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(*R*)-3-(*N*-Methylpyrrolidin-2-ylmethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole Derivatives as High Affinity h5-HT$_{1B/1D}$ Ligands

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Abstract—A series of (*R*)-3-(*N*-methylpyrrolidin-2-ylmethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives (**2**) have been prepared using parallel synthesis, and their structure–activity relationship studied. High affinity human 5-HT$_{1B/1D}$ (h5-HT$_{1B/1D}$) ligands have been identified.

Migraine is a chronic disease characterized by episodic attacks of intense, unilateral headache pain. Often associated with the attack are secondary symptoms that include nausea and vomiting, photophobia, and phonophobia. Although the episode will resolve on its own in a few hours to a few days, the debilitating nature of the attacks necessitates treatment to alleviate the discomfort experienced. It is estimated that over 200 million people worldwide suffer from migraine headaches in one form or another.[1,2]

Sumatriptan has for years been the treatment of choice for migraine sufferers. It is a potent h5-HT$_{1B/1D}$ receptor agonist, with K_i values of 3.4 and 7.7 nM at the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors, respectively.[3] Despite its success, sumatriptan possesses several shortcomings that have spurred the search for better therapies. These shortcomings include poor oral bioavailability, short half-life and the tendency for migraine attacks to reoccur, and angina-like side effects, possibly resulting from coronary artery vasoconstriction.[4] Due to this, the use of sumatriptan for patients with coronary heart disease is contraindicated.[5] While a new generation of triptan drugs have shown significant improvement in bioavailability and duration of action, the majority of them have still been shown to contract the human coronary artery in vitro,[6] and up to 40% of all attacks and up to 25% of all patients do not respond to any of these drugs.[7]

Although 5-HT$_{1B}$ receptors are found in human trigeminal ganglia, they are also abundantly expressed in vascular smooth muscle. It is now postulated that much of the vasoconstrictive liability of the triptans is a result of their high 5-HT$_{1B}$ affinity. 5HT$_{1D}$ receptors appear to be absent in vascular tissue, but are identified in the trigeminal ganglia. Electrical stimulation of the trigeminal nerves induces release of neuropeptides such as calcitonin gene-related peptide (CGRP). Subsequently, plasma protein extravasation into the dura occurs, resulting in vasodilation, inflammation and pain. Consistent with this model is the fact that the elevated levels of CGRP observed during a migraine attack are normalized by sumatriptan, with concurrent relief of the migraine. Although still under debate,[8,9] this neurogenic hypothesis has been the impetus for the search for h5-HT$_{1D}$ agonists that are selective over h5-HT$_{1B}$.[4]

Our efforts in the field of h5-HT$_{1D}$ selective agonists led to the discovery of ALX-0646 (**1**). This potent and selective ligand has a K_i of 8 ± 1 and 610 ± 147 nM for the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors, respectively.[10,11] It is currently in clinical trials for the treatment of acute migraine.[12]

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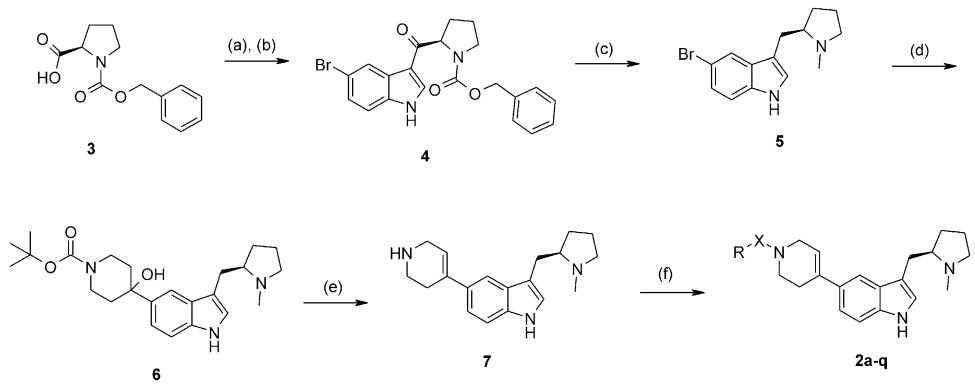
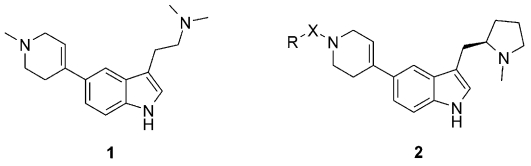


Scheme 1. (a) Oxalyl chloride, DMF, CH_2Cl_2; (b) 5-bromoindole, CH_2Cl_2; (c) $LiAlH_4$, THF, Δ; (d) ^{t}BuLi, THF, −78 °C, then *N*-Boc-4-piperidone; (e) 30% TFA/CH_2Cl_2, Δ; (f) RNCO, CH_2Cl_2, or RNCS, CH_2Cl_2, or RSO_2Cl, Et_3N, CH_2Cl_2.

Table 1. Binding profile of series **2** at the cloned human 5-HT_{1B} and 5-HT_{1D} receptors

Compd	X	R	h5-HT_{1D} K_i (nM)[a]	h5-HT_{1B} K_i (nM)[a]	K_i (h5-HT_{1B})/ K_i (h5-HT_{1D})
Sumatriptan			3.4[3]	7.7[3]	2.2
2a	SO_2	4-MeOPh	0.76±0.27	14±3	19
2b	SO_2	1-Napthyl	0.88±0.16	23±5	26
2c	SO_2	4-MePh	0.80±0.19	17±5	21
2d	NHCO	4-ClPh	0.38±0.00	3.8±1.4	10
2e	NHCO	Cyclohexyl	3.0±1.8	14±5	4.6
2f	NHCO	1-Adamantyl	4.0±1.1	11±4	2.8
2g	NHCO	Ph	0.45±0.10	4.8±1.2	11
2h	NHCO	4-MeOPh	0.42±0.01	4.2±0.8	10
2i	NHCO	4-MePh	0.31±0.00	3.0±0.4	9.7
2j	NHCO	1-Napthyl	0.45±0.14	3.8±1.6	8.4
2k	NHCS	Cyclohexyl	2.0±0.8	13±5	6.3
2l	NHCS	1-Adamantyl	5.6±1.2	39±10	7.0
2m	NHCS	Ph	0.68±0.16	5.8±2.0	8.5
2n	NHCS	4-ClPh	0.56±0.12	1.5±0.4	2.7
2o	NHCS	4-MeOPh	0.46±0.02	2.4±0.6	5.2
2p	NHCS	4-MePh	0.38±0.06	1.5±0.3	3.9
2q	NHCS	1-Napthyl	0.70±0.18	3.2±0.6	4.6

[a] K_i values are reported as the mean of two independent determinations±SEM.



As a continuation of our efforts in this area, this paper describes the results of one of our endeavors to investigate the effect of changing both the *N*,*N*-dialkylethylamine substituent at position 3 of the indole nucleus, and the substituent on the nitrogen of the tetrahydropyridine ring of **1**, providing compounds of the general structure **2**.

The series was prepared starting with (*R*)-*N*-Cbz-proline (**3**), the acid chloride of which was condensed with 5-bromoindole to yield ketone **4** (Scheme 1).[13,14] The ketone and the carbamate were simultaneously reduced with $LiAlH_4$. Lithium halogen exchange with three equivalents of ^{t}BuLi and trapping provided alcohol **6**. It was found to be unnecessary to protect the indole nitrogen prior to the lithiation. Treatment of **6** with TFA induced elimination and deprotection to provide the secondary amine **7**. This amine was reacted with various electrophiles in parallel to generate the compounds for this study (**2a–q**).

The receptor binding affinities of compounds **2a–q** are depicted in Table 1. All compounds reported here exhibited high affinity for the h5-HT_{1D} receptor, with K_i values ranging from 0.31 nM (compound **2i**) to 5.6 nM (compound **2l**). Selectivity over h5-HT_{1B} was modest, however, with compound **2b** having the best selectivity, an h5-$HT_{1B/1D}$ ratio of 26:1. Due to this, the functional activity of this series of compounds was not investigated. There was no significant difference between the ureas and thioureas, while the sulphonamides were typically less potent but more selective. The affinities of the compounds were not found to be particularly sensitive to the nature of the lipophilic R group; however, aromatic groups were somewhat preferred over aliphatic groups.

While we failed in our initial goal to produce a series of h5-HT_{1D} ligands selective over h5-HT_{1B}, to date the efficacy of highly selective h5-HT_{1D} compounds has yet to be demonstrated in clinical trials. If the mechanism of action of triptan antimigraine drugs is indeed due to a direct vasoconstrictive effect rather than, or in addition

to, inhibition of neuropeptide release, then some combination of h5-$HT_{1B/1D}$ activity is in fact desirable.[15]

In summary, a series of highly affinitive h5-$HT_{1B/1D}$ ligands have been identified using parallel synthesis techniques. Several compounds with subnanomolar affinity for the human 5-HT_{1D} receptor were developed.

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