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5-Alkyltryptamine Derivatives as Highly Selective and Potent 5-HT_{1D} Receptor Agonists

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Abstract—A series of 5-alkyltryptamines (**6**) and the corresponding conformationally constrained analogues (**8**) have been synthesized. The structure–activity relationships (SAR) at the 5-position of the indole skeleton and the ethylamine side chain have been studied. Functional activities were assessed using isolated rabbit saphenous vein. Potent, selective ligands were found (**6e**, K_i 2.5 nM, 5-HT_{1B}/5-HT_{1D} 125-fold) that have potential for treating acute migraine. © 2000 Elsevier Science Ltd. All rights reserved.

Migraine is a common, highly distressing disorder affecting normal daily life and economic productivity.[1] Approximately 8.7 million women and 2.6 million men in the United States suffer from migraine headaches.[2] The introduction of sumatriptan[2] (**1**) into clinical practice has revolutionized migraine drug discovery and spurred further research for better treatments.[3] While sumatriptan is effective as a migraine abortive agent, about 15% of patients fail to respond to treatment and up to 40% may suffer from recurrence of headache within 24 h.[4,5] Similar rates of headache recurrence have also been observed with other antimigraine treatments such as naratriptan (**2**) and eletriptan (**3**) (Fig. 1). These antimigraine drugs, collectively known as "triptans", bind to the 5-HT_{1D} (5-$HT_{1D\alpha}$ previously), 5-HT_{1B} (5-$HT_{1D\beta}$ previously) and 5-HT_{1F} receptors with high affinities.[3]

Although the exact pathophysiology of migraine is not completely understood, it appears that the pain of migraine may in part derive from stimulation of the trigeminal sensory system, which innervates meningeal and cerebral arteries.[3,6] Cranial vasodilation or neural stimulation or both have been suggested as possible mechanisms by which the pain is generated.[3,6,7] It is generally accepted that one or more of the three receptors to which the triptans bind is involved in migraine. While all three receptors (5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F}) have been found in human trigeminal ganglia, only 5-HT_{1B} and 5-HT_{1F} receptors are clearly present in cerebral blood vessels.[8] The vasoconstrictor effect could be mediated by the 5-HT_{1B} or 5-HT_{1F} receptors while the neurogenic effect could be mediated by any of the three. It has been proposed that selective agonists of the 5-HT_{1D} site might be effective in ameliorating migraine symptoms.[7,9] The same lines of argument have been used for the development of 5-HT_{1F} receptor selective agonists since the 5-HT_{1F} receptor appears to be present on trigeminal nerve terminals but is not vasoconstrictive on blood vessels.[10] An advanced compound in this class was LY334370 that was known to be potent in the dural extravasation assay[11] and had shown satisfactory phase II results, but was abandoned for safety reasons. In addition, it has been shown that adverse cardiovascular effects associated with sumatriptian can be attributed to its 5-HT_{1B} receptor binding.[11] Other members of the triptan class also bind to the 5-HT_{1B} receptor and will likely cause the same cardiovascular side effects. Thus, the search for the next generation of antimigraine drugs has focused on achieving 5-HT_{1B}/5-HT_{1D} selectivity. To this end, selectivity over 300-fold has been achieved in the indole series[12] and over 6000-fold in a nonindole series.[13] Since it is not certain that the 5-HT_{1D} receptor alone is involved in the pathogenesis and/or treatment of migraine, it will be very interesting to see if highly selective compounds show efficacy in humans.

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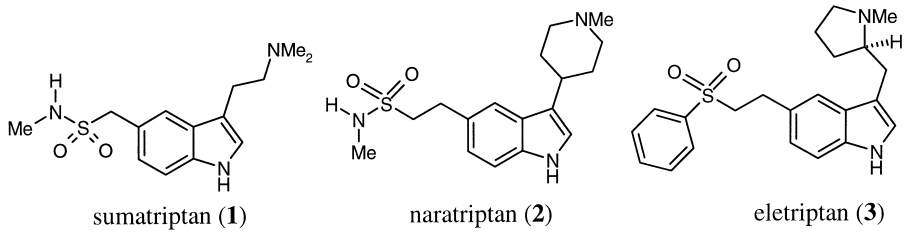
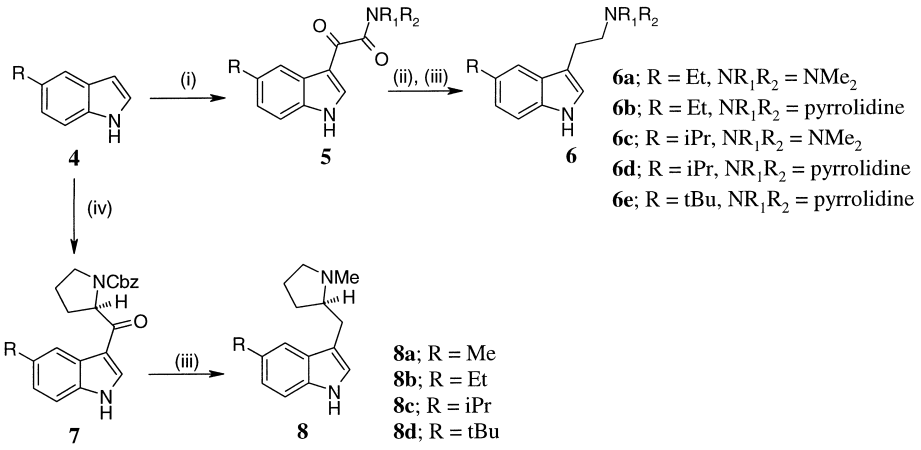


Figure 1.



Scheme 1. Reagent and conditions: (i) oxalyl chloride, diethyl ether, 0 °C, then reflux overnight; (ii) R_1R_2NH, Et_3N, THF, rt, 2 h; (iii) LAH, THF, reflux, 4 h; (iv) (a) EtMgBr, THF, 0 °C, 30 min; (b) Cbz-proline-acid chloride, THF, 0 °C, 1.5 h.

As a continuation of our efforts to develop highly potent selective 5-HT_{1D} ligands for the treatment of migraine,[14] this communication describes the synthesis and biological evaluation of a series of 5-alkyltryptamines (**6**) and conformationally constrained 5-alkyl-3-(N-methylpyrrolidin-2-yl-methyl) analogues (**8**) (Scheme 1).

Acylation of 5-alkylindole (**4**) by treatment with oxalyl chloride in diethyl ether at 0 °C and refluxing overnight afforded the corresponding acid chloride as intermediate,[15] which was further reacted with an excess amount of *N,N*-dimethylamine or pyrrolidine to give the key intermediates (**5**) (Scheme 1). In parallel, the same 5-alkylindole (**4**) was deprotonated using a Grignard reagent and trapped with the acid chloride of Cbz-D-proline[16] to afford the corresponding intermediate (**7**). Finally, the reduction of **5** and **7** with 4 equivalents of lithium aluminum hydride in refluxing tetrahydrofuran gave the targeted 5-alkyltryptamines (**6**) and 5-alkyl-3-(*N*-methylpyrrolidin-2-yl-methyl) derivatives (**8**), respectively, as final products suitable for biological evaluation (Table 1).

The binding affinities of 5-alkylindole derivatives (**6a–e** and **8a–d**) and sumatriptan have been determined at the cloned human 5-HT_{1D} and 5-HT_{1B} receptors. Most of these compounds exhibited very high binding affinities for the human 5-HT_{1D} receptor compared to sumatriptan, with improved 5-HT_{1B}/5-HT_{1D} selectivity (Table 1). It has been recently shown that the steric size of the lipophilic substituent at the 5-position of indole has a significant impact on the 5-HT_{1D} affinity, with enhanced potency as the size increased.[17] For example, *N*-methyl-5-*tert*-butyltryptamine (MBT) showed very potent binding (K_i 0.45 nM) but poor selectivity over 5-HT_{1B} (1.9-fold). In line with this finding, we were able to demonstrate that the 5-isopropyl substituents in **6c**,[18] **6d** and **8c** were more potent than their corresponding 5-ethyl analogues (**6a**, **6b**, and **8b**). Similar trends were observed in going from 5-isopropyl to the corresponding *tert*-butyl groups (**6d** to **6e** and **8c** to **8d**). However, in contrast to the previous finding of poor selectivity with MBT, the use of larger tertiary amine side chains provided much greater binding selectivity for 5-HT_{1D}. Compounds in each amine side chain series ((i) **6a** and **6c**; (ii) **6b**, **6d** and **6e**; (iii) **8a–d**)) showed better selectivities (17.8 to 125-fold)

Table 1. Binding profile of 5-alkyltryptamine derivatives **6** and **8** in comparison with sumatriptan at the cloned human 5-HT_{1D} and 5-HT_{1B} receptors, and rabbit saphenous vein (RSV) functional data

Compound[a]	5-HT_{1D} (K_i, nM)[a]	5-HT_{1B} (K_i, nM)[a]	5-HT_{1B}/ 5-HT_{1D}	RSV (EC_{50}, nM)[b]
Sumatriptan	5.5	47.9	8.7	173.5
6a	16	286	17.8	350
6b	45	1625	36	NA[c]
6c	0.4	14.2	34.6	NA
6d	5.3	472	89	440
6e	2.5	312	125	1167
8a	3.5	118	33.7	101.5
8b	0.97	47	49	14.7
8c	0.29	10.4	36	28.6
8d	0.25	15.5	62	51.8

[a] K_i values are given as the mean of at least two independent determinations performed in duplicate.
[b] None of the compounds demonstrated any antagonist activity with sumatriptan as agonist.
[c] Not available.

than sumatriptan (8.7-fold), with a general trend for increasing selectivity with increasing size of alkyl group (Et, *i*Pr, *t*Bu).

The functional activities of selected compounds (**6d**, **6e**, **8a**–**8d** and sumatriptan) were evaluated both as antagonists and as agonists using isolated rabbit saphenous vein (RSV) preparation as measures of functional activity. All compounds showed agonist activity with EC_{50} values (Table 1), with no demonstrated antagonist activity.

In summary, a series of highly potent and selective 5-alkyltryptamine derivatives have been developed using a variety of tertiary amine side chains. The constrained analogues derived from D-proline provided several compounds with subnanomolar potency and high selectivity. Compound **6e** is currently being further evaluated in animal models for the treatment of migraine.

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