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Substituted furo[3,2-*b*]pyridines: novel bioisosteres of 5-HT$_{1F}$ receptor agonists

Brian M. Mathes,[a,*] Kevin J. Hudziak,[a] John M. Schaus,[a] Yao-Chang Xu,[a] David L. Nelson,[a] David B. Wainscott,[a] Suzanne E. Nutter,[a] Wendy H. Gough,[a] Theresa A. Branchek,[b] John M. Zgombick[b,†] and Sandra A. Filla[a,‡]

[a]*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*
[b]*Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, NJ 07652, USA*

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Abstract—Synthesis and evaluation of a series of 2,3,5- and 3,5-substituted furo[3,2-*b*]pyridines were undertaken in order to investigate their utility as bioisosteres of 5-HT$_{1F}$ receptor agonist indole analogues, **1**–**3**. The replacement proved to be effective, providing compounds with similar 5-HT$_{1F}$ receptor affinity and improved selectivity when compared with the indole analogues. Through these studies we identified 4-fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-furo[3,2-*b*]pyridin-5-yl]-benzamide (**5**), a potent and selective 5-HT$_{1F}$ receptor agonist with the potential to treat acute migraine.

Serotonin (5-HT) is a neurotransmitter involved in the regulation of a number of physiological functions in the central nervous system and peripheral tissues.[1] Molecular cloning has identified seven 5-HT receptor subfamilies (5-HT$_1$–5-HT$_7$), subdivided based on receptor sequence homology, coupling to second messengers, and physiological effects. The 5-HT$_1$ receptor family has been further sub-classified into the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$ and 5-HT$_{1F}$ receptor subtypes.[2] Sumatriptan was the first 5-HT$_1$ receptor agonist approved for the treatment of migraine.[3] Its clinical efficacy was initially attributed to its 5-HT$_{1B/1D}$ receptor agonist activities, in large part because it is a potent agonist at these receptor subtypes. However, sumatriptan is a potent 5-HT$_{1F}$ receptor agonist as well.[4] Receptor mapping studies have shown that the 5-HT$_{1D}$ receptor resides only in neural tissues, whereas the 5-HT$_{1B}$ is distributed throughout neural and vascular tissues.[5] Thus activation of the 5-HT$_{1B}$ receptor has been implicated as a cause of vasoconstrictive properties and subsequent adverse cardiovascular effects associated with sumatriptan and other 5-HT$_1$ receptor agonist triptans.[6]

Phebus and colleagues reported that a compounds affinity for the 5-HT$_{1F}$ receptor was correlated to its potency to inhibit dural plasma protein extravasation (PPE) following electrical stimulation of the trigeminal ganglion in the guinea pig, an effect predictive of clinical efficacy to ameliorate migraine symptoms.[7] This correlation suggested that a potent and selective 5-HT$_{1F}$ receptor agonist might be a novel anti-migraine therapeutic devoid of the cardiovascular liabilities of non-selective 5-HT$_1$ agonist triptans. We have previously reported several 3-alkylamino-5-arylamido-indole analogues as potent and selective 5-HT$_{1F}$ receptor agonists.[8,9,10] Compound **1** (LY334370) exhibited high 5-HT$_{1F}$ receptor affinity and selectivity over the 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors, but showed appreciable affinity for the 5-HT$_{1A}$ receptor (Table 1). This compound was efficacious in the PPE migraine model[4] and was clinically effective in treating migraine pain.[11] Subsequent SAR studies focused on improving 5-HT$_{1F}$ receptor selectivity while maintaining high 5-HT$_{1F}$ receptor binding affinity and intrinsic agonist efficacy. Replacing the indole nucleus with pyrrolo[3,2-*b*]pyridine, providing **2**, resulted in a 5-fold decrease in 5-HT$_{1F}$ receptor affinity (Table 1).[9] While this analogue was more selective over the 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors than **1**, it showed no improvement in its selectivity over the 5-HT$_{1A}$ receptor. On the other hand, investigation of a series of C-5 arylamido tryptamines identified **3**, which

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* Corresponding author. Tel.: +1-317-277-7720; fax: +1-317-276-7600; e-mail: mathes_brian_m@lilly.com
† Deceased, 8 November 2002.
‡ E-mail: filla_sandra_a@lilly.com

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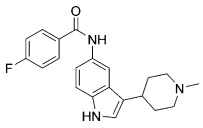
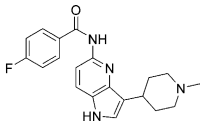
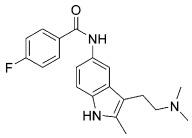
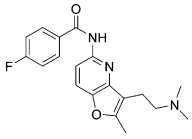
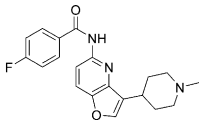
Table 1. Comparison of the 5-HT_{1F} receptor binding affinity and selectivity of 5-arylamido analogues of **1**[a]

Structure	Cpd	5-HT_{1F} K_i (nM)	5-HT selectivity ratio[b] 1A/1F	1B/1F	1D/1F
	**1**	1.6 (±0.4)	7	85	86
	**2**	7.6 (±1.2)	7.3	160	960
	**3**	8.2 (±1.2)	32	130	200
	**4**	13.5 (±1.8)	65	42	19
	**5**	3.1 (±0.7)	134	>1000	>1000

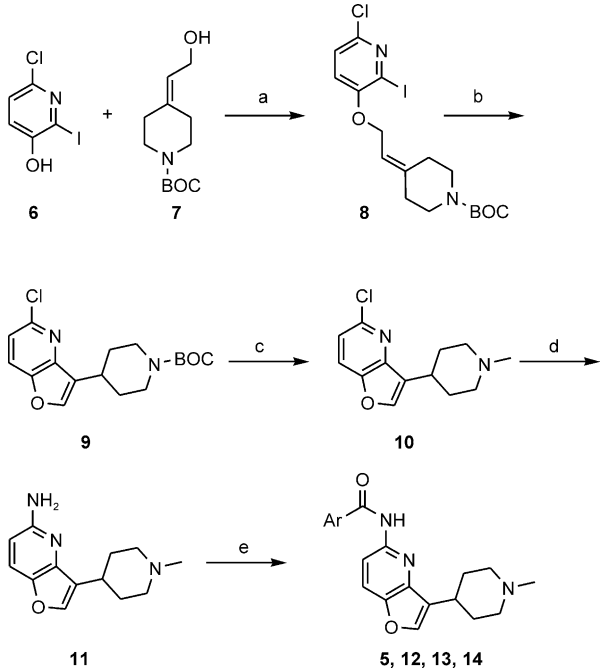
[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human 5-HT receptor.[21–23] Values are means of three or more experiments, SEM is given in parentheses.

[b] Ratio of the K_i value (derived from two or more experiments) for the 5-HT_{1A}, 5-HT_{1B} or 5-HT_{1D} receptor versus the 5-HT_{1F} receptor.

in addition to increased selectivity over the 5-HT_{1B} and 5-HT_{1D} receptors, also demonstrated a marked improvement in selectivity over the 5-HT_{1A} receptor.[10] However, this compound, like **2**, also showed a 5-fold decrease in 5-HT_{1F} receptor binding affinity when compared to **1**.

As a continuation of our efforts in this area, we were interested in investigating furo[3,2-*b*]pyridine as a bioisostere of the indole nucleus. Furo[3,2-*b*]pyridine retains the geometric and conformational attributes of indole, but has differing physicochemical and electronic properties that may result in differences in 5-HT receptor subtype recognition and subsequent activation. There have been few reports regarding the successful replacement of indole with benzofuran.[12–15] Typically, benzofuran isosteres of ligands targeting serotonergic receptors exhibited decreased biological activity relative to the indole analogues. However, these reports also noted that there were 5-HT receptor subtype selectivity differences with this bioisosteric replacement. Russell et al. reported that the benzofuran analogue of 5-carboxamidotryptamine demonstrated reduced 5-HT_{1A} and 5-HT_{1D} receptor binding affinities but increased 5-HT_{2A} receptor affinity, when compared with the indole parent compound.[12] They proposed this biological variation to be based on differences between the preferred C-5 amide conformations of the indole versus the benzofuran analogues. Furthermore, Nichols and co-workers observed that the 5-HT_{1A} receptor was less discriminating than the 5-HT_2 subtype in its preference for 5-methoxy-*N*,*N*-dimethyltryptamine and 5-methoxy-α-methyltryptamine compared to their benzofuran analogues.[13] In an effort to optimize for 5-HT_{1F} receptor affinity and selectivity, we considered that a bioisosteric replacement of this type might lead to variability between the 5-HT_1 receptor subtype affinities. We found no reports in the literature discussing the effect of bioisosteric replacements of the indole nucleus on a ligands 5-HT_{1F} receptor affinity. Thus, we investigated the bioisosteric replacement of furan for the pyrrole ring of the pyrrolo[3,2-*b*]pyridine nucleus, targeting compounds **4** and **5**. This report describes the synthesis and SAR studies of these compounds.

We recently disclosed the synthesis of the C-3 *N*,*N*-dimethylaminoethyl furo[3,2-*b*]pyridine analogue **4**.[16] Compounds **5**, **12**, **13**, and **14** were prepared in a similar fashion, using the six step synthesis shown in Scheme 1. Beginning with iodopyridine **6**,[16] a Mitsunobu coupling with **7**[17] yielded iodo aryl allyl ether intermediate **8**. Palladium-promoted cyclization, utilizing the method described by Larock,[18] afforded furo[3,2-*b*]pyridine **9** in moderate yield. Studies suggested that the piperidine nitrogen of the acylic precursor must be non-basic, as is in the case of the *N*-Boc-protected allyl ether **8**, in order for cyclization to be effected to any appreciable extent. For example, attempts to cyclize the analogous *N*-methyl or *N*-H substituted analogues of **8** resulted in very low isolated yields (ca. 10%) of cyclized product. Reduction of the Boc protecting group of **9** to the desired methyl group with $LiAlH_4$ provided **10**. The C-5



Scheme 1. Reagents and conditions: (a) PPh_3, DEAD, THF, room temp, 89%; (b) $Pd(OAc)_2$, Na_2CO_3, *n*-Bu_4NCl, NaO_2CH, DMF, 80 °C, 60%; (c) $LiAlH_4$, Et_2O, 35 °C, 61%; (d) (i) benzophenone imine, $Pd_2(dba)_3$, (±)-BINAP, NaO*t*Bu, toluene, 80 °C; (ii) 1 N HCl/THF (1:1), room temp, 73% (two steps); (e) ArCOCl, pyridine, 55 °C.

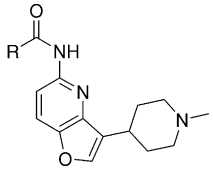
chloro substituent was converted to the corresponding amine **11** utilizing a palladium-mediated amination procedure that employed benzophenone imine as an ammonia equivalent, followed by acid hydrolysis.[19,20] Acylation of the C-5 amine, providing **5**, **12**, **13**, and **14**, completed the synthesis.

Given the favorable 5-HT_{1F} receptor selectivity profile of tryptamine **3** versus C-3 piperidinyl analogues **1** and **2**, we initially targeted C-3 *N,N*-dimethylaminoethyl furo[3,2-*b*]pyridine **4** for study. Evaluation of the 5-HT_1 receptor binding affinities of **4** indicated that like the pyrrolo[3,2-*b*]pyridine analogue **2**, this compound also exhibited decreased 5-HT_{1F} receptor affinity, and in fact was about 2-fold less potent than **2** (Table 1). In addition, **4** showed less selectivity over the 5-HT_{1B} and 5-HT_{1D} receptors when compared to either **1** or **2** or tryptamine analogue **3**. On the other hand, this compound was more selective for the 5-HT_{1F} receptor versus the 5-HT_{1A} receptor than **1**–**3**. We subsequently evaluated the C-3 piperidinyl-furo[3,2-*b*]pyridine **5**. Surprisingly, this analogue demonstrated a notable increase in 5-HT_{1F} receptor binding affinity when compared with any of the other analogues of **1**. Moreover, **5** was also markedly more selective for the 5-HT_{1F} receptor versus the other 5-HT_1 receptor subtypes tested, including the 5-HT_{1A} receptor. We further evaluated the 5-arylamido-3-piperidinyl-furo[3,2-*b*]pyridine series by preparing **12**, **13**, and **14** (Table 2). Like **5**, these compounds also demonstrated high 5-HT_{1F} receptor binding affinity. While they demonstrated decreased selectivity over the other 5-HT_1 receptors as compared to **5**, they were nevertheless more selective for the 5-HT_{1F} receptor, particularly versus the 5-HT_{1A} receptor, when compared to the indole analogues in Table 1. All of these compounds showed good intrinsic efficacy in the 5HT_{1F} GTP-γ-S functional assay, and were full agonists at the 5-HT_{1F} receptor.

Evaluation of the furo[3,2-*b*]pyridine nucleus as a bioisosteric replacement for indole identified a novel series of 5-arylamido-3-piperidinyl-furo[3,2-*b*]pyridines. These studies demonstrated that the 5-HT_{1F} receptor was less discriminating in its preference for the indole nucleus versus the furo[3,2-*b*]pyridine nucleus, as compared to other 5-HT_1 receptor subtypes, and in particular the 5-HT_{1A} receptor. This difference in selectivity suggested that there is perhaps a significant interaction between the indole NH and the receptor of some 5-HT_1 receptor subtypes that is not present in the case of the 5-HT_{1F} receptor–ligand interaction. Alternatively, the conformational preference of the C-5 amide of the furo[3,2-*b*]pyridine and indole analogues may differ, and the 5-HT_{1F} receptor may preferentially favor the low energy conformation of the furo[3,2-*b*]pyridine analogue.

We have identified a clear difference in the 5-HT_1 receptor subtype affinities of furo[3,2-*b*]pyridine biosiosteres versus those of the parent indole analogues. Thus, we have uncovered a novel approach to identify compounds with high affinity and selectivity for the 5-HT_{1F} receptor. From these SAR studies, we identified 4-fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-furo[3,2-*b*]pyridin-5-yl]-benzamide **5**, a novel, potent and selective 5-HT_{1F}

Table 2. Comparison of the 5-HT_{1F} receptor binding affinity, selectivity and functional activity of 5-arylamido-3-piperidinyl-furo[3,2-*b*]pyridine analogues[a]



		5-HT_{1F}	5-HT selectivity ratio			5-HT_{1F} GTP-γ-S	
Cpd	R	K_i (nM)	1A/1F	1B/1F	1D/1F	EC_{50} (nM)[b]	E_{max} (% 5-HT)[c]
5		3.1 (±0.7)	134	>1000	>1000	66.0 (±5.3)	88
12		2.3(±0.2)	57	181	62	91.7 (±1.5)	87
13		2.9 (±0.2)	103	164	31	68.7 (±7.5)	87
14		3.0 (±0.5)	47	177	165	27.7 (±1.0)	92

[a] See footnote of Table 1 for 5-HT receptor binding parameters.
[b] Stimulation of [^{35}S]GTP-γ-S binding in mouse LM(tk$^-$) cells expressing the human 5-HT_{1F} receptor.[24] Values are expressed as mean values from at least two separate experiments performed in triplicate, SEM is given in parentheses.
[c] Maximum stimulation of [^{35}S]GTP-γ-S binding expressed relative to the maximal effect of 5-HT.

receptor agonist that may have potential as a therapeutic for acute treatment of migraine.

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