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Novel 1-aminoethyl-3-arylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridines are potent 5-HT$_6$ agonists

Ronald C. Bernotas [a,*], Steven Lenicek [b], Schuyler Antane [b], Derek C. Cole [c], Boyd L. Harrison [b], Albert J. Robichaud [b], Guo Ming Zhang [d], Deborah Smith [d], Brian Platt [d], Qian Lin [d], Ping Li [d], Joseph Coupet [d], Sharon Rosenzweig-Lipson [d], Chad E. Beyer [d], Lee E. Schechter [d]

[a] *Chemical Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*
[b] *Chemical Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543-8000, USA*
[c] *Chemical Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*
[d] *Neuroscience, Wyeth Research, CN 8000, Princeton, NJ 08543-8000, USA*

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ABSTRACT

A series of 1-aminoethyl-3-arylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridines **10a–z** was prepared as novel 5-HT$_6$ ligands. The best compounds were high affinity, full agonists at 5-HT$_6$ receptors. Several agonists demonstrated good selectivity over other serotonergic and dopaminergic receptors. Acute administration of selective agonist **10e** significantly increased extracellular GABA concentrations in rat frontal cortex. This compound also reduced adjunctive drinking behavior in the rat schedule-induced polydipsia assay, possibly predictive of efficacy in obsessive compulsive disorder and other anxiety related disorders.

1. Introduction

Considerable attention has been focused on the 5-HT$_6$ receptor due to its CNS localization and the therapeutic implications of its proposed role in learning and memory.[1] This intense interest in the 5-HT$_6$ receptor has led to the discovery of several classes of high affinity ligands from Roche, SmithKline, and others. Roche identified sulfonamides including Ro 04-6790 (**1**) as selective 5-HT$_6$ antagonists (Fig. 1).[2] In 1998, scientists at SmithKline described a series of arylsulfonamide-substituted arylpiperazines from which SB-271046 (**2**) was identified as a potent, selective 5-HT$_6$ antagonist.[3] These compounds incorporate a common feature of many 5-HT$_6$ selective ligands: an arylsulfonyl group.

Several series of 5-HT$_6$ agonists based on an indole core have also been identified in the last decade (Fig. 2). Among these are moderately selective 2-alkyl-5-methoxy-tryptamines **3a** and **3b**,[4] 1-aminoethyl-6-arylsulfonamido-indoles **4**,[5] and 5-arylsulfonamido-3-(2-(*R*)-pyrrolidinomethyl)-indoles **5**.[6] A constrained basic side chain was incorporated with an indole in **6** to give 5-HT$_6$ agonists[7] while Alcalde has recently shown that even indenes **7** have agonist activity.[8] Various 1-arylsulfonyl-tryptamines **8** are also 5-HT$_6$ agonists.[9] Such agonists may help elucidate the biological roles of 5-HT$_6$ receptors and may possibly be therapeutic agents in their own right.

One approach to developing novel 5-HT$_6$ ligands, and one we have undertaken, is to reverse the relative roles of the 1- and 3-positions on the indole ring. In such ligands, the location of the

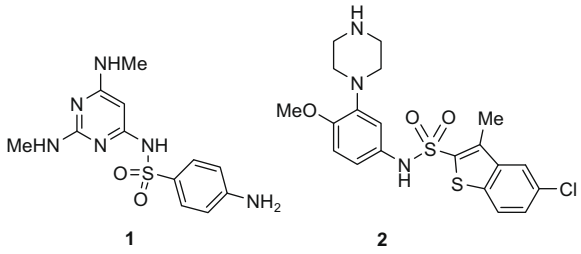

Figure 1. Early 5-HT$_6$ antagonists.

* Corresponding author. Tel.: +1 484 865 2168.
E-mail address: bernotr@wyeth.com (R.C. Bernotas).

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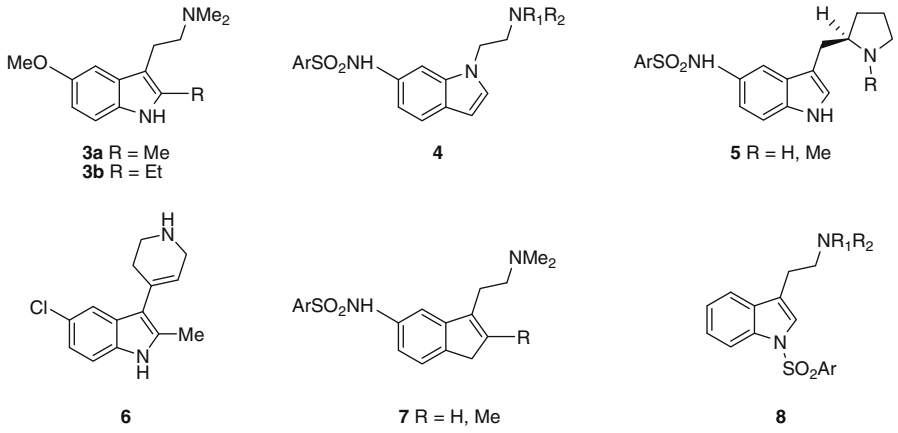


Figure 2. 5-HT_6 agonists.

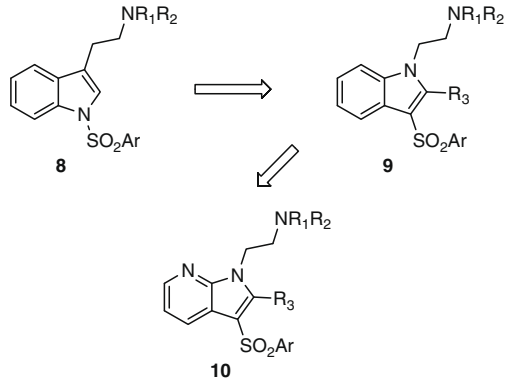
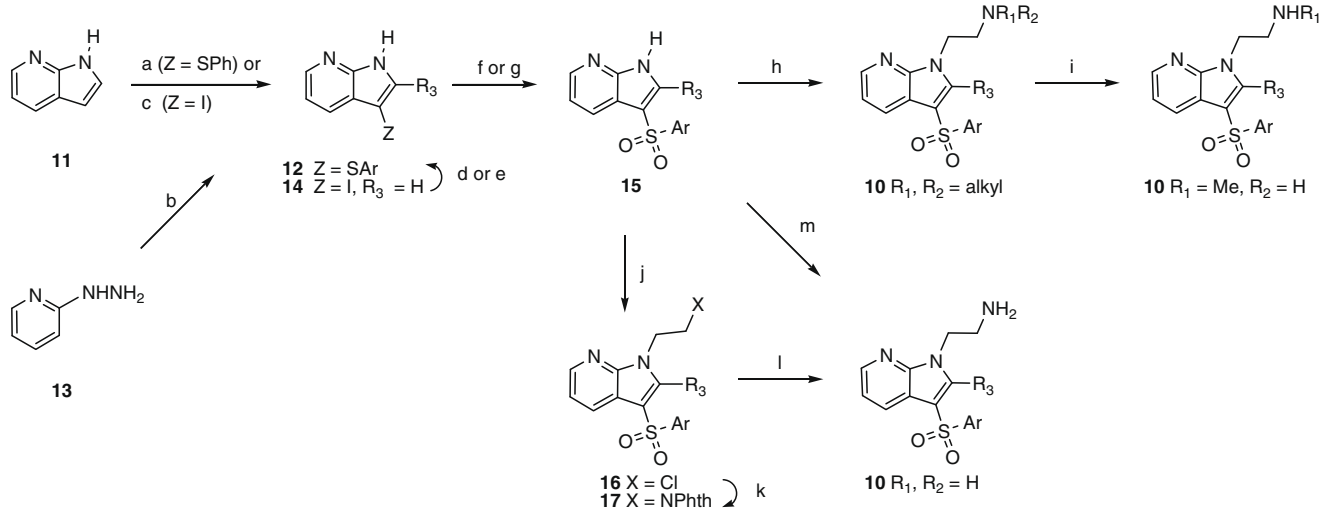


Figure 3. Genesis of pyrrolo[2,3-*b*]pyridines **10** as 5-HT_6 ligands.

aminoethyl side chain is reversed or 'flipped' from the carbon at the 3-position of the indole ring to the indole nitrogen itself. Recently, we described the application of this method to 1-arylsulfonyl-tryptamines **8** to provide 1-aminoethyl-3-arylsulfonyl-1*H*-indoles **9** (Fig. 3).[10] Compounds **9** proved to have comparable affinity for 5-HT_6 receptors relative to tryptamines **8**. We have extended this approach to pyrrolo[2,3-*b*]pyridines **10**, which incorporate an additional nitrogen in the core heterocycle. This replacement of a pyrrolo[2,3-*b*]pyridine for an indole led to a series of high affinity 5-HT_6 ligands, many of which performed as full agonists in a 5-HT_6 functional assay.

2. Chemistry

Our initial target in this series was 1-(*N*,*N*-dimethylaminoethyl)-3-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine **10a,** which should form upon alkylation of 3-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine. However, when we began this work, 3-(arylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridines were essentially unknown. The first synthesis of this system relied on direct arylthiolation of pyrrolo[2,3-*b*]pyridine **11** using methylphenylsulfoxide under Pummerer-type conditions. This approach has been used on indole to provide 3-(phenylthio)-1*H*-indole.[11] However, only a low yield (13%) of 3-(phenylthio)-1*H*-pyrrolo[2,3-*b*]pyridine (**12a** Ar = Ph, R_3 = H) was realized (Scheme 1). 2-Methyl-3-(thiophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine **12b** was prepared in 20% yield by a Fischer indole approach starting with 2-hydrazinopyridine **13**. An alternative



Scheme 1. Reagents and conditions: (a) $PhS(O)CH_3$, TFAA, CH_2Cl_2, −78 °C, then Et_3N, rt, 3 d; (b) $PhSCH_2C(O)Me$, EtOH, reflux, then 1,3-propanediol, reflux; (c) I_2, KI, EtOH; (d) ArSH, K_2CO_3, CuI, DMF, 65 °C, 4 h; (e) ArSH, NaO^{t}Bu, $Pd(PPh_3)_3$, EtOH, heat; (f) $MnSO_4$, 30% H_2O_2, aq $NaHCO_3$, ^{t}BuOH; (g) OXONE®, aq $NaHCO_3$, acetone; (h) NaH, $R_1R_2NCH_2CH_2Hal$, DMF; (i) $CH_3CHClOC(O)Cl$, DCE, reflux, 3 h, then EtOH, reflux, 2 h; (j) DCE, $CH_3N[(CH_2)_7CH_3]_3Cl$, NaOH, H_2O, 60 °C; (k) potassium phthalimide, DMF, 115 °C; (l) hydrazine, dioxane, heat; (m) $ClCH_2CH_2NH_2{\cdot}HCl$, NaOH, $(n\text{-}Bu)_4NHSO_4$.

method tried was Harris' arylthiolation procedure developed for indoles.[12] Treatment of **11** and thiophenol with iodine and potassium iodide afforded only trace amounts of **12a**, accompanied by large amounts of 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine **14**. Ready isolation of **14** suggested it could serve as an intermediate for the preparation of **12**. Thus, treatment of **14** with arylthiols in the presence of copper iodide gave **12d** and **12e** in moderate to good yield.[13] Alternatively, the coupling could be accomplished using $Pd(PPh_3)_4$ as a catalyst and NaO^{t}Bu as the base in hot ethanol to give **12**. Oxidation of sulfides **12** to sulfones **15** was accomplished using $MnSO_4/H_2O_2$ or, preferably, OXONE®.[14]

With the core 3-arylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridines in hand, we turned to installation of the basic side chain. In the presence of NaH, direct alkylation of **15** with aminoethylchlorides or bromides ($R_1R_2N(CH_2)_2Hal$), as the HCl or HBr salts, provided targets **10** (R_1, R_2 = alkyl), sometimes accompanied by a small amount of the regioisomer from alkylation at the other nitrogen. Secondary amines **10** (R_1 = Me, R_2 = H) were prepared from tertiary amines **10** (R_1, R_2 = Me) by monodealkylation with 1-chloroethyl chloroformate as described by Olofson.[15] Initially, primary amines **10** (R_1, R_2 = H) were prepared by Gabriel synthesis via chloroethyl intermediates **16**, which were converted to the corresponding phthalimides **17** and deprotected using hydrazine to afford **10** (R_1, R_2 = H). Direct alkylation using sodium hydroxide, 2-aminoethylchloride hydrochloride with $(n\text{-Bu})_4NHSO_4$ as a phase transfer catalyst, as reported by Alvarez-Builla for pyrroles,[16] proved much more efficient and was used to prepare most of the primary amines.

To facilitate SAR studies, a direct sulfonylation approach was developed to more quickly prepare tertiary amines **10** (Scheme 2). Commercial pyrrolo[2,3-*b*]pyridine **11** was alkylated with *N*,*N*-dimethylaminoethylchloride to provide **18** which was treated with arylsulfonyl chloride at elevated temperatures in nitrobenzene in the presence of silver triflate.[17] This two-step approach provided targets **10** (R_1, R_2 = Me) in poor to good yield and allowed the rapid expansion of the arylsulfonyl SAR to include more substituted phenyl rings as well as heterocycles such as thiophenes. Secondary amines **10** (R_1 = Me, R_2 = H) were prepared as described in Scheme 1.

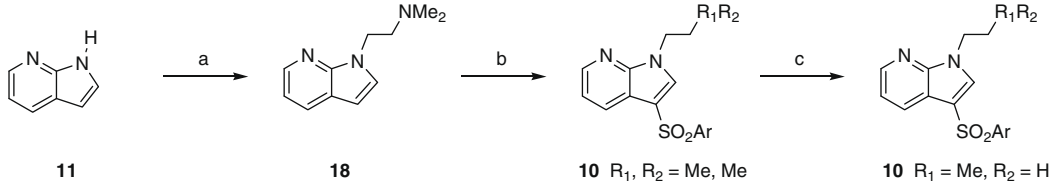
Table 1
5-HT_6 receptor binding and adenylyl cyclase activation assays[18,9]

	Ar	R_1	R_2	R_3	5-HT_6 K_i (nM)	cAMP assay for 5-HT_6	
						EC_{50} or IC_{50} (nM)	E_{max} or I_{max} (%)
9a	Ph	Me	Me	H	20 (±0.2)	366 (±23)	63
9b	Ph	H	H	H	25 (±2)	178 (±19)	67
10a	Ph	Me	Me	H	23 (±2)	25 (±0.1)	94
10b	Ph	H	H	H	5.5 (±0.6)	27 (±4)	100
10c	Ph	H	H	Me	4.2 (±0.4)	20 (±0.3)	85
10d	Ph	Me	Me	Me	4.7 (±0.1)	47 (±19)	100
10e	3-FPh	Me	Me	H	4.8 (±0.3)	7.3 (±1.6)	100
10f	3-FPh	Me	H	H	1.0 (±3.4)	6.2 (±0.1) (ant)	93 (ant)
10g	3-FPh	H	H	H	4.7 (±0.6)	24 (±3)	100
10h	3-FPh	$-(CH_2)_4-$		H	88 (±3)	Not tested	Not tested
10i	3-ClPh	Me	Me	H	2.3 (±0.2)	15 (±0.4)	86
10j	3-ClPh	Me	H	H	0.3 (±0)	8.3 (±0.6) (ant)	100 (ant)
10k	3-ClPh	H	H	H	2.0 (±0.3)	18 (±5)	94
10l	3-ClPh	$-(CH_2)_4-$		H	45 (±1)	Not tested	Not tested
10m	4-FPh	Me	Me	H	45 (±5)	30 (±3)	84
10n	4-FPh	H	H	H	22 (±3)	166 (±2)	100
10o	2-CF_3Ph	H	H	H	2.1 (±0.1)	85 (±4)	97
10p	3-CF_3Ph	H	H	H	2.1 (±0.1)	110 (±0.3)	83
10q	3,5-DiClPh	Me	Me	H	4.3 (±0.4)	28 (±6)	80
10r	3,5-DiClPh	H	H	H	2.9 (±0.4)	35 (±10)	65
10s	2,5-DiClPh	Me	Me	H	11.7 (±4)	15 (±2) (ant)	97 (ant)
10t	2,6-DiClPh	Me	Me	H	9.0 (±2)	31 (±11)	66
10u	1-Naphthyl	Me	Me	H	1.0 (±0.2)	51 (±3)	63
10v	1-Naphthyl	H	H	H	1.6 (±0)	63 (±23)	65
10w	2-Thienyl	Me	Me	H	15 (±2)	154 (±32)	74
10x	5-Cl-thien-2-yl	Me	Me	H	3.3 (±0)	32 (±8)	93
10y	6-Cl-imidazo[2,1-*b*][1,3]thiazo-5-yl	Me	Me	H	0.9 (±0.1)	120 (±5)	71
10z	6-Cl-imidazo[2,1-*b*][1,3]thiazo-5-yl	Me	H	H	0.9 (±0.2)	5.4 (±7.2) (ant)	89 (ant)

5-HT_6 receptors were human clones stably expressed in Hela cells using [^{3}H]LSD as the radioligand. IC_{50} and I_{max} values for antagonists in the adenylyl cyclase assay are indicated by 'ant' following the value.

3. In vitro biological assays

Final compounds **10** were tested for 5-HT_6 affinity in a standard radioligand binding assay[18] using human-cloned 5-HT_6 receptors stably transfected in Hela cells (Table 1). Comparison of 1-(aminoethyl)-3-phenylsulfonyl-*1H*-indoles **9a** and **9b** with their direct analogs (**10a** and **10b**, respectively) demonstrates that introduction of the second (pyridyl) nitrogen gave comparable or increased affinity for 5-HT_6 receptors. In this instance, the primary amine had modestly higher affinity compared to the tertiary amine but, in general, there was little difference in affinity between these basic groups. Methyl substitution at the 2-position (**10c**, **10d**) also provided high affinity ligands. Several modifications of the arylsulfonyl by halogen substitution were examined. Introduction of a meta-fluorine (**10e–g**) on the arylsulfonyl group maintained or slightly increased affinity. Interestingly, secondary amine **10f** had particularly high affinity with a K_i = 1 nM. 3-Chloro substitution (**10i–k**) provided a 2–3-fold increase in affinity relative to the 3-fluoro compounds and the same trend toward higher affinity for monomethylamines (**10j**) was observed. In fact, **10j** had a K_i = 0.3 nM, the best 5-HT_6 affinity for any compound described here. In contrast, larger basic groups such as pyrrolidine (**10h**, **10l**) or substitution at the 4-position of the arylsulfonyl (**10m**, **10n**) resulted in compounds with considerably weaker 5-HT_6 receptor affinity. Other modifications including trifluoromethyl (**10o**, **10p**) and dichloro substitution (**10q–t**) were well tolerated by the receptor. Replacing the phenyl with a 1-naphthyl group gave high affinity ligands **10u** and **10v**, a result consistent with trends seen in the 1-(aminoethyl)-3-phenylsulfonyl-*1H*-indole series we reported earlier.[10] Finally, heterocycles including thiophenes (**10w**, **10x**) and imidazothiazoles (**10y**, **10z**) also provided ligands with excellent 5-HT_6 affinity.



Scheme 2. Reagents and conditions: (a) NaH, $Me_2NCH_2CH_2Cl$, DMF, rt, 18 h; (b) $ArSO_2Cl$, AgOTf, $PhNO_2$, 100–125 °C, 20–25 h; (c) $CH_3CHClOC(O)Cl$, DCE, reflux, concentrate, then EtOH, reflux.

Nearly all the compounds were further tested in an adenylyl cyclase assay[19] to determine whether the pyrrolo[2,3-*b*]pyridine ligands were able to modulate 5-HT$_6$ function in vitro. *Remarkably, most of the primary* (R_1, R_2 = H) *and tertiary amines* (R_1, R_2 = Me) *in the series were potent and efficacious agonists.* Thus, introduction of the additional nitrogen provided full agonists in the adenylyl cyclase assay compared to the parent indole-based series (**9**), which at best were weak partial agonists. Favored substitutions for the most potent agonists were the 3-fluorophenylsulfonyl and 3-chlorophenylsulfonyl groups, which resulted in potent, full agonists. Among these compounds, **10e** (**WAY-208466**) was a standout with an EC_{50} = 7.3 nM and E_{max} = 100% and was chosen for further studies.[20] Most other substitution patterns in the primary and tertiary amines still provided agonists except for 2,5-dichlorophenylsulfonyl **10s**, which was an antagonist. Interestingly, high affinity monomethylamines **10** (R_1 = Me, R_2 = H) were potent *antagonists* in the adenylyl cyclase assay, regardless of the arylsulfonyl group. For example, in the 3-fluorophenyl and 3-chlorophenyl series, primary amines were full, potent agonists, secondary amines were full, potent antagonists, and tertiary amines reverted back to being full agonists. The reasons for this empirical observation are under investigation.

Selected compounds were further tested for binding selectivity against other serotonergic and dopaminergic receptors (Table 2). Binding selectivity of >50-fold for 5-HT$_6$ receptors compared to other serotonin and dopamine receptors was observed for four compounds. In contrast, **10k** was less selective, especially against 5-HT$_2$ receptors.

4. In vivo biological assays

The in vivo activity of **10e** (**WAY-208466**) was also evaluated.[21] Microdialysis techniques were used to show the neurochemical effects of **WAY-208466** in vivo. In the rat frontal cortex, acute treatment with **WAY-208466** (30 mg/kg, sc) significantly ($P < 0.05$) increased extracellular GABA concentrations (Fig. 4, top panel) without altering levels of glutamate (Fig. 4, bottom panel). These results show a unique profile of **WAY-208466** to preferentially elevate cortical GABA levels, which is consistent with the in vivo activity of other selective 5-HT$_6$ receptor agonists.[9c,20] Consistent with this neurochemical effect, **WAY-208466** was shown to reduce adjunctive drinking behavior in the rat schedule-induced polydipsia (SIP) assay (Fig. 5), a model considered to be predictive for efficacy in obsessive compulsive disorder (OCD) and related anxiety disorders. In a non-scheduled control comparing vehicle to **WAY-208466**, the test compound did not increase water intake.

Table 2
Binding affinity for serotonin and dopamine receptors (IC_{50} values in nM, or % inhibition at 1 μM)

	10b	10e	10i	10k	10u
5-HT$_6$	5.5	4.8	2.3	2.0	1.0
5-HT$_{1B}$	11%	30%	46%	nt	40%
5-HT$_{1D}$	16%	16%	10%	nt	0%
5-HT$_{1F}$	14%	22%	29%	nt	10%
5-HT$_{2A}$ (ag)	>5000	351	131	11	938
5-HT$_{2C}$ (ag)	>5000	644	477	44	1135
5-HT$_7$	>5000	4764	1217	1362	511
D_2	>5000	>5000	>5000	>5000	>5000
D_3	>5000	>5000	>5000	>5000	1558
D_4	>5000	>5000	>5000	>5000	>5000

Receptors were all human clones stably expressed in CHO cells (5-HT receptors) or CHO-K1 cells (dopamine receptors) except 5-HT$_6$ receptors (Hela cells). Radioligands were as follows: 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$, 5-HT$_{2C}$: [^{3}H]-5-HT: 5-HT$_{2A}$: [1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane ([^{125}I]DOI); 5-HT$_6$, 5-HT$_7$: [^{3}H]LSD; dopamine D_2, D_3, and D_4: [^{3}H]spiperone. ag = agonist.

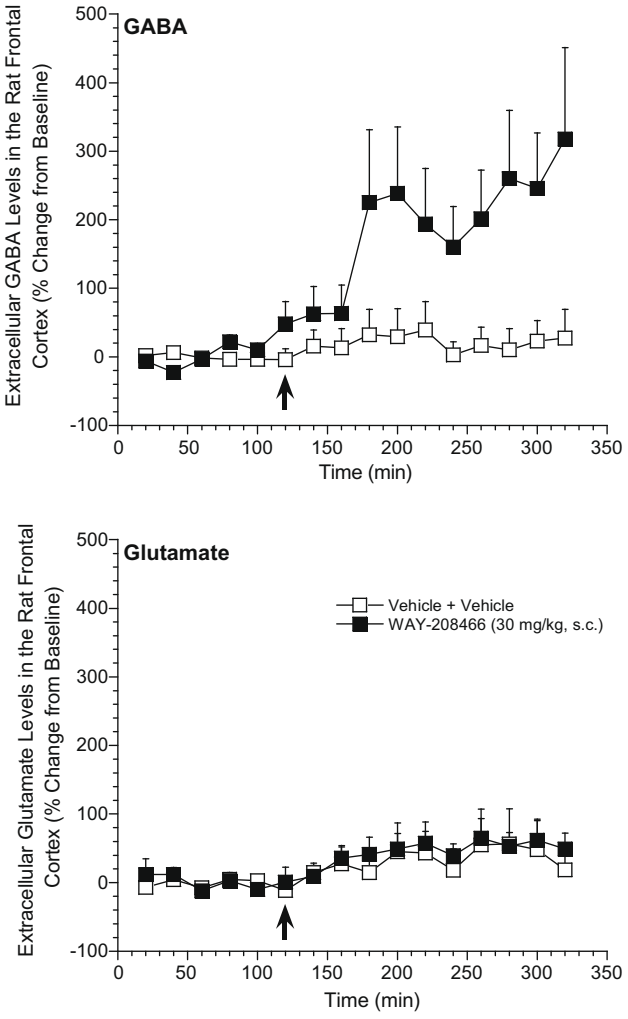


Figure 4. GABA and glutamate levels in the rat frontal cortex following acute treatment with **WAY-208466**. Arrows represent time of 5-HT$_6$ agonist administration. $^*P < 0.05$ compared to vehicle treatment.

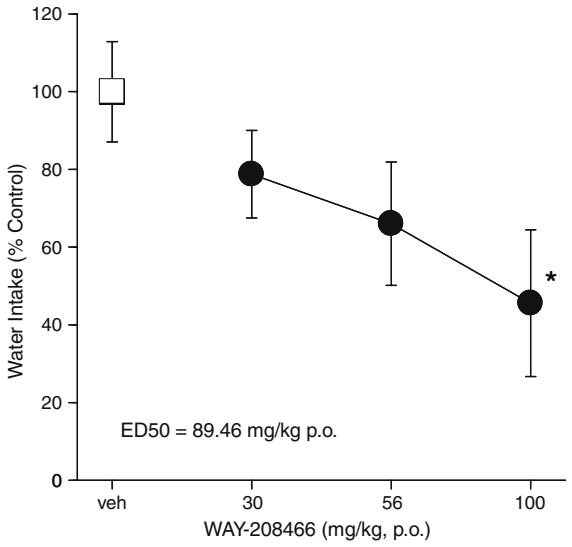


Figure 5. Schedule-induced polydipsia (SIP) in rats after oral dosing with **WAY-208466**. $^*P < 0.05$ compared to vehicle treatment.

5. Conclusions

In summary, novel 1-aminoethyl-3-arylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridines **10** were prepared by several routes. These compounds invert the relative positions of the basic side chain and arylsulfonyl group in known indole-based 5-HT_6 ligands and then introduce an additional nitrogen to the core structure. Binding assays indicated these compounds had generally high affinity for the target receptors, especially **10f**, **10j**, **10y** and **10z** with K_i values of 1.0 nM or less. Some exhibited excellent selectivity versus dopaminergic and other serotonergic receptors. All but one of the primary and *N*,*N*-dimethyl amines were agonists with intrinsic activity of 63% or better, including several full, potent agonists. Of particular note is compound **10e** (**WAY-208466**), which was a selective, full agonist of excellent potency in a 5-HT_6 functional assay (adenylyl cyclase activation) with an EC_{50} = 7.3 nM and E_{max} = 100%. Moreover, this compound displayed in vivo activity consistent with other selective 5-HT_6 receptor agonists. Further explorations of this and related series will be reported in the near future.

6. Experimental

6.1. General experimental

Solvents and chemicals were purchased from EM Sciences, VWR, and Aldrich Chemical Co. and used without further purification. High-resolution mass spectra were obtained on a Waters LC-TOFMS instrument and were measured to within 5 ppm of calculated values. ^{1}H NMR spectra were taken on a Bruker DPX300 (300 MHz) or Varian (400 MHz) instruments. NMR data are given as delta values (δ) ppm using tetramethylsilane as an internal standard (δ = 0 ppm). In the peak shape descriptions, v is very, br is broad, fc indicates very fine coupling, and app is apparent. Chromatography refers to purification on flash silica gel. Compounds with HRMS data were also run on an Agilent 1200H-MSD2 reverse phase analytical HPLC column (Xterra RP18, 3.5 u, 150 × 4.6 mm), detecting at 210–370 nM, and eluting with a 85:15–5:95 gradient of 10 mM aq ammonium formate/50:50 acetonitrile/water. Purity in this assay is given as HPLC purity.

6.1.1. *N*,*N*-Dimethyl-*N*-{2-[3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethyl}amine hydrochloride (10a)

Compound **15a** (400 mg, 1.55 mmol) in dry DMF (5 mL) stirred at 0 °C was treated with sodium hydride (60% in oil, 97 mg, 2.43 mmol). The reaction was stirred 3 h at 20 °C, then cooled to −20 °C and treated with 2-(dimethylamino)ethyl chloride hydrochloride (336 mg, 2.33 mmol). After heating at 60 °C for 16 h, the reaction was cooled, quenched with H_2O (150 mL), and extracted with ethyl acetate (3 × 150 mL). The organic phases were washed with brine and dried over $MgSO_4$. Concentration in vacuo afforded the free amine **10a** as a yellowish gum (150 mg, 29%, $R_f \sim 0.1$ in 1:49 methanol/CH_2Cl_2), which was dissolved in ethanol and treated with 1 N aqueous HCl (4 mL, 4 mmol). Concentration in vacuo to dryness followed by crystallization of the residue from ethanol/ether gave **10a** dihydrochloride as a light tan solid (111 mg). Mp: 214–217 °C. ^{1}H NMR (DMSO-d_6): 10.4 (1H, br s), 8.59 (1H, s), 8.44 (1H, d, *J* = 4.7 Hz), 8.22 (1H, d, *J* = 8.0 Hz), 8.01 (2H, d, *J* = 8.4 Hz), 7.55–7.65 (3H, m), 7.36 (1H, m), 4.74 (2H, t, *J* = 6.5 Hz), 3.64 (2H, m), 2.81 (6H, d, *J* = 4.8 Hz). MS (ES+): 330 (100%, M+H). Anal. Calcd for $C_{17}H_{19}N_3O_2S{\cdot}2HCl$: C, 50.75; H, 5.26; N, 10.44. Found: C, 50.88; H, 5.35; N, 10.25.

6.1.2. 2-[3-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethylamine hydrochloride (10b)

A solution of **17a** (4.54 g, 10.5 mmol) in dioxane (80 mL) was treated with anhydrous hydrazine (8.3 mL, 265 mmol). The solution was heated at 50 °C for 3 h and concentrated in vacuo. The residue was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The extracts were dried over $MgSO_4$ and concentrated in vacuo to a clear gum. Chromatography, eluting with 10:90 methanol/CH_2Cl_2, gave the free amine of **10b** as a clear gum (2.90 g, 92%, $R_f \sim 0.6$ in 15:85 methanol/CH_2Cl_2). The free amine was dissolved in ethanol and acidified with 2 N aqueous HCl (15 mL, 30 mmol). Concentration in vacuo to dryness and crystallization from ethanol/ether gave the dihydrochloride of **10b** as a white solid (3.20 g, 81%). Mp: 195–197 °C. ^{1}H NMR (DMSO-d_6): 8.51 (1H, s), 8.42 (1H, d, *J* = 4.7 Hz), 8.21 (1H, d, *J* = 8.0 Hz), 8.2 (3H, br s), 8.01 (2H, d, *J* = 7.9 Hz), 7.66–7.55 (3H), 7.35 (1H, dd, *J* = 4.7, 7.9 Hz), 4.60 (2H, t, *J* = 6.0 Hz), 3.36 (2H, m). MS (ES+): 302 (100%, M+H). Anal. Calcd for $C_{15}H_{15}N_3O_2S{\cdot}2HCl$: C, 48.13; H, 4.58; N, 11.23. Found: C, 47.95; H, 4.59; N, 10.95.

6.1.3. 2-[2-Methyl-3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethylamine hydrochloride (10c)

Prepared from **15b** in a manner analogous to that of **10g** affording **10c** as a hygroscopic white solid in 40% yield. Mp >250 °C. ^{1}H NMR (DMSO-d_6): 8.34 (1H, d, *J* = 4.7 Hz), 8.27 (1H, d, *J* = 8.0 Hz), 8.20 (3H, v br s), 7.95 (2H, d, *J* = 7.5 Hz), 7.62 (1H, app t, *J* = 6.6 Hz), 7.57 (2H, app t, *J* = 7.0 Hz), 7.32 (1H, m), 4.52 (2H, t, *J* = 6.7 Hz), 3.24 (2H, m), 2.81 (3H, s). MS (ES+): 316 (M+H). Anal. Calcd for $C_{16}H_{17}N_3O_2S{\cdot}2HCl$: C, 49.49; H, 4.93; N, 10.82. Found: C, 49.74; H, 4.80; N, 10.82.

6.1.4. *N*,*N*-Dimethyl-*N*-{2-[2-methyl-3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethyl}amine hydrochloride (10d)

Prepared from **15b** by the procedure of **10a** except purifying by chromatography eluting with 3:5:92 methanol/concd NH_4OH/dichloromethane, then by chromatography eluting with 2:1:97 ethanol/triethylamine/ethyl acetate to afford the free amine of **10d** (128 mg, 51%). The free amine was converted to the hydrochloride by dissolving in ethanol, treating with excess 1 M aqueous HCl, and concentrating to dryness. The residue was crystallized from ether/ethanol to afford the title compound as a hygroscopic white solid (138 mg). Mp: 210–214 °C. ^{1}H NMR (DMSO-d_6): 10.53 (1H, br s), 8.36 (1H, dd, *J* = 1.5, 4.7 Hz), 8.29 (1H, dd, *J* = 1.5, 7.9 Hz), 7.96 (2H, d, *J* = 7.3 Hz), 7.63 (1H, app t, *J* = 7.3 Hz), 7.57 (2H, app t, *J* = 7.8 Hz), 7.33 (1H, dd, *J* = 4.7, 7.9 Hz), 4.69 (2H, t, *J* = 6.9 Hz), 3.46 (2H, m), 2.84 (9H, m). MS (ES+): 343 (M+H). Anal. Calcd for $C_{18}H_{21}N_3O_2S{\cdot}1.5HCl{\cdot}0.4H_2O$: C, 53.34; H, 5.79; N, 10.37. Found: C, 53.00; H, 5.33; N, 10.11.

6.1.5. *N*-(2-{3-[(3-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10e)

A stirred solution of **18** (1.66 g, 8.8 mmol) in nitrobenzene (30 mL) under nitrogen was treated with 3-fluorophenylsulfonyl chloride (1.88 g, 9.7 mmol). Silver trifluoromethylsulfonate (2.94 g, 11.4 mmol) was added, producing an immediate precipitate. The reaction was heated at 100 °C for 22 h, then cooled and filtered through a cotton plug. The filtrate was treated with water (30 mL) and saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed eluting with 2:98 concentrated ammonium hydroxide/ethanol, isolating the component with $R_f \sim 0.2$ as a viscous oil which solidified (1.25 g, 41%). The free amine was dissolved in warm ethanol (25 mL), treated with 4 M HCl in dioxane (2.5 mL) and the resulting pale yellow solid was suction filtered to afford **10e** as the dihydrochloride (1.07 g, 29%). Mp: 191–192 °C. ^{1}H NMR (DMSO-d_6): 10.53 (1H, br s), 8.60 (1H, s), 8.41 (1H, dd, *J* = 1.6, 4.8 Hz), 8.22 (1H, dd, *J* = 1.6, 7.9 Hz), 7.83 (1H, app d, *J* = 6.8 Hz), 7.79 (1H, app dt, *J* = 1.6, 8.4 Hz), 7.61 (1H, m), 7.47 (1H, m), 7.33 (1H, dd, *J* = 4.8, 7.9 Hz), 4.72 (2H, t, *J* = 6.5 Hz), 3.61 (2H, m), 2.78 (6H, d, *J* = 4.8 Hz). MS (ES+): 348 (M+H). Anal. Calcd

for $C_{17}H_{18}FN_3O_2S{\cdot}2HCl$: C, 48.58; H, 4.80; N, 10.00. Found: C, 48.55; H, 4.73; N, 9.90.

6.1.6. *N*-(2-{3-[(3-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*-methylamine hydrochloride (10f)

Compound **10f** was prepared from the free amine of **10e** by the procedure of **10j** to give a white solid in 57% yield. Mp 260–262 °C. ^{1}H NMR (DMSO-d_6): 8.80 (2H, v br s), 8.52 (1H, s), 8.40 (1H, dd, J = 1.5, 4.7 Hz), 8.22 (1H, dd, J = 1.5, 7.9 Hz), 7.84 (1H, ddd, J = 0.9, 1.7, 7.8 Hz), 7.78 (1H, d with fc, J = 8.3 Hz), 7.62 (1H, m), 7.47 (1H, m), 7.33 (1H, dd, J = 4.8, 7.9 Hz), 4.62 (2H, t, J = 5.8 Hz), 3.45 (2H, br t, J = 5.6 Hz), 2.53 (3H, s). MS (ES+): 334.1 (M+H). Anal. Calcd for $C_{16}H_{16}FN_3O_2S{\cdot}HCl$: C, 51.96; H, 4.63; N, 11.36. Found: C, 51.55; H, 4.71; N, 11.15.

6.1.7. 2-{3-[(3-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethylamine hydrochloride (10g)

Essentially following the general procedure of Alvarez-Builla,[16] compound **15c** (270 mg, 0.98 mmol), 2-chloroethylamine hydrochloride (147 mg, 1.27 mmol), tetrabutylammonium sulfate (85 mg, 0.25 mmol), and powdered NaOH (157 mg, 3.92 mmol) in dioxane (3.0 mL) was heated at reflux for 22 h. The reaction was cooled and diluted with ethyl acetate and filtered. The filtrate was concentrated in vacuo and the residue purified by chromatography eluting with 4:5:91 methanol/concd NH_4OH/dichloromethane to give the free amine of **10g** as a light yellow solid (154 mg, 49%). The hydrochloride was prepared to give **10g** as a white, hygroscopic solid (158 mg). Mp: 202–204 °C. ^{1}H NMR (DMSO-d_6): 8.55 (1H, s), 8.43 (1H, dd, J = 1.4, 4.7 Hz), 8.24 (1H, dd, J = 1.6, 7.9 Hz), 8.14 (3H, v br s), 7.87 (1H, dd, J = 0.9, 7.8 Hz), 7.81 (1H, sl. br d, J = 8.4 Hz), 7.64 (1H, m), 7.50 (1H, app dt, J = 2.4, 8.5 Hz), 7.36 (1H, dd, J = 4.7, 7.9 Hz), 4.60 (2H, t, J = 6.0 Hz), 3.37 (2H, m). MS (ES+): 320 (M+H). Anal. Calcd for $C_{15}H_{14}FN_3O_2S{\cdot}1.5HCl$: C, 48.17; H, 4.18; N, 11.23. Found: C, 48.43; H, 4.33; N, 11.07.

6.1.8. 3-[(3-Fluorophenyl)sulfonyl]-1-(2-pyrrolidin-1-ylethyl)-1*H*-pyrrolo[2,3-*b*]pyridine hydrochloride (10h)

Prepared as in **10a** except using **15c** and 1-(2-chloroethyl)pyrrolidine hydrochloride as reactants and crystallizing from ethanol/ether to afford **10h** as an off-white solid (66% yield). Mp: 198–200 °C. ^{1}H NMR (DMSO-d_6): 10.64 (1H, br s), 8.66 (1H, s), 8.46 (1H, dd, J = 1.4, 4.7 Hz), 8.28 (1H, dd, J = 1.5, 7.9 Hz), 7.88 (1H, d with fc, J = 8.1 Hz), 7.84 (1H, d with fc, J = 8.2 Hz), 7.66 (1H, m), 7.52 (1H, m), 7.39 (1H, dd, J = 4.7, 7.9 Hz), 4.75 (2H, t, J = 6.6 Hz), 3.70 (2H, m, obscured by water peak), 3.56 (2H, m), 3.05 (2H, m), 2.00 (2H, m), 1.83 (2H, m). MS (ES+): 374.1 (M+H). Anal. Calcd for $C_{19}H_{20}FN_3O_2S{\cdot}2HCl$: C, 51.13; H, 4.97; N, 9.41. Found: C, 51.03; H, 5.14; N, 9.20.

6.1.9. *N*,*N*-Dimethyl-*N*-(2-{3-[(3-chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)amine hydrochloride (10i)

Prepared from **15d** (170 mg, 0.58 mmol) in a manner analogous to that of **10a** affording the free amine **10i** as an off-white solid (140 mg, 66%). The HCl salt was made in the same manner as in **10b** to give **10i** dihydrochloride as an off-white solid (106 mg). Mp: 182–186 °C. ^{1}H NMR (DMSO-d_6): 10.3 (1H, br s), 8.60 (1H, s), 8.45 (1H, d, J = 4.7 Hz), 8.23 (1H, d, J = 8.1 Hz), 8.15–8.05 (2H, m), 7.43 (2H, t, J = 8.8 Hz), 7.37 (1H, m), 4.74 (2H, t, J = 6.5 Hz), ~3.6 (2H, obscured by H_2O), 2.83 (6H, d, J = 4.8 Hz). MS (ES+): 364 (100%, M+H). Anal. Calcd for $C_{17}H_{18}ClN_3O_2S{\cdot}2HCl$: C, 46.75; H, 4.62; N, 9.62. Found: C, 47.06; H, 4.41; N, 9.34.

6.1.10. *N*-(2-{3-[(3-Chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*-methylamine hydrochloride (10j)

To a stirred solution under nitrogen of **10i** (0.540 g, 1.49 mmol) in 1,2-dichloroethane (10 mL) was added 1-chloroethyl chloroformate (0.40 mL, 3.7 mmol). The reaction was heated at reflux for 2 h, cooled, and concentrated in vacuo. The residue was treated with ethanol (10 mL), heated at reflux for 2 h, and concentrated in vacuo. The residue was chromatographed using 2:98 concentrated ammonium hydroxide/ethanol as eluent, isolating the component with $R_f \sim 0.2$ as a semi-solid (311 mg, 60%). The free amine was dissolved in ethanol (10 mL), treated with 4 M HCl in dioxane (0.50 mL) and the resulting pale yellow solid was suction filtered to afford **10j** hydrochloride (274 mg, 48%). Mp: 263–265 °C (dec.). ^{1}H NMR (DMSO-d_6): 8.79 (2H, v br s), 8.53 (1H, s), 8.40 (1H, dd, J = 1.5, 4.6 Hz), 8.22 (1H, dd, J = 1.5, 7.9 Hz), 7.97 (2H, m), 7.68 (1H, ddd, J = 1.2, 2.1, 8.0 Hz), 7.58 (1H, app t, J = 8.1 Hz), 7.34 (1H, dd, J = 4.6, 7.9 Hz), 4.62 (2H, t, J = 6.0 Hz), 3.43 (2H, br m), 2.53 (3H, br t, J = 5.1 Hz). MS (ES+): 348 (100%, M+H). Anal. Calcd for $C_{16}H_{16}ClN_3O_2S{\cdot}HCl$: C, 49.75; H, 4.44; N, 10.88. Found: C, 49.73; H, 4.11; N, 10.75.

6.1.11. 2-{3-[(3-Chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethylamine hydrochloride (10k)

Compound **10k** was prepared from **17b** (778 mg, 1.67 mmol) in the same manner as **10b** to give an off-white solid (369 mg, 1.10 mmol, 66%, $R_f \sim 0.3$ in 10:90 methanol/CH_2Cl_2). The dihydrochloride salt of **10k** was prepared as in **10a** to afford a white solid (353 mg, 52%). Mp: 203–206 °C. ^{1}H NMR (DMSO-d_6): 8.56 (1H, s), 8.44 (1H, d, J = 4.7 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.1 (3H, br s), 7.95–8.05 (2H, m), 7.70–7.75 (1H, m), 7.63 (1H, t, J = 8.2 Hz), 4.60 (2H, t, J = 6.0 Hz), 3.38 (2H, m). MS (ES+): 336 (100%, M+H). Anal. Calcd for $C_{15}H_{14}ClN_3O_2S{\cdot}2HCl$: C, 44.08; H, 3.95; N, 10.28. Found: C, 44.37; H, 3.96; N, 10.33.

6.1.12. 3-[(3-Chlorophenyl)sulfonyl]-1-(2-pyrrolidin-1-ylethyl)-1*H*-pyrrolo[2,3-*b*]pyridine hydrochloride (10l)

Prepared from **15d** in the same manner as **10h** to afford the free amine as an amber solid (155 mg, 73%) and the dihydrochloride as a white solid. Mp: 183–185 °C. ^{1}H NMR (DMSO-d_6): 10.67 (1H, br s), 8.67 (1H, s), 8.47 (1H, dd, J = 1.4, 4.6 Hz), 8.28 (1H, dd, J = 1.5, 8.1 Hz), 8.02 (2H, m), 7.73 (1H, d with fc, J = 7.2 Hz), 7.64 (1H, app t, J = 8.1 Hz), 7.39 (1H, dd, J = 4.7, 7.9 Hz), 4.75 (2H, t, J = 6.4 Hz), 3.73 (2H, m, partly obscured by water peak), 3.56 (2H, m), 3.05 (2H, m), 1.98 (2H, m), 1.84 (2H, m). MS (ES+): 390 (M+H). Anal. Calcd for $C_{19}H_{20}ClN_3O_2S{\cdot}2HCl{\cdot}0.4H_2O$: C, 48.55; H, 4.89; N, 8.94. Found: C, 48.54; H, 4.84; N, 8.85.

6.1.13. *N*,*N*-Dimethyl-*N*-(2-{3-[(4-fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)amine hydrochloride (10m)

Compound **10m** was prepared from **15e** (160 mg, 0.60 mmol) in a manner analogous to that of compound **10a** to give the free amine as an off-white solid (109 mg, 52%). The dihydrochloride of **10m** was made in the same manner as compound **10b** affording an off-white solid (119 mg). Mp: 189–192 °C. ^{1}H NMR (DMSO-d_6): 10.3 (1H, br s), 8.60 (1H, s), 8.45 (1H, d, J = 4.7 Hz), 8.23 (1H, d, J = 8.1 Hz), 8.15–8.05 (2H, m), 7.43 (2H, app t, J = 8.8 Hz), 7.37 (1H, m), 4.74 (2H, app t, J = 6.5 Hz), ~3.6 (2H, obscured by H_2O), 2.83 (6H, d, J = 4.8 Hz). MS (ES+): 348 (100%, M+H). Anal. Calcd for $C_{17}H_{18}N_3O_2S{\cdot}2HCl$: C, 48.58; H, 4.80; N, 10.00. Found: C, 48.40; H, 4.89; N, 9.77.

6.1.14. 2-{3-[(4-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethylamine hydrochloride (10n)

A suspension of **17c** (723 mg, 1.61 mmol) and anhydrous hydrazine (1.00 mL, 1.02 g, 32 mmol) in dioxane (20 mL) was stirred for 16 h at 20 °C. The reaction mixture was concentrated in vacuo, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 phases were dried over $MgSO_4$ and concentrated to a white gum. This intermediate product was resubmitted to reaction by dissolving in ethanol (20 mL), treating with anhydrous

hydrazine (0.50 mL, 0.50 g, 16 mmol), and heating for 4 h at 40 °C. The cooled reaction mixture was concentrated in vacuo, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed eluting with 3:97 methanol/CH_2Cl_2 to afford the free amine as an off-white solid (375 mg, 73%, $R_f \sim 0.3$ in 10:90 methanol/CH_2Cl_2). The hydrochloride was made as in **10b**, to obtain the title compound as a white solid (385 mg). Mp: 193–197 °C. ^{1}H NMR (DMSO-d_6): 8.51 (1H, s), 8.43 (1H, d, J = 4.7 Hz), 8.22 (1H, d, J = 7.9 Hz), 8.05–8.15 (5H), 7.43 (2H, app t, J = 8.9 Hz), 7.36 (1H, m), 4.59 (2H, t, J = 6.0 Hz), 3.38 (2H, m). MS (ES+): 320 (M+H). Anal. Calcd for $C_{15}H_{14}FN_3O_2S{\cdot}1.5HCl{\cdot}0.5H_2O$: C, 47.03; H, 4.34; N, 10.97. Found: C, 47.11; H, 4.24; N, 10.95.

6.1.15. 2-(3-{[2-(Trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethylamine hydrochloride (10o)

The free amine **10o** was prepared in 32% yield from **15f** using the procedure for **10g**. The dihydrochloride was obtained as a white hygroscopic solid. Mp: 182–185 °C. ^{1}H NMR (DMSO-d_6): 8.52 (1H, s), 8.46 (1H, dd, J = 1.4, 4.7 Hz), 8.40 (1H, d, J = 7.5 Hz), 8.19 (1H, dd, J = 1.5, 8.1 Hz), 8.05 (3H, v br s), 8.01 (1H, d, J = 7.5 Hz), 7.92–7.85 (2H), 7.38 (1H, dd, J = 4.7, 7.9 Hz), 4.63 (2H, t, J = 6.1 Hz), 3.39 (2H, t, J = 5.9 Hz). MS (ES+): 370 (M+H). HRMS: calcd for $C_{16}H_{14}F_3N_3O_2S + H^+$, 370.0831; found (ESI, $[M+H]^+$), 370.0826. HPLC purity = 100%.

6.1.16. 2-(3-{[3-(Trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethylamine hydrochloride (10p)

The free amine of **10p** was prepared in 51% yield as a light yellow gum from **15g** using the procedure for **10g**. The hydrochloride was obtained as a white hygroscopic solid. Mp: 179–183 °C. ^{1}H NMR (DMSO-d_6): 8.62 (1H, s), 8.45 (1H, dd, J = 1.4, 4.7 Hz), 8.30 (1H, dd, J = 1.5, 8.1 Hz), 8.27 (1H, s), 8.09 (3H, v br s), 8.06 (1H, d, J = 7.9 Hz), 7.87 (1H, app t, J = 7.9 Hz), 7.40 (1H, dd, J = 4.6, 7.9 Hz), 4.61 (2H, t, J = 6.0 Hz), 3.39 (2H, m). MS (ES+): 370 (M+H). HRMS: calcd for $C_{16}H_{14}F_3N_3O_2S + H^+$, 370.0831; found (ESI, $[M+H]^+$), 370.0828. HPLC purity = 97.4%.

6.1.17. *N*-(2-{3-[(3,5-Dichlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10q)

Compound **10q** was prepared from **15h** by the procedure of **10a** affording a white hygroscopic solid in 50% yield. Mp: 227–232 °C. ^{1}H NMR (DMSO-d_6): 10.32 (1H, br s), 8.70 (1H, s), 8.34 (1H, dd, J = 1.5, 7.9 Hz), 8.04 (1H, app t, J = 0.7 Hz), 7.96 (1H, s with fc), 7.41 (1H, dd, J = 4.7, 7.9 Hz), 4.76 (2H, t, J = 6.4 Hz), 3.68 (2H, m), 2.84 (6H, d, J = 4.7 Hz). MS (ES+): 398 (M+H). Anal. Calcd for $C_{17}H_{17}Cl_2N_3O_2S{\cdot}2HCl$: C, 43.33; H, 4.06; N, 8.92. Found: C, 42.96; H, 3.89; N, 8.69.

6.1.18. 2-{3-[(3,5-Dichlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethylamine hydrochloride (10r)

The free amine **10r** was prepared in 53% yield from **15h** using the procedure for **10g** except using acetonitrile as the solvent. The hydrochloride was obtained as a white hygroscopic solid. Mp: 136–140 °C. ^{1}H NMR (DMSO-d_6): 8.61 (1H, s), 8.46 (1H, dd, J = 1.4, 4.7 Hz), 8.32 (1H, dd, J = 1.5, 8.1 Hz), 8.12 (3H, v br s), 8.02 (2H, d, J = 1.8 Hz), 7.96 (1H, t, J = 1.9 Hz), 7.40 (1H, dd, J = 4.7, 7.9 Hz), 4.62 (2H, t, J = 6.0 Hz), 3.40 (2H, m). MS (EI+): 370 (M+H). Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_2S{\cdot}HCl{\cdot}H_2O$: C, 42.42; H, 3.80; N, 9.89. Found: C, 42.20; H, 3.67; N, 9.77.

6.1.19. *N*-(2-{3-[(2,5-Dichlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10s)

Using the procedure for **10e**, compound **10s** was prepared from 2,5-dichlorophenylsulfonyl chloride and **18** to give a white hygroscopic solid (8%). Mp: 136–140 °C. ^{1}H NMR (DMSO-d_6): 10.35 (1H, br s), 8.75 (1H, s), 8.42 (1H, dd, J = 1.5, 4.8 Hz), 8.29 (1H, d, J = 2.6 Hz), 8.13 (1H, dd, J = 1.6, 7.9 Hz), 7.72 (1H, dd, J = 2.6, 8.5 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 4.7, 7.9 Hz), 4.75 (2H, t, J = 6.3), 3.62 (2H, br t, 6.1 Hz), 2.78 (6H, s). MS (ES+): 397.9 (M+H). HRMS: calcd for $C_{17}H_{17}Cl_2N_3O_2S + H^+$, 398.0491; found (ESI, $[M+H]^+$), 398.0491. HPLC purity = 100%.

6.1.20. *N*-(2-{3-[(2,6-Dichlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10t)

Compound **10t** was prepared from 2,6-dichlorophenylsulfonyl chloride and **18** using the procedure of **10e** to give a white solid (19%). ^{1}H NMR (DMSO-d_6): 10.35 (1H, br s), 8.75 (1H, s), 8.42 (1H, dd, J = 1.5, 4.8 Hz), 8.29 (1H, d, J = 2.6 Hz), 8.13 (1H, dd, J = 1.6, 8.1 Hz), 7.74 (1H, dd, J = 2.6, 8.5 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 4.6, 7.9 Hz), 4.72 (2H, t, J = 5.5), 3.60 (2H, m), 2.79 (6H, s). MS (ES+): 397.9 (M+H). HRMS: calcd for $C_{17}H_{17}Cl_2N_3O_2S + H^+$, 398.0491; found (ESI, $[M+H]^+$), 398.0489. HPLC purity = 100%.

6.1.21. *N*,*N*-Dimethyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethyl}amine hydrochloride (10u)

Prepared as in the procedure of **10a** by alkylation of **15i** to afford a white, hygroscopic solid in 68% yield. Mp: 203–206 °C. ^{1}H NMR (DMSO-d_6): 10.35 (1H, br s), 8.86 (1H, s), 8.73 (1H, d, J = 8.6 Hz), 8.49 (1H, dd, J = 1.2, 7.5 Hz), 8.35 (1H, dd, J = 1.5, 4.6 Hz), 8.22 (1H, d, J = 8.2 Hz), 8.05–8.02 (2H), 7.71–7.63 (2H), 7.59 (1H, m), 7.25 (1H, dd, J = 4.7, 8.1 Hz), 4.71 (2H, t, J = 6.3 Hz), 3.60 (2H, m), 2.75 (6H, d, J = 4.7 Hz). MS (ES+): 380 (M+H). HRMS: calcd for $C_{21}H_{21}N_3O_2S{+}H^+$, 380.1426; found (ESI, $[M+H]^+$), 380.1426. HPLC purity = 100%.

6.1.22. 2-[3-(1-Naphthylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethylamine hydrochloride (10v)

Prepared as in **10g** by alkylation of **15i** to afford a white solid in 59% yield. ^{1}H NMR (DMSO-d_6): 8.77 (1H, s), 8.76 (1H, d, partly overlapping with 8.77 singlet), 8.46 (1H, dd, J = 1.1, 7.3 Hz), 8.34 (1H, dd, J = 1.6, 4.7 Hz), 8.21 (1H, d, J = 8.3 Hz), 8.10 (3H, v br s), 8.04 (2H, m), 7.70–7.64 (2H), 7.59 (1H, app t with fc, J = 7.0 Hz), 7.25 (1H, dd, J = 4.6, 7.9 Hz), 4.57 (2H, t, J = 6.1 Hz), 3.36 (2H, m, partly obscured by water peak). MS (ES+): 352 (M+H). HRMS: calcd for $C_{19}H_{17}N_3O_2S + H^+$, 352.1113; found (ESI, $[M+H]^+$), 352.1111. HPLC purity = 99.3%.

6.1.23 *N*,*N*-Dimethyl-*N*-{2-[3-(thien-2-ylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethyl}amine hydrochloride (10w)

Prepared by alkylation of **15j** according to the procedure of **10a** to afford **10w** in 72% yield as a white solid. Mp: 212–216 °C. ^{1}H NMR (DMSO-d_6): 10.38 (1H, br s), 8.59 (1H, s), 8.46 (1H, dd, J = 1.5, 4.7 Hz), 8.25 (1H, dd, J = 1.5, 7.9 Hz), 7.98 (1H, dd, J = 1.4, 5.0 Hz), 7.85 (1H, dd, J = 1.4, 3.8 Hz), 7.39 (1H, dd, J = 4.7, 7.9 Hz), 7.17 (1H, dd, J = 3.8, 4.9 Hz), 4.74 (2H, t, J = 6.6 Hz), 3.64 (2H, m), 2.82 (6H, d, J = 4.9 Hz). MS (ES+): 336 (M+H). HRMS: calcd for $C_{15}H_{17}N_3O_2S_2 + H^+$, 336.0835; found (ESI, $[M+H]^+$), 336.0842. HPLC purity = 100%.

6.1.24. *N*-(2-{3-[(5-Chlorothien-2-yl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10x)

The free amine of **10x** was prepared in 42% yield from 5-chlorothien-2-ylsulfonyl chloride and **18** using the procedure of **10e**. The dihydrochloride was obtained by treating an ethanolic solution of the free amine with 3 equiv of 4 N HCl in dioxane and isolating the white solid precipitate that formed after several hours by suction filtration. Mp: 169–171 °C. ^{1}H NMR (DMSO-d_6): 10.53 (1H, br s), 8.59 (1H, s), 8.44 (1H, dd, J = 1.6, 4.7 Hz), 8.21 (1H, dd, J = 1.5, 7.9 Hz), 7.74 (1H, d, J = 4.0 Hz), 7.38 (1H, dd, J = 4.7, 8.1 Hz), 7.21

(1H, d, J = 4.0 Hz), 4.72 (2H, t, J = 5.5 Hz), 3.60 (2H, m), 2.78 (6H, d, J = 4.9). MS (ES+): 370 (M+H). Anal. Calcd for $C_{15}H_{16}ClN_3O_2S_2{\cdot}2HCl$: C, 40.69; H, 4.10; N, 9.49. Found: C, 40.54; H, 3.98; N, 9.40.

6.1.25. *N*-(2-{3-[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*,*N*-dimethylamine hydrochloride (10y)

Prepared from 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride and **18** using the procedure of **10e** to afford the free amine after chromatography eluting with 2:98 triethylamine/ethanol and crystallizing the compound from hot ethyl acetate (45% yield). A portion of the free amine was dissolved in warm ethyl acetate, treated with 4 N HCl in dioxane (2.4 equiv), and concentrated in vacuo to obtain the dihydrochloride as a white hygroscopic solid. Mp: 180–182 °C. ^{1}H NMR (DMSO-d_6): 10.41 (1H, br s), 8.80 (1H, s), 8.42 (1H, m), 8.23–8.20 (2H, m), 7.63 (1H, d, J = 4.4 Hz), 7.36 (1H, dd, J = 4.8, 7.9 Hz), 4.72 (2H, t, J = 6.3 Hz), 3.60 (2H, m), 2.76 (6H, d, J = 4.8). MS (EI−): 410 (M−H). Anal. Calcd for $C_{16}H_{16}ClN_5O_2S_2{\cdot}2HCl{\cdot}0.25H_2O$: C, 39.43; H, 3.83; N, 14.37. Found: C, 39.34; H, 3.74; N, 13.98.

6.1.26. *N*-(2-{3-[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-*N*-methylamine hydrochloride (10z)

Compound **10z** was prepared from **10y** as in the procedure of **10j** except using 4 equiv of 1-chloroethyl chloroformate to afford an off-white solid in 71% yield. Mp: 182–186 °C (foamed on melting, darkens, not well-defined). ^{1}H NMR (DMSO-d_6): 8.98 (2H, v br s), 8.77 (1H, s), 8.41 (1H, dd, J = 1.5, 4.8 Hz), 8.23 (1H, dd, J = 1.6, 7.9 Hz), 8.20 (1H, d, J = 4.5 Hz), 7.61 (1H, d, J = 4.7 Hz), 7.36 (1H, dd, J = 4.6, 8.0 Hz), 4.64 (2H, t, J = 5.9 Hz), 3.43 (2H, m), 2.51 (3H, t, J = 5.3 Hz). MS (ES+): 396 (M+H). Anal. Calcd for $C_{15}H_{14}ClN_5O_2S_2{\cdot}2HCl{\cdot}0.25H_2O$: C, 38.06; H, 3.51; N, 14.80. Found: C, 38.25; H, 3.61; N, 14.41.

6.1.27. 3-(Phenylthio)-1*H*-pyrrolo[2,3-*b*]pyridine (12a)

A solution of methyl phenyl sulfoxide (8.33 g, 59.4 mmol) in CH_2Cl_2 (175 mL) was chilled to −78 °C and treated dropwise with trifluoroacetic anhydride (4.1 mL, 5.3 mmol). After 30 min, a solution of **11** (5.20 g, 44.0 mmol) in CH_2Cl_2 (25 mL) was added followed 30 min later by triethylamine (74 mL, 534 mmol). The reaction was stirred at ambient temperature for 84 h, then concentrated in vacuo, treated with saturated aqueous $NaHCO_3$ (300 mL), and extracted with CH_2Cl_2 (2 × 300 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from methanol/water and then crystallized from CH_2Cl_2/hexane. Vacuum drying gave **12a** as an off-white solid (1.26 g, 13%, $R_f \sim 0.5$ in ethyl acetate). Mp: 188–189 °C. ^{1}H NMR (DMSO-d_6): 12.3 (1H, br s), 7.91 (1H, s), 7.78 (1H, d, J = 7.9 Hz), 7.25–7.17 (2H, m), 7.15–7.00 (4H, m). MS (ES+): 227 (100%, M+H). MS (ES−): 225 (100%, M−H). Anal. Calcd for $C_{13}H_{10}N_2S{\cdot}0.1H_2O$: C, 68.45; H, 4.51; N, 12.28. Found: C, 68.39; H, 4.37; N, 12.22.

6.1.28. 2-Methyl-3-(phenylthio)-1*H*-pyrrolo[2,3-*b*]pyridine (12b)

1-(Phenylthio)-2-propanone and **13** were heated in ethanol at reflux for 24 h, then concentrated in vacuo. The resulting mixture was treated with 1,3-propanediol and heated at reflux for 3 h, affording **12b** as an off-white solid. Mp: 180–181 °C. ^{1}H NMR ($CDCl_3$): 11.91 (1H, br s), 8.30 (1H, dd, J = 1.4, 4.7 Hz), 7.87 (1H, dd, J = 1.4, 7.8 Hz), 7.17 (2H, app t, J = 7.3 Hz), 7.12 (1H, dd, J = 4.7, 7.8 Hz), 7.08–7.03 (3H), 2.65 (3H, s). MS (ES−): 239 (100%, M−H). Anal. Calcd for $C_{14}H_{12}C_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 69.90; H, 4.95; N, 11.57.

6.1.29. 3-[(3-Fluorophenyl)thio]-1*H*-pyrrolo[2,3-*b*]pyridine (12c)

A stirred mixture **14** (500 mg, 2.05 mmol), 3-fluorothiophenol (395 mg, 3.08 mmol), sodium *tert*-butoxide (591 mg, 6.15 mmol), and $Pd(PPh_3)_4$ (118 mg, 0.10 mmol) in ethanol (20 mL) was heated at reflux for 16 h. The reaction was concentrated to dryness and then treated with ethyl acetate. The resulting suspension was filtered through a bed of Celite® and the filtrate washed with water (20 mL) and then brine (20 mL). The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was crystallized from a mixture of dichloromethane and hexanes to afford **12c** as an off-white solid (277 mg, 55%). Mp: 158–160 °C. ^{1}H NMR (DMSO-d_6): 12.34 (1H, br s), 8.32 (1H, dd, J = 11.5, 4.7 Hz), 7.96 (1H, s), 7.79 (1H, dd, J = 1.5, 7.9 Hz), 7.25 (1H, m), 7.14 (1H, dd, J = 4.7, 7.0 Hz), 6.90 (1H, m), 6.86 (1H, d, J = 7.9 Hz), 6.77 (1H, finely coupled doublet, J = 9.8 Hz). MS (ES−): 243 (100%, M−H). HRMS: calcd for $C_{13}H_9FN_2S + H^+$, 245.0542; found (ESI, $[M+H]^+$), 245.0540. HPLC purity = 100%.

6.1.30. 3-[(3-Chlorophenyl)thio]-1*H*-pyrrolo[2,3-*b*]pyridine (12d)

The title compound was prepared from **14** (3.00 g, 12.3 mmol) and 3-chlorobenzenethiol (2.68 g, 18.5 mmol) in a manner analogous to **12e** except heating at 75 °C for 5 h. Chromatography (1:99 methanol/CH_2Cl_2) gave a pinkish solid (2.60 g, $R_f \sim 0.2$ in 1:99 methanol/CH_2Cl_2) which was shown by NMR to be a mixture of **12d** (60%) along with **11** (40%). This mixture was used in the subsequent oxidation. A small portion (140 mg) of impure product was crystallized from CH_2Cl_2/hexane to afford an analytically pure sample (90 mg) of **12d** as a tan solid. Mp: 156–158 °C. ^{1}H NMR (DMSO-d_6): 12.4 (1H, br s), 8.33 (1H, br s), 7.97 (1H, d, J = 2.8 Hz), 7.80 (1H, dd, J = 1.1, 7.8 Hz), 7.24 (1H, dt, J = 1.2, 7.9 Hz), 7.16–7.13 (2H, m), 7.04–6.98 (2H, m). MS (ES+): 262 (100%, M+H). Anal. Calcd for $C_{13}H_9ClN_2S{\cdot}0.5H_2O$: C, 57.88; H, 3.74; N, 10.38. Found: C, 57.94 H, 3.20; N, 10.28.

6.1.31. 3-[(4-Fluorophenyl)thio]-1*H*-pyrrolo[2,3-*b*]pyridine (12e)

A solution of **14** (4.0 g, 16.4 mmol) in DMF (40 mL) was treated with 4-fluorobenzenethiol (2.09 mL, 19.7 mmol), potassium carbonate (3.40 g, 24.6 mmol), and copper iodide (4.21 g, 22.1 mmol). The reaction mixture was heated at 65 °C for 4 h, then cooled and diluted with concd aqueous NH_4OH (100 mL). The mixture was extracted with ethyl acetate (3 × 200 mL) and the extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Chromatography (1:50 methanol/CH_2Cl_2) followed by crystallization from methanol/H_2O gave **12e** as an off-white solid (3.56 g, 89%). Mp: 183–184 °C. ^{1}H NMR (DMSO-d_6): 12.26 (1H, br s), 8.30 (1H, dt, J = 1.5, 5.5 Hz), 7.92 (1H, s), 7.79 (1H, dd, J = 1.5, 7.6 Hz), 7.15–7.03 (5H). MS (ES−): 243 (60%, M−H). Anal. Calcd for $C_{13}H_9FN_2S$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.59; H, 3.66; N, 11.35.

6.1.32. 3-{[2-(Trifluoromethyl)phenyl]thio}-1*H*-pyrrolo[2,3-*b*]pyridine (12f)

Prepared essentially as in **12c** in 48% yield except using 2-(trifluoromethyl)benzenethiol and recrystallizing from dichloromethane/hexane to give an orange solid. Mp: 222–225 °C. ^{1}H NMR (DMSO-d_6): 12.38 (1H, br s), 8.29 (1H, d, J = 4.8 Hz), 7.98 (1H, m), 7.70–7.67 (2H), 7.34 (1H, app t, J = 7.3 Hz), 7.11 (1H, dd, J = 4.7, 7.9 Hz), 6.84 (1H, d, J = 8.1 Hz). MS (ES−): 293 (100%, M−H). Anal. Calcd for $C_{14}H_9F_3N_2S{\cdot}0.3H_2O$: C, 56.11; H, 3.23; N, 9.35. Found: C, 56.19; H, 3.02; N, 9.25.

6.1.33. 3-{[3-(Trifluoromethyl)phenyl]thio}-1*H*-pyrrolo[2,3-*b*]pyridine (12g)

Prepared in 59% yield essentially as in **12c** except using 3-(trifluoromethyl)benzenethiol and recrystallizing from dichlorometh-

ane/hexanes to give an light yellow solid. Mp: 132–133 °C. ^{1}H NMR (DMSO-d_6): 12.33 (1H, br s), 8.29 (1H, dd, J = 1.6, 4.7 Hz), 7.96 (1H, s), 7.76 (1H, dd, J = 1.6, 7.8 Hz), 7.43–7.38 (2H), 7.29 (1H, s), 7.24 (1H, m), 7.16–7.13 (2H, m), 7.11 (1H, dd, J = 4.6, 7.9 Hz). MS (ES−): 293 (100%, M−H). Anal. Calcd for $C_{14}H_9F_3N_2S$: C, 57.14; H, 3.08; N, 9.52. Found: C, 56.88; H, 2.97; N, 9.34.

6.1.34. 3-[(3,5-Dichlorophenyl)thio]-1*H*-pyrrolo[2,3-*b*]pyridine (12h)

Prepared essentially as in **12c** except using 3,5-dichlorobenzenethiol to give **12h** as an orange solid in 59% yield. Mp: 206–208 °C. ^{1}H NMR (DMSO-d_6): 12.45 (1H, br s), 8.35 (1H, dd, J = 1.5, 4.7 Hz), 8.03 (1H, s), 7.84 (1H, dd, J = 1.5, 7.8 Hz), 7.33 (1H, m), 7.18 (1H, dd, J = 4.7, 7.9 Hz), 7.10 (2H, s). MS (ES−): 293 (100%, M−H). Anal. Calcd for $C_{13}H_8Cl_2N_2S{\cdot}0.2H_2O$: C, 52.26; H, 2.83; N, 9.37. Found: C, 52.30; H, 2.81; N, 9.29.

6.1.35. 3-(1-Naphthylthio)-1*H*-pyrrolo[2,3-*b*]pyridine (12i)

Prepared essentially as in **12c** except using naphthalene-1-thiol to give **12i** as an orange solid in 77% yield. Mp: 197–199 °C. ^{1}H NMR (DMSO-d_6): 12.32 (1H, br s), 8.37 (1H, d, J = 8.4 Hz), 8.30 (1H, dd, J = 1.5, 4.7 Hz), 8.00 (1H, d, J = 1.5 Hz), 7.94 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 1.2, 7.8 Hz), 7.67 (1H, app t, J = 8.2 Hz), 7.63 (1H, d, J = 8.2 Hz), 7.58 (1H, app t, J = 7.0 Hz), 7.27 (1H, app t, J = 7.7 Hz), 7.10 (1H, dd, J = 4.7, 7.9 Hz), 6.89 (1H, d, J = 7.3 Hz). MS (ES−): 275 (100%, M−H). Anal. Calcd for $C_{17}H_{12}N_2S{\cdot}0.2H_2O$: C, 73.41; H, 4.42; N, 10.07. Found: C, 73.14; H, 4.48; N, 10.00.

6.1.36. 3-(Thien-2-ylthio)-1*H*-pyrrolo[2,3-*b*]pyridine (12j)

Prepared essentially as in **12c** except using thiophene-2-thiol to give **12j** as a pink solid in 65% yield. Mp: 192–193 °C. ^{1}H NMR (DMSO-d_6): 12.14 (1H, br s), 8.28 (1H, dd, J = 1.4, 4.7 Hz), 7.99 (1H, dd, J = 1.5, 7.9 Hz), 7.89 (1H, s), 7.45 (1H, dd, J = 1.2, 5.3 Hz), 7.20 (1H, dd, J = 1.2, 2.5 Hz), 7.16 (1H, dd, J = 4.6, 7.9 Hz), 6.5 (1H, dd, J = 3.5, 5.2 Hz). MS (ES+): 233 (M+H). Anal. Calcd for $C_{11}H_8N_2S_2$. 0.1 H_2O: C, 56.43; H, 3.53; N, 11.97. Found: C, 56.32; H, 3.37; N, 11.81.

6.1.37. 3-Iodo-1*H*-pyrrolo[2,3-*b*]pyridine (14)

A solution of **11** (20.0 g, 169 mmol) in ethanol (800 mL) was treated with iodine (57.9 g, 228 mmol), potassium iodide (37.8 g, 228 mmol), and 1 N aqueous NaOH (204 mL, 204 mmol). After stirring for 4 h at 20 °C, the reaction was diluted with H_2O (500 mL) and extracted with ethyl acetate (3 × 1 L). The organic phases were combined and concentrated in vacuo. The residue was crystallized from methanol/H_2O. Vacuum drying gave **14** as a pink-white solid (35.4 g, 86%). Mp: 201–204 °C. ^{1}H NMR (DMSO-d_6): 12.1 (1H, br s), 8.25 (1H, d, J = 4.7 Hz), 7.70 (1H, s), 7.67 (1H, d, J = 7.9 Hz), 7.15 (1H, m). MS (ES+): 245 (100%, M+H). MS (ES−): 243 (100%, M−H). Anal. Calcd for $C_7H_5IN_2$: C, 34.45; H, 2.07; N, 11.48. Found: C, 34.58; H, 1.96; N, 11.40.

6.1.38. 3-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15a)

A solution of **12a** (100 mg, 0.44 mmol) in *t*-butyl alcohol (10 mL) was treated with $MnSO_4{\cdot}H_2O$ (4 mg, 0.020 mmol) and cooled to 0 °C. A mixture of 30% aqueous hydrogen peroxide (500 mg, 4.41 mmol) and 0.2 N aqueous $NaHCO_3$ (7.5 mL) was added dropwise. The reaction was stirred for 23 h at 20 °C, then diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Chromatography (1:50 methanol/CH_2Cl_2) gave crude product which was crystallized from CH_2Cl_2/hexane. Vacuum drying gave **15a** as a pink-white solid (58 mg, 50%, $R_f \sim 0.4$ in ethyl acetate). Mp: >250 °C. ^{1}H NMR (DMSO-d_6): 12.9 (1H, br s), 8.35 (2H, m), 8.18 (1H, d, J = 7.9 Hz), 8.00 (2H, d, J = 8.1 Hz), 7.65–7.55 (3H, m), 7.26 (1H, dd, J = 4.7, 7.9 Hz). MS (ES+): 300 (100%, M+CH_3CN (carrier solvent)+H), 259 (20%, M+H). MS (ES−): 257 (100%, M−H). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.11; H, 3.68; N, 10.82.

6.1.39. 2-Methyl-3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15b)

Prepared from **12b** using the procedure of **15e** to give a 32% yield of **15b** as a white solid. Mp: 252–253 °C. ^{1}H NMR (DMSO-d_6): 12.70 (1H, br s), 8.26 (1H, dd, J = 1.5, 4.8 Hz), 8.17 (1H, dd, J = 1.5, 7.9 Hz), 7.92 (1H, app d, J = 7.5 Hz), 7.61 (1H, t, J = 7.2 Hz), 7.55 (2H, app t, J = 7.4 Hz), 7.21 (1H, dd, J = 4.7, 7.9 Hz), 2.68 (3H, s). MS (ES−): 271 (100%, M−H). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.34; H, 4.46; N, 10.17.

6.1.40. 3-[(3-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (15c)

Prepared from **12c** using the procedure of **15e** to give **15c** as a white solid in 27% yield. Mp: >250 °C. ^{1}H NMR (DMSO-d_6): 12.97 (1H, br s), 8.41 (1H, s), 8.37 (1H, dd, J = 1.5, 4.7 Hz), 8.22 (1H, dd, J = 1.5, 8.0 Hz), 7.83 (2H), 7.63 (1H, m), 7.48 (1H, app dt, J = 4.7, 8.1 Hz), 7.28 (1H, dd, J = 4.7, 8.1 Hz). MS (ES+): 277 (100%, M+H). MS (ESI−): 275 (M−H). Anal. Calcd for $C_{13}H_9FN_2O_2S$: C, 56.51; H, 3.28; N, 10.14. Found: C, 56.09; H, 3.40; N, 10.04.

6.1.41. 3-[(3-Chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (15d)

Prepared from **12d** by the procedure of **15e** to give **15d** as an off-white solid in 24% yield. The crude filtered solid was triturated with CH_2Cl_2, washed with hexane, and vacuum dried to afford **15d**. Mp: 232–233 °C. ^{1}H NMR (DMSO-d_6): 13.0 (1H, br s), 8.43 (1H, s), 8.38 (1H, d, J = 4.7 Hz), 8.22 (1H, d, J = 8.0 Hz), 8.01 (1H, t, J = 1.9 Hz), 7.97 (1H, d, J = 7.9 Hz), 7.69 (1H, d, J = 9.2 Hz), 7.60 (1H, app t, J = 7.9 Hz), 7.25–7.30 (1H, m). MS (ES−): 291 (100%, M−H). Anal. Calcd for $C_{13}H_9ClN_2O_2S$: C, 53.34; H, 3.10; N, 9.57. Found: C, 53.01; H, 2.86; N, 9.41.

6.1.42. 3-[(4-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (15e)

A solution of **12e** (3.36 g, 13.8 mmol) in acetone (200 mL) was treated with $NaHCO_3$ (2.90 g, 34.5 mmol) dissolved in H_2O (175 mL). The reaction was then treated with Oxone® (25.5 g, 41.4 mmol) and stirred for 3 h at 20 °C. The reaction mixture was diluted with H_2O and chilled in an ice-water bath. The solids were filtered, washed with H_2O and vacuum dried to give **15e** as a white solid (1.73 g, 45%). Mp: 212–213 °C. ^{1}H NMR (DMSO-d_6): 12.9 (1H, s), 8.35 (2H, m), 8.18 (1H, d, J = 8.0 Hz), 8.0–8.1 (2H, m), 7.40 (2H, t, J = 8.9 Hz), 7.27 (1H, m). MS (ES−): 275 (100%, M−H). HRMS: calcd for $C_{13}H_9FN_2O_2S + H^+$, 277.0441; found (ESI, $[M+H]^+$), 277.0439. HPLC purity = 98.5%.

6.1.43. 3-{[2-(Trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrolo[2,3-*b*]pyridine (15f)

Prepared from **12f** using the procedure of **15e** to give **15f** as a pale orange solid in 37% yield. Mp: 222–223 °C. ^{1}H NMR (DMSO-d_6): 13.03 (1H, s), 8.40–8.37 (2H), 8.33 (1H, s), 8.35 (2H, m), 8.11 (1H, dd, J = 1.3, 8.0 Hz), 7.96 (1H, d, J = 7.2 Hz), 7.27 (1H, ddd, J = 1.1, 4.7, 8.1 Hz). MS (ESI-): 325 (M−H). HRMS: calcd for $C_{14}H_9F_3N_2O_2S + H^+$, 327.0409; found (ESI, $[M+H]^+$), 327.0405. HPLC purity = 97.5%.

6.1.44. 3-{[3-(Trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrolo[2,3-*b*]pyridine (15g)

Prepared from **12g** using the procedure of **15e** to give **15g** as a white solid. Mp: 214–217 °C. ^{1}H NMR (DMSO-d_6): 13.02 (1H, s), 8.49 (1H, s), 8.38 (1H, dd, J = 1.4, 4.6 Hz), 8.32 (1H, d, J = 7.8 Hz),

8.26 (1H, s), 8.23 (1H, dd, J = 1.5, 7.9 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.82 (1H, app t, J = 7.6 Hz), 7.30 (1H, m). MS (ESI-): 325 (M−H). Anal. Calcd for $C_{14}H_9F_3N_2O_2S$: C, 51.53; H, 2.78; N, 8.51. Found: C, 51.28; H, 2.71; N, 8.41.

6.1.45. 3-[(3,5-Dichlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (15h)

Prepared from **12h** using the procedure of **15e** to give **15h** as an off-white solid in 64% yield. Mp: >250 °C. ^{1}H NMR (DMSO-d_6): 13.07 (1H, br s), 8.51 (1H, s), 8.41 (1H, dd, J = 1.5, 4.7 Hz), 8.29 (1H, app d, J = 8.1 Hz), 8.03 (2H, s), 7.93 (1H, m), 7.32 (1H, dd, J = 4.7, 8.1 Hz). MS (ESI-): 325 (M−H). Anal. Calcd for $C_{13}H_8Cl_2N_2O_2S$: C, 47.72; H, 2.46; N, 8.56. Found: C, 47.67; H, 2.41; N, 8.53.

6.1.46. 3-(1-Naphthylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15i)

Prepared from **12i** using the procedure of **15e** except using 3 equivalents of Oxone® to give **15i** as a tan solid in 57% yield, crystallized from methylene chloride/hexanes. Mp: 234–236 °C. ^{1}H NMR (DMSO-d_6): 12.90 (1H, s), 8.79 (1H, d, J = 8.7 Hz), 8.66 (1H, s), 8.51 (1H, dd, J = 1.2, 7.5 Hz), 8.30 (1H, dd, J = 1.6, 4.5 Hz), 8.23 (1H, d, J = 8.4 Hz), 8.03 (2H, m), 7.72 (1H, app t, J = 7.7 Hz), 7.66 (1H, m), 7.60 (1H, app t, J = 7.0 Hz), 7.20 (1H, dd, J = 4.7, 7.9 Hz). MS (ESI−): 307 (M−H). HRMS: calcd for $C_{17}H_{12}N_2O_2S + H^+$, 309.0691; found (ESI, $[M+H]^+$), 309.0690. HPLC purity = 98.1%.

6.1.47. 3-(Thien-2-ylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15j)

Prepared from **12j** using the procedure of **15e** to give **15j** as a pink solid crystallized from methylene chloride/hexane in 62% yield. Mp: 249–250 °C. ^{1}H NMR (DMSO-d_6): 12.94 (1H, s), 8.40 (1H, dd, J = 1.5, 4.6 Hz), 8.37 (1H, s), 8.21 (1H, dd, J = 1.5, 7.9 Hz), 7.95 (1H, dd, J = 1.3, 4.9 Hz), 7.82 (1H, dd, J = 1.3, 3.6 Hz), 7.31 (1H, dd, J = 4.6, 8.0 Hz), 7.16 (1H, dd, J = 3.8, 4.9 Hz). MS (ESI-): 263 (M−H). HRMS: calcd for $C_{11}H_8N_2O_2S_2 + H^+$, 265.0099; found (ESI, $[M+H]^+$), 265.0097. HPLC purity = 100%.

6.1.48. 1-(2-Chloroethyl)-3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (16a)

A solution of **15a** (4.30 g, 16.6 mmol) in 1,2-dichloroethane (33 mL, 420 mmol) was treated with trioctylmethylammonium chloride (6.9 g) and 50% aqueous NaOH (1.6 g, 20 mmol) and heated 6 h at 45 °C. The cooled solution was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to a brown gum. The gum was chromatographed eluting with 1:4 ethyl acetate/hexanes and crystallized from ethyl acetate/hexane to give a white solid (3.84 g, 72%, $R_f \sim 0.6$ in 1:1 ethyl acetate/hexanes). Mp: 117–119 °C. ^{1}H NMR (DMSO-d_6): 8.55 (1H, s), 8.42 (1H, d, J = 4.7 Hz), 8.22 (1H, d, J = 7.9 Hz), 7.99 (2H, d, J = 7.3 Hz), 7.65–7.55 (3H), 7.33 (1H, m), 4.68 (2H, t, J = 6.0 Hz), 4.11 (2H, t, J = 6.0 Hz). MS (ES+): 321 (100%, M+H); HRMS: calcd for $C_{15}H_{13}ClN_2O_2S + H^+$, 321.0458; found (ESI, $[M+H]^+$), 321.0456. HPLC purity = 100%.

6.1.49. 1-(2-Chloroethyl)-3-[(3-chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16b)

Prepared from **15d** (0.85 g, 2.90 mmol) by the procedure of **16a**, giving a colorless gum (77%, $R_f \sim 0.5$ in 1:1 ethyl acetate/hexane), characterized only by NMR. ^{1}H NMR (DMSO-d_6): 8.57 (1H, s), 8.38 (1H, m), 8.23 (1H, m), 7.97–7.85 (2H), 7.65 (2H, m), 7.58 (1H, m), 4.64 (2H, m), 4.10 (2H, m).

6.1.50. 1-(2-Chloroethyl)-3-[4-(fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16c)

Prepared from **15e** in a manner analogous to the preparation of **16a** to give a white solid (78%, $R_f \sim 0.5$ in 1:1 ethyl acetate/hexanes), characterized only by NMR. ^{1}H NMR (DMSO-d_6): 8.52 (1H, s), 8.39 (1H, app d), 8.18 (1H, m), 8.00 (2H, m), 7.42–7.23 (3H), 4.63 (2H, m), 4.06 (2H, m).

6.1.51. 2-{2-[3-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (17a)

A solution of **16a** (3.84 g, 12.0 mmol) and potassium phthalimide (2.78 g, 15.0 mmol) in DMF (50 mL) was heated at 115 °C for 16 h. The cooled reaction was diluted with H_2O (200 mL), extracted into ethyl acetate (3 × 200 mL), and the combined extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration in vacuo followed by crystallization from CH_2Cl_2/hexane gave **17a** as a white solid (4.54 g, 88%, $R_f \sim 0.5$ in 1:1 ethyl acetate/hexanes). The product was characterized only by ^{1}H NMR and then carried on. ^{1}H NMR (DMSO-d_6): 8.48 (1H, s), 8.00 (2H, m), 7.80–7.42 (9H, m), 7.12 (1H, m), 4.55 (2H, m), 3.98 (2H, m).

6.1.52. 2-(2-{3-[(3-Chlorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione (17b)

Prepared from **16b** (790 mg, 2.22 mmol) in a similar manner to **17a**. The crude product is crystallized from CH_2Cl_2/hexane to afford a white solid (89%). Mp: 155–157 °C. ^{1}H NMR (DMSO-d_6): 8.60 (1H, s), 8.10 (1H, d, J = 8.0 Hz), 8.07 (1H, d, J = 4.7 Hz), 7.89 (1H, t, J = 1.8 Hz), 7.87 (1H, d, J = 7.8 Hz), 7.75–7.80 (2H, m), 7.65–7.72 (3H, m), 7.60 (1H, t, J = 8.0 Hz), 7.15–7.20 (1H, m), 4.59 (2H, t, J = 1.6 Hz), 4.04 (2H, t, J = 1.5 Hz). MS (ES+): 466 (100%, M + H). Anal. Calcd for $C_{23}H_{16}ClN_3O_4S{\cdot}0.4H_2O$: C, 58.39; H, 3.58; N, 8.88. Found: C, 58.47; H, 3.36; N, 8.82.

6.1.53. 2-(2-{3-[(4-Fluorophenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione (17c)

Prepared from **16c** in a manner analogous to that of **17a**, except crystallizing from CH_2Cl_2/hexane to give a white solid in 80% yield. Mp: 164–165 °C. ^{1}H NMR (DMSO-d_6): 8.54 (1H, s), 8.08–8.03 (2H, m), 7.98–7.93 (2H, dd, J = 5.0, 9.0 Hz), 7.80–7.75 (2H, m), 7.73–7.65 (2H, m), 7.40 (2H, t, J = 8.9 Hz), 7.15 (1H, dd, J = 4.7, 7.8 Hz), 4.59 (2H, m), 4.03 (2H, m). MS (ES+): 450 (100%, M + H). Anal. Calcd for $C_{23}H_{16}FN_3O_4S \cdot 0.2\ H_2O$: C, 60.97; H, 3.65; N, 9.27. Found: C, 60.89; H, 3.66; N, 9.18.

6.1.54. *N*,*N*-Dimethyl-*N*-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethyl]amine (18)

A stirred solution of **11** (2.50 g, 21.2 mmol) in DMF (100 mL) under nitrogen treated with sodium hydride (3.00 g, 75 mmol) in portions over about 2 min (gas evolved). After 1 h, the reaction was treated with 2-(dimethylamino)ethyl chloride hydrochloride (3.20 g, 22.2 mmol). Gas evolved. After 18 h, the reaction was treated with water (10 mL) and saturated aqueous NH_4OAc (5 mL). After gas evolution ceased, the reaction was concentrated in vacuo at ca. 50 °C, to reduce the volume to 25 mL. Half-saturated brine (100 mL) was added and the mixture extracted with ethyl acetate (2 × 100 mL). The dried ($MgSO_4$) extracts were concentrated in vacuo, then chromatographed with a gradient of 10:90:0 to 100:0:0 to 95:0:5 ethanol/ethyl acetate/concd NH_4OH. The resulting oil was dissolved in dichloromethane and filtered through a pad of $MgSO_4$ on a filter to remove any impurities from the column, affording **18** as a nearly colorless liquid (2.55 g, 64%). ^{1}H NMR (DMSO-d_6): 8.23 (1H, dd, J = 1.5, 4.7 Hz), 7.94 (1H, dd, J = 1.5, 7.8 Hz), 7.56 (1H, d, J = 3.5 Hz), 7.06 (1H, dd, J = 4.6, 7.8 Hz), 6.44 (1H, d, J = 3.5 Hz), 4.34 (2H, t, J = 6.7 Hz), 2.65 (2H, t, J = 6.7 Hz), 2.18 (6H, s). MS (ES+): 190.1 (100%, M+H). HRMS: calcd for $C_{11}H_{15}N_3 + H^+$, 190.1339; found (ESI, $[M+H]^+$), 190.1340. HPLC purity = 98.9%.

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