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# 2,7-DIAZABICYCLO[3.3.0]OCTANES AS NOVEL h5-HT$_{1D}$ RECEPTOR AGONISTS

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**Abstract**: The conformational restriction of a (benzylamino)methyl substituted pyrrolidine to form 2,7-diazabicyclo[3.3.0]octanes has led to a series of compounds with high affinity at the h5-HT$_{1D}$ receptor as well as dramatically increased concentrations in the hepatic portal vein following oral administration. 

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

Studies using h5-HT$_{1D}$ and h5-HT$_{1B}$ receptor-specific antibodies (previously termed 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ respectively[11]) suggest that the former receptors are responsible for blocking the release of peptides in the peripheral meningeal arteries and also for inhibiting neurotransmitter release within the brainstem and interrupting central pain transmission.[12] On the other hand, h5-HT$_{1B}$ receptors appear to be involved in direct vasoconstriction.

None of the "triptans" mentioned above, however, have significant selectivity between the h5-HT$_{1D}$ and h5-HT$_{1B}$ subtypes. If inhibition of peptide release is important in the therapeutic action of these agents, it might be expected that a selective h5-HT$_{1D}$ receptor agonist should still provide adequate pain relief without vasoconstrictor effects. This prompted us to seek to identify a selective h5-HT$_{1D}$ receptor full agonist in order to confirm the target tissue for antimigraine drugs and potentially develop a second generation antimigraine agent.

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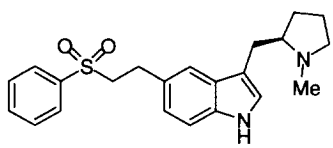
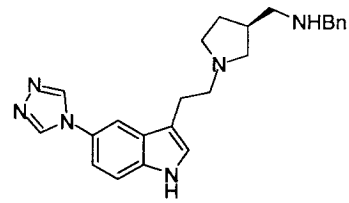
In this regard, we have previously communicated[13,14] the identification of a series of 3-substituted 3-[2-pyrrolidin-1-yl)ethyl]indoles as selective h5-$HT_{1D}$ receptor agonists. In particular, the analogue (**2**; L-760,790) having a benzylaminomethyl substituent with the (*R*)-stereochemistry at the pyrrolidine C-3 chiral centre had subnanomolar affinity, high selectivity over the h5-$HT_{1B}$ receptor subtype, and was a full agonist. The analogue in which the exocyclic nitrogen atom was methylated had similar properties. It was hypothesised that a similar substitution at the 4-position of the pyrrolidine ring in the (*2R*)-pyrrolidin-2-ylmethyl side chain of eletriptan may lead to compounds with the desired selectivity profile.

**Chart 1**




**1**: eletriptan



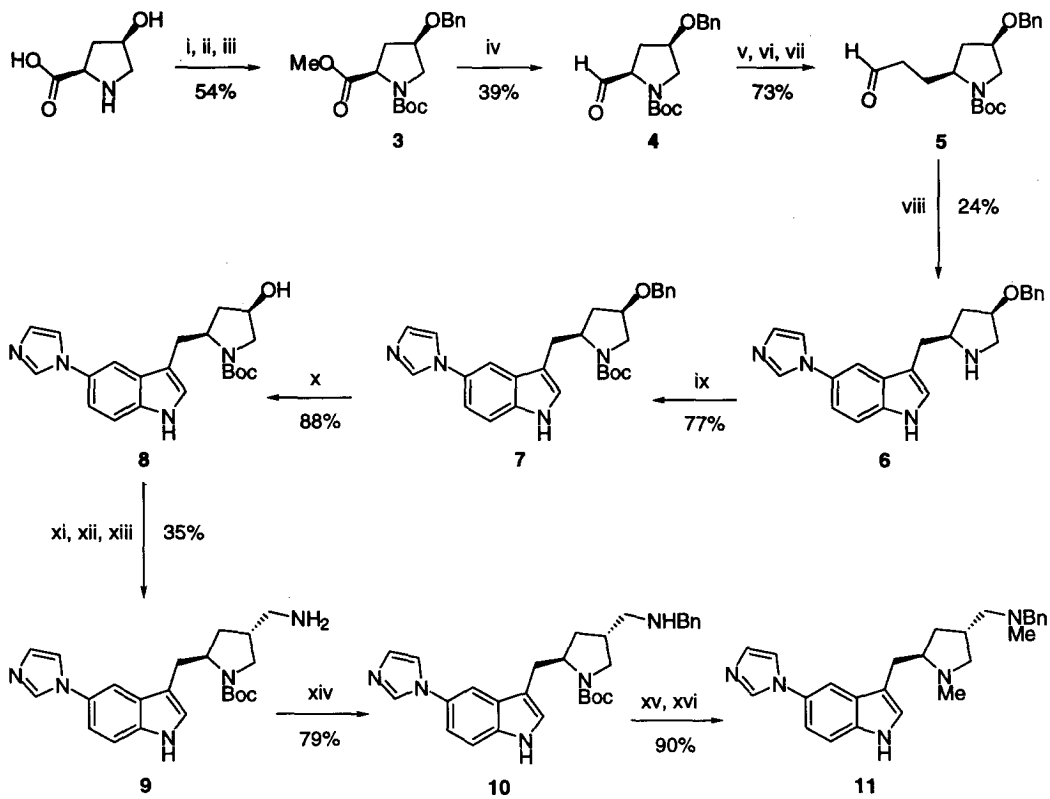

**2: L-760,790**

Thus, aldehyde (**5**) was prepared from cis-4-hydroxy-D-proline using standard chemistry (Scheme 1). Fischer indolisation with 4-(imidazol-1-yl)phenylhydrazine gave indole (**6**), which was reprotected on the pyrrolidine N atom and O-debenzylated to give alcohol (**8**). Treatment of this material with mesyl chloride and triethylamine gave an intermediate mesylate, which was utilised crude in the next reaction, after an aqueous work up. Displacement of the mesylate with tetrabutylammonium cyanide proceeded in moderate yields in DMF at 65 °C. Temperature control during the reaction was mandatory to avoid epimerisation of the nitrile. Catalytic hydrogenation over platinum gave 4-(aminomethyl)pyrrolidine (**9**), which was then reductively benzylated to afford **10**. The Boc group was then removed and both secondary amines were reductively methylated to give **11**. The other diastereomer (**12**) could be obtained by performing the cyanide displacement reaction so that epimerisation occurred, then carrying through a mixture of diastereomers, and separating the final compounds by HPLC.[15] The compounds were evaluated for their affinity to cloned h5-$HT_{1D}$ and h5-$HT_{1B}$ receptors stably expressed in CHO cells.[16]

Unfortunately, although the two diasteomers showed excellent h5-$HT_{1D}$ receptor affinity, there was no appreciable selectivity over the h5-$HT_{1B}$ receptor subtype (Table 1). In addition, an oral absorption screen was performed in which rats were dosed orally (3 mg/kg, 5 mL/kg dose volume; aqueous formulation) with the test compound. Drug concentrations were measured in plasma samples originating from the hepatic portal vein (hpv) and by cardiac puncture (systemic) at 0.5 and 2 h post administration. It was found that, like **2**, the levels

of **11** in the hpv plasma were low at both time points, and levels in the systemic circulation were below the limits of detection.

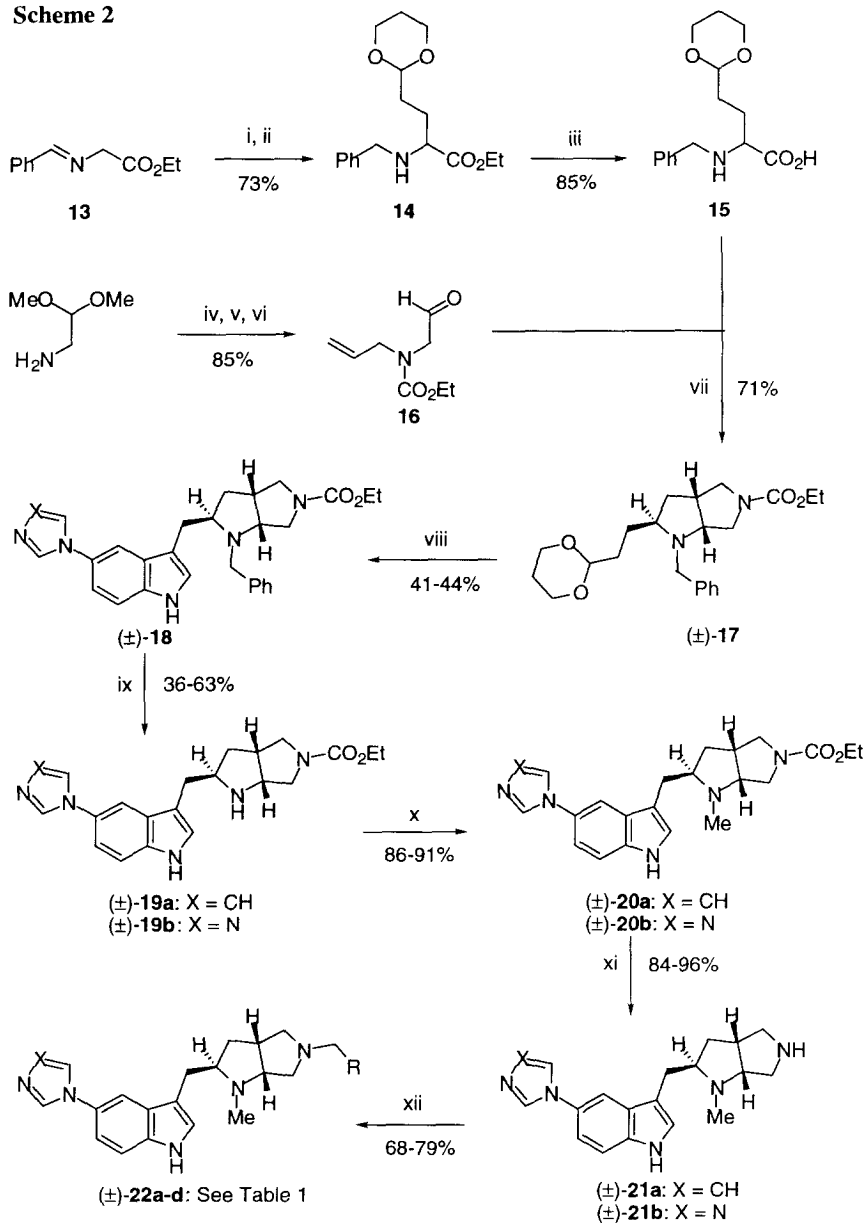
**Scheme 1**




Reagents: (i) $SOCl_2$, MeOH, –20 °C to rt, 19 h; (ii) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, rt, 3 h; (iii) NaH, BnBr, DMF, 5 °C, 4 h; (iv) DIBALH, toluene, –78 °C, 2.25 h; (v) $(MeO)_2P(O)CH_2CO_2Me$, KHMDS, THF, –78 °C to rt, 3 h; (vi) $H_2$, $PtO_2$, EtOAc, 12 psi, 40 min; (vii) DIBALH, toluene, –81 °C, 2 h; (viii) 4-(imidazol-1-yl)phenylhydrazine hydrochloride, 4% $H_2SO_4$(aq), reflux, 20 h; (ix) $Boc_2O$, THF, rt, 4 h; (x) $HCO_2NH_4$, 10% Pd/C, MeOH, 55-62 °C, 6 h; (xi) MsCl, $Et_3N$, THF, rt, 2 h; (xii) $Bu_4NCN$, DMF, 65 °C, 12 h; (xiii) $H_2$, $PtO_2$, $CHCl_3$, EtOH, 50 psi, 17 h; (xiv) PhCHO, $NaCNBH_3$, AcOH, MeOH, rt, 1.75 h; (xv) TFA, $CH_2Cl_2$, rt, 1 h; (xvi) $CH_2O$, $NaCNBH_3$, NaOMe, AcOH, MeOH, rt, 2.5 h.

In order to explore the effect on selectivity by reducing the conformational mobility of the (benzylamino)methyl substituent, a series of 2,7-diazabicyclo[3.3.0]octanes was designed and synthesised as shown in Scheme 2. The highly functionalised 2,7-diazabicyclo[3.3.0]octane (**17**) was prepared as one diastereomer in excellent yield by the thermolysis of an equimolar mixture of aldehyde (**16**)[17] and aminoacid (**15**) (synthesised in two steps from *N*-benzylideneglycine, ethyl ester[18]).

**Scheme 2**




Reagents: (i) (a) NaH, DMSO, rt, 35 min; (b) 2-(2-bromoethyl)-1,3-dioxane, rt, 2 h; (ii) $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt, 1.5 h; (iii) $LiOH.H_2O$, MeOH-THF-$H_2O$, rt, 3 d; (iv) $ClCO_2Et$, NaOH, $H_2O$, toluene, 10 °C to rt, 3 h; (v) allyl bromide, $BnEt_3NCl$, KOH, toluene, rt, 3 d; (vi) 90% $HCO_2H$(aq), 100 °C, 1 h; (vii) toluene, reflux, 24 h; (viii) 4-(heteroaryl)phenylhydrazine dihydrochloride, 4% $H_2SO_4$ (aq), reflux, 15-20 h; (ix) $HCO_2NH_4$, 10% Pd/C, MeOH, 5 N HCl(aq), reflux, 75-100 min; (x) $CH_2O$, $NaCNBH_3$, AcOH, MeOH, rt, 2-3.5 h; (xi) concd HCl, reflux, 40-48 h; (xii) RCHO, $NaCNBH_3$, AcOH, MeOH, rt, 12-20 h.

Indolisation of **17** with the appropriate 4-substituted phenylhydrazine, followed by standard functional group manipulations gave the 7-unsubstituted 2,7-diazabicyclo[3.3.0]octanes (**21**). This was then reductively alkylated with various aldehydes to give compounds **22a-d** as racemates.[19] The relative stereochemistry of **22a** was confirmed by COSY and NOESY NMR experiments.[20]

The 5-(imidazol-1-yl) analogue **22a** had high affinity at the h5-$HT_{1D}$ receptor but with little selectivity over the h5-$HT_{1B}$ subtype, although this might be improved upon resolution. However, in the oral absorption screen **22a** exhibited a vast increase in hpv concentrations compared to **11**, suggesting much improved absorption. This increase in hpv concentration also led to improved levels in the systemic circulation, although a significant degree of first-pass metabolism appears to be occurring. The intrinsic efficacy was measured in the same cell line using agonist-induced [$^{35}$S]GTPγS binding and expressed as % of the maximal 5-HT response. Although **22a** was only a partial agonist, this had also been observed in a previous series in which the corresponding 5-(1,2,4-triazol-4-yl) analogue was a full agonist.[21] Thus, derivatives **22b-d** incorporating this triazole group were prepared in an attempt to improve the efficacy. It was found that **22b** was a full agonist, although there was no significant improvement in the selectivity of any of these analogues. These analogues also had efficacy at h5-$HT_{1B}$ receptors similar to their efficacies at h5-$HT_{1D}$ receptors so were not functionally selective either.

**Table 1.** Binding, Efficacy and Absorption Data for Test Compounds[a].

| | | | | | | | [drug] (ng/mL) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $IC_{50}$ (nM)[b] | selectivity[c] | $EC_{50}$ (nM)[d] | efficacy[e] | 0.5 h | | 2.0 h | |
| compd[f] | X[g] | R[g] | h5-$HT_{1D}$ | 1B/1D | h5-$HT_{1D}$ | % 5-HT | hpv | systemic | hpv | systemic |
| **2** | | | 0.6 (0.7, 0.5) | 62 | 0.8 (1.3, 0.5) | 102±5 | <5 | <5 | <5 | <5 |
| **11** | | | 0.9 (0.5, 1.5) | 6.9 | | | 21±9 | <4 | 30±10 | <4 |
| **12** | | | 3.3 (2.4, 4.6) | 6.7 | | | | | | |
| (±)-**22a** | CH | Ph | 0.7 (0.3, 1.4) | 8.4 | 1.2 (0.8, 1.7) | 69±5 | 558±66 | 47±33 | 105±8 | 10±2 |
| (±)-**22b** | N | Ph | 0.9 (0.7, 1.1) | 6.7 | 0.5 (0.3, 0.9) | 96±4 | | | | |
| (±)-**22c** | N | 4-F-$C_6H_4$ | 0.8 (0.8, 0.9) | 13 | 2.9 (1.9, 4.4) | 88±7 | | | | |
| (±)-**22d** | N | 3-F-$C_6H_4CH_2$ | 1.2 (1.0, 1.5) | 15 | 1.9 (1.3, 2.8) | 63±4 | | | | |

[a] For full experimental details see reference 14. [b] Displacement of [$^3$H]-5-HT binding to cloned h5-$HT_{1D}$ receptors stably expressed in CHO cells. The figures are the geometric means of at least three independent experiments performed in duplicate. The numbers in parentheses are the upper and lower limits derived as a result of the SEM. In each case the radioligand concentration used was approximately at the $K_D$ for the receptor. [c] Binding selectivity for h-5-$HT_{1D}$ receptors obtained by dividing the mean $IC_{50}$ values for the respective receptors. [d] Measurement of agonist induced [$^{35}$S]GTPγS binding in CHO cells stably transfected with h5-$HT_{1D}$ receptors. The numbers in parentheses are the upper and lower limits derived as a result of the SEM. [e] Maximum stimulation of [$^{35}$S]GTPγS binding expressed relative to the maximal effect produced by 5-HT. Values are the arithmetic mean ±SEM of at least three independent experiments. [f] Satisfactory spectral and microanalytical data were obtained for all these compounds. [g] See Scheme 2.

In conclusion, conformational restriction of the amino side chain as 2,7-diazabicyclo[3.3.0]octanes has led to compounds with high affinity at the h5-$HT_{1D}$ receptor as well as a dramatic increase in hpv exposure.

This increase in exposure is not due to a change in the $pK_a$ of the most basic N atom since these were measured for **11** and **22b** and found to be 8.7 and 8.5 respectively. One possible explanation is that the conformationally restricted compound is less susceptible to gut wall metabolism. However, another possibility is that the amphoteric nature and/or the shape of the rigid analogue may be such that it can pass through the gut wall without having to make so many entropically unfavourable conformational changes.

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