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Discovery of selective *N*-[3-(1-methyl-piperidine-4-carbonyl)-phenyl]-benzamide-based 5-HT$_{1F}$ receptor agonists: Evolution from bicyclic to monocyclic cores

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ABSTRACT

Preclinical experiments and clinical observations suggest the potential effectiveness of selective 5-HT$_{1F}$ receptor agonists in migraine. Identifying compounds with enhanced selectivity is crucial to assess its therapeutic value. Replacement of the indole nucleus in **2** (LY334370) with a monocyclic phenyl ketone moiety generated potent and more selective 5-HT$_{1F}$ receptor agonists. Focused SAR studies around this central phenyl ring demonstrated that the electrostatic and steric interactions of the substituent with both the amide CONH group and the ketone C=O group play pivotal roles in affecting the adopted conformation and thus the 5-HT$_{1F}$ receptor selectivity. Computational studies confirmed the observed results and provide a useful tool in the understanding of the conformational requirements for 5-HT$_{1F}$ receptor agonist activity and selectivity. Through this effort, the 2-F-phenyl and *N*-2-pyridyl series were also identified as potent and selective 5-HT$_{1F}$ receptor agonists.

Serotonin (5-hydroxytryptamine, 5-HT), a neurotransmitter widely distributed in the brain and peripheral tissue, produces its effects through a variety of membrane-bound receptors.[1–3] Among these 5-HT receptors, the 5-HT$_1$ class of receptors appears to be the most complex and has been further classified into 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$ and 5-HT$_{1F}$ subtypes.[4–6] The 5-HT$_{1F}$ receptor was first identified and cloned in 1993.[5,6] The mRNA for the human receptor protein has been identified in the brain, mesentery and uterus. Based on the localization of the 5-HT$_{1F}$ receptor, a number of therapeutic indications have been proposed for both agonists and antagonists at this receptor.[7–11] One proposed indication for the 5-HT$_{1F}$ receptor agonists is the treatment of acute migraine.

Sumatriptan (**1**) was the first 5-HT$_1$ receptor agonist marketed for the clinical treatment of migraine, and has high affinity for 5-HT$_{1B}$, 5-HT$_{1D}$ and 5HT$_{1F}$ receptors (Fig. 1).[7] LY334370 (**2**), a potent and selective 5-HT$_{1F}$ receptor agonist,[12–15] is also clinically effective in ending migraine attacks.[16,17] Unlike sumatriptan and other 5-HT$_{1B/1D}$ receptor agonist 'triptans', selective 5-HT$_{1F}$ receptor agonists do not contract the rabbit saphenous vein, an effect that correlates well with contractile responses in the human coronary artery.[18,19] This indicates that the anti-migraine effect may be achieved through 5-HT$_{1F}$ activation, and thus avoid cardiovascular side-effects caused by 5-HT$_{1B/1D}$ activation.[10] However, LY334370, like the 'triptans', possesses an indole core structure, and also has appreciable 5-HT$_{1A}$ receptor affinity (K_i = 22.1 nM), a possible cause for observed adverse effects such as asthenia, dizziness and somnolence.

The goal of subsequent SAR studies was to improve 5-HT$_{1F}$ receptor selectivity while maintaining high 5-HT$_{1F}$ receptor binding affinity and intrinsic efficacy. We chose to focus on identifying 5-HT$_{1F}$ receptor agonists without the indole nucleus which could provide opportunities to improve selectivity over indole derivatives and further differentiate from known triptans. We have previously reported that pyrrolo[3,2-*b*]pyridine,[20] furo[3,2-*b*]pyridine,[21] indazole and 'inverted' indazole, benzo[*d*]isoxazole[22] systems can serve as replacements for the central indole ring and provide potent and selective 5-HT$_{1F}$ receptor agonists.

In the synthesis of the previously reported indazole analogs,[22] oxidative cleavage of the indole ring in LY334370 (**2**) followed by hydrolysis provided compound **3** (Scheme 1). Interestingly, this

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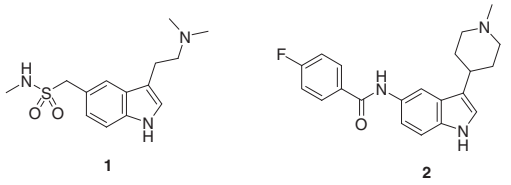
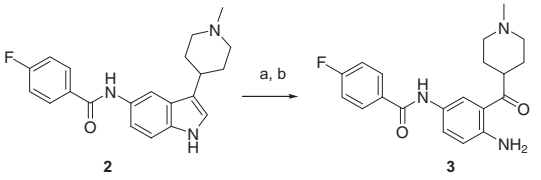


Figure 1. Structures of sumatriptan (**1**) and LY 334370 (**2**).

compound showed nanomolar affinity at the 5-HT_{1F} receptor (K_i = 64 nM). This finding prompted us to study the effects of central indole ring replacement with a mono-cyclic aromatic moiety on 5-HT_{1F} receptor binding affinity and selectivity.

The 4-fluoro-*N*-(3-(1-methyl-piperidine-4-carbonyl)-phenyl)-benzamide (**8**) was synthesized from bromoaniline **4** (Scheme 2). Protection of the amino group of **4** followed by lithium-bromo exchange generated an anion which was reacted with Weinreb amide **5** to provide intermediate **6**. Hydrolysis of **6** followed by acylation generated compound **8**. Different synthetic approaches were used to prepare the substituted phenyl analogs (Schemes 3 and 4). The phenyl anions obtained through either mono-lithium-bromo exchange (for **9a**,**c**–**e**) of dibromo compounds, or selective deprotonation[11] of **9f**, were treated with Weinreb amide **5** to provide **10a**,**c**–**f**. Buchwald reactions followed by hydrolysis generated the corresponding amines **11a**,**c**–**f**. Treatment of amines **11a**,**c**–**f** with 4-fluorobenzoyl chloride provided **12a**, **c**–**f**. Demethylation of **12a** with



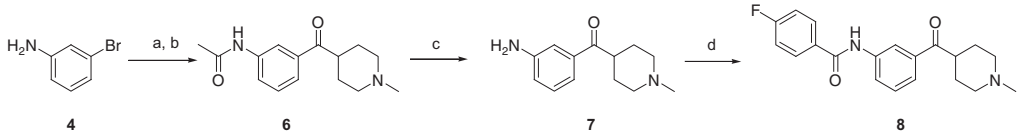
Scheme 1. Reagents and conditions: (a) $NaIO_4$, MeOH, room temp, 51%; (b) 5 N NaOH, MeOH, 45 °C, 51%.

BBr_3 yielded **12b**. Compound **15** was synthesized in three steps from 4-bromo-1-fluoro-2-nitrobenzene (**13**) (Scheme 4): reduction of the nitro group followed by acylation yielded compound **14**. Treatment of **14** with *n*-butyl lithium followed by Weinreb amide **5** provided compound **15**. For compound **18**, analogous to the approach in Scheme 3, 1-bromo-4-fluorobenzene (**16**) was converted to intermediate **17**[23], which was further transformed into **18** through a Buchwald-hydrolysis-acylation sequence.

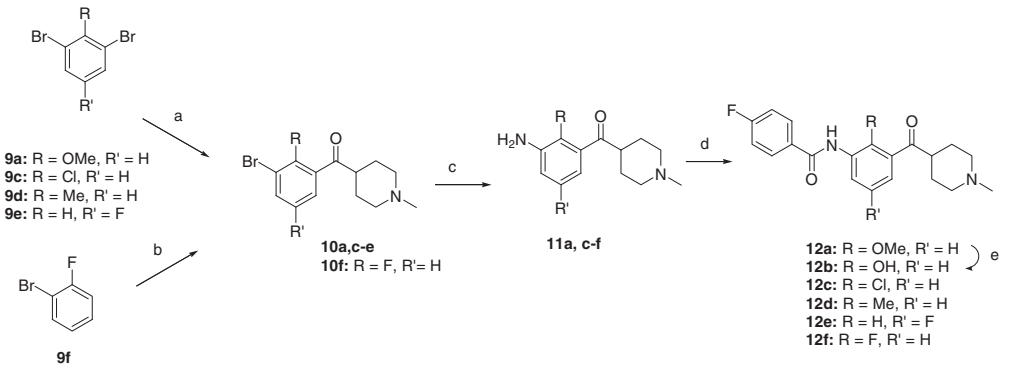
The pyridyl analogs were synthesized according to Scheme 5. The halo-pyridinyl-(1-methyl-piperidin-4-yl)-methanones **20a**–**b** and **23a**–**b** were obtained from either halo-pyridines **19a**–**b** or halo-pyridine carboxylic acids **22a**–**b**. Conversion of the halo groups to the amino groups through Buchwald amination followed by acylation afforded **21a**–**b** and **24a**–**b**.

The binding affinity of this series for the 5-HT_{1F}, receptor as well as selectivity ratio over 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is reported in Table 1. The unsubstituted parent compound **8** showed high affinity at the 5-HT_{1F} receptor and increased selectivity at the 5-HT_{1A} receptor than LY334370 (**2**). With this positive result, a focused SAR was conducted to explore the substituent-based effects on the preferred conformation of the new series so that it would mimic the more rigid conformation of compound **2** to have a strong binding affinity to the 5-HT_{1F} receptor, yet be structurally different enough to have improved receptor selectivity. Considering the strong electronegativity of the fluorine atom, it was hypothesized that its incorporation would change the electron density distribution of the molecule, favoring certain conformations over others.[24,25] Thus a fluorine walk around the central phenyl ring was performed (**12e**,**f**, **15**, **18**) and the results indicated that the 2-position of the phenyl ring would be an important position to explore. Interestingly, substitution with other groups (**12a**–**d**) at the 2-position all resulted in the loss of binding affinity at the 5-HT_{1F} receptor.

Conformational analysis of these compounds indicates that there are four distinctive low-energy conformations, *cis*–*trans* (*ct*), *cis*–*cis* (*cc*), *trans*–*trans* (*tt*) and *trans*–*cis* (*tc*) (Fig. 2).[26] The ab initio calculations at B3LYP/6-31G* level of theory using Gaussian 98[27] reveal that for compound **12f**, the *ct* form is the



Scheme 2. (a) AcCl, Et_3N, THF, room temp, 16 h, 75%; (b) MeLi, THF, −78 °C; then *t*-BuLi, 1-methyl-piperidine-4-carboxylic acid methoxy-methyl-amide (**5**), 81%; (c) 6 N HCl, reflux, 1.75 h, 76%; (d) 4-fluorobenzoyl chloride, Et_3N, THF, room temp, 98%.



Scheme 3. (a) *n*-BuLi, −78 °C, **5**, 21–80%; (b) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, **5**, −78 °C, 35%; (c) (i) benzophenone imine, *t*-BuONa, $Pd_2(dba)_3$, BINAP, 80 °C, 8 h; (ii) 1 M HCl, THF, 1 h; two-step: 37–80%; (d) 4-fluorobenzoyl chloride, dioxane, reflux, 3 h, 69–99%; (e) BBr_3, $CHCl_3$, 0 °C, 1.5 h, 60%.