Enhancement of Oral Absorption in Selective 5-HT$_{1D}$ Receptor Agonists: Fluorinated 3-[3-(Piperidin-1-yl)propyl]indoles

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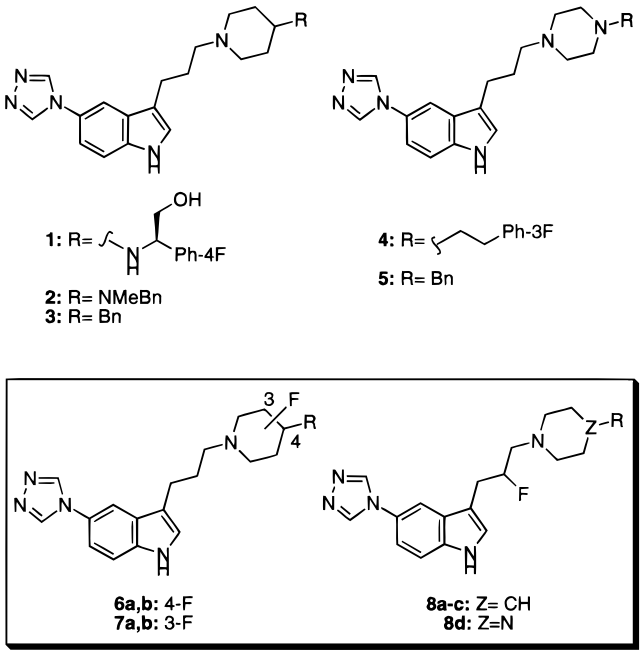
The discovery and introduction into clinical practice of selective serotonin 5-HT$_{1D/B}$ receptor agonists has revolutionized the acute treatment of migraine headache.[1] However, the exact mechanism of action of this class of compounds, collectively referred to as "triptans" (e.g., sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan), is still a matter of debate. Because all of the triptan agents so far developed bind with almost equal affinities to human 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors,[2] both a direct vasoconstrictor effect on cranial blood vessels[3] (5-HT$_{1B}$ mediated) and/or an inhibition of neurogenic inflammation[4] in the dura matter (5-HT$_{1D/B}$ mediated) have been proposed as potential pathways for headache pain relief by these agents. A central antinociceptive component has also been advanced as a key contributor in their mechanism of action.[5]

Although the side effect profile of these compounds is extremely good, the potential exists for coronary vasoconstriction (5-HT$_{1B}$ mediated) that precludes their use in patients with known heart disease.[6] This fact, coupled to the mechanistic uncertainties described above, prompted us to seek the development of selective 5-HT$_{1D}$ receptor agonists as a potential second generation migraine therapy devoid of vasoconstrictor liabilities. In this regard, we have recently disclosed the discovery of the first 5-HT$_{1D}$ agonists with up to 200-fold binding selectivity over the 5-HT$_{1B}$ subtype.[7,8] Compounds such as **1** (L-772,405) and **4** (L-775,606) were highlighted from this work (Chart 1). While **1** was found to have an almost ideal in vitro profile, and to be rapidly absorbed by the subcutaneous route in rats (*F*, 88%; C_{max}, 320 ng/mL; T_{max}, 10 min; dose, 3 mg/kg), its oral bioavailability was extremely low (<5%). The lack of good systemic exposure after oral dosing was a differentiating factor between compounds belonging to the piperidine series (e.g., **1**, **2**, **3**) and those incorporating a piperazine moiety (e.g., **4**, **5**; *F*, 27 and 21%, respectively; rat, 3 mg/kg). Extensive pharmacokinetic and metabolism studies with **1** and related compounds showed that their low oral bioavailablity was most probably due to deficient oral absorption rather than metabolic instability. For example, concentrations of **1** in hepatic portal vein (hpv) at 0.5 and 2 h post 3 mg/kg po in rats were extremely low (Table 1), and this poor absorption correlated well with epithelial transport studies carried out in Caco-2 cells.[9] In addition, **1** was not extensively metabolized in rat liver microsomes or fresh rat and human liver slices. It was, therefore, of particular interest to try to understand the reasons behind the different absorption behavior of the piperidines and piperazines (e.g., compare **3** vs **5**, Table 1) in order to introduce oral bioavailability into the former series. It was speculated that in the more basic piperidine series (e.g., **3**, pK_a 9.7 vs **5**, pK_a 8.2) a smaller proportion of uncharged species would exist at the physiological pHs encountered in the small intestine, leading to reduced passive diffusion across the gut wall.[10] To test this idea, modulation of the pK_a of the piperidine moiety was undertaken, and here we report on the synthesis and biological evaluation of three series of fluorinated compounds (see structures **6**, **7**, and **8**; Chart 1) which indeed showed enhanced absorption properties when compared to their unsubstituted analogues.

Chart 1



Introduction of fluorine was first targeted at C-4 of the piperidine for two reasons. First, this modification would not introduce a chiral center in the molecule, and in addition, it was thought that perhaps the electrostatic potential generated by the electronegative fluorine[11] could better mimic the region around N-4 of the piperazine moiety in **5**. Because this transformation would probably compromise the stability of compounds bearing a nitrogen substituent at C-4 of the piperidine (e.g., **1**, **2**), fluorination of the ring was also pursued at C-3, although the achiral advantage of the previous substitution was lost. Compounds of general structure **6** were prepared from the corresponding 4-hydroxypiperidine analogues by treatment with DAST.[12] Thus, ring opening of oxirane **9**[13] with 3-fluorophenethylmagnesium bromide afforded **10** in moderate yield, which was

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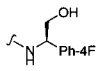
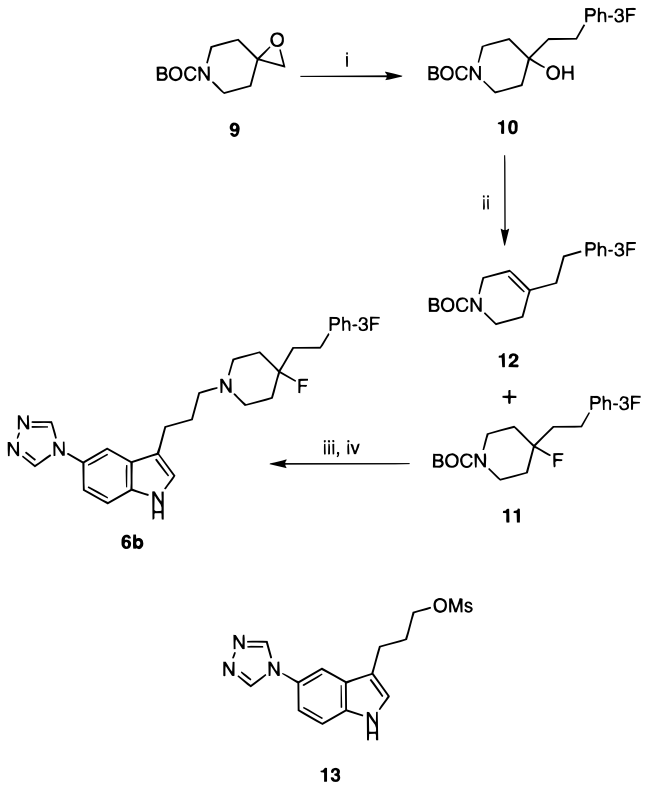
Table 1. Human 5-HT_{1D} Receptor Binding and Absorption Data for Fluorinated Piperidines and Reference Compounds

Compound	R	Z	Stereo[a]	IC_{50} (nM)[b] h5-HT_{1D}	Selectivity[c]	EC_{50} (nM,[d] %5-HT[e]) h5-HT_{1D}	[Drug] (ng/mL)[f] at 0.5 h post 3 mg/kg p.o. hpv	systemic	pK_a[g]
6a	Bn			1.0	16	0.50 (58)	570± 119	52± 21	8.8
6b	CH_2CH_2Ph-3F			0.75	30	5.1 (71)			
7a	NMeBn		3,4-cis	13	18		216± 67	2± 1	8.0
7b	NMeBn		3,4-trans	2.2	6				
8a	Bn	CH		0.95	65	11 (61)	781± 171	196± 60	8.7
8b	NMeBn	CH		5.4	230	18 (104)	57± 15	2±1	
8c		CH		1.4	225	1.7 (95)	5± 1	<1	
8d	CH_2CH_2Ph-3F	N		3.7	324	4.4 (98)			
1				0.90	206	1.1 (104)	<2	<2	
2				2.2	66	1.6 (94)	4± 1	<1	
3				0.35	57	0.60 (62)	25± 4	<2	9.7
4				0.60	125	1.2 (88)			
5				0.20	40	0.1 (56)	178± 40	42± 24	8.2

[a] Where applicable, all compounds are racemic. [b] Displacement of [^{3}H]-5-HT binding to cloned human 5-HT_{1D} receptors stably expressed in CHO cells.[7] The figures are the mean of two to four independent determinations performed in duplicate. In each case the radioligand concentration was used at the K_D for the receptor. The maximum variance from the mean of the log (IC_{50}) values was 3.5%. [c] Binding selectivity for 5-HT_{1D} over 5-HT_{1B} receptors. [d] Measurement of agonist induced [^{35}S]GTPγS binding in CHO cells.[7] [e] Efficacy relative to 5-HT. Values are the mean of two independent determinations. [f] Concentration of compound in rat plasma obtained from hepatic portal vein (hpv) and cardiac (systemic) blood samples following po administration at 3 mg/kg (four animals per group). Measured by electrospray mass spectrometry. [g] Determined by potentiometric titration as previously described.[17]

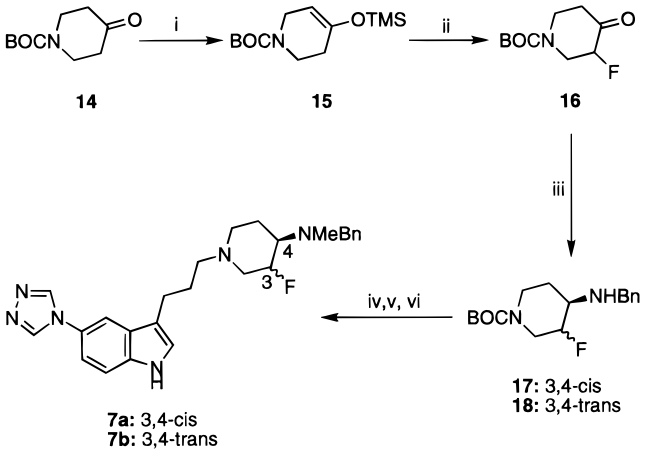
Scheme 1[a]



[a] Reagents: (i) 3-fluorobenzyl bromide, Mg, Et_2O; then add **9**, −30 °C; (ii) DAST, CH_2Cl_2, −78 to 0 °C; (iii) TFA, CH_2Cl_2; (iv) **13**, K_2CO_3, 2-propanol, reflux.

converted into a mixture of **11** and **12** by reaction with DAST at low temperature (Scheme 1). Chromatographic separation of the fluorinated compounds from the tetrahydropyridine side products was facilitated by epoxidation of the crude mixture with *m*-chloroperoxybenzoic acid. Removal of the BOC protecting group

Scheme 2[a]



[a] Reagents: (i) TMSCl, Et_3N, DMF, 80 °C; (ii) Selectfluor, MeCN, room temperature; (iii) RNH_2, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; or $NaCNBH_3$, AcOH, MeOH, room temperature; (iv) TFA, CH_2Cl_2; (v) **13**, K_2CO_3, 2-propanol, reflux; (vi) CH_2O, $NaCNBH_3$, AcOH, MeOH.

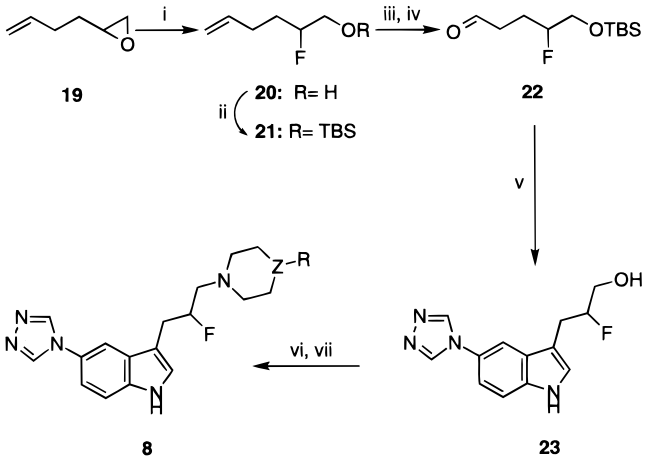
followed by reaction of the resulting piperidine with mesylate **13**[14] finally afforded **6b**. In a similar manner **6a** was prepared from 4-hydroxybenzylpiperidine. Preparation of 3-fluoro-4-aminopiperidines **7** was achieved as shown in Scheme 2, the key step being the treatment of trimethylsilyl enol ether **15** with a source of electrophilic fluorine such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor)[15] to cleanly afford **16** in 91% yield. Reductive amination of this ketone under different conditions gave varying mixtures[16] of racemic cis and trans products **17** and **18** which, after separation, could be converted into the required targeted compounds **7a,b** as described above.

It can be seen from the data in Table 1 that fluorination at C-4 of the piperidine is well tolerated by the

5-HT_{1D} receptor and both **6a** and **6b** bind with affinities comparable to those of the unsubstituted analogue **3** and piperazine **4**, respectively. A similar result was observed for the 3-fluoro-4-aminopiperidines **7a** and **7b**, although the former 3,4-cis isomer showed a 6-fold reduction in affinity compared to **2**. In addition, **6a** was as efficacious as **3** in the [^{35}S]GTPγS assay[7] while **6b** behaved as a partial agonist when compared to **4**. It can also be seen in Table 1 that introduction of fluorine into the piperidine ring reduced the basicity of the molecules by aproximately one pK_a unit,[17] bringing it closer to that found in the piperazines. Thus, although **6a,b** and **7a,b** had reduced selectivity for 5-HT_{1D} over 5-HT_{1B} receptors compared to the unfluorinated analogues, it was of interest to determine the effect of this pK_a modulation on their oral absorption profiles. Rats were dosed orally (3 mg/kg, 5 mL/kg dose volume; aqueous formulation) with the test compound, and blood samples were removed from the hpv and by cardiac puncture at 0.5 and 2 h postadministration (four rats per time point). Drug concentrations measured in plasma samples originating from hpv blood would reflect the levels of absorbed compound, which might be augmented by additional drug present in the systemic circulation (after successful avoidance of first-pass metabolism). The concentrations arising from cardiac blood samples would give an indication of systemic exposure and therefore of bioavailability of the compound. It is clear from the data in Table 1 that reduction of the pK_a of the piperidine results in increased oral absorption. Thus, **6a** and **7a** showed much improved levels of compound in hpv plasma when compared to **3** and **2**, respectively. Moreover, **6a** was also found to be present in the systemic circulation at reasonable concentrations both at 0.5 and 2 h (57 and 37 ng/mL, respectively). The enhanced absorption seen with **7a** did not translate, however, into appreciable oral bioavailability for this compound.

Encouraged by the above data, modulation of the pK_a was sought by fluorination of the propyl linking chain because previous structure−affinity relationships data indicated that substitution at this position could be less detrimental for 5-HT_{1D} over 5-HT_{1B} receptor selectivity. Ring opening of commercially available 1,2-epoxy-5-hexene (**19**) with 70% HF−pyridine occurred at the most substituted end of the epoxide[18] to give **20** in 30% yield (Scheme 3). Protection of the primary alcohol as the TBS derivative was then followed by ozonolysis of the olefin to afford aldehyde **22** in 54% yield.[19] Fischer indolization with 4-(1,2,4-triazol-4-yl)phenylhydrazine[20] under acidic conditions gave fluorinated homotryptol **23** in low yield (15%). Activation of the primary alcohol followed by reaction with the appropriate amines finally afforded compounds **8a**−**d** in moderate yields (50−55%). It can be seen (Table 1) that fluorination of the propyl chain or the piperidine ring led to a similar reduction in pK_a (e.g., **6a** vs **8a**). Compounds **8a**−**d** bound with high affinity to 5-HT_{1D} receptors and, in contrast to the above fluorinated piperidine analogues **6a,b** and **7a,b**, they showed high levels of selectivity over the 5-HT_{1B} subtype. In the case of **8b** and **8d** the selectivity was even improved ~3-fold over the unfluorinated analogues **2** and **4**, and it is tempting to speculate that this might be due to a change in binding mode for these two compounds. Thus, one would anticipate that the presence of the fluorine atom in **8d** would make N-1 of the piperazine (the nitrogen atom joined to the indole nucleus) less basic than N-4 and, therefore, **8d** would bind to helix-3 aspartate in 5-HT_{1D} receptors through a protonated N-4 nitrogen atom rather than N-1 as in **4**. The same argument could probably be applied to the 4-aminopiperidine **8b** but would be absent in the monobasic 4-benzylpiperidine analogue **8a**. In the functional GTPγS assay **8a** behaved as a partial agonist while **8b**−**d** were full agonists. Gratifyingly, the enhanced oral absorption seen with the previous fluorinated compounds was also maintained in this series and, for example, **8a** rapidly achieved high plasma levels in both hpv and systemic blood which compared very favorably with those obtained for **3**. In full pharmacokinetic studies, **8a** and **8d** were found to be orally bioavailable in rats (**8a**: *F*, 14%; $t_{1/2}$, 1.2 h. **8d**: *F*, 7%; $t_{1/2}$, 1.2 h).

Scheme 3[a]



[a] Reagents: (i) 70% HF-Py, CH_2Cl_2, −10 °C; (ii) TBSCl, imidazole, DMF; (iii) O_3, CH_2Cl_2; then Me_2S, room temperature, 3 h; (iv) Et_3N (2 equiv), CH_2Cl_2, room temperature, 2 h; (v) 4-(1,2,4-triazol-4-yl)phenylhydrazine, 4% H_2SO_4, reflux; (vi) MsCl, Et_3N, THF; (vii) R'_2NH, K_2CO_3, 2-propanol, reflux.

In summary, three related series of fluorinated 3-[3-(piperidin-1-yl)propyl]indoles were developed as selective 5-HT_{1D} agonists with the aim of enhancing oral absorption by modulation of the amine pK_a. Particularly interesting are compounds where fluorine was introduced on the propyl chain, some of which did indeed show improved absorption profiles while retaining or enhancing 5-HT_{1D} over 5-HT_{1B} receptor selectivity and agonist properties. In addition, fluorination of the piperidine ring at C-4 (e.g., **6a**) led to a similar reduction in basicity of approximately one pK_a unit, bringing it closer to that of the corresponding piperazine analogue **5**. This latter modification, which also generates a region of electrostatic potential around C-4 of the piperidine, may indeed provide a useful piperazine replacement for drug discovery.

Supporting Information Available: Experimental procedures for the preparation of **6b**, **7a**, and **8a** (14 pages). Ordering information is given on any current masthead page.

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