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4-Hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidines: Selective h5-HT$_{1D}$ Agonists for the Treatment of Migraine.

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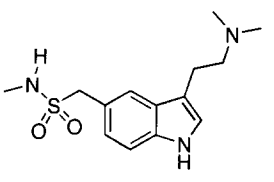
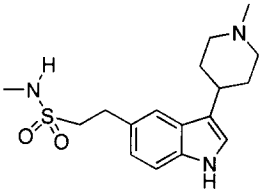
Abstract: A series of 4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl] piperidines was investigated as potential selective h5-HT$_{1D}$ agonists for the treatment of migraine. The 4-[(N-benzyl-N-methyl)amino]methyl analog **12a** was found to be a full agonist at the h5-HT$_{1D}$ receptor with good binding selectivity over the h5-HT$_{1B}$ receptor.

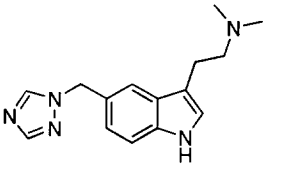
Following the discovery of sumatriptan (**1a**),[1] an antimigraine agent which acts as an agonist at h5-HT$_{1D/1B}$ receptors, considerable effort has been made to find alternative drugs for the treatment of this common condition. All the currently used "triptan" drugs (including naratriptan (**1b**)[2] and rizatriptan(**1c**)[3]) have a selectivity profile similar to sumatriptan at the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors i.e. none of these more recently introduced compounds has selectivity for the h5-HT$_{1D}$ receptor over the h5-HT$_{1B}$ subtype. In the case of sumatriptan extensive research suggests that the coronary artery vasoconstriction seen in a small number of patients could potentially be due to the drug's affinity for the h5-HT$_{1B}$ receptor.[4]



1a



1b



1c

In previous reports,[5,6] we have described the discovery of several compounds with indoles as the core scaffold which act as agonists at the h5-HT$_{1D}$ receptor. As a result of this work we decided to further investigate the structural diversity around the amine portion of the molecule. Our latest research effort has focussed on

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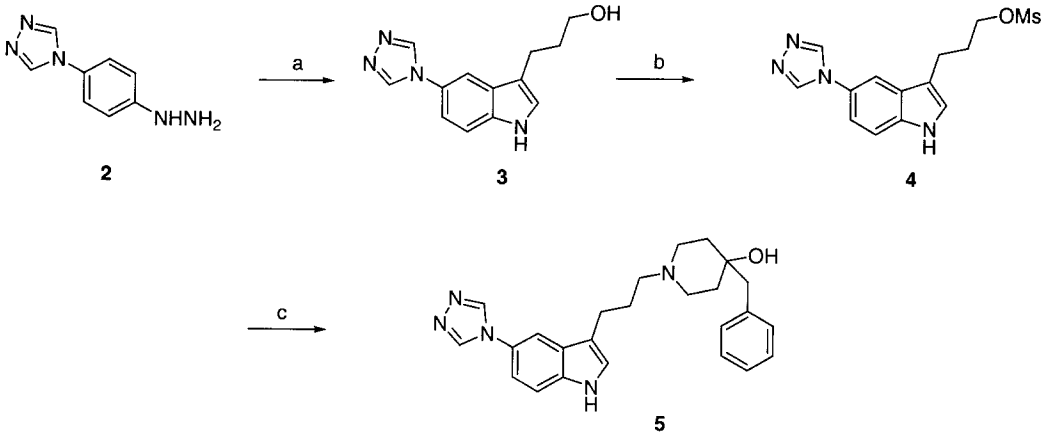
identifying a new class of selective h5-HT_{1D} agonists which possess a hydroxy group at the 4-position of a piperidine.

Chemistry.

Scheme 1 shows the synthetic route to the 4-benzyl-4-hydroxy-1[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine **5**. The hydrazine **2**[7] was treated with dihydropyran and 1N HCl in dioxane at reflux to give **3** in one step. The mesylate **4** (which was used crude due to its instability) was prepared by reacting **3** with methanesulfonyl chloride in THF. Coupling of 4-benzyl-4-hydroxypiperidine with **4**, to afford the final compound **5**, was achieved using potassium carbonate in isopropyl alcohol (IPA) at reflux.

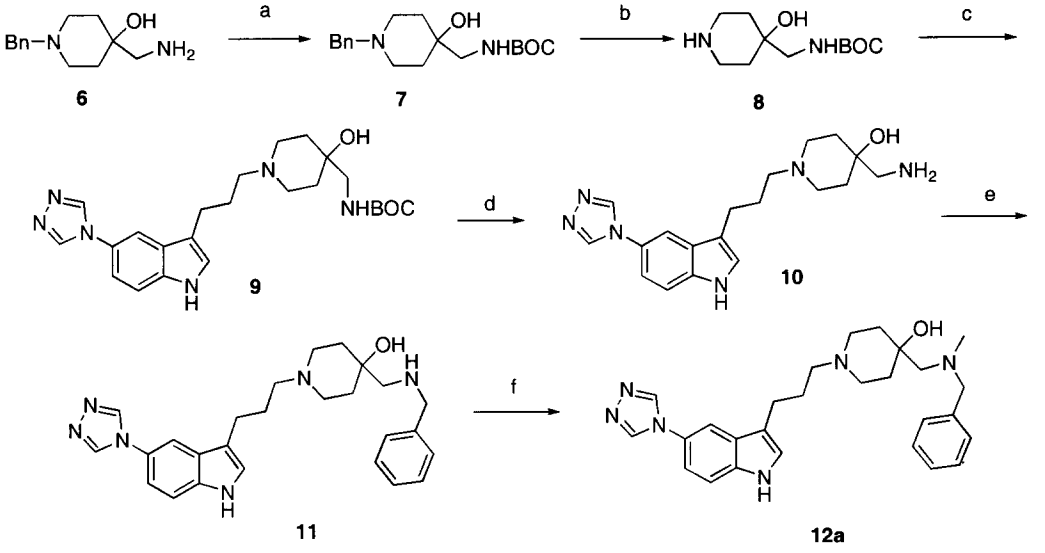
Scheme 1.



Reagents: a) Dihydropyran, dioxane, 1N HCl, reflux, 30%; b) Et_3N, methanesulfonyl chloride, THF, 0°C; c) K_2CO_3, 4-benzyl-4-hydroxypiperidine, IPA, reflux, (59%, from **3**).

Scheme 2 illustrates the synthesis of compounds **9, 11** and **12a-f**. Protection of the primary amine of the piperidine **6**[8] was carried out using BOC-anhydride in dichloromethane and deprotection of the secondary amine was achieved in methanol by transfer hydrogenation with ammonium formate in the presence of 10% palladium on carbon. The 4-hydroxypiperidine **8** was coupled with **4** using potassium carbonate in IPA to yield the piperidine **9**. The amine was deprotected with trifluoroacetic acid in dichloromethane to give the 4-aminomethyl-4-hydroxypiperidine **10**. Reductive alkylation of **10** with benzaldehyde (0.9 equivalent to avoid dialkylation), sodium cyanoborohydride and acetic acid in methanol gave the secondary amine **11**. Finally a second reductive alkylation with formaldehyde afforded 4-[(N-benzyl-N-methyl)amino]methyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl]piperidine **12a**.

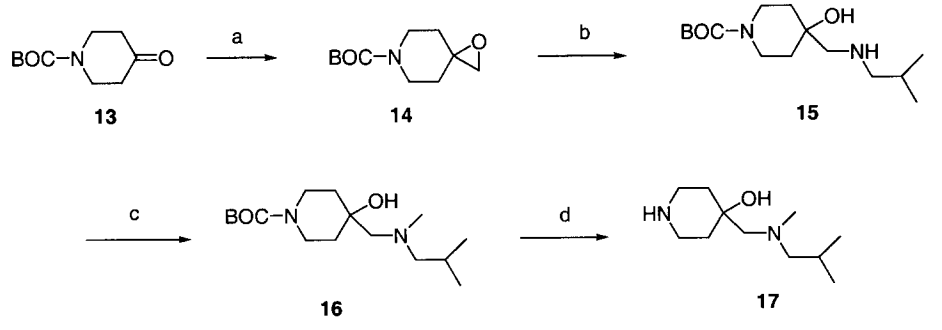
Scheme 2.



Reagents: a) BOC-anhydride, CH_2Cl_2, RT, 70%; b) 10% Pd on C, ammonium formate, MeOH, RT, 78%; c) **4**, K_2CO_3, IPA, reflux, (60%, from **8**); d) TFA, CH_2Cl_2, RT; e) Benzaldehyde, AcOH, $NaCNBH_3$, MeOH, RT, (41%, from **9**); f) formaldehyde, AcOH, $NaCNBH_3$, MeOH, RT, 83%.

Scheme 3 exemplifies the alternative route to the 4-hydroxypiperidine moieties used to synthesize compounds **12g-l**. The piperidone **13** was treated with a mixture of sodium hydride, DMSO and trimethylsulphoxonium iodide at 5°C to give the epoxide **14**. Opening of the epoxide with isobutylamine in ethanol yielded the 4-hydroxy-4-aminomethylpiperidine **15** which was reacted with formaldehyde in the presence of sodium cyanoborohydride and acetic acid in methanol. The free amine **17** was obtained by treatment of **16** with trifluoroacetic acid in dichloromethane and was coupled as described in Scheme **2**.

Scheme 3.

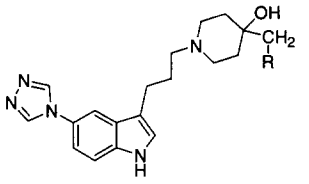


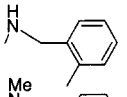
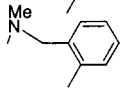
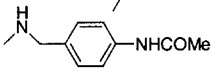
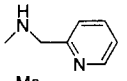
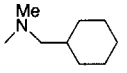
Reagents: a) NaH, Me_3SI, DMSO, 5°C, 55%; b) Isobutylamine, EtOH, RT, 85%; c) Formaldehyde, AcOH, $NaCNBH_3$, MeOH, RT, 76%; d) TFA, CH_2Cl_2, RT, 85%.

Results and discussion.

The compounds described in this article were tested *in-vitro* for their abilities to displace [^{3}H]-5-HT from recombinant human h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors stably expressed in CHO cells[9]. Their intrinsic efficacies, as determined using agonist-induced [^{35}S]GTPγS binding[10], is expressed as a percentage of the maximal stimulation seen with 5-HT.

The simple 4-hydroxybenzylpiperidine **5** has very good affinity for the h5-HT$_{1D}$ receptor and excellent selectivity over the h5-HT$_{1B}$ receptor, but as with other 5-HT$_{1D}$ ligands devoid of a nitrogen in the side chain[11] **5** is a partial agonist. Addition of an amine in the side chain, as in **11,** increases the efficacy whilst retaining binding selectivity for the h5-HT$_{1D}$ receptor. Methylating the side chain nitrogen gives **12a** which has good affinity and selectivity for the h5-HT$_{1D}$ receptor whilst being a full agonist (**12a**, IC$_{50}$ 1.2nM; 1B/1D 80; ED$_{50}$ 3.8nM(91%)). Substitution on the phenyl ring with an ortho methyl moiety (**12b**) decreases the affinity by 10 fold at the h5-HT$_{1D}$ receptor (relative to **11**) but addition of a methyl group on the chain nitrogen provides a compound (**12c**) with a similar binding profile to **12a**. Addition of a para acetamido group leads to a decrease in h5-HT$_{1D}$ affinity and selectivity but provides compound **12d** with excellent efficacy. Replacement of the phenyl ring in **11** with a 2-pyridyl entity (**12e**) leads to a decrease in both affinity at and selectivity for the h5-HT$_{1D}$ receptor. In this series, where an aromatic group is used, the presence or the absence of a methyl group on the chain nitrogen does not seem to follow any trend. For example with the simple benzyl substituent the NH compound **11** has higher affinity than the N methylated variant (**12a**), whereas methylation of the nitrogen of **12b** leads to poorer affinity. Following the discovery of the residual affinity of intermediate **9** for the h5-HT$_{1D}$ receptor we decided to investigate a small series of compounds with an alkyl amine substituent. The 3,3-dimethylpiperidine **12l** and the N-methyl-N-neopentyl compound (**12h**) have good affinity for the h5-HT$_{1D}$ receptor but lack sufficient selectivity and efficacy for the h5-HT$_{1D}$ receptor. In contrast, the N-isobutyl-N-methylamine **12k** has excellent affinity and moderate selectivity for the h5-HT$_{1D}$ receptor whilst being a full agonist. The cyclic analog of **12k**, the N-cyclopropylmethyl-N-methylamine **12j**, shows a marginal decrease in affinity and selectivity at the h5-HT$_{1D}$ receptor with similar efficacy. **12f**, the saturated version of **12a**, has identical affinity for the h5-HT$_{1D}$ receptor but much reduced selectivity and efficacy. These results suggest that functional activation of the receptor has specific steric requirements. For example both **12a** (N-Bn) and **12k** (N-iBu) are tolerated and give full agonism whilst the more bulky compounds such as **12f** (N-cyHex) and **12g** (N-neoPent) still bind at the h5-HT$_{1D}$ receptor but do not enable the receptor to fully functionally couple. Unlike in the aromatic series, the presence or the absence of a methyl group on the chain nitrogen does seem to follow a trend. Both analogs without a methyl group (**12g** and **12i**) have reduced affinity and selectivity for the h5-HT$_{1D}$ receptor.



	R^b	mp (°C)	IC_{50} (nM)[a]		1B/1D[c]	ED_{50} (nM[d], %5-HT[e])
			h5-HT_{1D}	h5-HT_{1B}		h5-HT_{1D}
5	—Ph	117-119	0.1	32	251	0.25 (64)
9	—$NHCO_2$t-Bu	>86 dec	21	340	16	9.7 (86)
11	—NHBn	>60 dec	0.45	47	106	2.2 (79)
12a	—NMeBn	>132 dec	1.2	96	80	3.8 (91)
12b		>138 dec	4.0	83	21	
12c		>110 dec	1.3	89	68	3.7(90)
12d		>110 dec	11	30	3	14 (102)
12e		>55 dec	3.2	55	17	3.2 (96)
12f		110-115	1.2	27	22	1.4 (69)
12g		>55 dec	7.3	85	12	
12h		>70 dec	1.8	61	34	1.6 (60)
12i		>207 dec	4.5	57	13	
12j		>79 dec	1.35	27	20	1.1(79)
12k		>60 dec	0.65	30	47	1.7 (95)
12l		125-132	0.65	19	29	0.9(67)

[a]Displacement of [^{3}H]5-HT binding to cloned h5-HT_{1D} and h5-HT_{1B} receptors stably expressed in CHO cells. In each case the radioligand concentration used was at the K_D for the receptor. [b]Satisfactory spectral and microanalytical data were obtained for all compounds. [c]Binding selectivity for h5-HT_{1D} receptors. [d]Measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells stably transfected with h5-HT_{1D} receptors. [e]Maximum stimulation of [^{35}S]GTPγS binding expressed relative to the maximal effect produced by 5-HT. These values are the mean of at least 2 experiments. The maximum deviation from the mean for log(IC_{50}) and log(ED_{50}) values is 5%. For the efficacy data the maximum deviationfrom the mean is 6% except for 11 anf 12f where it is 15%.

Conclusion.

In summary, a new series of 4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidines has been designed, synthesised and evaluated at the h5-HT_{1D} receptor. From this series we identified two compounds, one from the aromatic series (**12a**) and one from the aliphatic series (**12k**), which are full agonists at the h5-HT_{1D} receptor and possess moderate to excellent selectivity over the h5-HT_{1B} receptor.

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