Novel Potent 5-HT_{1F} Receptor Agonists: Structure−Activity Studies of a Series of Substituted *N*-[3-(1-Methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amides§

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Compound **1a** (LY334370), a selective 5-HT_{1F} receptor agonist (SSOFRA), inhibited dural inflammation in the neurogenic plasma protein extravasation model of migraine and demonstrated clinical efficacy for the acute treatment of migraine. Although **1a** was greater than 100-fold selective over both the 5-HT_{1B} and 5-HT_{1D} receptors, it exhibited appreciable 5-HT_{1A} receptor affinity. Described here is the synthesis and evaluation of a series of pyrrolo-[2,3-*c*]pyridine and pyrrolo[3,2-*b*]pyridine (**2a** and **3a**) as well as pyrrolo[3,2-*d*]pyrimidine (**4a**) analogues of **1a**, compounds prepared in an effort to identify SSOFRAs with improved selectivity over other 5-HT_1 receptor subtypes. The pyrrolo[3,2-*b*]pyridine analogue **3a** showed high 5-HT_{1F} receptor affinity but offered no improvement in selectivity compared to **1a**. However, the C-5 acetamide derivative, **3b**, was greater than 100-fold selective over the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors. SAR studies of this series determined that alkylamides in particular exhibited high selectivity for the 5-HT_{1F} receptor. Replacement at C-5 with other substituents decreased affinity or selectivity. These SAR studies identified SSOFRAs that demonstrated oral activity in the neurogenic plasma protein extravasation model, a model indicative of antimigraine activity.

Introduction

Sumatriptan, a nonselective 5-$HT_{1B/1D}$ agonist, is an effective therapeutic for the acute treatment of migraine.[1] The vasodilatory hypothesis of migraine suggests that the dilatation of cranial blood vessels is a primary cause of pain during migraine, and Sumatriptan's efficacy has been attributed to its ability to constrict cranial blood vessels.[2] Sumatriptan is also a potent vasoconstrictor of human arteries,[3] as are other 5-$HT_{1B/1D}$ agonists that have recently been developed. It and other agents within this triptan class of antimigraine compounds exhibit some effects that include dizziness, tingling, and chest tightness/pressure.[1] In addition, there have been reported incidences of coronary vasoconstriction, and the use of drugs such as Sumatriptan is contraindicated in patients with known heart disease.[4]

The mechanism of action of 5-HT_1 agonists in acute migraine treatment has been widely debated,[5] and the ability of these compounds to block dural inflammation mediated by trigeminal afferents might also account for their antimigraine activity. Stimulation of the trigeminal nerve results in vasodilatation and plasma protein extravasation in the dura, causing inflammation and pain. Inhibition of neuropeptide release and plasma protein extravasation in the dural membrane blocks neurogenic inflammation and central pain transmission, resulting in alleviation of migraine pain.[6] In fact, the triptans were all effective in blocking dural plasma protein extravasation (PPE) following electrical stimulation of the trigeminal ganglion in guinea pigs,[7] a model that, although controversial,[8] is believed to be predictive of clinical efficacy for migraine treatment.[9] This effect of the triptans is likely mediated through activation of the 5-HT_{1F} receptor. Phebus et al. reported a distinct correlation between a compound's potency in the PPE model and its affinity for the 5-HT_{1F} receptor but not other 5-HT_1 receptors.[9a] In addition, 5-HT_{1F} receptor agonists did not contract the rabbit saphenous vein,[10] an effect that correlated well with contractile responses in the human coronary artery.[11] Recent reports demonstrated that the 5-HT_{1B} receptor mediated vascular contractile responses to triptans[12] and supported the contention that it also mediated vascular responses in the rabbit saphenous vein,[11] suggesting that this receptor subtype was responsible for the triptans' vasoconstrictive properties. On the basis of these studies, we proposed that a compound selective for the 5-HT_{1F} receptor may provide an effective treatment for migraine without cardiovascular side effects. We have recently reported on the first of these SSOFRAs (selective serotonin one F receptor agonists).[13] Compound **1a** (LY334370) exhibited high affinity for the 5-HT_{1F} receptor as well as high selectivity over the 5-HT_{1B} and

§ Dedicated to our talented and energetic colleague, Dr. John Zgombick, 1958−2002.

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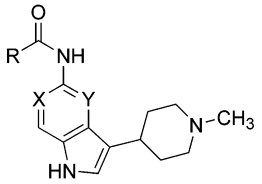
Table 1. Comparison of in Vitro Binding Affinities of 5-Acylaminopyrrolopyridine/Pyrrolopyrimidine Analogues vs 5-Acylaminoindole Analogues



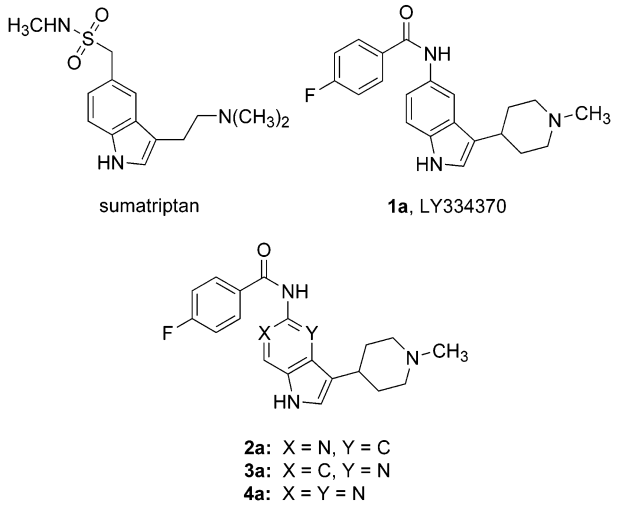
				binding affinity[a] K_i (nM)			
compd	R	X	Y	5-HT$_{1F}$	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$
1a	4-F-phenyl	C	C	2.1(0.6)	22(4.4)	240(33)	430(30)
2a	4-F-phenyl	N	C	13(1.2)	17(3.1)	80(6.4)	53(6.4)
3a	4-F-phenyl	C	N	7.6(1.0)	56(5.1)	1200(150)	730(9)
4a	4-F-phenyl	N	N	67(6.5)	200(31)	6000(540)	1900(270)
1b	methyl	C	C	9.7(2.3)	68(8.0)	390(18)	150(4.0)
2b	methyl	N	C	210(48)	2.0(1.0)	ND[b]	39(10)
3b	methyl	C	N	5.0(0.5)	620(37)	270(47)	250(38)
4b	methyl	N	N	220(37)	780(100)	2900(550)	470(65)

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

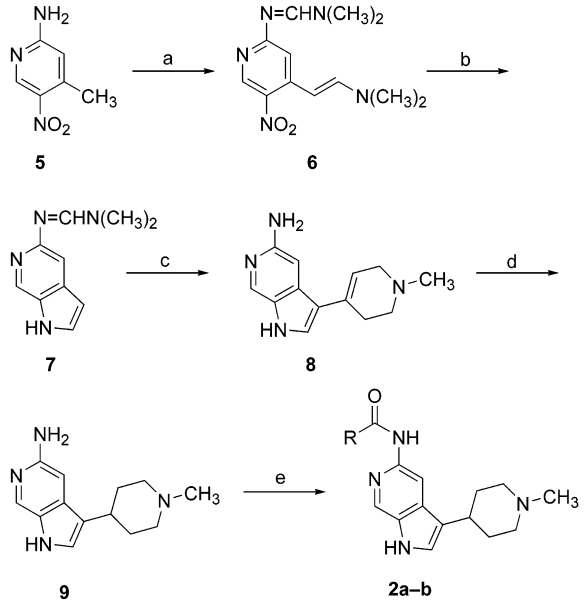
5-HT$_{1D}$ receptors, although it demonstrated appreciable affinity for the 5-HT$_{1A}$ receptor (Table 1).[14] It did not contract the rabbit saphenous vein, yet was effective in the PPE model of migraine.[9a,14b] Compound **1a** also significantly inhibited activation of second-order neurons in the trigeminal nucleus caudalus produced by electrical stimulation of the dura mater in rats, another well-accepted model of migraine.[15] In addition, **1a** demonstrated clinical efficacy as a treatment for migraine without the cardiovascular side effects observed with nonselective 5-HT$_1$ receptor agonists.[16]

Our subsequent focus in this program turned to identifying potential SSOFRAs with improved 5-HT receptor selectivity, particularly against the 5-HT$_{1A}$ receptor. As a continuation of our structure−activity relationship (SAR) studies, we proposed to survey replacement of the indole nucleus of **1a** with various pyrrolopyridine nuclei. Pyrrolopyridines retain the geometric and conformational attributes of indole but have different physicochemical properties, which may alter their biological activity. In addition to an additional heteroatom that itself may participate in a hydrogen-bonding interaction with the receptor, we anticipated that replacement of a carbon atom with nitrogen adjacent to the C-5 amide bond might impact the pK_a of the amide proton as well as potentially affect the conformation of this amide group (vide infra). We prepared 4-fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]benzamide (**2a**), 4-fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]benzamide (**3a**), and 4-fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]benzamide (**4a**) and determined the 5-HT receptor binding affinities of these analogues (Chart 1). From these studies, we identified a series of novel and highly selective 5-HT$_{1F}$ receptor agonists. We report here the synthesis of these compounds and their pharmacologic profiles and describe the SAR studies that led to the identification of potent and selective 5-HT$_{1F}$ receptor agonists with potential for acute treatment of migraine.

Chart 1



Scheme 1[a]

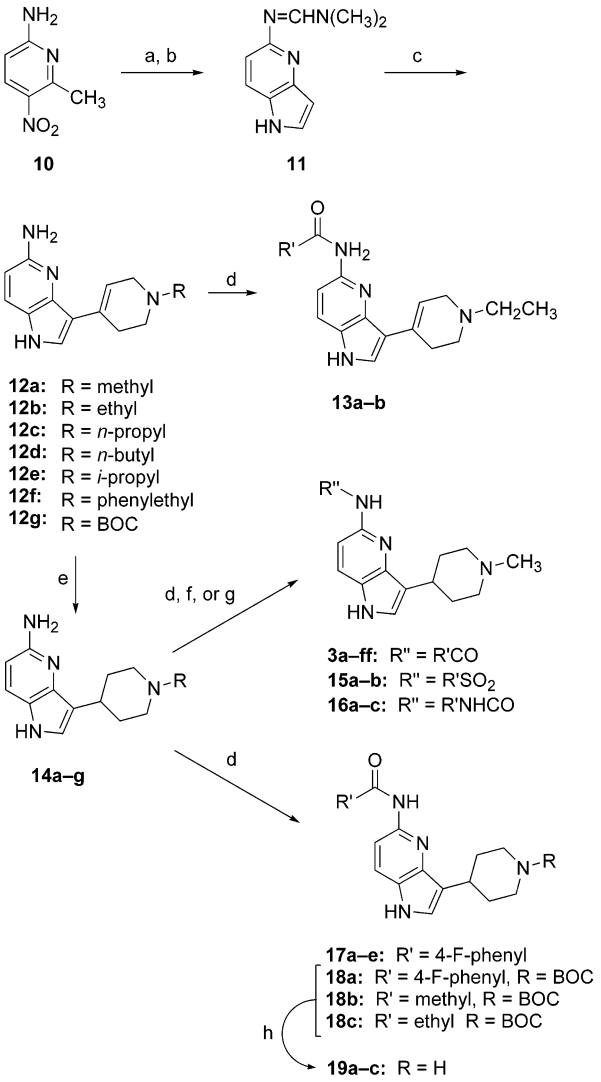


[a] Reagents: (a) DMFDMA, DMF, 110 °C; (b) 10% Pd/C, H_2 (40 psi), EtOH, room temp; (c) Na^0, MeOH, 1-methyl-4-piperidone, 75 °C; (d) 10% Pd/C, H_2 (60 psi), EtOH, 40 °C; (e) RCOCl, pyridine, room temp.

Chemistry

Each of the three 5-substituted pyrrolopyridine and pyrrolopyrimidine nuclei (**7**, **11**, and **24**) was prepared through a modified Batcho−Leimgruber indole synthesis. The preparation of the pyrrolo[2,3-*c*]pyridine derivatives is illustrated in Scheme 1. Treatment of 2-amino-4-methyl-5-nitropyridine **5** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in DMF provided eneamine **6**. Reductive cyclization (H_2, Pd/C) yielded the C-5 formamidine pyrrolo[2,3-*c*]pyridine nucleus **7**. Condensation of **7** with 1-methyl-4-piperidone in sodium methoxide/methanol introduced the 1,2,5,6-tetrahydropyridyl moiety at C-3 with concomitant hydrolysis of the C-5 amidine group, providing amine **8**. The desired 5-acylaminopyrrolo[2,3-*c*]pyridine analogues **2a**,**b** were subsequently prepared from **8** by hydrogenation of the olefin to **9** followed by acylation with the requisite acid chloride in pyridine.

Scheme 2[a]

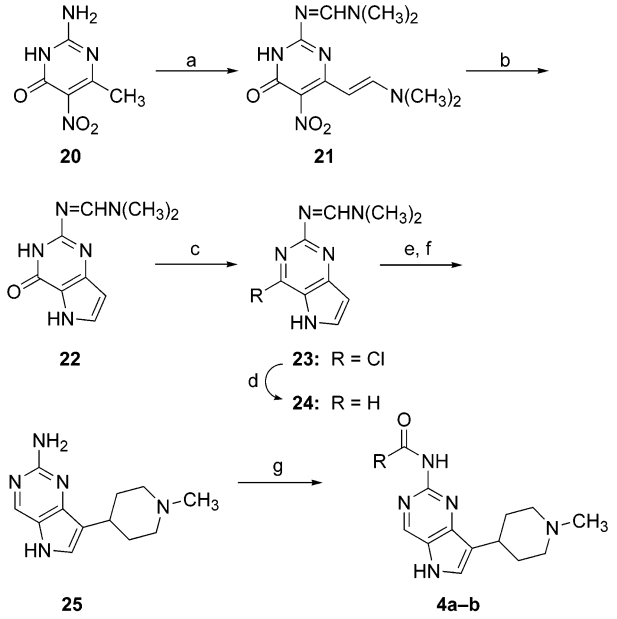


[a] Reagents: (a) DMFDMA, DMF, 110 °C; (b) 10% Pd/C, H_2 (40 psi), EtOH, room temp; (c) KOH, MeOH, 1-*R*-4-piperidone, 75 °C; (d) R′COCl, pyridine, 55 °C; (e) 10% Pd/C, H_2 (40 psi), THF/EtOH, room temp; (f) R′SO_2Cl, pyridine, 55 °C; (g) R′NCO, THF/DMF, room temp; (h) TFA, CH_2Cl_2, room temp.

The 5-substituted pyrrolo[3,2-*b*]pyridine nucleus **11** was synthesized in an analogous fashion starting with 2-amino-6-methyl-5-nitropyridine **10** (Scheme 2).[17] Condensation of **11** with an *N*-alkyl-4-piperidone or with 1-(*tert*-butoxycarbonyl)-4-piperidone under basic conditions provided 1,2,5,6-tetrahydropyridyl intermediates **12a**−**g**, which were either acylated at the C-5 amine to prepare derivatives **13a**,**b** or hydrogenated to yield the corresponding N-substituted piperidinyl C-5 amines **14a**−**g**. Reaction of the C-5 amine of **14a** (R = CH_3) with an acid chloride, sulfonyl chloride, or isocyanate provided amides **3a**−**ff**, sulfonamides **15a**,**b**, and ureas **16a**−**c**. Likewise, acylation of the other N-substituted piperidinyl C-5 amines **14b**−**g** using the same conditions provided analogues **17a**−**e** and **18a**−**c** (Scheme 2). The piperidine-BOC protecting group of compounds **18a**−**c** was subsequently removed with TFA to generate **19a**−**c**.

The preparation of the pyrrolo[3,2-*d*]pyrimidine analogues **4a**,**b** is described in Scheme 3. In this case, we opted to start with 2-amino-6-methyl-5-nitro-4(3*H*)-oxopyrimidine **20**,[18] since attempts to nitrate 2-amino-6-methylpyrimidine directly proved to be unsuccessful. This strategy necessitated removal of the undesired carbonyl functionality at some stage of the synthesis. Treatment of **20** with DMFDMA or DMFDEA resulted in formation of the desired C-6 eneamine but with appreciable amounts of N-3 alkylation. Use of tris(dimethylamino)methane, however, circumvented this problem, and compound **21** was isolated as the sole product. Reductive cyclization provided the 2-formamidino-9-deazaguanine intermediate **22**. The C-6 oxo group was removed in a two-step sequence. Halogenation with phosphorus oxychloride yielded **23** without loss of the C-2 amidine-protecting group. Hydrogenolysis then gave the pyrrolo[3,2-*d*]pyrimidine intermediate **24**. This compound was converted to the desired analogues **4**,**b** using the three-step sequence described previously. In this case, selective acylation of the C-2 amine of **25** proved to be difficult because of the electron-withdrawing character of the adjacent nitrogen atoms. Under optimized conditions, treatment of **25** with the requisite acid chloride in pyridine at 50 °C provided **4a**,**b** in modest yields, accompanied by some diacylated product as well as unreacted starting amine.

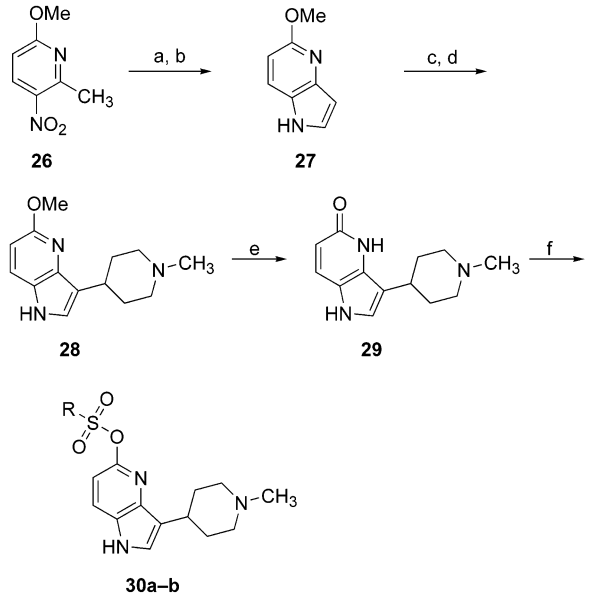
Scheme 3[a]



[a] Reagents: (a) $[(CH_3)_2N]_3CH$, DMF, 100 °C; (b) 5% Pd/C, H_2 (60 psi), THF/EtOH, room temp; (c) $POCl_3$, 115 °C; (d) 10% Pd/C, H_2 (40 psi), $NaHCO_3$, EtOH, room temp; (e) Na^0, MeOH, 1-methyl-4-piperidone, 75 °C; (f) 10% Pd/C, H_2 (60 psi), EtOH, room temp; (g) RCOCl, pyridine, 50 °C.

We replaced the C-5 amide with representative non-hydrogen-bond-donating groups to evaluate what role the N−H functionality at this position played in 5-HT_{1F} receptor binding. The compounds of interest were prepared from common intermediate 5-methoxypyrrolo[3,2-*b*]pyridine **27**, which was prepared in a manner analogous to the synthesis of **11**. Compound **27** was then subjected to standard conditions to provide **28**. Hydrolysis of the methyl ether with HBr/HOAc gave **29**, which was converted to sulfonate ester derivatives **30a**,**b** (Scheme 4).

Scheme 4[a]



[a] Reagents: (a) DMFDMA, Et_3N, DMF, 120 °C; (b) 10% Pd/C, H_2 (40 psi), EtOH, room temp; (c) KOH, MeOH, 1-methyl-4-piperidone, 75 °C; (d) 10% Pd/C, H_2 (40 psi), THF/EtOH, room temp; (e) HBr/HOAc, 105 °C; (f) $(RSO_2)_2O$ or RSO_2Cl, pyridine, 60 °C.

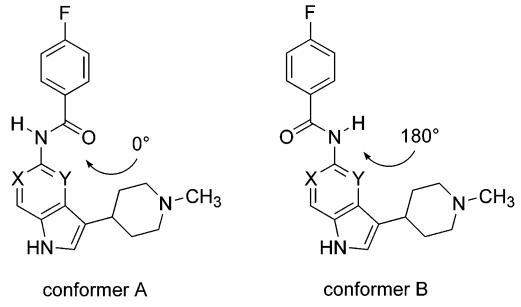
Pharmacology

Affinities of compounds for receptors, expressed in K_i (nM), were determined in vitro by radioligand binding assays using cell lines expressing the human 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$ receptors.[19−21] Intrinsic efficacy at the 5-HT$_{1F}$ receptor was evaluated in a cell-based measure of receptor activation via stimulation of [^{35}S]GTP-γ-S binding.[22] The vascular contractile effects of 5-HT$_{1F}$ agonists with high affinity and selectivity for the 5-HT$_{1F}$ receptor were assessed in vitro using ring preparations of rabbit saphenous vein.[10] Finally, compounds with minimal in vitro vascular contractile activity were tested in vivo in the guinea pig PPE model of migraine.[7,23] Unilateral stimulation of the trigeminal ganglia caused the release of inflammatory neuropeptides such as CGRP and substance P from the trigeminal nerve terminals, resulting in the leakage (extravasation) of plasma proteins labeled with Evan's blue fluorescent dye.[23] The inhibition of this extravasation was quantified by measurement of the ratio of fluorescence from the stimulated versus the unstimulated side of the dural tissue. Data are reported as a ratio of plasma protein extravasation on the stimulated versus unstimulated side.

Results and Discussion

Evaluation of Pyrrolopyridine and Pyrrolopyrimidine Analogues of 1a. Compounds **2a**, **3a**, and **4a**, the 4-fluorobenzamide analogues of **1a**, were screened at a number of 5-HT$_1$ receptor subtypes to compare their affinity and selectivity for the 5-HT$_{1F}$ receptor (Table 1). The pyrrolo[2,3-*c*]pyridine and the pyrrolo[3,2-*d*]-pyrimidine analogues (**2a** and **4a**) suffered diminished affinity and selectivity. On the other hand, the pyrrolo-[3,2-*b*]pyridine analogue **3a** showed a slight decrease in 5-HT$_{1F}$ receptor affinity compared with **1a** but retained selectivity. We further explored these nuclei

Chart 2



by comparing the C-5 acetyl analogues (**2b**, **3b**, and **4b**) with the corresponding indole derivative **1b** (Table 1). Again, we observed that the pyrrolo[3,2-*b*]pyridine analogue **3b** retained high affinity for the 5-HT$_{1F}$ receptor. Furthermore, this analogue possessed improved selectivity at the 5-HT$_{1A}$ receptor versus **1b** and in fact was more selective than **1a**, indicating that this new series may exhibit an improved pharmacologic profile over the indole series.

We sought to rationalize the effect of the nitrogen atom in the heterocyclic nuclei of **2a**, **3a**, and **4a** on the compounds' 5-HT receptor affinities. Assuming that each analogue bound to the receptor in a similar fashion with respect to the basic piperidine nitrogen and the heterocyclic moiety, the binding affinity differences could be ascribed to direct van der Waal or hydrogen-bonding interactions of the pyrrolopyridine or pyrrolopyrimidine nucleus with the receptor. This explanation was not satisfactory, however, in light of the data at hand. In both acylamino series tested, the pyrrolo[3,2-*b*]pyridine analogues (**3a** and **3b)** exhibited higher affinity at the 5-HT$_{1F}$ receptor than the pyrrolo[2,3-*c*]-pyridine derivatives (**2a** and **2b**). While an added favorable interaction between the nitrogen in the 4-position of the heterobicycle (Y = N) and the receptor in **3a**,**b** could explain the increased affinity, it would not explain the high affinity observed with the indole analogues (**1a** and **1b**). Consequently we proposed that rather than directly influencing receptor binding through electronic effects, perhaps the ring nitrogen indirectly affected binding affinity by changing the conformational preference of the C-5 amide bond. We examined this possibility by comparing the rotational barriers of each of the 4-fluorobenzamide analogues. For **1a**−**4a**, the ring nitrogen (i.e., torsion Y−C−N−C) bond was driven from 0° to 360° at 10° increments using Macromodel (Chart 2).[24] The MM3* force field was utilized, and water solvation effects were modeled using the GB/SA method.[25] The resulting relative energy versus torsion angle plots are shown in Figure 1. Minima existed close to 0° (20° and 340° for conformer A) and 180° (160° and 200° for conformer B) for the highest affinity 5-HT$_{1F}$ receptor analogue **1a**, which was consistent with resonance stabilization of the amide unit by the indole aromatic system. On the other hand, the two pyrrolopyridine isomers, **2a** and **3a**, had significant energy differences ($\sim$3.5 kcal mol^{-1}) between their 0° and 180° conformations. The more active isomer **3a** favored the 180° conformation (conformer B), while the less active isomer **2a** favored the 0° conformation (conformer A), presumably because of dipole minimization or lone pair repulsion between the amide carbonyl and the pyrrolopyri-

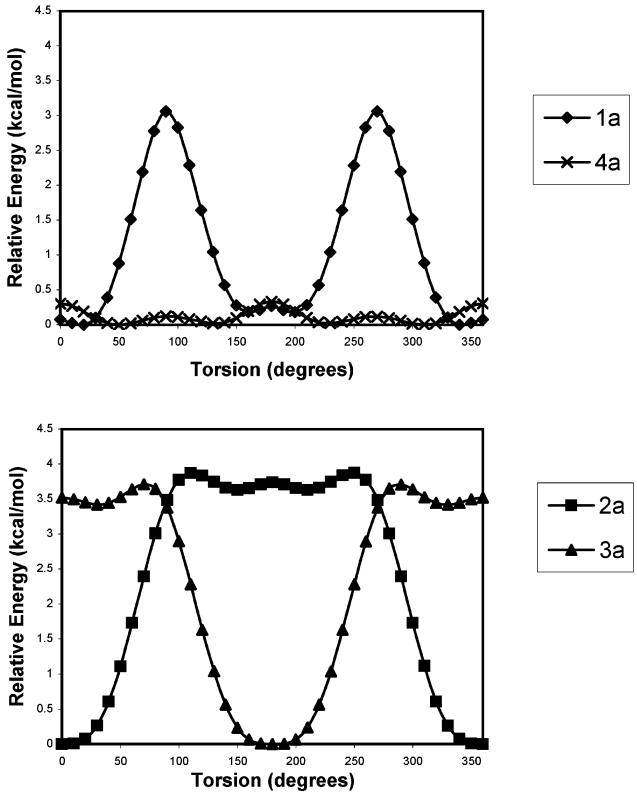
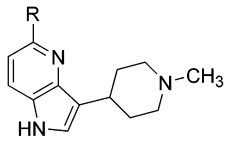


Figure 1. MM3*(GB/SA) relative energy versus torsion angle for 4-fluorobenzamidoindole analogues **1a**−**4a**.

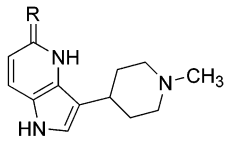
dine nitrogen atom. Furthermore, analyses of available crystal structures (Cambridge Structural Database[26]) of structurally related 2-acylaminopyridines were consistent with our calculations. Approximately 90% of the over 270 compounds evaluated adopted the conformer represented by conformer B in Chart 2 (where X = C; Y = N). This difference in conformational preference between **2a** and **3a** may point to conformer B as important for 5-HT_{1F} receptor binding, possibly directing either the amide carbonyl oxygen or the nitrogen proton to a favorable interaction with the receptor. Conformer A may be relevant for high binding affinity at the other 5-HT_1 receptors, accounting for the decreased 5-HT_{1F} selectivity of analogues **1a**,**b** and **2a**,**b**. As a result of the in vitro binding analysis of the pyrrolopyridine and pyrrolopyrimidine analogues, we decided to investigate the pyrrolo[3,2-*b*]pyridine series in an effort to identify potent and selective 5-HT_{1F} receptor agonists. We focused primarily on varying amine-substituted groups at C-5. In addition, we also evaluated substituent effects on N-1 of the 4-piperidine moiety at C-3.

SAR Summary of the Pyrrolo[3,2-*b*]pyridine Series. In Vitro Binding and Functional Activities. On the basis of SAR studies that identified **1a**, we determined that C-5 substituents bearing a hydrogen bond donor and acceptor were optimal. This trend carried over to the pyrrolo[3,2-*b*]pyridine series, since compounds devoid of this functionality at C-5 showed greatly reduced 5-HT_{1F} receptor affinity or selectivity (Table 2). Amine substitution at C-5 (**14a**) reduced 5-HT_{1F} receptor affinity compared with the C-5 amide analogues. While this functional group could participate as a hydrogen bond donor, it lacked the corresponding hydrogen bond accepting carbonyl unit. Alternatively,

Table 2. In Vitro Binding Affinities of Substituted *N*-[3-(1-Methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amides: Various C-5 Substituents



28, 31, 14a, 30a–b



29

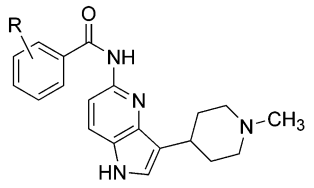
		binding affinity[a] K_i (nM)		
compd	R	5-HT_{1F}	5-HT_{1B}	5-HT_{1D}
14a	NH_2	100(8.6)	800(30)	420(75)
28	OCH_3	23(4.5)	110(24)	23(5.3)
29	O	100(13)	ND[b]	ND[b]
30a	OSO_2CH_3	4.7(1.6)	25(2.2)	8.0(1.1)
30b	$OSO_2C_6H_4$−4-F	7.5(0.2)	ND[b]	30(2.0)

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

perhaps its increased basicity accounted for the compound's diminished activity. Sulfonate esters **30a**,**b** exhibited high 5-HT_{1F} receptor affinity, but their affinities for the 5-HT_{1B} and 5-HT_{1D} receptors were also high. This suggested that perhaps hydrogen bond donation might not be necessary for 5-HT_{1F} receptor activity but was advantageous for selectivity over other 5-HT_1 receptor subtypes. We concluded that retaining the hydrogen bond donating/accepting character of the C-5 substituent was critical. Thus, we initiated SAR studies at the C-5 amine of 3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-ylamine (**14a**), preparing multiple C-5 amide, sulfonamide, and urea derivatives from this intermediate.

In light of the reasonable affinity and selectivity of **3a**, we focused initially on substituted benzamides (Table 3). Small substituents at the meta or para position were generally preferred. In all cases, the ortho-substituted benzamides possessed diminished affinity for the 5-HT_{1F} receptor. Compound **3a**, the pyrrolo[3,2-*b*]pyridine analogue of **1a**, was selective for the 5-HT_{1F} receptor over the 5-HT_{1B} and 5-HT_{1D} receptors (160- and 96-fold, respectively) and was a full agonist (EC_{50} = 4.1 nM, E_{max} = 96% maximal response to 5-HT) in the 5-HT_{1F} [^{35}S]GTP-γ-S assay. Other 4-substituted (**3m**,**n**) and the unsubstituted (**3c**) benzamides also had high 5-HT_{1F} receptor affinity and were full agonists (data not shown); however they possessed high 5-HT_{1A} receptor affinity. In fact, appreciable affinity at the 5-HT_{1A} receptor accompanied this entire series of compounds. For example, the 2,4-dichloro derivative **3p** had high affinity for the 5-HT_{1F} receptor but was nonselective versus the 5-HT_{1A} receptor. In the best case, we observed a 5-HT_{1A}/5-HT_{1F} receptor affinity selectivity ratio of 17 with **3k**; however, this compound was only a partial 5-HT_{1F} receptor agonist (EC_{50} = 22 nM, E_{max} = 60% maximal response to 5-HT). On the other hand, most compounds within this series were quite selective for the 5-HT_{1F} receptor over the 5-HT_{1B} receptor, the receptor that concerned us most regarding potential cardiovascular liabilities.[27]

Table 3. In Vitro Binding Affinities of Substituted *N*-[3-(1-Methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amides: Substituted Benzamides



3a, c–p

		binding affinity[a] K_i (nM)			
compd	R	5-HT$_{1F}$	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$
3a	4-F	7.6(1.0)	56(5.1)	1200(150)	730(9)
3c	H	7.3(0.6)	72(15)	820(100)	1000(180)
3d	2-F	19(2.5)	42(7.0)	ND[b]	ND[b]
3e	2-NO_2	19(3.5)	64(17)	ND[b]	170(21)
3f	2-OCH_3	20(3.7)	20(3.5)	750(66)	ND[b]
3g	2-CH_3	12(1.7)	106(11)	150(57)	440(100)
3h	3-F	11(2.0)	135(4.8)	1600(370)	690(91)
3i	3-NO_2	42(23)	130(23)	390(61)	330(39)
3j	3-OCH_3	16(2.3)	98(16)	ND[b]	ND[b]
3k	3-CH_3	5.8(0.5)	100(16)	1200(200)	490(150)
3l	3-CN	11(0.9)	100(3.0)	590(170)	ND[b]
3m	4-CN	7.2(1.6)	31(5.0)	310(24)	380(100)
3n	4-NO_2	7.7(1.7)	38(4.8)	270(24)	340(42)
3o	4-CH_3	12(2.2)	30(3.2)	ND[b]	ND[b]
3p	2,4-di-Cl	4.1(0.9)	5.1(0.9)	ND[b]	83(22)

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19–21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

Table 4 summarizes the 5-HT$_{1F}$ receptor affinity of heteroaromatic and alkyl amides at C-5. Isosteric heteroaryl amide groups such as thienyl and furyl amides proved to be more selective for the 5-HT$_{1F}$ receptor than the benzamide derivatives, particularly regarding their 5-HT$_{1A}$ receptor affinities. Both the 3-thienyl (**3q**) and the 2-thienyl (**3r**) derivatives were >35-fold more selective for the 5-HT$_{1F}$ receptor over the 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1D}$ receptors. Interestingly, **3r** was only a partial agonist in the 5-HT$_{1F}$ receptor functional [^{35}S]-GTP-γ-S assay, whereas **3q** showed better intrinsic efficacy. The furyl derivatives **3s** and **3t** were highly selective and were also full 5-HT$_{1F}$ agonists in the [^{35}S]-GTP-γ-S functional assay. Two pyridyl derivatives (**3u** and **3v**) were also prepared. These compounds showed activity similar to that of the benzamides, possessing only about a 4-fold difference in 5-HT$_{1A}$ versus 5-HT$_{1F}$ receptor affinity. Given the high affinity and selectivity of **3b** (Table 1), we also investigated a series of simple alkylamides (Table 4). Small alkyl and cycloalkyl groups were tolerated and showed very little affinity for other 5-HT receptors, including the 5-HT$_{1A}$ receptor. As the chain length or ring size was increased, however, 5-HT$_{1F}$ receptor affinity correspondingly decreased. Chain branching (**3z**) also diminished 5-HT$_{1F}$ receptor affinity. The acetamide (**3b**) and propionamide (**3w**) were the most selective compounds identified in this series and were full agonists at the 5-HT$_{1F}$ receptor. Three other compounds from this series, **3x**, **3cc**, and **3dd**, also possessed high 5-HT$_{1F}$ receptor affinity and exhibited reasonable 5-HT$_{1F}$ receptor intrinsic efficacy in the GTP-γ-S assay.

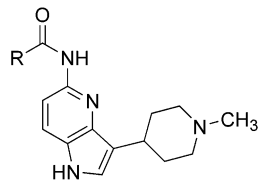
Representative alternative hydrogen bond donating/accepting substituents at the C-5 amino position, specifically sulfonamides (**15a**,**b**) and ureas (**16a**−**c**), were investigated (Table 5). The slightly more acidic sulfonamide derivatives exhibited reduced 5-HT$_{1F}$ receptor affinity relative to compounds in the amide series. On the other hand, the urea compounds showed high 5-HT$_{1F}$ receptor affinity but had high 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor affinities as well. As a result of this study, we concluded that C-5 amide substituents in the pyrrolo[3,2-*b*]pyridine series were preferred, since these analogues exhibited superior 5-HT$_{1F}$ receptor affinity and selectivity compared to compounds with other C-5 substituents.

A focused SAR study evaluated whether the *N*-methyl-4-piperidinyl moiety at C-3 was optimal in the pyrrolo[3,2-*b*]pyridine series (Table 6). We evaluated the effect of varying the N-1 alkyl substituent on the 4-piperidinyl moiety in the C-5 4-fluorobenzamide series. Increasing the chain length at N-1 decreased 5-HT$_{1F}$ receptor affinity (**17a**−**e**), as did chain branching (**17d**). The unsubstituted piperidinyl (**19a**) as well as the *N*-ethyl-1,2,3,6-tetrahyropyridyl (**13a**) analogues showed reasonable affinity for the 5-HT$_{1F}$ receptor, and we evaluated some C-5 alkyl amide derivatives in each case in an attempt to optimize these two series (**13b**, **19b**,**c**). We were particularly interested in investigating the latter platform, given the dramatic difference in binding affinity between piperidinyl compound **17a** and its tetrahydropyridyl analogue **13a**. None of the compounds prepared showed increased 5-HT$_{1F}$ receptor affinity, suggesting that the methyl group was optimal at N-1 of the 4-piperidinyl moiety at C-3.

SAR Summary of the Pyrrolo[3,2-*b*]pyridine Series. Efficacy in the Rabbit Saphenous Vein and Migraine Models. We evaluated compounds that were potent full agonists at the 5-HT$_{1F}$ receptor and exhibited greater than 30-fold selectivity over other 5-HT$_1$ receptor subtypes for vasocontractility in the rabbit saphenous vein and then further for in vivo efficacy in the neurogenic PPE migraine model. Contractile response of the rabbit saphenous vein to 5-HT receptor agonists correlated with serotonin agonist induced contractility of human coronary arteries.[27] Sumatriptan, as well as the other 5-HT$_{1B}$/5-HT$_{1D}$ receptor agonists, contracted the rabbit saphenous vein, an effect potentially mediated by the 5-HT$_{1B}$ receptor,[11] whereas the SSOFRAs did not.[10,13] To identify compounds that would not have the cardiovascular liabilities associated with the triptans, we used contractile response in the rabbit saphenous vein as a predictor of vasoconstrictive activity. In general, these 5-HT$_{1F}$ receptor agonists did not markedly contract the rabbit saphenous vein; however, as a means to prioritize compounds, we characterized compounds as vasoactive if they contracted the rabbit saphenous vein at >10% maximal contraction relative to KCl-induced (67 mM) contraction. Of the benzamides evaluated (**3a**, **3c**, **3m**), only the 4-fluorobenzamide **3a** contracted the rabbit saphenous vein (Table 7). Two of the alkyl derivatives, **3x** and **3dd**, were also vasoactive, whereas alkylamides **3b**, **3w**, and **3cc** showed minimal contractile activity.

Compounds devoid of contractile activity were tested for in vivo efficacy in the guinea pig neurogenic PPE

Table 4. In Vitro Binding Affinities (K_i, nM) and in Vitro Functional Activity of Substituted *N*-[3-(1-Methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amides: Heteroaromatic and Alkyl Amides

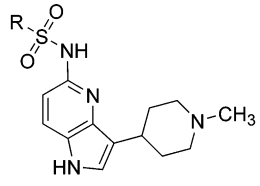


3b, q–ff

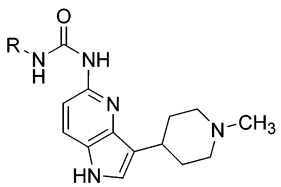
		binding affinity[a] K_i (nM)					
compd	R	5-HT_{1F}	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	EC_{50} [b] (nM)	E_{max} [c] (%)
3q	3-thienyl	7.4(1.9)	400(53)	1000(120)	810(76)	9.4(0.5)	84(0.7)
3r	2-thienyl	7.1(1.5)	350(65)	390(19)	650(130)	15(1.1)	61(2.3)
3s	3-furyl	4.6(0.3)	840(130)	930(300)	1100(250)	11(2.2)	88(2.4)
3t	2-furyl	13(5)	560(20)	1100(64)	930(16)	11(1.5)	82(2.3)
3u	2-pyridyl	6.3(1.5)	41(3.9)	1000(480)	820(55)	25(3.2)	63(1.6)
3v	4-pyridyl	8.4(2.1)	40(1.7)	330(24)	420(42)	11(2.4)	97(1.3)
3b	methyl	5.0(0.5)	620(37)	270(47)	250(38)	36(1.5)	98(1.8)
3w	ethyl	5.5(0.6)	1000(270)	720(220)	730(55)	32(3.8)	88(1.1)
3x	*n*-propyl	6.9(0.5)	ND[d]	ND[d]	ND[d]	13(0.5)	94(0.2)
3y	*n*-butyl	14(5.0)	ND[d]	ND[d]	ND[d]		
3z	*tert*-butyl	62(20)	ND[d]	ND[d]	ND[d]		
3aa	*n*-pentyl	13(3.0)	ND[d]	ND[d]	ND[d]		
3bb	*n*-heptyl	20(5.2)	ND[d]	32(12)	110(28)		
3cc	cyclopropyl	9.8(1.4)	1400(520)	1700(150)	1800(270)	34(5.7)	77(0.7)
3dd	cyclobutyl	8.7(1.6)	2000(290)	380(52)	900(150)	21(3.5)	81(1.0)
3ee	cyclopentyl	11(2.7)	2000(400)	640(110)	740(86)		
3ff	cyclohexyl	20(5.0)	660(71)	ND[d]	ND[d]		

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] EC_{50} (nM) for stimulation of [^{35}S]GTP-γ-S binding in mouse LM(tk$^-$) cells expressing the human 5-HT_{1F} receptor.[22] Values are the mean of at least three determinations. SEM is shown in parentheses. [c] Maximum stimulation of [^{35}S]GTP-γ-S binding expressed relative to the maximal effect of 5-HT. [d] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

Table 5. In Vitro Binding Affinities of 5-Substituted *N*-[3-(1-Methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridines: Sulfonamides and Ureas



15a–b



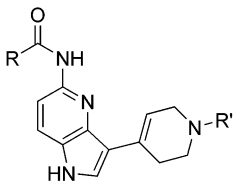
16a–c

		binding affinity[a] K_i (nM)		
compd	R	5-HT_{1F}	5-HT_{1B}	5-HT_{1D}
15a	4-fluorophenyl	27(4.6)	ND[b]	ND[b]
15b	methyl	19(5.8)	610(260)	380(57)
16a	4-fluorophenyl	11(0.6)	3.2(0.6)	3.8(0.7)
16b	methyl	2.5(0.6)	14(1.4)	8.5(1.3)
16c	ethyl	3.8(0.4)	ND[b]	40(8.8)

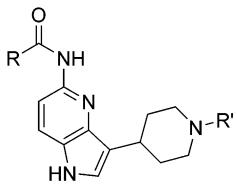
[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

migraine model. A rapid screening procedure using this model was developed to evaluate the oral activity and duration of action of potent and selective 5-HT_{1F} receptor agonists in the pyrrolo[3,2-*b*]pyridine series. Initially, we were interested in identifying compounds that demonstrated complete blockade of plasma protein extravasation upon oral administration with a long duration of action. Sumatriptan was reported to have a

Table 6. In Vitro 5-HT_{1F} Receptor Binding Affinity of Substituted *N*-[3-(1-Substituted 4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amides: N-1 Substituent Effects



13a–b



17a–e
19a–c

			binding affinity[a] K_i (nM)
compd	R	R′	5-HT_{1F}
17a	4-F-phenyl	ethyl	170(58)
13a	4-F-phenyl	ethyl	25(5.5)
17b	4-F-phenyl	*n*-propyl	18(5.7)
17c	4-F-phenyl	*n*-butyl	14(4.7)
17d	4-F-phenyl	isopropyl	30(8.6)
17e	4-F-phenyl	phenylethyl	75(32)
19a	4-F-phenyl	H	9.5(2.7)
19b	methyl	H	45(22)
19c	ethyl	H	35(14)
13b	methyl	ethyl	21(5.4)

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses.

short plasma/tissue half-life in humans, and frequently additional doses were required because of recurrence of migraine pain.[28] Since the normal duration of a migraine headache is 4−72 h,[29] a therapeutic agent with

Table 7. In Vitro Contractile Response in Rabbit Saphenous Vein and in Vivo Efficacy in Neurogenic Plasma Protein Extravasation Screen

	rabbit saphenous vein[a]		neurogenic PPE screen[b]	
compd	contractile response (%)	concn of max response (M)	ratio at 1 h postdose	ratio at 24 h postdose
3a	16(2.3)	10^{-4}		
3b	5.7(1.7)	3×10^{-5}	1.0	1.1
3c	0	10^{-4}	1.1	1.6
3m	1.1(0.8)	3×10^{-5}	1.5	
3q	0	10^{-4}	1.0	1.6
3w	3.0(1.5)	10^{-4}	1.2	1.0
3x	12.4(5.0)	10^{-4}		
3cc	2.3(1.2)	10^{-4}	1.4	
3dd	17(5.2)	10^{-4}		

[a] Maximal contraction relative to KCl-induced (67 mM) contraction in the rabbit saphenous vein.[10] Values are the mean (SEM in parentheses) of three to seven determinations. [b] Dural extravasation ratio (stimulated side/unstimulated side) approximated using the guinea pig neurogenic PPE assay (1 ng/kg, po).[23]

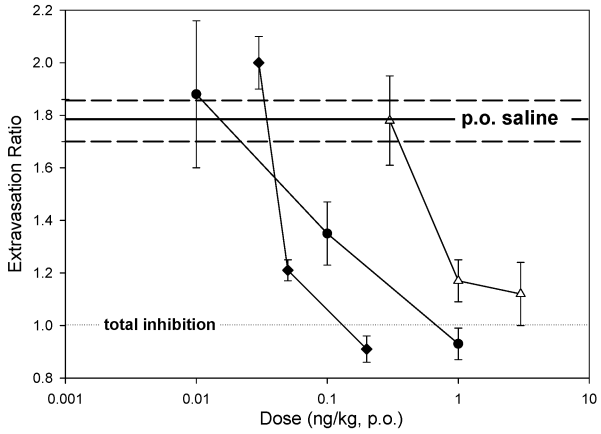


Figure 2. Dose−response curves of **1a**, **3b**, and **3w** in the PPE model after oral administration: (◆) **1a**; (●) **3b**; (△) **3w**. Values are the mean ratio of Evan's Blue dye extravasation in the stimulated side of the dura to that in the unstimulated side ± SEM (n = 3). A compound was considered fully efficacious at a ratio of approximately 1 and an ineffective at a ratio of approximately 1.8.

a long duration of action might minimize breakthrough headache. The compounds were tested at a single oral dose of 1 ng/kg, and the extravasation ratio was determined 1 h postdose (Table 7). For two compounds, **3m** and **3cc**, the stimulated/unstimulated extravasation ratio was greater than 1, indicating that these compounds had either limited oral activity at this dose or a short duration of action. Compounds **3b**, **3c**, **3q**, and **3w** were fully efficacious and were studied further. The arylamides **3c** and **3q** (dosed at 1 ng/kg, po) possessed a relatively long duration of action, exhibiting some effect 24 h postdose (Table 7). However, the acetamide derivative **3b** and propionamide derivative **3w** were both fully efficacious 24 h postdose, indicating that both compounds displayed excellent oral activity and duration of action in this model.

Full dose−response curves were generated for both compounds (Figure 2). While less potent than comparitor compound **1a**, both **3b** and **3w** decreased dural extravasation in a dose-related manner following oral administration (ID_{50} = 0.2 and 0.6 ng/kg, respectively). The duration of action of these compounds in the PPE model was compared to **1a** by administering an oral ID_{100} to fasted guinea pigs and determining the extravasation ratio at various times postdose (Figure 3). Both **3b** and **3w** (1 ng/kg, po) were effective at 1 and 24 h, but not 48 h, postdose. Thus, the long duration of action of **3b** and **3w** compared favorably to **1a** and indicated that these compounds may have a long duration of action in humans. As shown in Table 8, both compounds displayed greater than 50-fold selectivity over 10 other 5-HT receptor subtypes. In addition, these compounds were evaluated for affinity at 40 other neurotransmitter binding sites (receptors, ion channels, and transporters; data not shown). Neither compound demonstrated any notable affinity at any of the receptor sites tested. On the basis of these studies, we characterized **3b** and **3w** as potent and selective, as well as orally active and long acting, 5-HT$_{1F}$ receptor agonists (SSOFRAs) with the clinical potential to treat acute migraine.

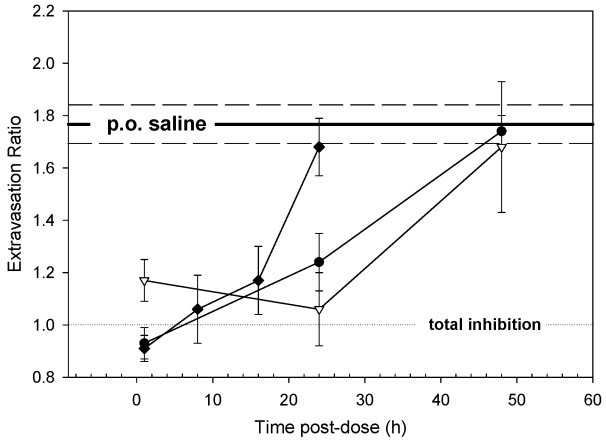


Figure 3. Duration of action curves of **1a**, **3b**, and **3w** in the PPE model: (◆) **1a**; (●) **3b**; (▽) **3w**. Fasted guinea pigs were given their approximate oral ID_{100}, the minimal dose that produced a full inhibition of extravasation 1 h postdose, and the extravasation ratio was determined at various time points. Data are expressed as the mean ± SEM (n = 3).

Table 8. 5-HT Receptor Binding Profile of **3b** and **3w**

	binding profile[a] K_i (nM)	
receptor	**3b**	**3w**
5-HT$_{1A}$	620(37)	1000(270)
5-HT$_{1B}$	270(47)	720(220)
5-HT$_{1D}$	250(38)	720(55)
5-HT$_{1E}$	660(110)	770(80)
5-HT$_{1F}$	5.0(0.5)	5.5(0.6)
5-HT$_{2A}$	4800(2000)	3400(1600)
5-HT$_{2B}$	>10000	>10000
5-HT$_{2C}$	1900(1600)	310(41)
5-HT$_4$	4000(350)	2400(740)
5-HT$_6$	>10000	1120(203)
5-HT$_7$	>5000	ND[b]

[a] Affinities for receptors were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptor.[19−21] Each value is the mean of at least three determinations. SEM is shown in parentheses. [b] ND = K_i not determined. <50% displacement of radioligand at 10^{-7} M test ligand.

Conclusions

We prepared a series of pyrrolopyridine and pyrrolopyrimidine analogues of SSOFRA **1a** (LY334370) in an effort to explore the structural motif required for 5-HT$_{1F}$ receptor affinity and selectivity and to identify compounds with an improved pharmacologic profile over **1a**. Evaluation of these analogues revealed the pyrrolo[3,2-

b]pyridine derivatives as a novel series of 5-HT_{1F} receptor agonists. From the SAR studies of this series coupled with in vivo pharmacologic evaluation, we have identified methyl-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]amide (**3b**) and ethyl-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]-amide (**3w**) as potent and selective 5-HT_{1F} receptor agonists.

Experimental Section

General Chemical Methods. All commercially available solvents and reagents were used as received. Reactions were conducted under a nitrogen atmosphere with magnetic stirring. Column chromatography was performed on E. Merck Kieselgel 230−400 mesh silica gel 60 using the solvent system described in parentheses. Melting points were obtained with a Gallenkamp digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz in the solvent noted in parentheses. Chemical shifts are reported in ppm (δ) relative to solvent. Mass spectrometry was performed using a Varian MAT 731 instrument. Elemental analyses were carried out by the Physical Chemistry Department at Lilly Research Laboratories.

***N,N*-Dimethyl-*N′*-[4-(2-(dimethylamino)vinyl)-5-nitropyridin-2-yl]formamidine (6).** To a solution of 2-amino-4-methyl-5-nitropyridine **5** (10.0 g, 65.3 mmol) dissolved in 90 mL of DMF was added in one portion *N,N*-dimethylformamide dimethyl acetal (87.0 mL, 653.0 mmol). The deep-red reaction mixture was heated at 110 °C overnight and then cooled to room temperature and concentrated in vacuo to provide 17.7 g (100%) of the title compound as a red solid. An analytical sample was purified by recrystallization from benzene: mp = 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.57 (s, 1H), 7.28 (d, J = 13.2 Hz, 1H), 6.82 (s, 1H), 6.03 (d, J = 13.6 Hz, 1H), 3.10 (s, 3H), 3.08 (s, 3H), 2.93 (s, 6H) ppm; MS (*m/e*) 263 (M^+). Anal. ($C_{12}H_{17}N_5O_2$) C, H, N.

***N,N*-Dimethyl-*N′*-(1*H*-pyrrolo[2,3-*c*]pyridin-5-yl)formamidine (7).** A mixture of **6** (8.0 g, 30.4 mmol) and 10% palladium on carbon (2.0 g) in 80 mL of EtOH was hydrogenated at room temperature under 40 psi of hydrogen pressure for 24 h, filtered through Celite, and concentrated in vacuo. The resulting dark-brown foam was chromatographed (10−20% 2 M NH_3−MeOH/CH_2Cl_2) to provide 3.4 g (60%) of a brown solid that was slurried in EtOAc (50 mL), filtered, and rinsed with cold EtOAc to provide the title compound as an ivory solid: mp = 162−166 °C; ^{1}H NMR (DMSO-d_6) δ 11.25 (s, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 7.46 (d, J = 2.6 Hz, 1 H), 6.94 (s, 1H), 6.31 (d, J = 2.6 Hz, 1H), 2.98 (s, 6H) ppm; MS (*m/e*) 188 (M^+). Anal. ($C_{10}H_{12}N_4$) C, H, N.

3-[1-Methyl-(1,2,3,6-tetrahydropyridin-4-yl)]-1*H*-pyrrolo-[2,3-*c*]pyridin-5-ylamine (8). Sodium metal (1.20 g, 52.6 mmol) was added in portions to MeOH (50 mL) cooled to 0 °C. When the sodium completely dissolved, **7** (2.48 g, 13.2 mmol) followed by 1-methyl-4-piperidone (2.4 mL, 19.8 mmol) was added. The reaction mixture was heated at 75 °C overnight, and then 1 mL of H_2O was added. The reaction mixture was heated at the same temperature for an additional 24 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between 3:1 $CHCl_3$/IPA and ice/water, and the aqueous phase was extracted with $CHCl_3$. The combined organics were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10−20% 2 M NH_3−MeOH/CH_2Cl_2) gave 2.59 g (86%) of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1H), 8.15 (s, 1H), 7.38 (s, 1H), 6.81 (s, 1H), 5.97 (br s, 1H), 5.04 (br s, 2H), 3.03 (m, 2H), 2.55−2.50 (m, 4H), 2.27 (s, 3H) ppm; MS (*m/e*) 229 (M^+). Anal. ($C_{13}H_{16}N_4$) C, H, N.

3-(1-Methylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-5-ylamine (9). A mixture of **8** (2.25 g, 5.0 mmol) and 10% palladium on carbon (0.56 g) in 200 mL of EtOH was hydrogenated at 60 psi at 40 °C for 24 h. The reaction mixture was filtered through Celite, the catalyst was washed with EtOAc, and the solution was concentrated in vacuo. Recrystallization from EtOAc provided the title compound as a white solid (1.81 g, 80%): mp = 196−199 °C; ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1H), 8.11 (s, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 4.92 (br s, 2H), 2.87−2.83 (m, 2H), 2.51−2.53 (m, 1H), 2.20 (s, 3H), 2.00−1.64 (m, 6H) ppm; MS (*m/e*) 231 (M^+). Anal. ($C_{13}H_{18}N_4 \cdot 0.1C_4H_8O_2$) C, H, N.

4-Fluoro-*N*-[3-(1-methylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]benzamide (2a). To a solution of **9** (0.14 g, 0.60 mmol) dissolved in pyridine (5 mL) was added 4-fluorobenzoyl chloride (0.09 mL, 0.71 mmol). The reaction mixture was stirred at room temperature for 4 h, concentrated in vacuo, and partitioned between CH_2Cl_2 and 1 N aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (5−20% 2 M NH_3−MeOH/CH_2Cl_2) provided the title compound (0.16 g, 77%) as a white solid: ^{1}H NMR (CD_3OD) δ 8.53 (s, 1H), 8.26 (s, 1H), 8.06 (dd, J = 5.3, 8.9 Hz, 2H), 7.47 (s, 1H), 7.26 (t, J = 8.7 Hz, 2H), 3.70−3.50 (m, 2H), 3.30−3.25 (m, 3H), 2.93 (s, 3H), 2.40−2.00 (m, 4H) ppm; MS (*m/e*) 252 (M^+). Anal. ($C_{20}H_{21}FN_4O$) C, H, N.

***N,N*-Dimethyl-*N′*-(1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)formamidine (11).** To a solution of **10**[17] (7.5 g, 49.0 mmol) dissolved in 35 mL of DMF was added in one portion DMFDMA (32.5 mL, 244.7 mmol). The deep-red reaction mixture was heated at 110 °C for 24 h, cooled to room temperature, and concentrated in vacuo to provide 12.5 g (97%) of the title compound as a red solid. An analytical sample was purified by recrystallization from benzene: mp = 159 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 12.5 Hz, 1H), 6.40 (d, J = 8.7 Hz, 1H), 6.39 (d, J = 12.5 Hz, 1H), 3.13 (s, 3H), 3.10 (s, 3H), 2.99 (s, 6H) ppm.

A mixture of this intermediate (7.2 g, 27.3 mmol) and 10% palladium on carbon (1.1 g) in 90 mL of EtOH was hydrogenated at room temperature under 40 psi of hydrogen pressure for 4 h, filtered through Celite, and concentrated in vacuo. The resulting dark-brown foam was chromatographed (5−20% 2 M NH_3−MeOH/CH_2Cl_2) to provide 3.8 g (74%) of a brown solid that was slurried in EtOAc (150 mL), filtered, and rinsed with cold EtOAc to provide the title compound as an ivory solid: mp = 187−189 °C; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1H), 8.42 (s, 1H), 7.58 (d, J = 8.5 Hz, H), 7.43 (m, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.32 (m, 1H), 3.06 (s, 3H), 2.96 (s, 3H) ppm. Anal. ($C_{10}H_{12}N_4$) C, H, N.

Representative Procedure for the Condensation of 1-Substituted 4-Piperidones with 11 (12a−g). Preparation of 3-[1-Methyl-(1,2,3,6-tetrahydropyridin-4-yl)]-1*H*-pyrrolo[3,2-*b*]pyridin-5-ylamine (12a). To a solution of KOH (4.0 g, 70.7 mmol) and **11** (3.8 g, 20.2 mmol) dissolved in MeOH (41 mL) was added 1-methyl-4-piperidone (3.2 mL, 26.3 mmol). The reaction mixture was heated at 75 °C for 24 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between 3:1 $CHCl_3$/IPA and ice/water, and the aqueous phase was extracted with $CHCl_3$. The combined organics were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10−20% 2 M NH_3−MeOH/CH_2Cl_2) followed by recrystallization (CH_3CN) provided 3.76 g (82%) of the title compound as an orange solid: mp = 199−202 °C; ^{1}H NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.23 (m, 1H), 7.04 (m, 1H), 6.32 (d, J = 8.6 Hz, 1H), 5.38 (br s, 2H), 3.00 (m, 2H), 2.55−2.45 (m, 4H), 2.26 (s, 3H) ppm; MS (*m/e*) 229 (M^+). Anal. ($C_{13}H_{16}N_4$) C, H, N.

Representative Procedure for Preparation of N-Substituted Piperidinyl Intermediates (14a−g). Preparation of 3-(1-Methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-ylamine (14a). A solution of **12a** (R = CH_3) (3.09 g, 13.9 mmol) and 10% palladium on carbon (0.46 g) in 130 mL of 1:1 THF/EtOH was hydrogenated at 40 psi for 24 h. The reaction mixture was filtered through Celite, the catalyst was washed with EtOAc, and the solution was concentrated in vacuo. The crude material was slurried in 30 mL of EtOAc, cooled, filtered, and rinsed with cold EtOAc, providing the title compound as a white solid (2.74 g, 88%): ^{1}H NMR (DMSO-d_6) δ 10.45 (s,

1H), 7.38 (d, J = 8.5 Hz, 1H), 7.02 (s, 1H), 6.28 (d, J = 8.5 Hz, 1H), 5.33 (br s, 2H), 2.90−2.86 (m, 2H), 2.70 (m, 1H), 2.24 (s, 3H), 2.10−1.95 (m, 4H), 1.67−1.64 (m, 2H) ppm; MS (*m*/*e*) 230 (M^+). Anal. ($C_{13}H_{18}N_4$) C, H, N.

Representative Procedure for the Synthesis of Substituted *N*-[3-(1-Substituted piperidin-4-yl)-1*H*-pyrrolo-[3,2-*b*]pyridin-5-yl]amides (3a−ff, 13a,b, 17a−e and 18a−c). Preparation of 4-Fluoro-*N*-[3-(1-methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]benzamide (3a). To a solution of **14a** (R = CH_3) (1.00 g, 4.30 mmol) dissolved in pyridine (85 mL) was added 4-fluorobenzoyl chloride (0.57 mL, 4.80 mmol). The reaction mixture was heated at 55 °C for 0.5 h, concentrated in vacuo, and partitioned between CH_2Cl_2 and 1 N aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (10−20% 2 M NH_3−MeOH/CH_2Cl_2) followed by recrystallization (EtOH/H_2O) provided the title compound (1.32 mg, 87%) as a white solid: mp = 118−121 °C; ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.47 (s, 1H), 8.14 (dd, J = 5.7, 9.0 Hz, 2H), 7.80 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.35 (m, 1H), 7.32 (t, J = 9.0 Hz, 2H), 2.86−2.79 (m, 3H), 2.19 (s, 3H), 2.03−1.94 (m, 4H), 1.79−1.67 (m, 2H) ppm; MS (*m*/*e*) 352 (M^+). Anal. ($C_{20}H_{21}FN_4O$) C, H, N.

Representative Procedure for the Synthesis of Substituted *N*-[3-(1-Methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]-pyridin-5-yl]sulfonamides (15a,b). Preparation of 4-Fluoro-*N*-[3-(1-methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]-pyridin-5-yl]benzenesulfonamide (15a). To a solution of **14a** (R = CH_3) (150 mg, 0.65 mmol) dissolved in pyridine (10 mL) was added 4-fluorobenzenesulfonyl chloride (152 mg, 0.78 mmol). The reaction mixture was heated at 55 °C for 2 h, concentrated in vacuo, and partitioned between 3:1 $CHCl_3$/IPA and 1 N aqueous NaOH. The pH of the aqueous layer was adjusted to ca. 11 with 1 N aqueous HCl and then extracted with 3:1 $CHCl_3$/IPA. The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (20% 2 M NH_3−MeOH/CH_2Cl_2) followed by recrystallization (EtOH/H_2O) provided the title compound (134 mg, 53%) as a white solid: mp = 152 °C; ^{1}H NMR (DMSO-d_6) δ 11.20 (br s, 1H), 11.03 (s, 1H), 7.97 (dd, J = 5.3, 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 1H), 7.33 (t, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.83 (dd, J = 9.0 Hz, 1H), 2.84−2.81 (m, 2H), 2.64 (m, 1H), 2.22 (s, 3H), 2.01−1.94 (m, 2H), 1.81−1.78 (m, 2H), 1.66−1.55 (m, 2H) ppm; MS (*m*/*e*) 388 (M^+). Anal. ($C_{19}H_{21}FN_4O_2S\cdot 1H_2O$) C, H, N.

Representative Procedure for the Synthesis of 1-Substituted 3-[3-(1-Methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]-pyridin-5-yl]ureas (16a−c). Preparation of 1-(4-Fluoro)-3-[3-(1-methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]urea (16a). To a solution of **14a** (R = CH_3) (150 mg, 0.65 mmol) dissolved in 5:1 THF/DMF (6 mL) was added 4-fluorophenyl isocyanate (0.10 mL, 0.85 mmol). The reaction mixture was stirred at room temperature overnight, concentrated in vacuo, and partitioned between 3:1 $CHCl_3$/IPA and 1 N aqueous NaOH. The aqueous layer was extracted with 3:1 $CHCl_3$/IPA, and the combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10% 2 M NH_3−MeOH/CH_2Cl_2) followed by recrystallization (MeOH) provided the title compound (176 mg, 74%) as a white solid: mp = 246 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.99 (br s, 1H), 11.01 (s, 1H), 9.54 (s, 1H), 7.74−7.71 (m, 3H), 7.34 (m, 1H), 7.15 (t, J = 8.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 2.90−2.75 (m, 3H), 2.25 (s, 3H), 2.03−1.82 (m, 6H) ppm; MS (*m*/*e*) 369 (M^+). Anal. ($C_{20}H_{22}FN_5O$) C, H, N.

Representative Procedure for the Synthesis of Substituted *N*-(3-Piperidin-4-yl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl]benzamides (19a−c). Preparation of 4-Fluoro-*N*-(3-piperidin-4-yl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)benzamide (19a). To **18a** (R′ = 4-fluorophenyl; R = BOC) (107 mg, 0.24 mmol) dissolved in 2 mL of CH_2Cl_2 was added an excess (0.5 mL) of TFA. The reaction mixture was stirred at room temperature for 1 h, concentrated in vacuo, and partitioned between $CHCl_3$ and 1 N aqueous NaOH. The aqueous layer was extracted with $CHCl_3$, and the combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10% MeOH/CH_2Cl_2−MeOH) provided the title compound (73 mg, 90%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.52 (s, 1H), 8.24 (m, 1H), 7.84 (m, 1H), 7.81−7.72 (m, 3H), 7.34 (m, 1H), 7.20 (t, J = 4.4 Hz, 1H), 3.33 (br s, 1H), 3.03−2.90 (m, 3H), 2.65−2.58 (m, 2H), 2.00−1.96 (m, 2H), 1.57−1.52 (m, 2H) ppm; MS (*m*/*e*) 339 (M^+). Anal. ($C_{19}H_{19}FN_4O$) C, H, N.

***N*-[4-(2-Dimethylaminovinyl)-5-nitro-6-oxo-1,6-dihydropyrimidin-2-yl]-*N*,*N*-formamidine (21).** To **20**[18] (7.0 g, 41.1 mmol) dissolved in 100 mL of DMF was added tris-(dimethylamino)methane (12.5 mL, 123.4 mmol). The reaction mixture was heated at 100 °C overnight and then concentrated in vacuo. Column chromatography (10% MeOH/CH_2Cl_2−MeOH) provided the title compound (6.5 g, 57%) as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H), 8.82 (s, 1H), 8.17 (d, J = 12.1 Hz, 1H), 5.48 (d, J = 12.1 Hz, 1H), 3.22 (s, 3H), 3.05 (s, 3H), 3.20−2.80 (m, 6H) ppm; MS (*m*/*e*) 281 (M^+). Anal. ($C_{11}H_{16}N_6O_3$) C, H, N.

***N*,*N*-Dimethyl-*N*′-(4-oxo-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]-pyrimidin-2-yl)formamidine (22).** To a solution of the enamine **21** (12.4 g, 44.1 mmol) dissolved in 1:1 THF/EtOH (140 mL) was added a slurry of 5% palladium on carbon (3.1 g) in EtOH. The reaction mixture was hydrogenated at 60 psi for 2 h, filtered through Celite, and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2−10% 2 M NH_3−MeOH/CH_2Cl_2) gave 4.8 g (53%) of an ivory solid that was recrystallized (MeOH): mp = 269−271 °C; ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1H), 10.96 (s, 1H), 8.54 (s, 1H), 7.18 (m, 1H), 6.09 (m, 1H), 3.11 (s, 3H), 2.99 (s, 3H) ppm; MS (*m*/*e*) 206 (M^+). Anal. ($C_9H_{11}N_5O$) C, H, N.

***N*,*N*-Dimethyl-*N*′-(4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)formamidine (23).** A mixture of **22** (2.2 g, 10.7 mmol) and phosphorus oxychloride (12.0 mL, 128.8 mmol) was stirred vigorously while being heated at 115 °C. Within 0.25 h, the reaction mixture became homogeneous. It was heated for an additional 0.25 h, then quickly cooled to 0 °C in an ice/water bath, basified with 5 N NaOH, and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. The residue was chromatographed (5% 2 M NH_3−MeOH/CH_2Cl_2) to give 1.4 g (59%) of an ivory solid: mp = 174 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1H), 8.53 (s, 1H), 7.75 (m, 1H), 6.42 (m, 1H), 3.11 (s, 3H), 2.99 (s, 3H), ppm; MS (*m*/*e*) 224 (M^+). Anal. ($C_9H_{10}ClN_5$) C, H, N.

***N*,*N*-Dimethyl-*N*′-(5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)formamidine (24).** A mixture of **23** (1.34 g, 6.0 mmol), $NaHCO_3$ (1.00 g, 12.0 mmol), and 10% palladium on carbon (0.60 g) in EtOH (20 mL) was hydrogenated at 40 psi for 2 h. The reaction mixture was filtered through Celite, concentrated in vacuo, chromatographed (5% 2 M NH_3−MeOH/CH_2Cl_2), and recrystallized (MeOH/EtOAc), providing the title compound (0.72 g, 64%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 11.43 (br s, 1H), 8.64 (s, 1H), 8.58 (s, 1H), 7.70 (m, 1H), 6.33 (m, 1H), 3.09 (s, 3H), 3.00 (s, 3H) ppm; MS (*m*/*e*) 190 (M^+). Anal. ($C_9H_{11}N_5\cdot 0.2H_2O$) C, H, N.

7-(1-Methylpiperidin-4-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-ylamine (25). Sodium metal (0.20 g, 8.46 mmol) was added in portions to MeOH (10 mL) cooled to 0 °C. When the sodium completely dissolved, **24** (0.40 g, 2.12 mmol) followed by 1-methyl-4-piperidone (0.39 mL, 3.18 mmol) was added. The reaction mixture was heated at 75 °C for 48 h, then cooled to room temperature, and concentrated in vacuo. The residue was partitioned between 3:1 $CHCl_3$/IPA and ice/water, and the aqueous phase was extracted with $CHCl_3$. The combined organics were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10−20% 2 M NH_3−MeOH/CH_2Cl_2) followed by recrystallization (MeOH) gave 0.33 g (68%) of the tetrahydropyridyl intermediate as yellow crystals: mp = 230−234 °C; ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 8.39 (s, 1H), 7.49 (s, 1H), 6.93 (s, 1H), 5.83 (br s, 2H), 3.00 (m, 2H), 2.59−2.38 (m, 4H), 2.27 (s,

3H) ppm. Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 63.09; H, 6.69; N, 30.69.

A mixture of this material (0.50 g, 2.18 mmol) and 10% palladium on carbon (0.13 g) in 35 mL of EtOH was hydrogenated at 60 psi overnight. The reaction mixture was filtered through Celite, the catalyst was washed with EtOAc, and the mixture was concentrated in vacuo to provide the title compound as a white solid (0.35 g, 69%) that was recrystallized from MeOH: ^{1}H NMR (DMSO-d_6) δ 10.79 (s, 1H), 8.34 (s, 1H), 7.30 (s, 1H), 5.73 (s, 2H), 2.80 (m, 2H), 2.62 (m, 1H), 2.50 (m, 2H), 2.18 (s, 3H), 1.96−1.90 (m, 4H), 1.68 (m, 2H) ppm; MS (*m*/*e*) 232 (M^+). Anal. ($C_{12}H_{17}N_5$) C, H, N.

4-Fluoro-*N*-[7-(1-methylpiperidin-4-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl]benzamide (4a). To a solution of **25** (0.36 g, 1.56 mmol) dissolved in 30 mL of pyridine was added 4-fluorobenzoyl chloride (0.37 mL, 3.11 mmol). The cloudy orange mixture was stirred at 50 °C overnight, then concentrated in vacuo, redissolved in MeOH, and placed on a 5 g Mega Bond Elut SCX column (Varian Sample Preparation Products). The column was washed with three volumes of MeOH, and the product was removed from the column with two volumes of 2 M NH_3−MeOH. The resulting organics were concentrated in vacuo. Radial chromatography (4 mm thickness, 5−25% 2 M NH_3−MeOH/CH_2Cl_2) provided the title compound as an ivory solid (0.34 g, 62%): ^{1}H NMR (DMSO-d_6) δ 11.50 (br s, 1H), 10.71 (s, 1H), 8.77 (s, 1H), 8.04 (dd, J = 3.3, 8.8 Hz, 2H), 7.65 (d, J = 1.5 Hz, 1H), 7.32 (t, J = 8.8, 2H), 2.84−2.81 (m, 2H), 2.75 (m, 1H), 2.19 (s, 3H), 2.01−1.94 (m, 4H), 1.79−1.67 (m, 2H) ppm; MS (*m*/*e*) 354 (M + 1). Anal. ($C_{19}H_{20}FN_5O$) C, H, N.

5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridine (27). To **26**[30] (29.4 g, 175 mmol) dissolved in 300 mL of DMF was added DMFDMA (120 mL, 896 mmol) and Et_3N (1 mL). The bright-red reaction mixture was heated at 120 °C for 2 h and then concentrated in vacuo to provide 38.9 g of a red solid, which was used in the subsequent reaction without purification: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 6.46 (d, J = 12.4 Hz, 1H), 6.20 (d, J = 12.4 Hz, 1H), 3.96 (s, 3H), 3.06 (s, 6H) ppm.

The crude enamine (38.8 g, 174 mmol) was dissolved in 1.2 L of EtOH and charged with 10% palladium on carbon (5.0 g). The mixture was hydrogenated at room temperature under 40 psi of hydrogen pressure for 4 h. After filtration through Celite and chromatography (50% EtOAc/hexane), the material was recrystallized from EtOAc/hexane to provide 19.6 g of an ivory solid (76%): mp = 113−114 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.15 (br s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.47 (m, 1H), 6.54 (d, J = 9.0 Hz, 1H), 6.39 (m, 1H), 3.84 (s, 3H) ppm; MS (*m*/*e*) 149 (M^+). Anal. ($C_8H_8N_2O$) C, H, N.

5-Methoxy-3-(1-methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (28). To a mixture of **27** (7.0 g, 47 mmol) and KOH (9.2 g, 165 mmol) in 350 mL of MeOH was added 1-methyl-4-piperidone (9.9 mL, 80 mmol) in one portion. The reaction mixture was heated at reflux temperature overnight and then cooled to room temperature. The resulting precipitate was collected, and the filtrate was concentrated to a minimal volume. A second crop of crystals was collected, washed with cold MeOH, and combined with the previous crop to afford 9.0 g (79%) of the tetrahydropyridyl intermediate as an ivory solid: mp = 203 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.10 (br s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.44 (m, 1H), 7.02 (m, 1H), 6.56 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 3.03 (m, 2H), 2.50−2.27 (m, 4H), 2.27 (s, 3H) ppm; MS (*m*/*e*) 243 (M^+). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.22; H, 7.13; N, 17.47.

The intermediate described above (9.0 g, 37 mmol) was dissolved in 190 mL of EtOH/THF/MeOH (10:10:1). A slurry of 10% palladium on carbon (2.2 g) in EtOH was added, and the reaction mixture was hydrogenated at 40 psi for 96 h. The mixture was filtered through Celite, the catalyst was washed with EtOH, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (5−10% 2 M NH_3−MeOH/CH_2Cl_2) to provide 8.79 g (97%) of the desired material: ^{1}H NMR (DMSO-d_6) δ 10.82 (br s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.22 (m, 1H), 6.49 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 2.88−2.85 (m, 2H), 2.75 (m, 1H), 2.22 (s, 3H), 2.09−1.98 (m, 3H), 1.83−1.75 (m, 3H) ppm; MS (*m*/*e*) 245 (M^+). Anal. ($C_{14}H_{19}N_3O$) C, H, N.

3-(1-Methylpiperidin-4-yl)-1,4-dihydropyrrolo[3,2-*b*]-pyridin-5-one (29). A solution of **28** (2.30 g, 9.4 mmol) in 30 mL of 30% HBr/HOAc was heated in a sealed tube at 105 °C for 72 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in H_2O, and the pH was adjusted to ca. 13 with 5 N aqueous NaOH. The mixture was concentrated in vacuo, and the residue was chromatographed (20% 2 M NH_3−MeOH/CH_2Cl_2). After concentration in vacuo, the product was dissolved in MeOH, charged with Dowex 50X8 (100−200) ion-exchange resin (25 g, prewashed with 200 mL of H_2O followed by 100 mL of MeOH), and stirred overnight at room temperature. The mixture was filtered, and the resin was washed with water and MeOH. The resin was then stirred overnight in 100 mL of 2 M NH_3−MeOH and filtered. The filtrate was concentrated in vacuo to provide 1.84 g (85%) of the desired material, which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 11.39 (br s, 1H), 10.85 (br s, 1H), 7.50 (d, J = 9.4 Hz, 1H), 6.96 (m, 1H), 5.97 (d, J = 9.4 Hz, 1H), 2.82−2.72 (m, 2H), 2.66 (m, 1H), 2.18 (s, 3H), 2.01−1.93 (m, 2H), 1.90−1.80 (m, 2H), 1.55−1.43 (m, 2H) ppm. Anal. ($C_{13}H_{17}N_3O$) C, H, N.

Methanesulfonic Acid 3-(1-Methylpiperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl Ester (30a). To a solution of **29** (0.25 g, 1.08 mmol) cooled to 0 °C in pyridine (25 mL) was added methanesulfonic anhydride (0.49 g, 2.81 mmol). The reaction mixture was warmed to room temperature over 2 h and then heated at 60 °C for an additional 2 h. The pyridine was removed, and the residue was partitioned between 3:1 $CHCl_3$/IPA and saturated aqueous $NaHCO_3$ and then extracted with 3:1 $CHCl_3$/IPA. The combined organics were washed with saturated aqueous NaCl, dried with Na_2SO_4, and concentrated in vacuo. Chromatography (20% 2 M NH_3−MeOH/CH_2Cl_2) provided 0.18 g (53%) of the title compound: mp = 142−144 °C; ^{1}H NMR (DMSO-d_6) δ 11.32 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 3.61 (s, 3H), 2.87−2.84 (m, 2H), 2.81−2.73 (m, 1H), 2.20 (s, 3H), 2.06−1.94 (m, 4H), 1.80 (dt, J = 3.0, 12.1 Hz, 2H) ppm; MS (*m*/*e*) 309 (M^+). Anal. ($C_{14}H_{19}N_3O_3S$) C, H, N.

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