieved an improved quality of life as the often painful and debilitating symptoms of the disease are controlled following acute treatment.[2] Rizatriptan[3] (**2**) and a number of other compounds in this class[4] (e.g., zolmitriptan,[5] naratriptan,[6] eletriptan,[7] almotriptan,[8] and frovatriptan[9]) have since been developed and have either received regulatory approval or are in late phase clinical development.



1 R = $SO_2N(H)Me$, sumatriptan
2 R = 1,2,4-triazol-1-yl, rizatriptan

There has been considerable speculation about the mode of action of this class of drugs, centered on the observation that the compounds so far developed bind with almost equal affinities to the two subtypes (formerly 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$) of the human 5-HT_{1D} receptor.[4] During recent revisions to the 5-HT receptor nomenclature made by the Serotonin Club Nomenclature Committee, these receptor subtypes[10] have been renamed as 5-HT_{1D} and 5-HT_{1B}, respectively. Current hypotheses suggest that direct vasoconstriction of the cranial blood vessels[11] (5-HT_{1B} mediated) and/or inhibition of neurogenic inflammation in the dura mater[12] (5-$HT_{1D/B}$ mediated) may account for the relief of headache pain by these drugs, although the extent and relative importance of these two mechanisms are still unclear. A central nociceptive component has also been proposed as a contributing factor in the action of some of these compounds.[13]

Despite an extremely good side effect profile for this class of therapy, there exists the potential for detrimental coronary vasoconstriction[14] (5-HT_{1B} mediated[15]) that precludes their use in patients with existing defects in cardiovascular function.[16] Receptor-mapping studies have indicated that 5-HT_{1B} receptors are expressed widely in the CNS in both neural and vascular tissue, whereas the 5-HT_{1D} subtypes are expressed preferentially in neural tissues.[17a] Further studies using h5-HT_{1B} and h5-HT_{1D} receptor-specific antibodies have shown that only the 5-HT_{1B} receptor protein is found on dural arteries, whereas only the 5-HT_{1D} receptor protein was detected on trigeminal sensory neurones.[17b] This, together with the uncertainty over the mechanism of action, has led to speculation that a compound which binds selectively to 5-HT_{1D} over the 5-HT_{1B} receptor would have a reduced cardiovascular side effect liability and might therefore give rise to a new generation of anti-migraine drugs.

With this strategy in mind we have recently reported the identification of **3**[18] as a 5-HT_{1D} selective agonist (Table 1). The majority of marketed products or products undergoing development as first-generation anti-migraine therapies all display remarkably similar molecular frameworks. While the most pronounced structural diversity occurs in the C-5 substituent of the indole,

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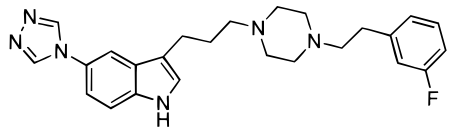
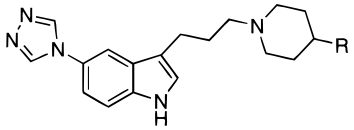


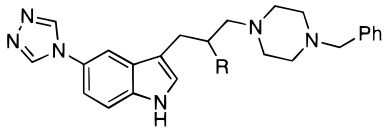
3

changes to the side chain attached to C-3 have been more conservative. However, the improvements in receptor subtype selectivity observed with **3** are attributable to modifications to the C-3 substituent, indicating that this is a profitable area for investigation. The distal amine of the piperazine would appear not to be necessary for binding since the corresponding piperidine analogues[19a] such as **4** were also shown to be ligands. The distal amine could also be moved to an exocyclic position to give a 4-aminopiperidine[20] (e.g., **5**) which would be expected to show subtle differences in pK_a relative to the parent piperazines (e.g., **6**).



4 R = CH_2Ph
5 R = $N(Me)CH_2Ph$

The pharmacokinetic advantages, in terms of oral absorption, of the propylpiperazines over the propylpiperidine 5-HT_{1D} receptor ligands are illustrated in Table 9.[19a] While the piperazine **6** is rapidly absorbed and is also orally bioavailable, the corresponding piperidine analogue **4** lacks good absorption and oral bioavailability. The reduced pK_a of the piperazine nitrogen com-



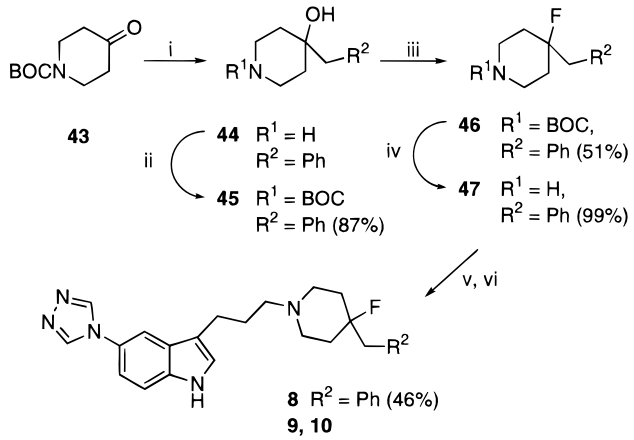
6 R = H
7 R = OH

pared to the piperidine may be one possible explanation for these differences. To investigate this idea, while at the same time mimicking the electrostatic properties of the second piperazine nitrogen, introduction of fluorine at the 4-position was investigated. Fluorine is commonly incorporated into biologically active molecules since it influences pK_a and routes of metabolism while having minimal steric requirements.[21]

The excellent in vitro profile of the 4-aminopiperidine **5**[20] was also overshadowed by poor absorption and low bioavailability. We speculated that modulation of the basicity of this series might also be advantageous to the absorption and bioavailability profiles. Accordingly, incorporation of fluorine was targeted at C-3 of the piperidine ring.

It had been demonstrated that **7**,[19b] which has a hydroxyl substituent in the propyl chain, retained binding affinity and selectivity. We inferred from this that the corresponding fluorinated analogues in both piperidine and piperazine series would also be tolerated while modulating the pK_a in the desired manner. Introduction of a *gem* difluoro substituent in the propyl chain was considered particularly advantageous since the absence of a chiral center would avoid the complexities of a chiral synthesis at a later stage.

Scheme 1[a]



[a] Reagents: (i) R^2CH_2Br, Mg, Et_2O; (ii) $(BOC)_2O$, CH_2Cl_2; (iii) DAST, CH_2Cl_2; (iv) TFA, CH_2Cl_2; (v) 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol,[23] MsCl, Et_3N; (vi) ^{i}PrOH, K_2CO_3, reflux.

Synthetic Chemistry

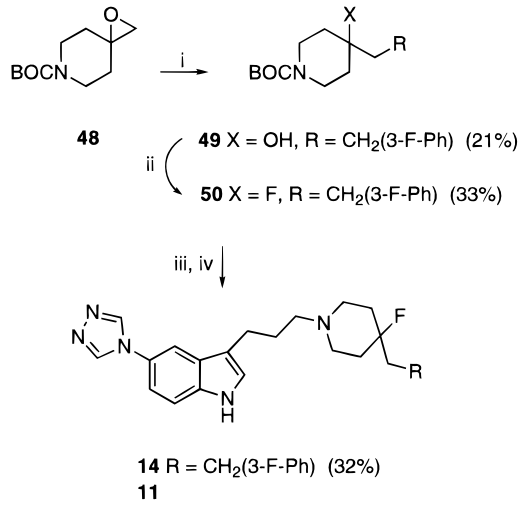
To synthesize these classes of compounds for biological and physicochemical evaluation, we developed chemistry to enable their preparation via convergent strategies. Representative syntheses to examples in each class of the fluorinated analogues are described below.

i. 4-Fluoropiperidines. The 4-fluoro-4-benzylpiperidine **8** was targeted as a direct analogue of **4**. Protection of 4-benzyl-4-hydroxypiperidine **44** as the *N*-*tert*-butylcarbamate followed by reaction with diethylaminosulfur trifluoride[22] (DAST) at low temperature gave a separable mixture of the tetrahydropyridine elimination product and the required fluorinated compound **46** (Scheme 1). Removal of the BOC protecting group followed by coupling to the mesylate of 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol[23] gave efficient access to **8**. Other analogues in this series with differing aryl substituents were prepared, starting with the addition of the appropriate benzylic Grignard reagent to *N*-*tert*-butoxycarbonyl piperidone **43**.

Alternatively, Grignard reagents or lithiated arenes, generated either by metalation of the appropriate aryl bromide or, where an *ortho* directing group was present, by direct deprotonation, were coupled with the epoxide **48**[24] (Scheme 2). For example, the (3-fluorophenyl)ethyl derivative **14** was prepared from the ring opening of epoxide **48** with 3-fluorobenzylmagnesium bromide to give the alcohol **49**. In contrast to our previous findings, reaction with DAST gave an inseparable mixture of the required fluorinated compound **50** and the corresponding tetrahydropyridine. Selective epoxidation of the crude mixture using mCPBA facilitated the isolation of the 4-fluoro-4-phenethylpiperidine **50** from the epoxide by column chromatography. This proved to be a useful general procedure for isolation of the pure fluorinated materials where simple separation of the tetrahydropyridine byproducts was not possible. Subsequent deprotection and coupling as described previously gave **14**.

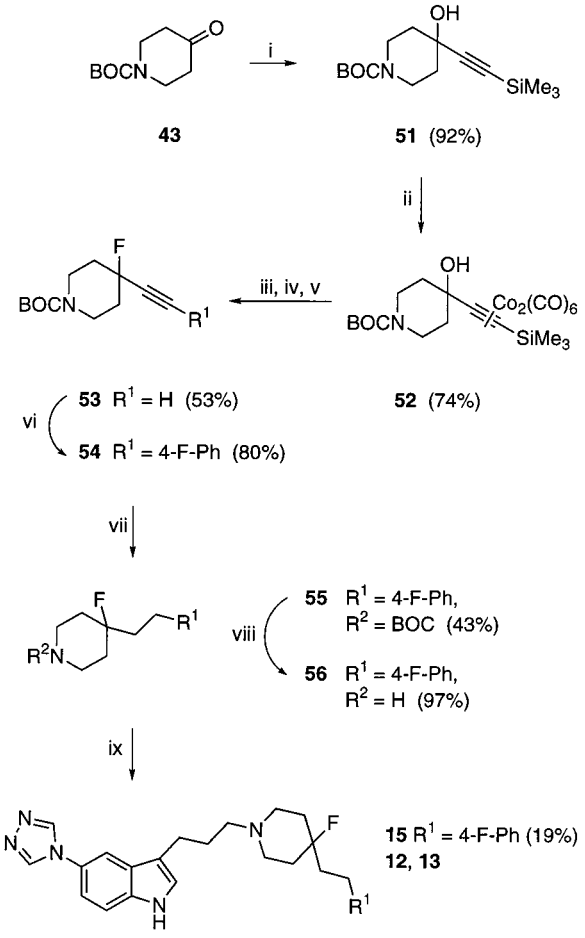
A more efficient strategy was developed which enabled the aryl ring to be incorporated at a late stage using the advanced intermediate **53** (Scheme 3). Addition of the anion of trimethylsilylacetylene to *N*-*tert*-

Scheme 2[a]



[a] Reagents: (i) Grignard reagent or aryllithium; (ii) (a) DAST, CH_2Cl_2 then (b) mCPBA, CH_2Cl_2; (iii) TFA, CH_2Cl_2; (iv) (a) 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propanol-1-ol,[23] MsCl, Et_3N then (b) ^{i}PrOH, K_2CO_3, reflux.

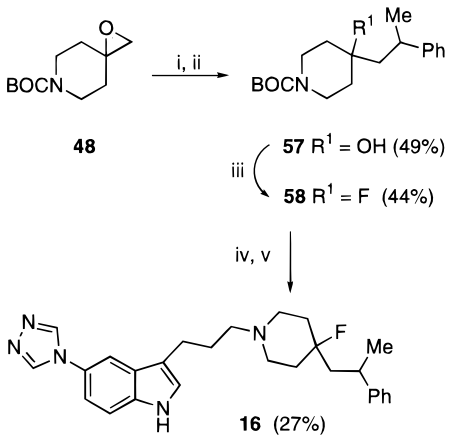
Scheme 3[a]



[a] Reagents: (i) trimethylsilylacetylene, THF, ^{n}BuLi; (ii) $Co_2(CO)_8$, Et_2O; (iii) DAST, CH_2Cl_2; (iv) CAN, acetone; (v) TBAF, THF; (vi) Et_2NH, CuI, $Pd(PPh_3)_2Cl_2$, RI or RBr; (vii) MeOH, AcOH, Pd−C, 50 psi H_2; (viii) TFA−CH_2Cl_2; (ix) (a) 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl-propan-1-ol,[23] MsCl, Et_3N then (b) ^{i}PrOH, K_2CO_3, reflux.

butoxycarbonylpiperidone **43** gave the 4-ethynyl-4-hydroxypiperidine **51**. The acetylene was protected as the cobalt complex before reaction of the tertiary alcohol with DAST. Decomplexation of the triple bond was achieved with ceric(IV) ammonium nitrate and the acetylenic silyl group was removed with TBAF to give the required advanced intermediate **53**. Palladium mediated coupling of **53** with aryl halides, followed by complete reduction of the triple bond and deprotection, afforded a versatile route to 4-fluoro-4-phenethylpiperidines.

Scheme 4[a]



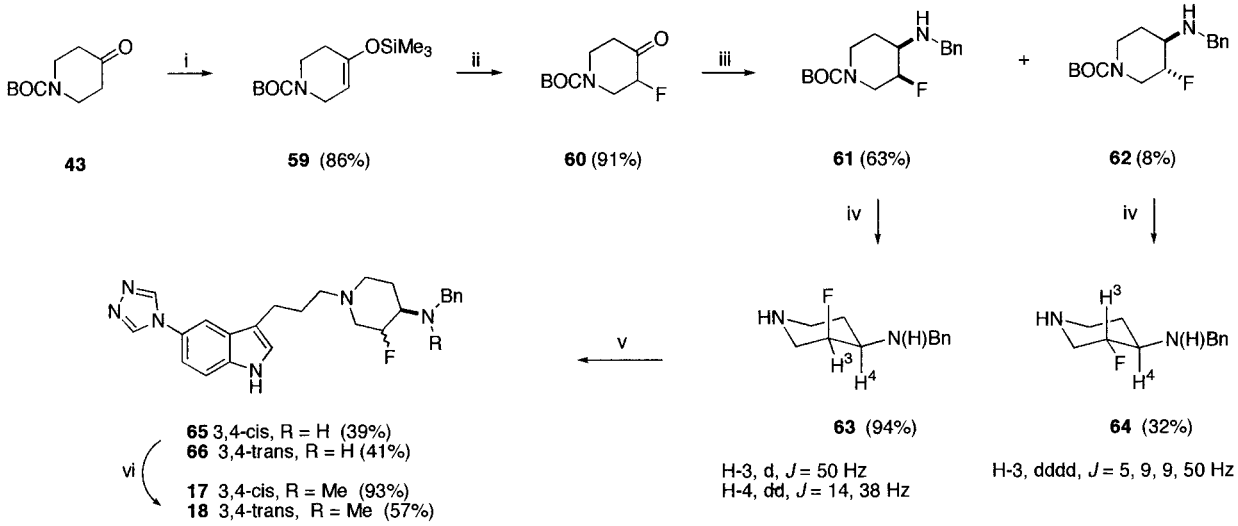
[a] Reagents: (i) ^{t}BuLi, α-bromostyrene, THF, −78 °C; (ii) 1 atm H_2, Pd−C, EtOAc; (iii) DAST, CH_2Cl_2; (iv) TFA−CH_2Cl_2; (v) (a) 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propanol-1-ol,[23] MsCl, Et_3N then (b) ^{i}PrOH, K_2CO_3, reflux.

The α-methylphenethyl derivative **16** was prepared by ring opening of the epoxide **48** using 1-phenylvinyllithium[25] (Scheme 4). Hydrogenation of the double bond followed by reaction with DAST gave the racemic 4-fluoropiperidine **58**. Deprotection and coupling using the conditions reported above gave **16**.

ii. 3-Fluoropiperidines. Fluorination of the silyl enol ether **59**[26] with 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (SELECTFLUOR) proceeded in high yield to give the corresponding α-fluoroketone **60** (Scheme 5).[27] Reductive amination with benzylamine afforded a mixture of *cis* and *trans* 4-amino-3-fluoro-piperidines **61** and **62** which were separated at this stage by chromatography and independently converted to the final target compounds. The identity of the two isomers was determined from the ^{1}H NMR spectra of the deprotected piperidines **63** and **64**.[28] After coupling of the piperidines to the intermediate mesylate, N-methylation of the 4-amino-3-fluoropiperidines **65** and **66** was achieved by reductive alkylation.

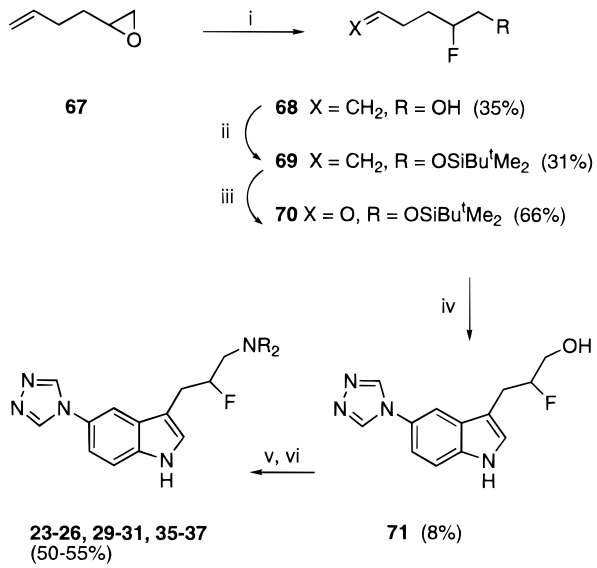
iii. 2-Fluoropropyl-Linked Piperazines and Piperidines. A versatile synthesis of the 2-fluoropropyl-linked compounds was devised that allowed incorporation of the amines at the final step (Scheme 6). Thus, reaction of 1,2-epoxy-5-hexene **67** with HF·pyridine at −78 °C gave the fluoro alcohol **68** which was protected as the silyl ether **69**. Ozonolysis of the olefin **69** proceeded smoothly, although the intermediate ozonide was remarkably stable to reduction using dimethyl sulfide even after reaction for 18 h. It was therefore decomposed using triethylamine, a reaction which was complete after less than 3 h.[29] Fischer indole synthesis using aldehyde **70** in dilute, refluxing sulfuric acid gave the advanced intermediate **71**. Formation of the primary mesylate followed by nucleophilic attack with an appropriate amine completed the synthesis. The reactivity

Scheme 5[a]



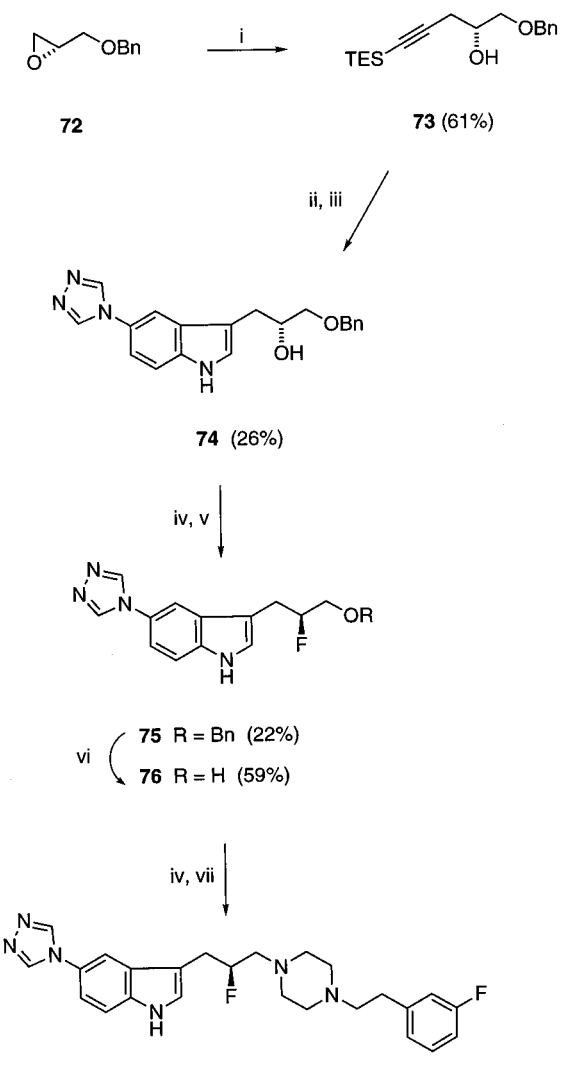
[a] Reagents: (i) DMF, TMSCl, Et_3N; (ii) CH_3CN, Selectfluor; (iii) $BnNH_2$, $Na(OAc)_3BH$, 1,2-dichloroethane; (iv) TFA, CH_2Cl_2; (v) (a) 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol,[23] MsCl, Et_3N then (b) ^{i}PrOH, K_2CO_3, reflux; (vi) AcOH, HCHO, $NaCNBH_3$, MeOH.

Scheme 6[a]



[a] Reagents: (i) HF·Py, CH_2Cl_2, −78 °C; (ii) TBSCl, imidazole, DMF; (iii) O_3, CH_2Cl_2, −78 °C then Et_3N, CH_2Cl_2, rt; (iv) 4-(1,2,4-triazol-4-yl)phenylhydrazine, HCl(aq), dioxane, reflux; (v) MsCl, Et_3N, THF; (vi) R_2NH, ^{i}PrOH, reflux.

Scheme 7[a]

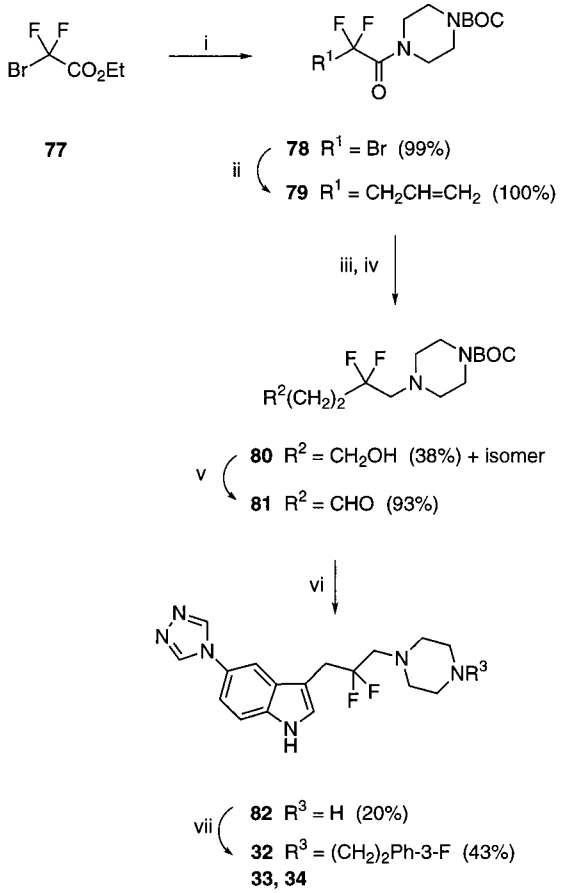


[a] Reagents: (i) TES−acetylene, ^{n}BuLi, BF_3·Et_2O, THF; (ii) 2-iodo-4-(1,2,4-triazol-4-yl)aniline, $Pd(OAc)_2$, K_2CO_3, DMF; (iii) HCl; (iv) MsCl, Et_3N, THF; (v) TBAF, DMF; (vi) NH_4HCO_2, $Pd(OH)_2$−C; (vii) 3-fluorophenethylpiperazine, K_2CO_3, ^{i}PrOH, reflux.

of the mesylate was much lower than that of the corresponding des-fluoro analogue, and extended reaction times were required to achieve full conversion.

A synthetic route which gave separate access to both enantiomers of **25** was devised starting from the commercially available enantiomers of benzyl glycidyl ether. Ring opening of the (*R*)-epoxide **72** using the anion of TES-acetylene, followed by a Larock reaction, gave the optically active intermediate **74** (Scheme 7). Activation of the secondary alcohol as the mesylate and fluoride displacement gave the fluoroalkane **75** which was debenzylated to give alcohol **76**. Both this compound and the enantiomer prepared from (*S*)-benzyl glycidyl ether had optical purities of >95% ee as determined by chiral HPLC, demonstrating stereospecific displacement of the intermediate mesylate, assumed to be through an S_N2 mechanism with inversion of configuration. Coupling of

Scheme 8[a]



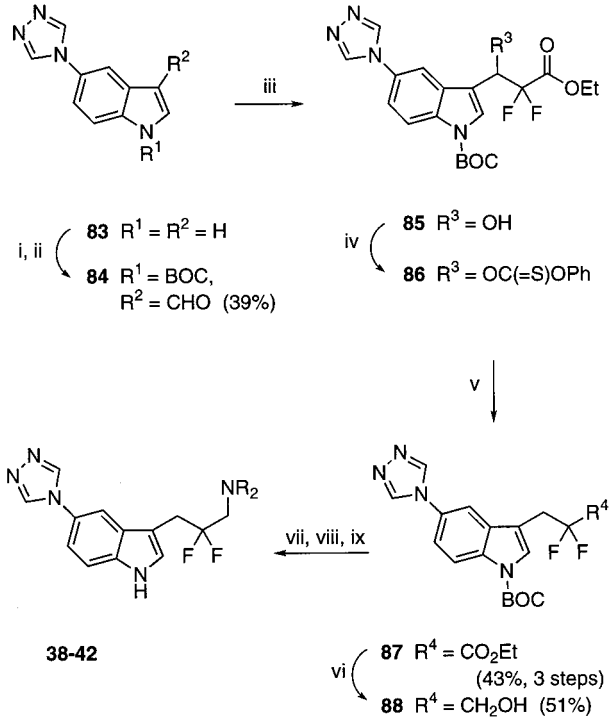
[a] Reagents: (i) *tert*-butyl 1-piperazinecarboxylate; (ii) AIBN, benzene, reflux, allyltributyltin; (iii) BH_3·THF, reflux; (iv) H_2O_2, NaOH; (v) SO_3·pyridine, DMSO, Et_3N; (vi) 4-(1,2,4-triazol-4-yl)phenylhydrazine, 4% H_2SO_4, reflux; (vii) $NaCNBH_3$, MeOH, AcOH, 3-fluorophenylacetaldehyde.

the chiral alcohols under the conditions described previously gave the two enantiomers **27** and **28**.

iv. 2,2-Difluoropropyl-Linked Piperazines and Piperidines. In the first approach to these targets, ethyl bromodifluoroacetate **77** was reacted with *tert*-butyl 1-piperazinecarboxylate to give the amide **78** (Scheme 8).[30] Subsequent radical coupling using allyltributyltin gave rapid and efficient access to the intermediate **79**. Hydroboration and concomitant reduction of the amide carbonyl using borane−THF gave a 3:1 mixture of primary and secondary alcohols, but exclusive formation of the primary alcohol **80** could be achieved using 9-BBN. Oxidation to the aldehyde **81** proceeded smoothly using sulfur trioxide−pyridine complex. On a larger scale, the use of tetrapropylammonium perruthenate (TPAP) was found to be more convenient and gave superior yields. Fischer indole synthesis using the aldehyde **81** gave access, albeit in modest yield, to the *gem*-difluoropropyl tryptamine **82**. Reductive amination using 3-fluorophenylacetaldehyde under Borch conditions[31] gave **32**, the *gem*-difluoro analogue of **3**. The piperazine **82** could also be alkylated under standard conditions.

While the route outlined in Scheme 8 provided sufficient material for the preparation of piperazine analogues via reductive amination or alkylation, the *gem*-difluoropropanol **88** (Scheme 9) was considered a more flexible intermediate. Accordingly, formylation of 5-(1,2,4-

Scheme 9[a]



[a] Reagents: (i) AcOH, H_2O, hexamethylenetetramine; (ii) $(BOC)_2O$, CH_2Cl_2; (iii) Zn, THF, DMF, BrF_2CCO_2Et, heat; (iv) phenylchlorothionoformate, THF, heat; (v) Bu_3SnH, AIBN, $PhCH_3$, heat; (vi) $NaBH_4$, MeOH; (vii) Tf_2O, pyridine, CH_2Cl_2; (viii) R_2NH, K_2CO_3, DMF, heat; (ix) CF_3CO_2H, CH_2Cl_2, rt.

triazolyl-4-yl)indole[32] **83** followed by protection of the indole N−H gave **84**, into which the propyl chain was introduced by Reformatski reaction with ethyl bromodifluoroacetate.[33] Addition of phenyl chlorothionoformate to the reaction when all the aldehyde had been consumed and additional heating gave the thionocarbonate **86**. Deoxygenation of **86** under radical conditions led to the ester **87**.[34] When these reactions were carried out sequentially with no purification of intermediates, the ester **87** was produced in 43% yield from **84**. Reduction using sodium borohydride gave access to the desired alcohol **88** which was activated to nucleophilic displacement by piperazines and piperidines through preparation of the triflate.

Biology

The approaches described above were used to prepare the analogues shown in Tables 2−6. A screening cascade was established in which compounds were first evaluated using a radioligand binding assay to measure affinity at human 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in Chinese hamster ovary (CHO) cells. Compounds with satisfactory binding affinity and selectivity over 5-HT_{1B} were then evaluated in a functional binding assay. Their intrinsic efficacy, expressed as a percentage of maximal 5-HT response, was determined in the same cell lines using agonist-induced [^{35}S]-GTPγS binding.[35] Results are given as the logarithmic mean of at least two independent determinations.

Results and Discussion

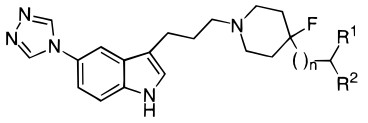
Binding Affinity and Selectivity. Although the binding affinity of the 4-fluoro-4-benzylpiperidines **8**−**11**

Table 1. 5-HT Receptor Binding Affinities of Reference Compounds

compd	IC_{50} (nM)[a] 5-HT_{1D}	5-HT_{1B}	selectivity[b] 1B/1D
3	0.5	72	140
4	0.3	19	63
5	2.1	140	67
6	0.14	11	79
7	1.8	360	200

[a] Displacement of specific [^{3}H]-5-HT binding to cloned human 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in CHO cells. The figures are the logarithmic mean of 2−5 independent determinations performed in duplicate. In each case the radioligand concentration was used at approximately the K_D for the receptor. The maximum variance from the mean of log(IC_{50}) values was 4%. [b] Binding selectivity for 5-HT_{1D} receptors.

Table 2. 5-HT Receptor Binding Affinities of Selected 4-Fluoropiperidines[a]



compd[b]	R^1	R^2	*n*	IC_{50} (nM) 5-HT_{1D}	5-HT_{1B}	selectivity 1B/1D
8	Ph	H	0	0.9	15	17
9	2-F-Ph	H	0	0.1	3.1	31
10	3-F-Ph	H	0	0.4	5.3	13
11	2-CF_3-Ph	H	0	0.3	14	47
12	Ph	H	1	2.0	49	25
13	2-F-Ph	H	1	0.8	16	20
14	3-F-Ph	H	1	0.7	22	31
15	4-F-Ph	H	1	1.0	25	25
16	Ph	CH_3	1	0.6	28	47

[a] See footnote to Table 1 for definitions of binding parameters. [b] Compounds **8**−**10** prepared by method described in Scheme 1; **11** and **14** prepared by method described in Scheme 2; **12**, **13**, and **15** prepared by method described in Scheme 3; **16** prepared by method described in Scheme 4.

and 4-fluoro-4-phenethylpiperidines **12**−**16** was excellent, the selectivity for 5-HT_{1D} over 5-HT_{1B} was reduced in comparison to the corresponding parent piperazine **3** (Tables 1 and 2). As was observed[18] in the parent piperazines, there was a preference at the 5-HT_{1D} receptor for electron-withdrawing substituents in the aryl ring. Introduction of an α-methyl group to the 4-phenethylpiperidine **12** to give **16** arguably led to somewhat improved affinity at the 5-HT_{1D} receptor. Determination of the basicity of representative compounds (Table 7) and molecular modeling studies (Figure 1) had indicated that 4-fluoropiperidine should be a good replacement for piperazine in terms of basicity and electron density distribution. This hypothesis was supported by the affinity of compounds **8**−**16** at the receptors, but the reduced selectivity implied that there may be a further property of the piperazines responsible for the selectivity of compounds such as **3**.

The 3-fluoro-4-aminopiperidines **17**−**22** (Table 3) also had reasonable binding affinities at the 5-HT_{1D} and 5-HT_{1B} receptors compared to the parent **5**, but again selectivity was poor. Neither introduction of electron-withdrawing substituents into the aryl ring nor N-methylation had a significant effect on the binding of these compounds. Importantly, the axially fluorinated

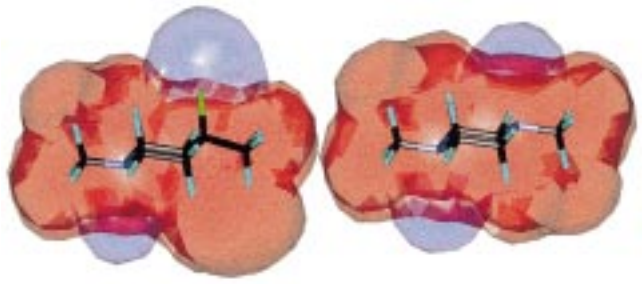
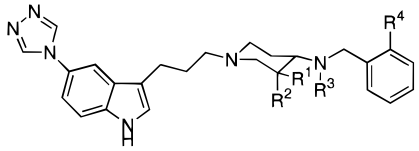


Figure 1. Calculated electrostatic potential contours of 4-fluoro-1,4-dimethylpiperidine (left) and 1,4-dimethylpiperazine (right). The contours are illustrated at +3 kcal/mol (red) and −3 kcal/mol (blue).

Table 3. 5-HT Receptor Binding Affinities of Selected 4-Amino-3-fluoropiperidines[a]



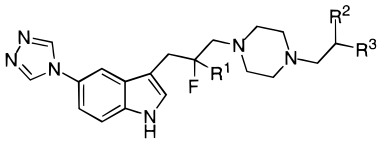
compd[b]	R^1	R^2	R^3	R^4	IC_{50} (nM) 5-HT_{1D}	5-HT_{1B}	selectivity 1B/1D
17	H	F	CH_3	H	12	220	18
18	F	H	CH_3	H	2.1	13	6
19	H	F	CH_3	CF_3	9.3	220	24
20	F	H	CH_3	CF_3	13	220	17
21	H	F	H	CF_3	13	300	23
22	F	H	H	CF_3	5.0	170	34

[a] See footnote to Table 1 for definitions of binding parameters. [b] Compounds **17**−**22** prepared by method described in Scheme 5.

piperidine **19** and its equatorially fluorinated counterpart **20** were shown to differ in basicity by almost one log unit (Table 7) but had identical binding profiles. In combination with the data from the 4-fluoropiperidines and the parent unfluorinated piperidines, this demonstrated the relative insensitivity of the receptors to changes in the basicity of the ligands within a pK_a range of ca. 7−10. Although the binding selectivities of the 4-fluoropiperidines and the 3-fluoro-4-aminopiperidines were low, the dramatically improved oral absorption of these compounds relative to the unfluorinated compounds **4** and **5** (see below) gave the first validation of our original hypothesis. Prior investigations of substitution of the propyl linker had revealed that the (2-hydroxy)propyl compound **7**[19b] was well tolerated at the 5-HT_{1D} receptor with good selectivity over 5-HT_{1B}. This encouraged us to explore the introduction of fluorine into the propyl linker.

Gratifyingly, given the low selectivities of the fluorinated heterocyles described above, monofluorination of the propyl chain of the propylpiperazines **23**−**31** related to **3** had a small detrimental effect on 5-HT_{1D} affinity but maintained the selectivity over 5-HT_{1B} (Table 4). The identical binding profiles of **27** and **28**, the individual enantiomers of **25**, and the good binding profile of the hydroxylated compound **7**, suggested that placing these small substituents at the 2-position of the propyl linker had little effect on the conformation of the ligands and thus no effect on their binding to the receptors. In

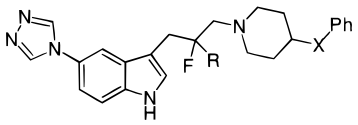
Table 4. 5-HT Receptor Binding Affinities of Selected 1-(2-Fluoropropyl)piperazines and 1-(2,2-Difluoropropyl)piperazines[a]



compd[b]	R^1	R^2	R^3	IC_{50} (nM) 5-HT_{1D}	IC_{50} (nM) 5-HT_{1B}	selectivity 1B/1D
23	H	H	Ph	6.8	930	137
24	H	H	2-F-Ph	4.7	520	111
25	H	H	3-F-Ph	3.5	1200	343
26	H	H	4-F-Ph	5.5	540	98
(*S*)-**27**	H	H	3-F-Ph	5.8	680	117
(*R*)-**28**	H	H	3-F-Ph	5.1	1000	196
29[c]	H	CH_3	2-F-Ph	1.0	380	380
30[c]	H	CH_3	3-F-Ph	0.9	280	311
31[c]	H	CH_3	4-F-Ph	1.0	310	310
32	F	H	3-F-Ph	15	1600	107
33	F	CH_3	Ph	6.2	1800	290
34	F	CH_3	4-F-Ph	1.8	1000	556

[a] See footnotes to Table 1 for definition of binding parameters. [b] Compounds **23**−**26** and **29**−**31** prepared by method described in Scheme 6; **27**−**28** prepared by method described in Scheme 7; **32**−**34** prepared by method described in Scheme 8. [c] Compound was prepared and tested as a mixture of two diastereoisomeric pairs.

Table 5. 5-HT Receptor Binding Affinities of Selected 1-(2-Fluoropropyl)piperidines and 1-(2,2-Difluoropropyl)piperidines[a]



compd[b]	R	X	IC_{50} (nM) 5-HT_{1D}	IC_{50} (nM) 5-HT_{1B}	selectivity 1B/1D
35	H	$-CH_2-$	0.9	62	69
36	H	$-OCH_2-$	30	3000	100
37	H	$-N(CH_3)CH_2-$	5.4	1200	22
38	F	$-CH_2-$	78	1300	17
39	F	$-OCH_2-$	8.5	1000	118
40	F	$-CH_2O-$	280	7200	26
41	F	$-CH_2CH_2-$	56	5800	104
42	F	$-N(CH_3)CH_2-$	35	2100	60

[a] See footnotes to Table 1 for definition of binding parameters. [b] Compounds **35**−**37** prepared by method described in Scheme 6; **38**−**42** prepared by method described in Scheme 9.

contrast, incorporation of an α-methyl substituent into the phenethyl moiety, as in **29**−**31**, gave slightly higher affinity for the 5-HT_{1D} receptor while maintaining the selectivity. This was analogous to the weak effect seen in the 4-fluoropiperidines and implies that the $5HT_{1D}$ and $5HT_{1B}$ receptors vary in their sensitivity to increases in steric bulk around the distal aryl ring, or to local changes in conformation of the ligand at this point produced by, for example, *ortho* substituents in the ring.

Monofluorination of the linker of the propylpiperidine **4** to give **35** (Table 5) gave little change in affinity and selectivity relative to the parent compound. Homologation to the benzyl ether **36** severely decreased 5-HT_{1D} affinity. In contrast, the monofluorinated 4-aminopiperidine **37** retained affinity and selectivity at 5-HT_{1D} relative to the parent **5**.

Substitution in the propyl chain of both propylpiperazines and propylpiperidines with a *gem*-difluoro group generally led to a decrease in binding affinity at the 5-HT_{1D} receptor (Tables 4 and 5). Thus the piperidine **38** was inferior when compared to the parent **4** or the monofluorinated analogue **35**. A similar outcome was seen for the 4-aminopiperidine **42** compared to **5** and **37** and also for the piperazine **32** compared to **3** and **25**. For the difluorinated piperidine **38**, the measured pK_a was found to be less than 7 (Table 7). These observations imply that difluorination of the linker reduces the basicity of the piperidines beyond a critical threshold, at which point binding to the receptors is compromised due to the lack of protonated ligand at physiological pH. This is consistent with the known importance of an ammonium ion binding site in the $5HT_{1D}$ and $5HT_{1B}$ receptors.[4] A surprising exception was the difluorinated benzyloxypiperidine **39** which showed an unexpectedly good binding profile relative to the monofluorinated benzyloxypiperidine **36**, especially in view of the very low pK_a (5.9) of this compound (Table 7). Translocation of the ether oxygen in this compound to give the phenoxide **40** or replacement by methylene to give the phenethyl analogue **41** gave a loss of binding affinity more in keeping with the low affinities of the other *gem*-difluorinated compounds. Interestingly, incorporation of the α-methyl substituent that had proved beneficial in previous series also improved the in vitro profile of the *gem*-difluoropropyl-linked compounds (Table 4). For example, the 2,2-difluoropropylpiperazine **34** showed excellent selectivity for 5-HT_{1D} over 5-HT_{1B}, comparable to that of the monofluorinated counterpart **31**. Therefore, it is possible that the general detrimental effect of very low basicity, and the subsequent reduction in ammonium ion binding, can be offset by optimizing the binding of the distal aryl substituent to the receptors.

For the piperazines and 4-aminopiperidines fluorinated in the propyl linker, it is possible that the second, distal nitrogen atom will be protonated at physiological pH in preference to the proximal nitrogen and as a result be involved in the binding interaction with the receptor (see below). This would be particularly likely for the monofluoropropyl- and *gem*-difluoropropyl-substituted piperazines. If this is the case, it would appear from the binding and selectivity data presented above that $5HT_{1D}$ receptors are better able to accommodate such alternative binding interactions than $5HT_{1B}$ receptors, even though the two receptors are highly homologous at the binding site. Thus the unfluorinated and monofluoropropyl piperazines show improved selectivity over the piperidine ligands, reflecting the increased potential for interaction with the distal nitrogen.

Efficacy. Selected compounds were evaluated in the 5-HT_{1D} and 5-HT_{1B} [^{35}S]-GTPγS functional assays[35] (Table 6). The 4-fluoro-4-benzylpiperidines **8** and **11** had partial agonism, equivalent to the unfluorinated parent 4-benzylpiperidine **4**, showing a limited role for the basicity of the compounds, as modulated by the introduction of fluorine, in determining efficacy in this series. The α-methyl substitution which had shown a small benefit in terms of the binding selectivity of **16** also engendered a modest increase in efficacy to levels

Table 6. Determination of Efficacy for Selected Compounds

	[^{35}S]-GTPγS 5-HT$_{1D}$		[^{35}S]-GTPγS 5-HT$_{1B}$	
compd	EC$_{50}$ (nM)[a]	% 5-HT[b]	EC$_{50}$ (nM)[c]	% 5-HT[b]
3	1.0	88	430	71
4	0.6	63	120	62
5	1.5	94	1400	77
8	0.4	58	66	67
11	0.2	61	290	91
14	5.0	71	440	88
16	2.6	86	510	85
25	3.8	99	810	25
30	1.9	112	1500	87
31	1.6	106	1700	79
32	35	78		
33	16	123	5100	53
35	0.9	61	450	77
37	18	104	10300	59
39	34	100	10000	78

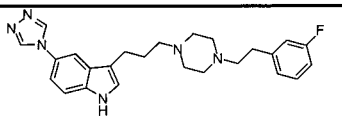
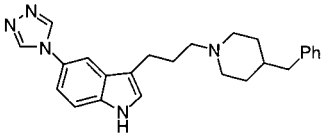
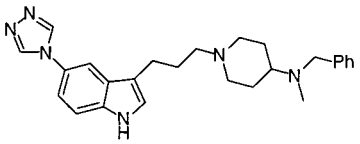
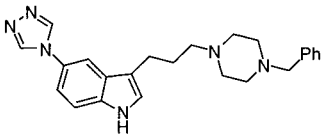
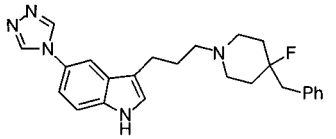
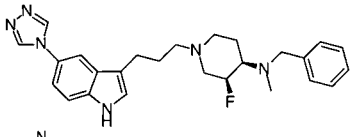
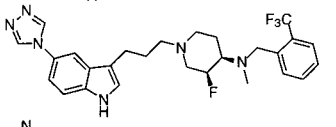
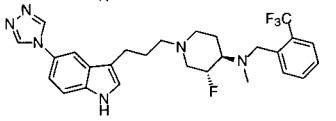
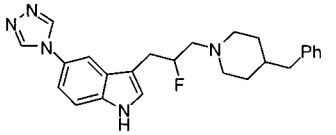
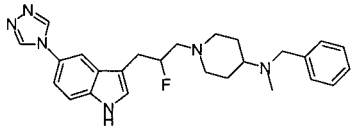
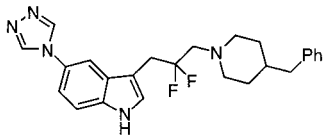
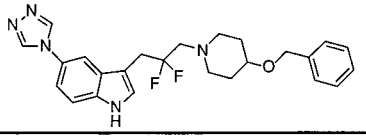
[a] Measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells stably transfected with human 5-HT$_{1D}$ receptors. The figures are the logarithmic mean of 2−3 independent determinations. The maximum variance of the individual log(EC$_{50}$) values from the mean was 4%. [b] Efficacy relative to 5-HT. Values are the mean of 2−3 independent determinations. The maximum variance of the individual relative efficacies from the mean was 16%. [c] Measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells stably transfected with human 5-HT$_{1D}$ receptors.

comparable to **3**. In the propylpiperazine series, monofluorination of **3** in the propyl linker gave **25**, which retained high levels of efficacy at 5-HT$_{1D}$. Substitution with α-methyl in the phenethyl side chain of this group of compounds was again found to be beneficial for efficacy. Thus both the monofluoro compounds **30** and **31** and the *gem*-difluoro analogue **33** were full agonists at 5-HT$_{1D}$. The piperidine **4** was a partial agonist and, as above, incorporation of a single fluorine into the propyl chain to give **35** did not alter this efficacy. The sensitivity of the functional behavior to the structure of the distal substituent was further demonstrated by the 4-benzyloxypiperidine **39** which was a full agonist. The prototypical 4-aminopiperidine **5** was a full agonist at 5-HT$_{1D}$ and this efficacy was maintained upon monofluorination of the propyl linker of the related compound **37**. In general, the changes in basicity due to fluorination had little effect on the efficacy of the compounds in any of the series investigated. Incorporation of α-methyl substitution was demonstrated to be a useful strategy for restoring efficacy. This supported earlier observations that the structure of the distal aryl substituent influences the efficacy of the compounds.

Physicochemical Properties. The role of fluorine substituents in modulating the pK_a of the basic amines was investigated by experimental determination of the pK_a for representative members of the different series[36] (Table 7). The prototypical 4-fluoropiperidine **8** was found to be significantly less basic than the parent **4**, with a pK_a closer to that of the piperazines **3** and **6**. The suitability of 4-fluoropiperidine as a piperazine replacement was further supported by calculations of the electrostatic potential surface for these groups using MOPAC 6.0[37] (Figure 1). The electron density due to the axial 4-fluoro substituent neatly mirrors that of the lone pair of the second piperazine nitrogen, although it does extend over a larger region of space.

Decreases in basicity were also seen for the 3-fluoropiperidines **17**, **19**, and **20** relative to the parent **5**. A significant difference in pK_a was observed between these

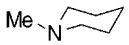
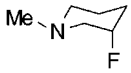
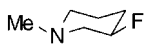
Table 7. Determination of pK_a for Selected Compounds

compound	structure	pKa[a]
3		8.3
4		9.7
5		9.3
6		8.2
8		8.8
17		8.0
19		7.7
20		6.9
35		8.7
37		8.5
38		6.7
39		5.9

[a] Determined by potentiometric titration.[36]

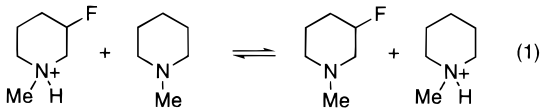
last two compounds, with the equatorially fluorinated *trans* isomer **20** having a pK_a almost one unit lower than the axially fluorinated *cis* isomer **19**. Calculations using AMSOL 5.4c[38] on the relative energies for the protonation of the equatorial and axial conformers of *N*-methyl-

Table 8. Relative Basicities of Equatorially and Axially Fluorinated *N*-Methyl-3-fluoropiperidine Calculated Using AMSOL 5.4c[a]

structure	relative protonation energy	pK_a units relative to *N*-methylpiperazine
	0	0
	2.50	−1.83
	4.42	−3.24

[a] See ref 38 for a description of the calculation methods.

3-fluoropiperidine, represented by the equilibrium (reaction 1), duplicated both the rank order of basicity of



(1)

the two isomers and also the magnitude of the difference in pK_a between them (Table 8). Neither examination of the bond orders and localized orbitals calculated for these species nor a visual examination of the electron density calculated from the molecular orbital output was able to explain the energy differences in terms of a hydrogen bond from the N−H hydrogen to the axial fluorine or via overlap of the antiperiplanar ring N−C bond with the C−F bond in the equatorial case. The simplest explanation of the discrimination is therefore probably a purely electrostatic one, in which for the axial case the dipoles of the N−H and C−F groups are parallel and opposed, hence compensating partially for the general loss of proton affinity produced by through-bond inductive effects. These observations are in accord with those previously made on the conformational preferences of protonated 3-fluoropiperidine itself[39] which has been shown to have a preference for the axial conformation both in experiment and in theoretical models (including an earlier AMSOL model). In the present case, the conformation is constrained (either experimentally by the presence of the 4-aminoalkyl group, or artificially in the theoretical model), and we are thus able to observe the difference in stability upon protonation of either species.

In the propylpiperidine series, the monofluorinated compound **35** had a pK_a one unit lower than the unfluorinated parent **4**, and addition of another fluorine to the propyl chain, as in **38**, gave a substantial further reduction in pK_a. As previously described, this appears to make the propylpiperidines sufficiently nonbasic to compromise binding to the receptors. Introduction of an electron-withdrawing oxygen atom into the 4-substituent caused a further significant decrease in basicity of **39**. However, this compound maintained binding affinity, indicating that the basicity of the amine is not the sole factor controlling the binding of these ligands. The basicity of the 4-aminopiperidine **37** was also reduced relative to the parent **5** by monofluorination in the propyl linker.

The magnitude of the reduction in pK_a upon fluorination of the propyl linker may also have consequences for the binding mode of the propylpiperazines. Site-directed mutagenesis studies have implicated an aspartate residue present in all G-protein coupled receptors as a key amino acid for ammonium ion binding, and the interaction of protonated, endogenous 5-hydroxytryptamine or drug ligands with aspartate 118 located on transmembrane helix III is thought to be critical for binding at the 5-HT_{1D} receptor.[4] Whereas protonation of the unfluorinated piperazines such as **3** and **6** will occur at the proximal nitrogen to the indole nucleus in a fashion similar to the simpler tryptamine derivatives **1** and **2**, fluorination in the linker would render the distal nitrogen more basic in compounds such as **25**. Thus at physiological pH a higher proportion of these ligands may be protonated at the distal nitrogen. Different interactions with Asp 118 in TM-III would be expected for these two series of compounds.[40] It appears from our data that interactions with the more remote protonated nitrogen are better accommodated by the $5HT_{1D}$ receptor than the $5HT_{1B}$ receptor, leading to the greater selectivity observed for the piperazines compared to the piperidines.

Table 9. Short Oral Absorption Study Data

	short oral absorption study plasma concentration (ng/mL)[a,b]			
	0.5 h		2 h	
compd	hpv	systemic	hpv	systemic
4	25 (±4)	<2	33 (±6)	<2
5	4 (±1)	<1	66 (±23)	5 (±2)
6	168 (±40)	42 (±24)	*c*	*c*
8	570 (±119)	52 (±21)	273 (±57)	35 (±7)
17	216 (±67)	2 (±1)	136 (±23)	3 (±0.3)
32	503 (±278)	<4	61 (±25)	<4
35	781 (±171)	196 (±60)	258 (±80)	46 (±22)
37	57 (±15)	2 (±1)	217 (±27)	10 (±3)

[a] Concentration of compound in rat plasma obtained from hepatic portal vein (hpv) and cardiac (systemic) blood samples following oral dosing at 3 mg/kg. Concentration determined by electrospray mass spectrometry. [b] Values in parentheses represent standard error in the mean. [c] Not determined.

Pharmacokinetic Determinations. Although the 5-$HT_{1D/1B}$ selectivity for the 4-fluoropiperidine **8** was reduced when compared to the corresponding piperazines and piperidines, it offered advantages in that it was effectively absorbed and retained measurable systemic levels after 2 h. (Table 9). Since the measured pK_a for **8** is substantially lower than that for the unfluorinated piperidine **4**, this provided support for our hypothesis that modulation of this physical property would enhance oral absorption. Fluorination at C-3 of the 4-aminopiperidines also lowered the pK_a of the heterocycle, and a corresponding improvement in oral absorption was seen with **17** compared to **5**. Despite this, the systemic exposure of **17** was very low, suggesting depletion by first-pass metabolism.

On the basis of observation that the monofluoropropylpiperidine **35** also had a measured pK_a of one unit lower than that for **4**, it was anticipated to be well absorbed, and this was indeed the case. This compound also showed moderate bioavailability (F = 14%). The monofluoropropyl 4-aminopiperidine **37** also had a significantly lower pK_a than the unfluorinated parent **5**, and this again translated into an improvement in oral absorption. However, like the 3-fluoro-4-aminopiperidine **17**, this compound appeared to suffer from extensive first-pass metabolism. Other ligands also demonstrated the importance of first-pass metabolism in

determining systemic penetration. For example, the difluoropropylpiperazine **32** showed excellent oral absorption but negligible bioavailability. The rate of clearance of this compound (Cl_p = 67 mL/min/kg), close to the rate of liver blood flow in the rat, was indicative of extensive metabolism. Other factors were observed to mitigate against such hepatic metabolism, since the parent compound **3** also had high clearance (Cl_p = 84 mL/mg/kg), but nevertheless achieved good oral bioavailability (F = 27%). In this case, it may be that very rapid absorption of the compound **3** leads to saturation of the metabolizing enzymes on first pass, resulting in good bioavailability despite high clearance. Interestingly, the piperidine **39**, with a pK_a of only 5.9 (Table 7), attained very high systemic levels (C_{max} = 157ng/mL) with moderate clearance (Cl_p = 43 mL/min/kg) and acceptable bioavailability (F = 11%), reconfirming the validity of our original hypothesis that reduction of the basicity of the piperidines would improve oral absorption.

Conclusions

We speculated that a reduction of the pK_a of the 3-(3-heterocyclylpropyl)indole 5-HT_{1D} ligands might lead to improvements in their oral absorption as a first step toward improving oral bioavailability. To investigate this idea, we proposed that fluorine could be incorporated into piperidines and piperazines to subtly modulate pK_a while having minimal steric requirements. Versatile synthetic chemistry was developed which enabled analogues to be prepared efficiently with fluorination either in the heterocyclic ring or in the propyl linker to the indole nucleus.

The novel series of 4-fluoropiperidines and 3-fluoro-4-aminopiperidines were shown to be ligands with high affinity for 5-HT_{1D} although with only moderate binding selectivity over 5-HT_{1B}. The measured pK_a for the 4-fluoropiperidine **8** was substantially lower than that for the unfluorinated piperidine **4** and the compound showed good oral absorption, providing the initial support for our hypothesis that modulation of pK_a may enhance oral absorption. While the 3-fluoro-4-aminopiperidine **17** showed much improved oral absorption compared to the parent **7**, the low systemic levels obtained with this compound illustrated that bioavailability may be compromised by metabolic instability. Incorporation of fluorine into the propyl chain led to the identification of a number of ligands, both piperidines and piperazines, with high affinity and selectivity for 5-HT_{1D} which also had high intrinsic efficacy in functional binding assays. These series provided further validation of our original hypothesis that reduction of basicity would lead to increased oral absorption with the observation that **35** was absorbed very effectively compared to **4**, and similarly **37** compared to **5**.

The increased complexity of the C-3 substituents on the indole has allowed successful discrimination between the highly homologous $5HT_{1D}$ and $5HT_{1B}$ receptors, in contrast to simple tryptamines such as **1** and **2**. In particular, the differences between the piperazine and piperidine ligands suggests that, despite close homology between the proteins, the $5HT_{1D}$ receptor is more tolerant of changes in the position of the basic nitrogen than the $5HT_{1B}$ receptor, and that this may be usefully exploited in improving the selectivity of ligands for the $5HT_{1D}$ receptor. Moderation of pK_a alters the equilibrium in favor of un-ionized species, and this will clearly influence tissue penetration although it will not necessarily affect adverse metabolic processes. Our data illustrates this and has shown that although incorporation of fluorine substituents into these classes of tryptamines can dramatically improve oral absorption by lowering the basicity of the compounds, the effects on oral bioavailability cannot always be predicted accurately across the series.

Experimental Section

pK_a Determinations. Potentiometric pK_a determinations were performed using a Sirius PCA-101 titrator (Sirius Analytical Instruments Ltd., East Sussex, England) equipped with a Ross combination type electrode calibrated for mixed solvent titrations. The mixed solvent approach was employed due to limited aqueous solubility across the pH range. A cosolvent of MeOH−H_2O, ionic strength adjusted with 0.15 M KCl, was used. Three separate titrations were determined for each compound with different water/cosolvent ratios to obtain pK_a values in the presence of cosolvent (psK_a values). Aqueous pK_a values were calculated by extrapolation to 100% H_2O using the Yasuda−Shedlovsky relationship: a linear plot of psK_a + log[H_2O] versus $1/\epsilon$ where ϵ is the dielectric constant of the water/cosolvent mixture.

Oral Absorption and Pharmacokinetic Determinations. Six male Sprague−Dawley rats (approximate weight 300 g) were deprived of food overnight. The tail artery of each animal was cannulated under isoflurane anaesthesia, and the animals were allowed to recover for a minimum of 30 min. Each animal was then given a 3 mg/kg dose of the test compound either i.v. (via bolus injection into tail vein) or orally (via gavage to the stomach), three animals per dose route. For i.v. dosing the test compounds were formulated as a solution (3 mg/mL) in a PEG 300 and 5 mM HCl (25:75 v/v) cosolvent. For oral administration the test compounds were formulated as a solution (0.6 mg/mL) in PEG 400:5 mM HCl (25:75 v/v). Serial blood samples (600 μL) were collected into heparinized tubes at several time points up to 6 h after dosing. Plasma was harvested from the blood samples by centrifugation, and the samples were stored at −20 °C until analysis.

In addition, a further six rats (without any surgical preparation) were fasted overnight and given a 3 mg/kg oral dose of the test compound, formulated as above. Terminal blood samples were obtained from the heart and hepatic portal vein, under isoflurane anaesthesia, at 0.5 and 2 h after administration (three animals per time point). Plasma was obtained from the blood samples as above.

Concentrations of test compounds in plasma were determined by solid phase extraction followed by reverse phase HPLC with fluorescence detection. A 0.2 mL aliquot of plasma sample was diluted with 1 mL of water and applied to a preconditioned (1 mL of MeOH followed by 1 mL of H_2O) solid phase extraction cartridge (BondElut C2, 50 mg, 1 mL). Following a cleanup with 1 mL of MeOH:water (70:30 v/v), the test compound was eluted with 1 mL of MeOH:0.1 M NH_4-OAc (80:20 v/v). The eluent was evaporated to dryness under N_2 at 65 °C. The residue was reconstituted in 0.3 mL of HPLC mobile phase (25 mM triethylamine phosphate pH 3 and 10 mM sodium dodecyl sulfate:acetonitrile 60:40 v/v). HPLC analysis was carried out on a Hichrom 5 μm RPB column (100 mm × 4.6 mm) at 45 °C with a flow rate of 1.5 mL/min and an injection volume of 100 μL. Detection of test compounds was achieved by monitoring the fluorescence of the eluent (λ_{ex} = 235 nm, λ_{em} = 370 nm). Quantitation of test compounds was achieved by comparing peak areas of samples against calibration curves obtained by spiking control rat plasma with known amounts of test compounds. All pharmacokinetic analysis was model independent and used standard formulas in a Microsoft Excel spreadsheet.

General Chemical Experimental Procedures. ^{1}H NMR spectra were recorded on Brucker AMX500, AM360, or AC250 spectrometers. Chemical shifts, from tetramethylsilane as internal standard, are given in ppm and coupling constants in hertz. Melting points were determined on a Reichert Thermovar hot stage apparatus and are uncorrected. Mass spectra were obtained with a VG Quattro spectrometer using electrospray in positive ion mode. Anhydrous THF, DMF, Et_2O, MeOH, and toluene were purchased from the Aldrich Chemical Co. Petroleum ether refers to the fraction boiling between 60 and 80 °C (glass distilled, Romil Chemicals). EtOH refers to absolute EtOH. Organic solutions were dried over dry Na_2SO_4 or $MgSO_4$. Flash chromatography and dry flash chromatography were performed on silica gel Fluka Art. No. 60738 and Merck 15111, respectively. Thin-layer chromatography (TLC) was carried out on Merck 5 cm × 10 cm plates with silica gel 60 F_{254} as sorbant. Preparative thin-layer chromatography was carried out using 20 cm × 20 cm silica gel GF tapered plates supplied by Analtech Inc, Newark. Alumina was obtained from ICN Biochemicals and was treated with water to give grade III activity. Microanalyses were determined by Butterworth Laboratories, 54−56 Waldegrave Road, Teddington, U.K. Where not described in the Experimental Section, amine fragments used for the preparation of the compounds shown in Tables 2−5 were commercially available or were prepared using standard literature procedures.

1-*tert*-Butyloxycarbonyl-4-benzyl-4-hydroxypiperidine (45). A solution of 4-benzyl-4-hydroxypiperidine **44** (14.50 g, 75.8 mmol) in CH_2Cl_2 (150 mL) was treated portionwise with di-*tert*-butyl dicarbonate (16.55 g, 75.8 mmol) and then stirred at room temperature for 4 h. The solution was washed with 10% aqueous citric acid (50 mL), dried, and evaporated to afford a gum which was purified by column chromatography using EtOAc−petroleum ether (1:1) as eluent to give **45** as a pale yellow solid (19.30 g, 87%): mp 87−88 °C; δ_H (360 MHz, DMSO-d_6) 1.32−1.37 (13 H, m), 2.67 (2 H, s), 2.98−3.05 (2 H, m), 3.63 (2 H, d, J = 12), 4.37 (1 H, s), 7.15−7.27 (5 H, m); m/z (ES+) 292 (M + H$^+$).

1-*tert*-Butyloxycarbonyl-4-benzyl-4-fluoropiperidine (46). A solution of **45** (0.70 g, 2.40 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise via cannula at −71 °C to a stirred solution of DAST (634 μL, 4.80 mmol) in dry CH_2Cl_2 (15 mL) under N_2. After 50 min at −75 °C the mixture was warmed to −10 °C and stirred for a further 2 h. H_2O (20 mL) and saturated K_2CO_3 (aqueous) (7 mL) were added, and products were extracted with Et_2O (70 mL). The organic solution was washed with brine (25 mL), dried, and concentrated. Flash column chromatography using hexanes−Et_2O (86:14) as eluent gave 1-*tert*-butyloxycarbonyl-4-benzyl-1,2,5,6-tetrahydropyridine (0.19 g, 29%) and **46** (0.36 g, 51%) as pale yellow oils: **46** δ_H (360 MHz, $CDCl_3$) 1.44 (9 H, s), 1.46−1.78 (4 H, m), 2.90 (2 H, d, J = 22), 2.98−3.08 (2 H, m), 3.86−3.94 (2 H, m), 7.16−7.34 (5 H, m); m/z (ES+) 294 (M + H$^+$).

4-Benzyl-4-fluoropiperidine (47). A solution of **46** (0.36 g, 1.23 mmol) in a mixture of CF_3CO_2H and CH_2Cl_2 (1:2; 12 mL) was allowed to stand at room temperature for 1 h. Solvents were removed under vacuum, and the residue was azeotroped with MeOH (2 × 25 mL). H_2O (10 mL), NaOH (aqueous) (4 M; 5 mL), and brine (15 mL) were added, and the product was extracted with EtOAc (2 × 50 mL). The combined organic solutions were dried and concentrated to give **47** as a pale yellow oil (0.24 g, 99%) which was used in the next step without further purification: δ_H (360 MHz, $CDCl_3$) 1.50−1.78 (4 H, m), 2.84−2.96 (6 H, m), 7.16−7.32 (5 H, m); m/z (ES+) 194 (M$^+$ + H$^+$).

4-Benzyl-4-fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (8). To a stirred suspension of 3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propanol-1-ol[23] (0.21 g, 0.85 mmol) in dry THF (35 mL) at room temperature under N_2 was added dry Et_3N (237 μL, 1.70 mmol) followed by MsCl (135 μL, 1.70 mmol). After 1.5 h, the mixture was diluted with EtOAc (100 mL), washed with brine (2 × 30 mL), dried, and concentrated (bath temperature 35 °C). The residue was dissolved in ^{i}PrOH (60 mL). K_2CO_3 (164 mg, 1.19 mmol) and a solution of **47** (0.23 g, 1.19 mmol) in ^{i}PrOH (10 mL) were added, and the mixture was refluxed for 18 h under N_2. Solvent was removed under vacuum, the residue was dissolved in H_2O (50 mL) and saturated K_2CO_3 (aqueous) (4 mL), and the product was extracted with EtOAc (2 × 80 mL). The combined extracts were washed with brine (35 mL), dried, and concentrated. Flash chromatography of the residue using CH_2Cl_2−MeOH−NH_3 (aqueous) (95:5:0.5) gave **8** as a white foam (0.16 g, 46%): oxalate salt, mp 79−85 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.84−2.10 (6 H, m), 2.76 (2 H, t, J = 7.2), 2.96−3.14 (6 H, m), 3.32−3.42 (2 H, m), 7.20−7.36 (7 H, m), 7.51 (1 H, d, J = 8.5), 7.80 (1 H, d, J = 2), 9.01 (2 H, s), 11.18 (1 H, s); m/z (ES+) 418 (M + H$^+$). Anal. ($C_{25}H_{28}FN_5$·2($C_2H_2O_4$)·0.5(H_2O)) C, H, N.

Compounds **9** and **10** were prepared using similar chemistry.

4-Fluoro-4-(2-fluorobenzyl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (9): oxalate salt, mp 84−89 °C (EtOH−Et_2O); δ_H (360 MHz, 9:1 $CDCl_3$−DMSO-d_6 + CF_3CO_2H) 1.92−2.00 (2 H, m), 2.25−2.56 (4 H, m), 2.84−3.12 (8 H, m), 3.40−3.50 (2 H, m), 7.04−7.30 (6 H, m), 7.51 (1 H, d, J = 8), 7.66 (1 H, s) and 8.80 (2 H, s); m/z (ES+) 436 (M + H$^+$). Anal. ($C_{25}H_{27}F_2N_5$·2($C_2H_2O_4$)·0.5(H_2O)) C, H, N.

4-Fluoro-4-(3-fluorobenzyl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propy)piperidine (10): oxalate salt, mp 80−83 °C (EtOH−Et_2O); δ_H (360 MHz, 9:1 $CDCl_3$-DMSO-d_6) 1.86−1.97 (2 H, m), 2.04−2.56 (4 H, m), 2.87−2.98 (6 H, m), 3.02−3.09 (2 H, m), 3.40−3.50 (2 H, m), 6.89−7.00 (3 H, m), 7.13 (1 H, dd, J = 8 and 2), 7.22−7.33 (2 H, m), 7.50 (1 H, d, J = 8), 7.55 (1 H, d, J = 2), 8.56 (2 H, s) and 10.30 (1 H, s); m/z (ES+) 436 (M + H$^+$). Anal. ($C_{25}H_{27}F_2N_5$·3($C_2H_2O_4$)·0.5($C_4H_{10}O$)·H_2O) C, H, N.

1-*tert*-Butyloxycarbonyl-4-(2-(3-fluorophenyl)ethyl)-4-hydroxypiperidine (49). To magnesium turnings (0.49 g), covered with dry Et_2O (3 mL), was added one crystal of iodine followed by a small amount (10%) of a solution of 3-fluorobenzyl bromide (4.12 g, 22 mmol) in dry Et_2O (8 mL). The mixture was warmed with a water bath (35 °C) to initiate Grignard formation, and then the remaining solution of 3-fluorobenzyl bromide was added dropwise over 30 min at the same temperature. Steady refluxing was observed, which ceased after 30 min. The resulting mixture was cooled to −30 °C and a solution of **48**[24] (3.0 g, 14.1 mmol) in dry Et_2O (8 mL) was added dropwise over 20 min. The mixture was stirred at −10 °C for a further 4.25 h and then quenched with saturated NH_4Cl (aqueous) (100 mL) and extracted with EtOAc (2 × 125 mL). The combined organic solutions were washed with brine (50 mL), dried, and concentrated. Flash chromatography of the residue using hexanes−Et_2O (50:50 to 30:70) as eluent afforded **49** (0.94 g, 21%): δ_H (250 MHz, $CDCl_3$) 1.47 (9 H, s), 1.54−1.64 (4 H, m), 1.72−1.82 (2 H, m), 2.66−2.78 (2 H, m), 3.12−3.26 (2 H, m), 3.78−3.90 (2 H, m), 6.82−7.00 (3 H, m), 7.18−7.30 (1 H, m); m/z (ES+) 324 (M + H$^+$).

1-*tert*-Butyloxycarbonyl-4-fluoro-4-(2-(3-fluorophenyl)-ethyl)piperidine (50). The alcohol **49** (0.93 g, 2.87 mmol) was reacted with DAST as described for **46**. Flash chromatography of the residue using hexanes−Et_2O (86:14) as eluent gave crude **50** (0.50 g) contaminated with 1-*tert*-butyloxycarbonyl-4-[2-(3-fluorophenyl)ethyl]-1,2,5,6-tetrahydropyridine (ca. 3:1). The mixture and mCPBA (80−85%; 0.40 g) were dissolved in CH_2Cl_2 (25 mL) and stood at room temperature for 12 h. Et_2O (150 mL) was added, and the solution was washed with 2 M NaOH (aqueous) (25 mL), 2 M NaOH−10% sodium thiosulfite (1:1, 30 mL), dried, and concentrated. Flash chromatography of the residue using hexanes−Et_2O (86:14) as eluent gave **50** as a colorless thick oil which solidified on standing (0.31 g, 33%): δ_H (250 MHz, $CDCl_3$) 1.47 (9 H, s), 1.50−2.00 (6 H, m), 2.68−2.78 (2 H, m), 3.02−3.16 (2 H, m), 3.90−4.00 (2 H, m), 6.84−7.00 (3 H, m), 7.18−7.30 (1 H, m); m/z (ES+) 326 (M + H$^+$).

4-Fluoro-4-[2-(3-fluorophenyl)ethyl]-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (14). Compound **50** was deprotected as described for **47** and coupled as described for **8**: oxalate salt, mp 70−80 °C (EtOH−Et_2O); δ_H

(360 MHz, DMSO-d_6) 1.86−2.14 (8 H, m), 2.65−2.82 (4 H, m), 3.00−3.20 (4 H, m), 3.30−3.46 (2 H, m), 6.96−7.12 (3 H, m), 7.26−7.36 (3 H, m), 7.50 (1 H, d, J = 9), 7.81 (1 H, s), 9.02 (2 H, s), 11.18 (1 H, s); m/z (ES+) 450 (M + H^+). Anal. ($C_{26}H_{29}F_2N_5 \cdot 2(C_2H_2O_4)$) C, H, N.

4-Fluoro-4-(2-(trifluoromethyl)benzyl))-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (11). Compound **11** was prepared by a route similar to that described for **14** starting from the anion generated by metalation of 2-bromo-trifluoromethylbenzene with ^{n}BuLi: oxalate salt, mp 88−91 °C (EtOH−Et_2O); δ_H (360 MHz, 9:1 $CDCl_3$ + DMSO-d_6) 1.58−1.66 (2 H, m), 1.90−2.10 (4 H, m), 2.54−2.60 (2 H, m), 2.65−2.78 (2 H, m), 2.80−2.87 (2 H, m), 2.91 (2 H, d, J = 24), 3.18−3.24 (2 H, m), 6.86 (1 H, dd, J = 9 and 1), 6.92 (1 H, s), 7.13 (1 H, dd, J = 8 and 8), 7.21−7.27 (4 H, m), 7.38 (1 H, d, J = 8), 8.30 (2 H, s), 10.25 (1 H, s); m/z (ES+) 486 (M + H^+). Anal. ($C_{26}H_{27}N_5F_4 \cdot 2(C_2H_2O_4) \cdot 0.5(C_4H_{10}O) \cdot 0.25(H_2O)$) C, H, N.

1-*tert*-Butyloxycarbonyl-4-hydroxy-4-(2-trimethylsilylethynyl)piperidine (51). A solution of ^{n}BuLi (96 mL, 2.5 M in hexanes, 241 mmol) was added slowly at −40 °C to a stirred solution of trimethylsilylacetylene (34 mL, 241 mmol) in dry THF (400 mL) under N_2. The mixture was stirred at −40 °C for 1 h then cooled to −78 °C, and a solution of 1-*tert*-butyloxycarbonyl-4-piperidone **43** (40 g, 201 mmol) in dry THF (250 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h and then at room temperature for 72 h. The reaction was quenched by the addition of saturated NH_4Cl (aqueous) (300 mL), the mixture was stirred for a further 10 min and poured into H_2O (500 mL), and the products extracted with EtOAc (3 × 300 mL). The combined organic solutions were washed with H_2O (500 mL) and brine (300 mL), dried, and evaporated to give **51** (55 g, 92%): mp 75 °C; δ_H (250 MHz, $CDCl_3$) 0.19 (9 H, s), 1.48 (9 H, s), 1.63−1.74 (2 H, m), 1.80−1.92 (2 H, m), 3.18−3.28 (2 H, m), 3.71−3.84 (2 H, m); m/z (ES+) 298 (M + H^+).

1-*tert*-Butyloxycarbonyl-4-hydroxy-4-(2-trimethylsilylethynyl)piperidine-dicobalt hexacarbonyl (52). Dicobalt octacarbonyl (70 g, 203 mmol) was added portionwise to a solution of **51** (55 g, 185 mmol) in Et_2O (1000 mL). The mixture was stirred at room temperature for 4.5 h and then concentrated. The residue was purified by column chromatography using hexane and then Et_2O−hexane (1:4) as eluent to give **52** as a red solid (80 g, 74%): δ_H (250 MHz, $CDCl_3$) 0.32 (9 H, s), 1.48 (9 H, s), 1.75 (4 H, m), 3.14 (2 H, m), 4.03 (2 H, m).

1-*tert*-Butyloxycarbonyl-4-ethynyl-4-fluoropiperidine (53). A solution of **52** (80 g, 137 mmol) in dry CH_2Cl_2 (400 mL) was added via cannula over 20 min to a solution of DAST (18.1 mL, 137 mmol) in dry CH_2Cl_2 (250 mL) at −78 °C under N_2. After 1 h at −78 °C, the mixture was warmed to room temperature and stirred for a further 2 h. Et_2O (1000 mL) was added, and the organic solution was washed with a mixture of H_2O (600 mL) and saturated K_2CO_3 (aqueous) (300 mL) then brine (1 × 300 mL), dried, and concentrated. The residue was dissolved in acetone (750 mL), and ceric ammonium nitrate (226 g, 412 mmol) was added in 5 g portions over 1 h. The mixture was stirred at room temperature for a further 3 h and then concentrated. H_2O (500 mL) was added, and the products were extracted with CH_2Cl_2 (3 × 300 mL). The combined organic solutions were washed with H_2O (1 × 400 mL) and brine (1 × 200 mL), dried, and concentrated. The residue was dissolved in dry THF (200 mL) at 0 °C, and a solution of TBAF (137 mL, 1.1 M in THF, 151 mmol) was added. The mixture was stirred at 0 °C for 1 h and then poured into H_2O (500 mL), and the products were extracted with EtOAc (3 × 200 mL). The combined organic solutions were washed with H_2O (1 × 400 mL) and brine (1 × 200 mL), dried, and concentrated. Flash chromatography of the residue using Et_2O−hexane (20:80) as eluent afforded **53** (20 g, 53%): mp 45 °C; δ_H (360 MHz, $CDCl_3$) 1.46 (9 H, s), 1.93−2.00 (4 H, m), 2.70 (1 H, d, J = 5), 3.45−3.60 (4 H, m).

1-*tert*-Butoxycarbonyl-4-fluoro-(2-(4-fluorophenyl)ethynyl)piperidine (54). A mixture of **53** (1.0 g, 4.4 mmol) and 4-fluoroiodobenzene (610 μL, 5.3 mmol) in *N*,*N*-diethylamine (20 mL) was flushed with N_2 for 15 min, and then palladium(II) bis(triphenylphosphine)dichloride (150 mg, 0.2 mmol) and copper iodide (42 mg, 0.2 mmol) were added. The mixture was stirred at room temperature under N_2 for 2 h and then evaporated. The residue was partitioned between H_2O (50 mL) and Et_2O (3 × 25 mL). The combined organic solutions were washed with H_2O (1 × 50 mL) and brine (1 × 20 mL), dried, and concentrated. Flash chromatography of the residue using EtOAc−hexane (1:9) as eluent gave **54** (1.30 g, 80%): δ_H (360 MHz, $CDCl_3$) 1.47 (9 H, s), 2.01−2.08 (4 H, m), 3.51−3.64 (4 H, m), 7.00−7.05 (2 H, m), 7.42−7.46 (2 H, m).

1-*tert*-Butoxycarbonyl-4-fluoro-4-(2-(4-fluorophenyl)-ethyl)piperidine (55). A solution of **54** in MeOH (20 mL) and glacial AcOH (1 mL) was hydrogenated over 10% Pd−C (0.5 g) at 50 psi for 5 h. The catalyst was removed by filtration, and the solvents were evaporated. The residue was dissolved in Et_2O (20 mL), washed with saturated $NaHCO_3$ (aqueous) (2 × 15 mL), dried, and concentrated to give **55** (430 mg, 43%) which was used in the next step without further purification: δ_H (360 MHz, $CDCl_3$) 1.46 (9 H, s), 1.48−1.67 (2 H, m), 1.82−1.93 (4 H, m), 2.68−2.73 (2 H, m), 3.05−3.20 (2 H, m), 3.90−3.99 (2 H, m), 6.94−6.99 (2 H, m), 7.11−7.15 (2 H, m): m/z (ES+) 326 (M + H^+).

4-Fluoro-4-(2-(4-fluorophenyl)ethyl)piperidine (56). A solution of **55** (430 mg, 1.3 mmol) was deprotected as described for **47** to give **56** (0.29 g, 97%) which was used in the next step without further purification: δ_H (360 MHz, $CDCl_3$) 1.52−1.71 (2 H, m), 1.82−1.92 (4 H, m), 2.68−2.73 (2 H, m), 2.93−3.00 (4 H, m), 6.94−6.99 (2 H, m), 7.12−7.16 (2 H, m); m/z (ES+) 226 (M + H^+).

The following compounds were prepared following a procedure similar to that described above and were coupled as described for compound **8**.

4-Fluoro-4-(2-phenylethyl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (12): oxalate salt, mp 212 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.84−2.14 (8 H, m), 2.64−2.69 (2 H, m), 2.77 (2 H, t, J = 7), 2.94−3.12 (4 H, m), 3.28−3.40 (2 H, m), 7.16−7.34 (7 H, m), 7.50 (1 H, d, J = 9), 7.81 (1 H, d, J = 2 Hz), 9.03 (2 H, s), 11.20 (1 H, broad s); m/z (ES+) 432 (M + H^+). Anal. ($C_{26}H_{30}FN_5 \cdot C_2H_2O_4 \cdot 0.25(H_2O)$ C, H, N.

4-Fluoro-4-(2-(2-fluorophenyl)ethyl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (13): oxalate salt, mp 144 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.84−2.14 (8 H, m), 2.69−2.73 (2 H, m), 2.75−2.79 (2 H, t, J = 7.4), 3.00−3.10 (4 H, m), 3.36−3.44 (2 H, m), 7.11−7.16 (2 H, m), 7.23−7.29 (1 H, m), 7.30−7.38 (4 H, m), 7.50 (1 H, d, J = 8.6), 7.81 (1 H, d, J = 1.9), 9.03 (2 H, s), 11.20 (1 H, broad s); m/z (ES+) 450 (M + H^+). Anal. ($C_{26}H_{29}F_2N_5 \cdot 1.5(C_2H_2O_4) \cdot 0.7(H_2O)$) C, H, N.

4-Fluoro-4-(2-(4-fluorophenyl)ethyl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (15): oxalate salt, mp 205 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.82−2.14 (8 H, m), 2.64−2.69 (2 H, m), 2.77 (2 H, t, J = 7.3), 2.92−3.16 (4 H, m), 3.28−3.40 (2 H, m), 7.09 (2 H, t, J = 8.8), 7.25−7.34 (4 H, m), 7.50 (1 H, d, J = 8.6), 7.81 (1 H, d, J = 1.8), 9.03 (2 H, s), 11.20 (1 H, broad s); m/z (ES+) 450 (M + H^+). Anal. ($C_{26}H_{29}F_2N_5 \cdot C_2H_2O_4$) C, H, N.

1-*tert*-Butyloxycarbonyl-4-(2-phenylprop-1-yl)-4-fluoropiperidine (58). A pentane solution of ^{t}BuLi (1.7 M, 11 mL, 18.7 mmol) was added dropwise at −78 °C to a stirred solution of α-bromostyrene (2.3 mL, 17.7 mmol) in dry THF (80 mL) under N_2. After 20 min, a solution of **48**[24] (2.0 g, 9.38 mmol) in dry THF (6 mL) was added. The black solution was warmed slowly to room temperature over 7 h. The mixture was diluted with saturated NH_4Cl (aqueous) (200 mL), and the products were extracted with EtOAc (100 mL). The extract was washed with brine (50 mL), dried, and concentrated. Flash column chromatography eluting with EtOAc−hexane (20:80) then (60:40) gave 1-*tert*-butyloxycarbonyl-4-(2-phenylprop-2-en-1-yl)-4-hydroxypiperidine (1.67 g, 56%) as a yellow oil: δ_H (360 MHz, $CDCl_3$) 1.39−1.47 (13 H, m), 1.57 (1 H, s), 2.74 (2 H, s), 2.98−3.10 (2 H, m), 3.70−4.02 (2 H, m), 7.26−7.42 (5 H, m); m/z (ES+) 318 (M + H^+). This material (1.67 g, 5.26 mmol) was

dissolved in EtOAc (25 mL) and hydrogenated over 10% Pd−C (0.8 g) at room temperature and 1 atm H_2 for 1.5 h. The mixture was filtered and concentrated to yield 1-*tert*-butyloxycarbonyl-4-(2-phenylprop-1-yl)-4-hydroxypiperidine **57** (1.47 g, 87%) as a pale yellow glass: δ_H (250 MHz, $CDCl_3$) 1.27 (3 H, d, J = 7), 1.36−1.60 (13 H, m), 1.73 (1 H, dd, J = 15 and 4), 2.01 (1 H, dd, J = 15 and 10), 2.98−3.06 (3 H, m), 3.60−3.88 (2 H, m), 7.16−7.36 (5 H, m); m/z (ES+) 320 ($M + H^+$). This material (1.47 g, 4.60 mmol) was reacted following a method similar to that described for **46** to give **58** (0.65 g, 44%): δ_H (250 MHz, $CDCl_3$) 1.28 (3 H, d, J = 7), 1.43 (9 H, s), 1.47−2.11 (6 H, m), 2.93−3.07 (3 H, m), 3.76−3.86 (2 H, m), 7.15−7.33 (5 H, m); m/z (ES+) 322 ($M + H^+$).

4-Fluoro-4-(2-phenylprop-1-yl)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (16). The piperidine **58** (0.64 g, 1.99 mmol) was treated in the same way as **47** to give 4-(2-phenylprop-1-yl)-4-fluoropiperidine (0.37 g, 85%): δ_H (360 MHz, $CDCl_3$) 1.28 (3 H, d, J = 7), 1.35−1.60 (2 H, m), 1.70−1.79 (2 H, m), 1.83−2.09 (2 H, m), 2.79−2.93 (4 H, m), 3.03 (1 H, qt, J = 7 and 7), 7.15−7.22 (3 H, m), 7.26−7.31 (2 H, m); m/z (ES+) 222 ($M + H^+$). This material was reacted following a method similar to that described for the preparation of **8** to give **16** (0.12 g, 32%): oxalate salt, mp 87−91 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.21 (3 H, d, J = 7), 1.60−2.10 (10 H, m), 2.75 (2 H, t, J = 8), 2.90−3.12 (4 H, m), 3.26−3.28 (1 H, m), 7.16−7.20 (1 H, m), 7.24−7.35 (6 H, m), 7.50 (1 H, d, J = 9), 7.79 (1 H, s), 9.01 (2 H, s), 11.17 (1 H, s); m/z (ES+) 446 ($M + H^+$). Anal. ($C_{27}H_{32}N_5F \cdot 2(C_2H_2O_4)$) C, H, N.

1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-(trimethylsilyloxy)pyridine (59). To a stirred solution of **43** (10.13 g, 50.8 mmol) in dry DMF (20 mL) under argon was added TMSCl (7.74 mL, 61.0 mmol) and then dry Et_3N (17.0 mL, 122 mmol), and the mixture was stirred at 80 °C for 16 h under argon. The mixture was diluted with hexane (60 mL) and washed with cold saturated $NaHCO_3$ (aqueous) (3 × 30 mL). The organic layer was dried and concentrated. Flash chromatography using EtOAc−petroleum ether (10:90) as eluent gave **59** (11.84 g, 86%) as a colorless oil: δ_H (250 MHz, $CDCl_3$) 0.20 (9 H, s), 1.47 (9 H, s), 2.11 (2 H, m), 3.52 (2 H, t, J = 5.8), 3.87 (2 H, m), 4.80 (1 H, m).

1-*tert*-Butoxycarbonyl-3-fluoro-4-piperidone (60). To a stirred solution of **59** (3.98 g, 14.7 mmol) in dry MeCN (160 mL) under N_2 was added Selectfluor reagent (5.74 g, 16.2 mmol), and the mixture was stirred for 75 min. The mixture was poured into EtOAc (600 mL), washed with dilute brine (300 mL) and then saturated brine (100 mL), dried, and concentrated. Flash chromatography on alumina using MeOH−EtOAc (0:100 then 5:95) as eluent gave **60** (2.91 g, 91%) as a colorless oil: δ_H (250 MHz, $CDCl_3$) 1.50 (9 H, s), 2.52−2.64 (2 H, m), 3.22−3.38 (2 H, m), 4.18 (1 H, m), 4.45 (1 H, m), 4.83 (1 H, m).

***cis*-4-Benzylamino-1-*tert*-butoxycarbonyl-3-fluoropiperidine (61) and *trans*-4-Benzylamino-1-*tert*-butoxycarbonyl-3-fluoropiperidine (62).** A mixture of **60** (0.11 g, 0.509 mmol), benzylamine (61 μL, 0.559 mmol), and $NaB(OAc)_3H$ (0.1628 g, 0.768 mmol) in dry 1,2-dichloroethane (2 mL) was stirred at room temperature under N_2 for 135 min. The reaction mixture was quenched with saturated K_2CO_3 (aqueous) (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried and evaporated. Flash column chromatography using EtOAc−hexane (50:50 then 100:0) as eluent gave **61** (*cis* isomer) (99.5 mg, 63%) and **62** (*trans* isomer) (12.7 mg, 8%) as colorless oils. **61** (*cis* isomer): δ_H (360 MHz, DMSO-d_6) 1.38 (9 H, s), 1.44 (1 H, m), 1.68 (1 H, m), 2.64 (1 H, m), 2.74 (1 H, m), 2.96 (1 H, m), 3.78 (1 H, m), 4.14 (1 H, m), 4.78 (1 H, m), 7.21 (1 H, m), 7.28−7.36 (4 H, m); m/z (ES+) 309 ($M + H^+$). **62** (*trans* isomer): δ_H (360 MHz, DMSO-d_6) 1.34 (1 H, m), 1.39 (9 H, s), 1.81 (1 H, m), 2.74 (1 H, m), 3.14 (1 H, m), 3.30 (1 H, m), 3.48 (1 H, m), 3.69 (1 H, m), 3.77 (2 H, m), 4.39 (1 H, m), 7.22 (1 H, m), 7.28−7.35 (4 H, m); m/z (ES+) 309 ($M + H^+$).

***cis*-4-Benzylamino-3-fluoropiperidine (63).** A solution of **61** (0.91 g, 2.95 mmol) was deprotected as described for **47** to give **63** as a colorless oil (0.58 g, 94%): δ_H (250 MHz, $CDCl_3$) 1.54 (1 H, qd, J = 12 and 4), 1.83 (1 H, m), 2.54−2.76 (3 H, m), 3.11 (1 H, m), 3.88 (2 H, m), 4.73 (1 H, m), 7.23−7.37 (5 H, m).

***cis*-4-Benzylamino-3-fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (65).** Compound **63** was coupled using a method similar to that described for **8** to give **65** as a colorless oil (0.21 g, 39%): oxalate salt, mp 141−149 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.86−2.00 (4 H, m), 2.34 (1 H, m), 2.60−2.75 (5 H, m), 3.10−3.26 (2 H, m), 3.40 (1 H, m), 4.12 (2 H, m), 5.13 (1 H, d, J = 48), 7.30−7.33 (2 H, m), 7.38−7.43 (3 H, m), 7.48−7.51 (3 H, m), 7.78 (1 H, d, J = 2), 11.14 (1 H, s); m/z (ES+) 433 ($M + H^+$). Anal. ($C_{25}H_{29}FN_6 \cdot 2(C_2H_2O_4) \cdot 1.7(H_2O)$) C, H, N.

***cis*-4-(*N*-Benzyl-*N*-methylamino)-3-fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (17).** Glacial AcOH (64 μL, 1.12 mmol), formaldehyde (37 wt % solution) (25 μL, 0.338 mmol), and $NaCNBH_3$ (0.02 g, 0.33 mmol) were added to a solution of **65** (0.12 g, 0.281 mmol) in dry MeOH (4 mL) under argon, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated K_2CO_3 (aqueous) (10 mL), and the products were extracted with EtOAc (2 × 25 mL). The combined extracts were dried and concentrated. Flash chromatography using CH_2Cl_2−MeOH−NH_3 (aqueous) (94:6:0.6 then 93:7:0.7) as eluent gave **17** as a colorless oil (0.12 g, 93%): oxalate salt, mp 111−115 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.87−2.12 (4 H, m), 2.24 (3 H, s), 2.74−3.04 (7 H, m), 3.38 (1 H, m), 3.59 (1 H, m), 3.71 (2 H, m), 5.24 (1 H, d, J = 50), 7.25−7.35 (7 H, m), 7.50 (1 H, d, J = 8.5), 7.80 (1 H, d, J = 2), 11.17 (1 H, s); m/z (ES+) 447 ($M + H^+$). Anal. ($C_{26}H_{31}FN_6 \cdot 2(C_2H_2O_4)$) C, H, N.

The *trans* isomers **64** and **66** were prepared using chemistry similar to that described for the preparation of the *cis* isomers **63** and **65**.

The following compounds were prepared using similar procedures.

***trans*-4-(*N*-Benzyl-*N*-methylamino)-3-fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)-piperidine (18):** oxalate salt, mp 98−100 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.7−1.85 (1 H, m), 1.9−2.06 (3 H, m), 2.25 (3 H, s), 2.50−2.80 (4 H, m), 2.80−3.00 (3 H, m), 3.20−3.30 (1 H, m), 3.48−3.60 (1 H, m), 3.74 (2 H, q, J = 17), 4.96 (1 H, broad d, J = 46), 7.26−7.34 (7 H, m), 7.49 (1 H, d, J = 7), 7.79 (1 H, d, J = 4), 9.01 (2 H, s), 11.14 (1 H, s); m/z (ES+) 447 ($M + H^+$). Anal. ($C_{26}H_{31}FN_6 \cdot 2.5(C_2H_2O_4) \cdot H_2O$) C, H, N.

***cis*-3-Fluoro-4-(*N*-methyl-*N*-(2-(trifluoromethyl)benzyl)amino)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)-piperidine (19):** oxalate salt, mp 95−97 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.89 (1 H, m), 1.98−2.10 (3 H, m), 2.22 (3 H, s), 2.76−3.10 (7 H, m), 3.42 (1 H, m), 3.62 (1 H, m), 3.83 (2 H, m), 5.25 (1 H, d, J = 48), 7.31−7.33 (2 H, m), 7.46 (1 H, t, J = 7), 7.50 (1 H, d, J = 9), 7.64−7.70 (2 H, m), 7.80−7.82 (2 H, m), 9.01 (2 H, s), 11.17 (1 H, s); m/e (ES+) 515 ($M + H^+$). Anal. ($C_{27}H_{30}F_4N_6 \cdot 1.7(C_2H_2O_4)$) C, H, N.

***trans*-3-Fluoro-4-(*N*-methyl-*N*-(2-(trifluoromethyl)benzyl)amino)-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (20):** oxalate salt, mp 80−96 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.76 (1 H, m), 1.88−2.00 (3 H, m), 2.21 (3 H, s), 2.58−2.84 (7 H, m), 3.18 (1 H, m), 3.52 (1 H, m), 3.94 (2H, s), 4.89 (1 H, m), 7.30−7.32 (2 H, m), 7.45 (1 H, t, J = 8), 7.49 (1 H, d, J = 9), 7.64−7.69 (2 H, m), 7.80−7.83 (2 H, m), 9.01 (2 H, s), 11.13 (1 H, s); m/z (ES+) 515 ($M + H^+$). Anal. ($C_{27}H_{30}F_4N_6 \cdot 1.5(C_2H_2O_4) \cdot 0.25(C_4H_{10}O)$) C, H, N.

***cis*-3-Fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)-propyl)-4-(2-(trifluoromethyl)benzylamino)piperidine (21):** oxalate salt, mp 116−120 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.81 (1 H, m), 1.92−2.03 (3 H, m), 2.69−3.12 (7 H, m), 3.30 (1 H, m), 3.60 (1 H, m), 3.99 (2 H, s), 5.04 (1 H, d, J = 46), 7.31−7.33 (2 H, m), 7.48−7.51 (2 H, m), 7.66−7.71 (2 H, m), 7.79 (1 H, s), 7.84 (1 H, d, J = 7), 9.01 (2 H, s), 11.17 (1 H, s); m/z (ES+) 501 ($M + H^+$). Anal. ($C_{26}H_{28}F_4N_6 \cdot 2(C_2H_2O_4)$) C, H, N.

***trans*-3-Fluoro-1-(3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)-propyl)-4-(2-(trifluoromethyl)benzylamino)piperidine (22):** oxalate salt, mp 127−129 °C (MeOH−Et_2O); δ_H (360

MHz, DMSO-d_6) 1.64 (1 H, m), 2.00 (3 H, m), 2.58−2.88 (7 H, m), 3.10 (1 H, m), 3.39 (1 H, m), 3.99 (2 H, s), 4.71 (1 H, m), 7.30−7.33 (2 H, m), 7.49−7.51 (2 H, m), 7.68−7.71 (2 H, m), 7.79−7.83 (2 H, m), 9.01 (2 H, s), 11.15 (1 H, s); *m*/*z* (ES+) 501 $(M + H)^+$. Anal. ($C_{26}H_{28}F_4N_6 \cdot 1.5(C_2H_2O_4) \cdot 0.25(H_2O)$) C, H, N.

2-Fluoro-hex-5-en-1-ol (68). 1,2-Epoxy-5-hexene **67** (12 g, 0.12 mol) was added dropwise over 20 min at −78 °C to a stirred mixture of HF·pyridine (30 mL) and dry CH_2Cl_2 (60 mL). After complete addition the reaction was warmed to room temperature over 20 min. The yellow solution was poured onto ice−H_2O (400 mL) containing NH_3 (aqueous) (57 mL) and extracted into Et_2O. The organic phase was washed with brine, dried, and concentrated to give **68** (5.02 g, 35%) as an oil which was used without further purification: δ_H (250 MHz, $CDCl_3$) 1.65−1.95 (2 H, m), 2.10−2.35 (2 H, m), 2.95−3.10 (1 H, br s), 3.60−3.82 (2 H, m), 4.40−4.76 (1 H, m), 4.95−5.10 (2 H, m), 5.75−6.00 (1 H, m).

***tert*-Butyl-(2-fluoro-hex-5-enyloxy)dimethylsilane (69).** *tert*-Butyldimethylsilyl chloride was added to a solution of **68** (14.42 g, 0.12 mol) and imidazole (24.92 g, 0.37 mol) in dry DMF (250 mL). The reaction was stirred for 22 h and then partitioned between H_2O and Et_2O. The organic phase was washed with 1 M HCl, $NaHCO_3$ (aqueous), brine, then dried and concentrated. Flash chromatography using petroleum ether−Et_2O (98:2) as eluent gave **69** (8.9 g, 31%) as a colorless oil: δ_H (360 MHz, $CDCl_3$) 0.06 (6H, s), 0.83−0.91 (9 H, m), 1.50−1.79 (2 H, m), 2.14−2.24 (2 H, m), 3.68 (2 H, dd, J = 5 and 24), 4.54 (1 H, dd, J = 171 and 4), 4.95−5.08 (1 H, m), 5.76−5.87 (1 H, m).

5-(*tert*-Butyldimethylsilanyloxy)-4-fluoropentanal (70). Ozone was bubbled through a stirred solution of **69** (8.9 g, 38 mmol) in dry CH_2Cl_2 (150 mL) at −78 °C until a blue coloration persisted. The reaction was blanketed with N_2, and dry Et_3N (10.7 mL, 78 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 1.5 h then concentrated. Flash chromatography using CH_2Cl_2 as eluent gave **70** (5.4 g, 66%) as a colorless oil: δ_H (250 MHz, $CDCl_3$) 0.0 (6 H, s), 0.82 (9 H, s), 1.80−1.98 (2 H, m), 2.43−2.64 (2 H, m), 3.62 (2 H, dd, J = 5 and 18), 4.27−4.59 (1 H, m), 9.74 (1 H, s).

(*R*,*S*)-2-Fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl-)-propanol (71). A solution of **70** (5.94 g, 25 mmol) and 4-(1,2,4-triazol-4-yl)phenyl hydrazine (4.89 g, 28 mmol) was stirred in dioxane−H_2O (8:1) for 15 min. HCl (2 M, 10.6 mL) was added, and the mixture was refluxed for 66 h and then concentrated. Flash chromatography using MeOH−CH_2Cl_2 (1:9) gave **71** (0.51 g, 8%) as a solid: δ_H (250 MHz, $CDCl_3$) 2.89−3.01 (2 H, m), 3.45−3.59 (4 H, m), 6.89 (1 H, dd, J = 7.5 and 2.5), 7.09 (1 H, s), 7.33 (1 H, d, J = 10), 7.48 (1 H, d, J = 2.5), 8.46 (2 H, s), 10.32 (1 H, broad s).

4-(Benzylmethylamino)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (37). Dry Et_3N (214 μL, 1.54 mmol) was added to a stirred suspension of **71** (0.20 g, 0.77 mmol) in dry THF (30 mL) under N_2, followed by addition of methanesulfonyl chloride (121 μL, 1.54 mmol). After being stirred at room temperature for 2.2 h, the mixture was diluted with EtOAc (125 mL), washed with brine−H_2O (1:1, 25 mL) and brine (25 mL), then dried, and concentrated. A mixture of the mesylate, dry K_2CO_3 (0.13 g, 0.93 mmol), and 4-(*N*-benzyl-*N*-methylamino)piperidine (0.80 g, 3.92 mmol) in ^{i}PrOH (35 mL) was refluxed under N_2 for 65 h. The solvents were removed under vacuum, the residue was dissolved in H_2O (40 mL), and the products were extracted with EtOAc (2 × 100 mL). The combined organic solutions were washed with brine (1 × 40 mL), dried, and concentrated. Flash chromatography using CH_2Cl_2−MeOH−NH_3 (aqueous) (95:5:0.5) as eluent, followed by purification on alumina (activity III) using CH_2Cl_2−MeOH−NH_3 (aqueous) (97:3:0.2) as eluent, and finally flash chromatography using CH_2Cl_2−MeOH (80:20) gave **37** (0.19 g, 55%): oxalate salt, mp 110−117 °C (EtOH−Et_2O); δ_H (360 MHz, D_2O) 2.08−2.24 (2 H, m), 2.36−2.48 (2 H, m), 2.75 (3 H, s), 3.10−3.34 (4 H, m), 3.38−3.58 (2 H, m), 3.62−3.92 (3 H, m), 4.28−4.50 (2 H, m), 5.26−5.48 (1 H, m), 7.32 (1 H, d, J = 9), 7.40−7.55 (6 H, m), 7.62 (1 H, d, J = 9), 7.77 (1 H, s), 8.92 (2 H, s); *m*/*z* (ES+) 447 $(M + H^+)$. Anal. ($C_{26}H_{31}FN_6 \cdot 2.0(C_2H_2O_4) \cdot 1.5H_2O$) C, H, N.

The following compounds were prepared using the conditions described above.

1-((*R*,*S*)-2-Fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)-propyl)-4-(2-phenylethyl)piperazine (23): oxalate salt, mp 194−196 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 2.8−3.3 (16 H, m), 4.9−5.2 (1 H, dm, J = 50), 7.2−7.4 (7 H, m), 7.5 (1 H, d, J = 9), 7.8 (1 H, s), 9.0 (2 H, s), 11.2 (1 H, broad s); *m*/*z* (ES+) 433 $(M + H^+)$. Anal. ($C_{25}H_{29}N_6F_2 \cdot 2(C_2H_2O_4) \cdot 0.5(C_4H_{10}O) \cdot H_2O$) C, H, N.

4-(2-(2-Fluorophenyl)ethyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (24): oxalate salt, white crystals, mp 197−210 °C (EtOH); δ_H (360 MHz, DMSO-d_6) 2.7−3.2 (16 H, m), 5.0−5.1 (1 H, dm, J = 48), 7.1 (2 H, m), 7.3−7.4 (4 H, m), 7.52 (1 H, d, J = 9), 7.84 (1 H, d, J = 2), 9.02 (2 H, s), 11.27 (1 H, broad s); *m*/*z* (ES+) 451 $(M + H^+)$. Anal. ($C_{25}H_{28}F_2N_6 \cdot 2(C_2H_2O_4) \cdot 0.2(H_2O)$) C, H, N.

4-(2-(3-Fluorophenyl)ethyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (25): oxalate salt, mp 193−195 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 2.64−3.20 (16 H, m), 5.04 (1 H, broad d, J = 50), 7.02−7.16 (3 H, m), 7.38−7.40 (3 H, m), 7.51 (1 H, d, J = 9), 7.83 (1 H, s), 9.01 (2 H, s), 11.25 (1 H, s); *m*/*z* (ES+) 451 $(M + H^+)$. Anal. ($C_{25}H_{28}F_2N_6 \cdot 2.5(C_2H_2O_4)$) C, H, N.

4-(2-(4-Fluorophenyl)ethyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (26): oxalate salt, white crystals, mp 188−190 °C (EtOH); δ_H (360 MHz, DMSO-d_6) 2.8−3.2 (16 H, m), 5.0−5.1 (1 H, dm, J = 50), 7.15 (2 H, t, J = 9), 7.2−7.3 (4 H, m), 7.51 (1 H, d, J = 9), 7.83 (1 H, d, J = 2), 9.01 (2 H, s), 11.26 (1 H, broad s); *m*/*z* (ES+) 451 $(M + H^+)$. Anal. ($C_{25}H_{28}F_2N_6 \cdot 2(C_2H_2O_4) \cdot 0.5(H_2O)$) C, H, N.

4-((*R*,*S*)-2-(2-Fluorophenyl)propyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (29): oxalate salt, white crystals, mp 185−186 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.2 (3 H, d, J = 7), 2.7−3.1 (13 H, m), 3.3−3.4 (2 H, m), 5.0−5.2 (1 H, dm, J = 50), 7.0−7.4 (6 H, m), 7.7 (1 H, d, J = 9), 7.8 (1 H, s), 9.0 (2 H, s), 11.2 (1 H, broad s); *m*/*z* (ES+) 465 $(M + H^+)$. Anal. ($C_{26}H_{30}N_6F_2 \cdot 2(C_2H_2O_4) \cdot 0.5(C_4H_{10}O) \cdot 0.5(H_2O)$ C, H, N.

4-((*R*,*S*)-2-(3-Fluorophenyl)propyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (30): oxalate salt, white crystals, mp 183−185 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.2 (3 H, d, J = 7) 2.7−3.1 (15 H, m), 5.0−5.2 (1 H, dm, J = 50), 7.0−7.4 (6 H, m), 7.5 (1 H, d, J = 9), 7.8 (1 H, s), 9.0 (2 H, s), 11.2 (1 H, broad s); *m*/*z* (ES+) 465 $(M + H^+)$. Anal. ($C_{26}H_{30}N_6F_2 \cdot 2(C_2H_2O_4) \cdot 0.5(C_4H_{10}O) \cdot 2(H_2O)$) C, H, N.

4-((*R*,*S*)-2-(4-Fluorophenyl)propyl)-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (31): oxalate salt, white crystals, mp 187−189 °C (MeOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.2 (3 H, d, J = 7) 2.7−3.1 (15 H, m), 5.0−5.2 (1 H, dm, J = 45), 7.15 (2 H, apparent t, J = 9), 7.25−7.4 (4 H, m), 7.5 (1 H, d, J = 9), 7.8 (1 H, s), 9.0 (2 H, s), 11.3 (1 H, broad s); *m*/*z* (ES+) 465 $(M + H^+)$. Anal. ($C_{26}H_{30}N_6F_2 \cdot 2(C_2H_2O_4) \cdot 0.5(C_4H_{10}O_4) \cdot H_2O$) C, H, N.

4-Benzyl-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (35): oxalate salt, mp 95−100 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.34−1.52 (2 H, m), 1.64−1.80 (3 H, m), 2.74−2.94 (2 H, m), 3.06−3.44 (8 H, m), 5.20−5.42 (1 H, dm, J = 47), 7.12−7.22 (3 H, m), 7.24−7.40 (4 H, m), 7.52 (1 H, d, J = 8.5), 7.84 (1 H, d, J = 2), 9.00 (2 H, s), 11.33 (1 H, s); *m*/*z* (ES+) 418 $(M + H^+)$. Anal. ($C_{25}H_{28}FN_5 \cdot 1.75(C_2H_2O_4)$ C, H, N.

4-Benzyloxy-1-((*R*,*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (36): oxalate salt, softens at 130 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.60−1.80 (2 H, m), 1.80−2.00 (2 H, m), 2.54−2.70 (2 H, m), 2.80−3.20 (6 H, m), 3.46−3.78 (1 H, m), 4.50 (2 H, s), 5.00−5.24 (1 H, m), 7.20−7.40 (7 H, m), 7.46−7.56 (1 H, m), 7.78 (1 H, s), 8.87 (2 H, s), 11.04 (1 H, s); *m*/*z* (ES+) 434 $(M + H^+)$. Anal. ($C_{25}H_{28}FN_5O \cdot 1.2(C_2H_2O_4) \cdot 0.4(H_2O)$) C, H, N.

(*R*)-5-Benzyloxy-4-hydroxy-1-triethylsilyl-1-pentyne (73). ^{n}BuLi (1.6 M, 48 mL) was added over 20 min to triethylsilylacetylene (10.7 g, 76.4 mmol) in dry THF (90 mL) at −78 °C. After 10 min BF_3·OEt_2 (10 mL, 82 mmol) was added, and then after another 10 min (−)-benzyl-(*R*)-glycidyl ether **72** (8.4 g, 51 mmol) in dry THF (20 mL) was added over 10 min. The mixture was stirred at −78 °C for 1 h and then at 0 °C for 20 min. Saturated NH_4Cl (aqueous) was added, and the mixture was extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried, evaporated, and purified by flash chromatography to give **73** (9.4 g, 61%): δ_H (250 MHz, $CDCl_3$) 0.53 (6 H, q, J = 8), 1.0 (9 H, t, J = 8) 2.50−2.53 (2 H, m), 3.48−3.65 ((2 H, m), 3.90−3.99 (1 H, m), 4.50 (2 H, s), 7.25−7.35 (5 H, m).

(*R*)-3-(3-Benzyloxy-2-hydroxyprop-1-yl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (74). A mixture of **73** (7.6 g, 25 mmol), 2-iodo-4-(1,2,4-triazol-4-yl)aniline (5.6 g, 19.6 mmol), LiCl (927 mg, 19.7 mmol), Na_2CO_3 (8.37 g, 79 mmol), and Ph_3P (1.0 g, 3.9 mmol) were stirred in DMF (200 mL) at room temperature for 2 h while N_2 gas was bubbled through the mixture. $Pd(OAc)_2$ (441 mg, 1.97 mmol) was then added, and the reaction was heated at 100 °C for 20 h. The mixture was cooled, filtered, and evaporated. The residue was partitioned between H_2O and EtOAc. The organic phase was separated and the aqueous phase re-extracted with EtOAc (5×). The combined organic layers were washed with H_2O and brine, dried, and concentrated. A mixture of EtOH and 5 M HCl (300 mL, 1:1 v/v) was added, and the solution stood at room temperature for 18 h and then was poured into saturated K_2CO_3 (aqueous) and extracted with EtOAc (3×). The organic layers were washed with H_2O and brine, dried, evaporated, and purified by flash chromatography, eluting with CH_2Cl_2:MeOH (92:8) to give **74** (1.8 g, 26%): δ_H (250 MHz, $CDCl_3$) 2.89−3.07 (2 H, m), 3.34−3.37 (2 H, m), 4.09−4.31 (2 H, m), 4.54 (2 H, s), 7.15 (1 H, dd, J = 2.5 and 10), 7.30−7.34 (5 H, m), 7.49 (1 H, d, J = 7.5), 7.65 (1 H, d, J = 2.5), 8.64 (1 H, s).

(*S*)-1-Benzyloxy-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propane (75). Compound **74** (1.81 g, 5.17 mmol) was reacted using conditions described for the preparation of **46** to give **75** (407 mg, 22%) as a colorless foam: δ_H (250 MHz, $CDCl_3$) 1.34−1.43 (1 H, m), 1.46−1.62 (1 H, m), 3.11−3.24 (2 H, m), 4.51 (2 H, s), 4.2−5.0 (1 H, m), 7.10−7.34 (6 H, m), 7.50−7.58 (1 H, m), 8.02 (1 H, s), 8.46 (1 H, d, J = 14), 9.41 (1 H, broad s), 9.48 (1 H, broad s).

(*S*)-2-Fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propanol (76). A solution of **75** (1.7 g, 4.88 mmol) in MeOH (40 mL) containing HCO_2NH_4 (0.72 g, 11.4 mmol) and $Pd(OH)_2$ (0.20 g) was heated to reflux for 18 h. The cooled reaction was filtered and the catalyst washed thoroughly with MeOH and H_2O. The filtrate was concentrated and purified by flash chromatography using CH_2Cl_2−MeOH−NH_3 (aqueous) (90:10:1) as eluent to give **76** (0.75 g, 59%) as a white solid. Comparison with the racemic material by chiral HPLC (Chiralpak AS, 15% EtOH and 0.1% DEA in hexane, 1 mL/min, 40 °C, UV 230 nm) showed **76** to have 95% enantiomeric excess: δ_H (360 MHz, DMSO-d_6) 3.32−3.6 (1 H, m), 3.74 (2 H, t, J = 7), 4.68 (1 H, t, J = 5), 4.81 (2 H, t, J = 5), 7.31−7.35 (2 H, m), 7.52 (1 H, d, J = 11), 7.87 (1 H, s), 9.01 (2 H, s), 11.24 (1 H, broad s).

4-(2-(3-Fluorophenyl)ethyl)-1-((*S*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (27). Compound **27** was prepared from **76** using the conditions described for the preparation of **8**: oxalate salt, mp 202−203 °C (EtOH); δ_H (360 MHz, DMSO-d_6) 2.68−3.2 (16 H, m), 4.88−5.16 (1 H, dm, J = 50), 7.04−7.16 (2 H, m), 7.3−7.4 (2 H, m), 7.51 (1 H, d, J = 10), 7.83 (1 H, s), 9.01 (2 H, s), 11.26 (1 H, s); m/z (ES+) 451 ($M + H^+$). Anal. ($C_{25}H_{28}F_2N_6$·2($C_2H_2O_4$)·0.7(H_2O)) C, H, N.

4-(2-(3-Fluorophenyl)ethyl)-1-((*R*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperazine (28). This was made in the same way as **27**, but starting with (+)-benzyl-(*S*)-glycidyl ether. Analysis of (*R*)-2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propanol using chiral HPLC under the conditions described for **96** showed the compound to have 95% enantiomeric excess. Spectroscopic data for **28** was identical to that quoted above for the *S* enantiomer **27**.

4-(Bromodifluoroacetyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (78). Ethyl bromodifluoroacetate **77** (5.0 g, 24.6 mmol) and *tert*-butyl piperazinecarboxylate (4.58 g, 24.6 mmol) were mixed and gently heated to melt the solid. The reaction was cooled, and trituration with petroleum ether gave **78** (8.4 g, 99%) as a colorless solid: δ_H (250 MHz, $CDCl_3$) 1.47 (9 H, s), 3.48−3.55 (4 H, m), 3.64−3.66 (4 H, m).

4-(2,2-Difluoropent-4-enoyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (79). A solution of allyltributyltin (4.5 mL) and **78** (5.0 g, 14.57 mmol) in degassed C_6H_6 (100 mL) was heated to reflux for 24 h under N_2 in the presence of AIBN (50 mg). The reaction was concentrated. Flash chromatography using EtOAc−petroleum ether (0:100 then 20:80) as eluent gave **79** (4.43 g, 100%) as an oil which crystallized slowly on standing: δ_H (250 MHz, $CDCl_3$) 1.47 (9 H, s), 2.83−3.01 (2 H, m), 3.44−3.48 (4 H, m), 3.59−3.63 (2 H, m), 3.67−3.71 (2 H, m), 5.24 (1 H, s), 5.28−5.31 (1 H, d, J = 7.5), 5.70−5.94 (1 H, m).

4-(2,2-Difluoro-5-hydroxypentyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (80). A solution of **79** (0.5 g, 1.7 mmol) in dry THF (20 mL) was treated with BH_3−THF (1 M, 8.2 mL). The reaction was heated to reflux for 18 h, cooled, and then concentrated. MeOH was added cautiously, the reaction reconcentrated, and MeOH added again. Concentration in vacuo gave a clear oil which was dissolved in THF (10 mL) and adjusted to pH 9 with 4 M NaOH. H_2O_2 (30 wt % solution, 1 mL) was added, and the reaction was stirred at room temperature for 2 h. The organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried, and concentrated. Flash chromatography using EtOAc−petroleum ether (30:70) as eluent gave **80** (0.19 g, 38%) as a clear oil: δ_H (250 MHz, $CDCl_3$) 1.45 (9 H, s), 1.70−1.82 (2 H, m), 1.96−2.28 (2 H, m), 2.54−2.64 (4 H, m), 2.70−2.81 (2 H, m), 3.43−3.47 (4 H, m), 3.67−3.72 (2 H, m); m/z (ES+) 309 ($M + H^+$).

4-(2,2-Difluoro-5-oxo-pentyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (81). A solution of **80** (1.28 g, 4.2 mmol) and Et_3N (4 mL) in dry DMSO (12 mL) was treated with portions of SO_3−pyridine complex (1.3 g) using occasional cooling in an ice−H_2O bath to moderate the exotherm. When addition was complete, the reaction was cooled in an ice−H_2O bath, quenched with H_2O, and extracted into EtOAc. The organic phase was dried and concentrated. Flash chromatography using EtOAc−petroleum ether (20:80 then 50:50) as eluent gave **81** (1.2 g, 93%) as a clear oil: δ_H (250 MHz, $CDCl_3$) 1.45 (9 H, s), 2.13−2.27 (2 H, m), 2.34−2.40 (4 H, m), 2.50−2.54 (2 H, m), 3.39−3.43 (4 H, m), 3.49 (2 H, br s), 9.81 (1 H, s); m/z (ES+) 307 ($M + H^+$).

3-(2,2-Difluoro-3-piperazin-1-ylpropyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (82). A solution of **81** (1.32 g, 4.3 mmol) and 4-(1,2,4-triazol-4-yl)phenylhydrazine (0.75 g) in 4% H_2SO_4 was stirred at room temperature for 20 min and then refluxed for 21 h. The reaction was cooled, the products were extracted into ^{n}BuOH, and the organic extracts were concentrated. Flash chromatography using MeOH−CH_2Cl_2−NH_3 (aqueous) (10:89:1) as eluent gave **82** (0.24 g, 20%) as a brown oil: δ_H (250 MHz, $CDCl_3$ + MeOH-d_4) 2.52−2.62 (6 H, m), 2.85−2.90 (4 H, m), 3.35−3.48 (2 H, t, J = 17.5), 7.12−7.16 (1 H, m), 7.30 (1 H, s), 7.49−7.52 (1 H, d, J = 7.5), 7.64−7.65 (1 H, d, J = 2.5), 8.5 (2 H, s); m/z (ES+) 347 ($M + H^+$).

3-(2,2-Difluoro-3-(4-(2-(3-fluorophenyl)ethyl)piperazin-1-yl)propyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (32). A solution of **82** (0.08 g, 0.2 mmol), AcOH (40 μL), and 3-fluorophenylacetaldehyde (0.035 g, 0.25 mmol) in MeOH (4 mL) was stirred for 10 min and then treated with sodium cyanoborohydride (0.015 g, 0.24 mmol). Further 3-fluorophenylacetaldehyde (0.008 g, 0.06 mmol) was added, and stirring was continued for 30 min. The reaction was quenched with 4 M NaOH, concentrated, and chromatographed to give **32** (47 mg, 43%): oxalate salt, mp 142−145 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 2.64−2.90 (6 H, m), 2.90−2.95 (2 H, m), 3.00−3.22 (6 H, m), 3.36−3.50 (2 H, d, J = 18), 7.06−7.15 (3 H, m), 7.32−

7.41 (3 H, m), 7.52−7.55 (1 H, d, J = 11), 7.82 (1 H, s), 8.99 (2 H, s), 11.37 (1 H, s); m/z (ES+) 469 (M + H^+). Anal. $C_{25}H_{27}N_6F_3 \cdot 1.25(C_2H_2O_4) \cdot H_2O$) C, H, N.

The following compounds were prepared similarly.

3-(2,2-Difluoro-3-(4-(2-phenyl-propyl)-piperazin-1-yl)-propyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (33): oxalate salt, softens at 109 °C (EtOH−Et_2O); free base δ_H (250 MHz, $CDCl_3$) 1.20 (3 H, d, J = 7), 2.24−2.59 (12 H, m), 2.87−2.93 (1 H, m), 3.31−3.34 (1 H, m), 3.42−3.49 (1 H, m), 7.14−7.3 (7 H, m), 7.51−7.54 (1 H, m), 7.83 (1 H, s), 8.9 (2 H, s); m/z (ES+) 465 (M + H^+). Anal. ($C_{26}H_{30}N_6F_2 \cdot C_2H_2O_4 \cdot 0.9(H_2O) \cdot 1.3(C_2H_6O)$) C, H, N.

(*R*,*S*)-3-(2,2-Difluoro-3-(4-(2-(4-fluorophenyl)propyl)-piperazin-1-yl)propyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (34): softens at 65 °C (EtOH−Et_2O); δ_H (500 MHz, DMSO-d_6) 1.14 (3 H, d, J = 7), 2.29−2.49 (10 H, m), 2.59 (2 H, t, J = 15), 2.91 (9 H, q, J = 5), 3.42 (2 H, t, J = 15), 7.09 (2 H, t, J = 5), 7.23−7.25 (2 H, m), 7.31 (1 H, dd, J = 10 and 5), 7.37 (1 H, d, J = 5), 7.51 (1 H, d, J = 5 Hz), 7.81 (1 H, d, J = 5), 8.97 (2 H, s), 11.31 (1 H, s); m/z (ES+) 483 (M + H^+). Anal. ($C_{26}H_{30}N_6F_3 \cdot 0.5(H_2O)$) C, H, N.

5-Formyl-5-(1,2,4-triazol-4-yl)-indole-1-carboxylic Acid *tert*-Butyl Ester (84). A solution of hexamethylene tetramine (12.0 g, 86 mmol) and 5-(1,2,4-triazol-4-yl)-1*H*-indole[32] **83** (10.5 g, 57.1 mmol) in AcOH (125 mL, 30% v/v) was heated at reflux for 3 h. The reaction was neutralized with K_2CO_3, and H_2O was removed in vacuo. The residue was triturated with H_2O, and the solid was collected to give 5-(1,2,4-triazol-4-yl)-1*H*-indole-3-carbaldehyde as a brown solid (6.0 g, 50%): δ_H (250 MHz, DMSO-d_6) 7.54 (1 H, dd, J = 2 and 9), 7.68 (1 H, d, J = 9), 8.24 (1 H, d, J = 2), 8.45 (1 H, s), 9.09 (2 H, s), 9.99 (1 H, s); m/z (ES+) 213 (M + H^+). A suspension of this material (1.01 g, 4.8 mmol), DMAP (47 mg, 0.39 mmol), and $(BOC)_2O$ (1.03 g, 4.7 mmol) in CH_2Cl_2 (25 mL) was stirred for 8 h at room temperature. Further quantities of DMAP (0.05 g, 0.41 mmol) and $(BOC)_2O$ (0.20 g, 0.9 mmol) were added after 1.5 h. The reaction was concentrated, and the solid was triturated with MeOH to give **84** (4.45 g, 51%) as a beige solid: δ_H (250 MHz, DMSO-d_6) 1.90 (9 H, s), 7.96−8.00 (1 H, m), 8.46 (1 H, d, J = 10), 8.54 (1 H, d, J = 3), 9.03 (1 H, s), 9.38 (2 H, s), 10.34 (1 H, s); m/z (ES+) 313 (M + H^+).

3-(2-Ethoxycarbonyl-2,2-difluoroethyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole-carboxylic Acid *tert*-Butyl Ester (87). A suspension of activated zinc dust (85 mg) and **84** (0.31 g, 1 mmol) in THF (3 mL) and DMF (0.1 mL) was refluxed under N_2. Ethyl bromodifluoroacetate (0.14 mL, 1.1 mmol) was added. After 15 min, a further aliquot (70 mL, 0.5 mmol) of ethyl bromodifluoroacetate was added, followed after 15 min by phenyl chlorothionoformate (0.18 mL, 1.3 mmol). The reaction was heated at reflux for 1.5 h then cooled and partitioned betwen H_2O and EtOAc. The combined organic phases were dried and concentrated. Flash chromatography using MeOH−CH_2Cl_2 (5:95) gave partially purified product **86**, which was heated to reflux in degassed toluene (15 mL) with Bu_3SnH (0.27 mL, 1 mmol) and AIBN (0.12 g). After 2.5 h the reaction was concentrated. Flash chromatography using MeOH−CH_2Cl_2 (2:98) to (5:95) gave **87** (0.18 g, 43%) as a yellow oil: δ_H (250 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.5), 1.69 (9 H, s), 3.49 (2 H, t, J = 15), 4.28 (2 H, q, J = 7.5), 7.30−7.35 (1 H, m), 7.56 (1 H, m), 7.67 (1 H, s), 8.30−8.34 (1 H, m), 8.50 (2 H, s); m/z (ES+) 421 (M + H^+).

3-(2,2-Difluoro-3-hydroxypropyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole-carboxylic Acid *tert*-Butyl Ester (88). A solution of **87** (0.18 g, 0.4 mmol) in EtOH (3 mL) was treated with $NaBH_4$ (20 mg, 0.53 mmol) at room temperature. When all the starting material was consumed, the reaction was quenched by addition of H_2O. EtOH was removed in vacuo, and the product was extracted with EtOAc. The organic phase was dried and concentrated. Flash chromatography using MeOH−CH_2Cl_2 (5:95) as eluent gave **88** (83 mg, 51%) as a yellow oil: δ_H (250 MHz, $CDCl_3$) 1.69 (9 H, s), 3.42 (2 H, t, J = 17.5), 3.77 (2 H, t, J = 12.5), 7.30−7.34 (1 H, m), 7.69 (1 H, s), 7.74 (1 H, s), 8.29−8.32 (1 H, m), 8.60 (2 H, broad s); m/z (ES+) 379 (M + H^+).

4-(*N*-Benzyl-*N*-methylamino)-1-(2,2-difluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl)piperidine (42). A solution of **88** (80 mg, 0.21 mmol) and pyridine (70 μL) in dry CH_2Cl_2 (10 mL) was cooled to an internal temperature of −50 °C under N_2. Trifluoromethanesulfonic anhydride (71 μL) was added, and the reaction mixture was stirred at −25 °C for 1.5 h. H_2O (5 mL) was added, and the mixture was warmed to room temperature. The organic phase was separated, dried, and concentrated. The crude triflate was dissolved in dry DMF (3 mL) and heated at 120 °C for 10 min with K_2CO_3 (58 mg, 0.42 mmol) and 4-(*N*-benzyl-*N*-methylamino)piperidine (86 mg, 0.42 mmol). The reaction was partitioned between EtOAc and H_2O. The organic phase was dried and concentrated. The residue was allowed to stand in CF_3CO_2H−CH_2Cl_2 (1:2) until deprotection was complete. The mixture was concentrated, basified with 4 M NaOH, and extracted into EtOAc. Flash chromatography using MeOH−CH_2Cl_2 (3:97) then MeOH−CH_2Cl_2−NH_3 (aqueous) (5:94:1) as eluent gave **42** (73 mg, 75%): oxalate salt, softens at 85 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.66−1.80 (2 H, m), 1.90−2.00 (2 H, m), 2.16−2.24 (2 H, m), 2.54 (3 H, s), 2.70 (2 H, t, J = 14), 2.90−3.00 (2 H, m), 3.06−3.20 (1 H, m), 3.44 (2 H, t, J = 14), 4.20−4.28 (2 H, m), 7.32−7.60 (8 H, m), 7.84 (1 H, s), 9.0 (2 H, s), 11.4 (1 H, s); m/z (ES+) 465 (M + H^+). Anal. ($C_{26}H_{30}F_2N_6 \cdot 3(C_2H_2O_4) \cdot 2(H_2O)$) C, H, N.

The following compounds were prepared using the above method.

3-(3-(4-Benzylpiperidin-1-yl)-2,2-difluoropropyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (38): oxalate salt, mp 100−115 °C (EtOH−Et_2O); δ_H (360 MHz, DMSO-d_6) 1.16−1.3 (2 H, m), 1.4−1.6 (3 H, m), 2.1−2.3 (2 H, m), 2.43−2.49 (2 H, m), 2.7−3.0 (4 H, m), 3.3−3.5 (2 H, m), 7.11−7.18 (3 H, m), 7.24−7.31 (3 H, m), 7.38−7.39 (1 H, m), 7.50−7.53 (1 H, m) 7.83−7.84 (1 H, m), 9.00 (2 H, s), 11.34 (1 H, s); m/z (ES+) 436 (M + H^+). Anal. ($C_{25}H_{27}N_5F_2 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

3-(3-(4-Benzyloxypiperidin-1-yl)-2,2-difluoropropyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (39): free base, mp 169−170 °C (EtOH); δ_H (360 MHz, DMSO-d_6) 1.49−1.52 (2 H, m), 1.80−1.90 (2 H, m), 2.22−2.32 (2 H, m), 2.60−2.78 (4 H, m), 3.31−3.45 (3 H, m), 7.26−7.38 (7 H, m), 7.50−7.52 (1 H, m), 7.81 (1 H, s), 8.98 (2 H, s), 11.32 (1 H, s); m/e (ES+) 452 (M + H^+). Anal. ($C_{25}H_{27}F_2N_5O$) C, H, N.

3-(2,2-Difluoro-3-(4-phenoxymethylpiperidin-1-yl)propyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (40): free base, mp 197−199 °C (EtOH); δ_H (500 MHz, DMSO-d_6) 0.87 (2 H, m), 1.29−1.34 (5 H, m), 1.65−1.71 (2 H, m), 2.13−2.17 (2 H, m), 2.63−2.69 (2 H, m), 3.38−3.45 (2 H, m), 6.91−6.93 (3 H, m), 7.26−7.53 (5 H, m), 7.69−7.71 (1 H, m), 7.83 (1 H, s), 8.88 (2 H, s); m/z (ES+) 452 (M + H^+). Anal. ($C_{25}H_{27}F_2N_5O$) C, H; N: calcd, 15.51; found, 14.24.

3-(3-(4-(2-Phenethyl)piperidin-1-yl)-2,2-difluoropropyl)-5-(1,2,4-triazol-4-yl)-1*H*-indole (41): oxalate salt, mp 110 °C (softens) (EtOH−Et_2O); δ_H (500 MHz, DMSO-d_6 + CF_3CO_2H, 300 °C) 1.4−1.7 (5 H, m), 1.8−1.95 (2 H, m), 2.5−2.6 (2 H, m), 3.0−3.15 (2 H, m), 3.4−3.6 (4 H, m), 3.7−3.9 (2 H, m), 7.15−7.20 (3 H, m), 7.25−7.28 (2 H, m), 7.45−7.46 (1 H, m), 7.51−7.55 (1 H, m), 7.62−7.64 (1 H, m), 7.98−8.05 (1 H, m), 9.0 (2 H, s), 11.34 (1 H, s); m/z (ES+) 450 (M + H^+). Anal. ($C_{26}H_{29}N_5F_2 \cdot C_2H_2O_4 \cdot 3(H_2O)$) C, H, N.

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Supporting Information Available: Experimental details for the preparation of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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using the ESP method and the electrostatic potential regenerated from these charges classically to produce the contours shown in Figure 1.

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