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3-(2-Pyrrolidin-1-ylethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives as high affinity human 5-HT$_{1B/1D}$ ligands

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Abstract—A series of 3-(2-pyrrolidin-1-ylethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives (**2**) has been prepared using parallel synthesis techniques, and their structure–activity relationships studied. High affinity human 5-HT$_{1B/1D}$ (h5-HT$_{1B/1D}$) ligands have been identified.
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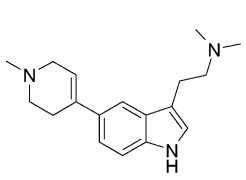
Migraine is a serious and debilitating disease with profound economic impacts. Over 200 million people worldwide suffer from at least occasional migraine attacks. The experience of these episodes varies, but can typically be characterized by intense unilateral headache pain, often accompanied by secondary symptoms including nausea and vomiting, photophobia, and phonophobia.[1,2] The prototypical pharmacotherapy for migraine is sumatriptan. It is a mixed 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] Sumatriptan is contraindicated in patients with coronary heart disease, as it can cause coronary artery constriction leading to angina-like effects.[4,5] It also possesses poor oral bioavailability and a limited half-life, leading to a tendency for the migraine attack to reoccur. These liabilities have left room for the introduction of several new antimigraine triptans. While these 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]

There are abundant levels of functional 5-HT$_{1B}$ receptors in vascular smooth muscle. This has led to the hypothesis that activity at this receptor might underlie the vasoconstrictive effects of the triptans, as many of these drugs are potent 5-HT$_{1B}$ agonists. Both 5-HT$_{1B}$ and 5-HT$_{1D}$ are found in human trigeminal ganglia. Electrical stimulation of the trigeminal nerves induces release of neuropeptides such as calcitonin gene-related peptide (CGRP). CGRP levels are found to be elevated during a migraine attack, and these levels are normalized by sumatriptan. Subsequently, plasma protein extravasation into the dura occurs, resulting in vasodilation, inflammation and pain. 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 h5-HT$_{1D}$ and h5-HT$_{1B}$ respectively, with a h5-HT$_{1B}$/h5-HT$_{1D}$ ratio of 76.[10,11] It is currently in development for the acute treatment of migraine.[12]



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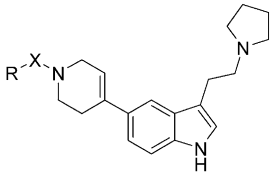

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As a continuation of our efforts in this field,[13] this paper relates the results of one of our endeavors to determine the effect of changing both the *N*,*N*-dialkylethylamine

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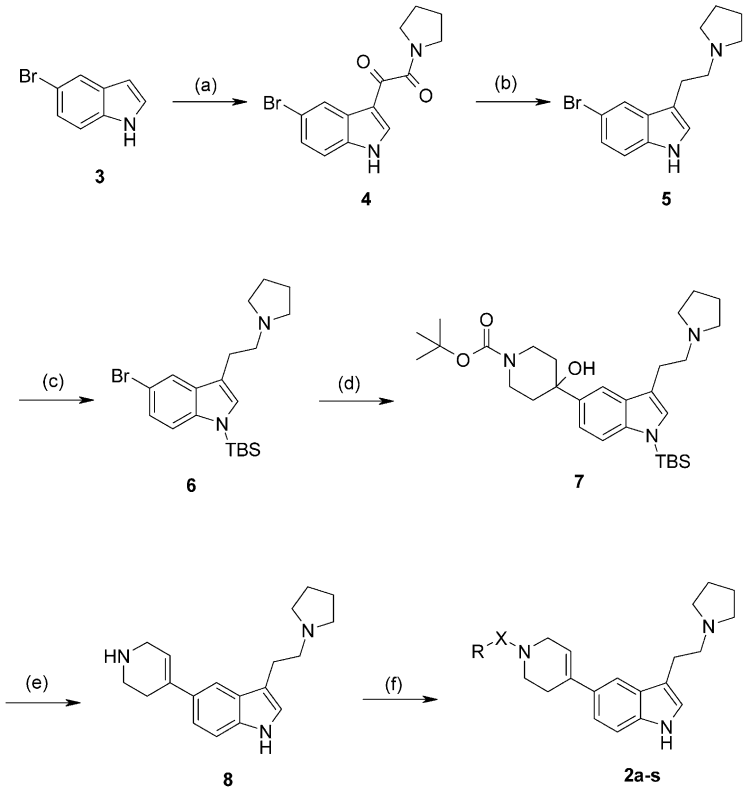

Scheme 1. (a) Oxalyl chloride, DMF, CH_2Cl_2, then pyrrolidine; (b) $LiAlH_4$, THF, Δ; (c) NaHMDS, TBSCl, DMF, 0 °C; (d) *t*BuLi, THF, −78 °C, then *N*-Boc-4-piperidone; (e) 30% TFA/CH_2Cl_2, Δ; (f) RNCO, CH_2Cl_2, or RNCS, CH_2Cl_2, or RSO_2Cl, Et_3N, CH_2Cl_2.

Table 1. Binding profile of series **2** at the cloned human h5-HT_{1B} and h5-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]	
2a	SO_2	4-MeOPh	11±0	140±40	13
2b	SO_2	1-Napthyl	27±0	410±100	15
2c	SO_2	4-ClPh	9.3±0.7	110±20	12
2d	SO_2	4-MePh	12±2	140±20	12
2e	SO_2	Ph	21±2	440±150	21
2f	NHCO	4-ClPh	6.1±2.6	82±18	13
2g	NHCO	cyclohexyl	29±9	130±0	4.4
2h	NHCO	1-Adamantyl	29±7	64±6	2.2
2i	NHCO	Ph	8.6±1.0	40±3	4.6
2j	NHCO	4-MeOPh	7.8±0.4	44±12	5.6
2k	NHCO	4-MePh	8.5±0.6	63±20	7.4
2l	NHCO	1-Napthyl	8.8±0.0	65±13	7.6
2m	NHCS	Cyclohexyl	11±0	38±8	3.5
2n	NHCS	1-Adamantyl	29±1	170±20	5.9
2o	NHCS	Ph	9.5±0.3	68±9	7.2
2p	NHCS	4-ClPh	12±2	36±8	3.0
2q	NHCS	4-MeOPh	6.2±1.5	58±8	9.3
2r	NHCS	4-MePh	7.4±0.6	32±4	4.4
2s	NHCS	1-Napthyl	16±2	95±1	6.0
8	H		74±6	760±40	10

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

substituent at position 3 of the indole nucleus, and the substituent on the nitrogen of the tetrahydropyridine ring of **1**, yielding compounds of the general structure **2**. Compounds for this study were prepared from 5-bromoindole as illustrated in Scheme 1. 5-Bromoindole (**3**) was acylated at the 3-position with oxalyl chloride, and the intermediate acid chloride was trapped in situ with pyrrolidine to provide the α-carbonyl amide **4**.[14] Following reduction with excess of $LiAlH_4$ and protection of the indole nitrogen,[15] lithium-halogen exchange and trapping with *N*-Boc-4-piperidone yielded the tertiary alcohol **7**.[16] Treatment of this compound with trifluoroacetic acid (TFA) simultaneously eliminated the alcohol, and removed the TBDMS and *t*-butoxycarbonyl protecting groups to provide the key intermediate **8**,[17] from which all of the compounds in this

series could be synthesized using standard parallel synthesis acylation techniques.[18]

The affinities of the compounds **2a**–**s** and the intermediate **8** for the cloned human 5-HT_{1B} and 5-HT_{1D} receptors are depicted in Table 1.[19] All final compounds reported here exhibited good affinity for the h5-HT_{1D} receptor, with K_i values ranging from 6.1 to 29 nM for compounds **2f** and **2h** respectively. Selectivity over h5-HT_{1B} was modest however, the best compound having an h5-HT_{1B}/h5-HT_{1D} ratio of 21:1 (compound **2e**). As a result, functional activity of this class of ligands 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. Smaller alkyl groups provided compounds with weak affinity (% inhibition data only, not shown), suggesting that the substituent at this position might be interacting with a hydrophobic pocket within the receptor. Compound **8**, where the substituent on the nitrogen was merely a hydrogen atom, exhibited an order of magnitude drop in affinity for both receptors.

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

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16. A solution of **6** (1.07 g, 2.63 mmol) in anhydrous THF (20 mL) was chilled in a dry ice/acetone bath. A 1.7 M solution of *t*-butyllithium in pentane (3.8 mL, 6.56 mmol) was added dropwise. After 1 h a solution of 4-oxopiperidine-1-carboxylic acid *t*-butyl ester (1.12 g, 5.65 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to room temperature. After 2 h the reaction was quenched with pH 7 buffer and extracted with EtOAc. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (1% NH_4OH, 4% MeOH, 95% CH_2Cl_2) provided **7** (0.67 g, 48%) as a yellow oil. **7:** ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 6H), 0.91 (s, 9H), 1.48 (s, 9H), 1.78–1.83 (m, 5H), 1.95–2.18 (m, 3H), 2.61 (s, 4H), 2.74 (t, 2H), 2.90 (t, 2H), 3.30 (t, 2H), 4.00 (br s, 2H), 6.98 (s, 1H), 7.28 (d, 1H), 7.42 (d, 1H), 7.70 (s, 1H).
17. Indole **7** (0.67 g, 1.27 mmol) was dissolved in CH_2Cl_2 (7 mL) and trifluoroacetic acid (3 mL). The solution was refluxed for 21 h, then cooled and washed with 1 M NaOH. The organic phase was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (1% NH_4OH, 2% MeOH, 97% CH_2Cl_2) provided **8** (113 mg, 30%) as an off-white solid. **8:** ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (t, 4H), 2.50 (t, 2H), 2.59 (t, 4H), 2.80 (t, 2H), 2.99 (t, 2H), 3.15 (t, 2H), 3.58 (t, 2H), 6.13 (s, 1H), 7.02 (s, 1H), 7.23–7.31 (m, 2H), 7.62 (s, 2H), 7.97 (br s, 1H).
18. As a representative procedure, **8** (20 mg, 0.068 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). 1-Napthyl isocyanate (9.7 μL, 11 mg, 0.068 mmol) was added. After 4 h a drop of methanol was added and the reaction mixture was concentrated to provide **2l** in quantitative yield. **2l:** ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 4H), 2.62 (s, 4H), 2.75 (s, 2H), 2.83 (t, 2H), 3.04 (t, 2H), 3.85 (t, 2H), 4.30 (s, 2H), 6.09 (s, 1H), 6.76 (s, 1H), 7.01 (s, 1H), 7.28–7.33 (m, 1H), 7.42–7.58 (m, 2H), 7.60–7.69 (m, 2H), 7.76 (d, 1H), 7.82–7.95 (m, 2H), 8.22 (s, 1H).
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