Bioorganic & Medicinal Chemistry Letters 19 (2009) 6935–6938

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

1-(2-Aminoethyl)-3-(arylsulfonyl)-1*H*-pyrrolopyridines are 5-HT$_6$ receptor ligands

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ARTICLE INFO

Article history:
Received 28 August 2009
Revised 14 October 2009
Accepted 15 October 2009
Available online 20 October 2009

Keywords:
Serotonin
5-HT6 receptor
Pyrrolo[2,3-*c*]pyridine
Pyrrolo[3,2-*b*]pyridine
Pyrrolo[3,2-*c*]pyridine
Agonist
Antagonist
Sulfone

ABSTRACT

1-(2-Aminoethyl)-3-(arylsulfonyl)-1*H*-pyrrolopyridines were prepared. Binding assays indicated they are 5-HT$_6$ receptor ligands, among which **6f** and **6g** showed high affinity for 5-HT$_6$ receptors with K_i = 3.9 and 1.7 nM, respectively.

The 5-hydroxytryptamine-6 (5-HT$_6$) receptor is believed to play a role in learning and memory and therefore its modulation has been investigated as a potential therapeutic target.[1] Intense interest in 5-HT$_6$ receptors has led to the discovery of several classes of high affinity ligands[2] including 1-arylsulfonyl-tryptamines **1** (Fig. 1) reported by Glennon and others.[3] One approach to the development of novel serotonergic ligands has been to reverse the relative roles of the 1- and 3-positions on the indole ring of this compound class. On this basis, we initially identified compounds **2** in which the location of the aminoethyl side chain is 'flipped' from the indole 3-position, as in serotonin, to the indole nitrogen.[4] Many of these compounds were high affinity 5-HT$_6$ ligands and served as the genesis of several ensuing novel derivative classes.

Further modification of the core heterocycle led to the identification of 5-HT$_6$ ligands exemplified by **3** (Fig. 2).[5] Here, substituting a pyrrolo[2,3-*b*]pyridine for an indole afforded ligands which had high affinity for the 5-HT$_6$ receptor, and showed an interesting variation in their functional efficacy. Depending on the substituents, these compounds behaved as either potent agonists or antagonists in a cyclase functional assay. These promising results led us to explore the synthesis and pharmacology of the regioisomeric pyrrolopyridines, which result from moving the nitrogen around to the various positions of the six-membered ring (**4**, **5** and **6**). In

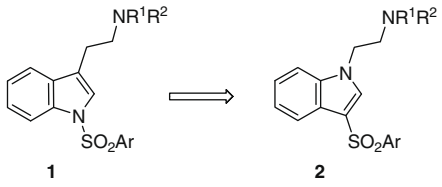

Figure 1. 'Flipped' 5-HT$_6$ ligands.

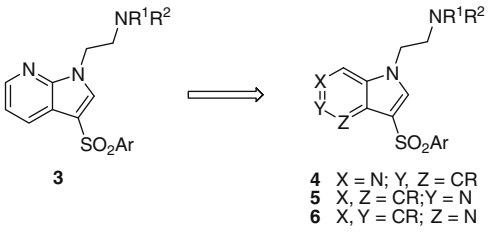

Figure 2. Regioisomeric 1-(2-aminoethyl)-3-arylsulfonyl-pyrrolopyridines.

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doi:10.1016/j.bmcl.2009.10.067

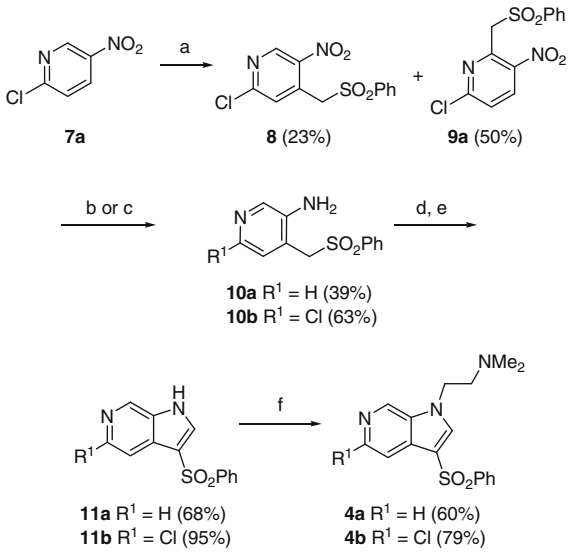
this Letter, we describe the preparation and biological activity of representative examples of these series.

To simplify SAR comparisons, we chose to initially target only compounds with 2-(dimethylamino)ethyl side chains. We knew from our previous work[5] that this side chain was easy to install and generally provided high affinity ligands. This group also did not seem to interfere with agonist activity determinations in the 5-HT_6 cyclase functional assay. Because direct alkylation of 3-arylsulfonyl-1*H*-pyrrolopyridines should provide compounds **4**–**6**, these core heterocycles became our penultimate targets. Several different routes were used to prepare the target compounds and are described here.

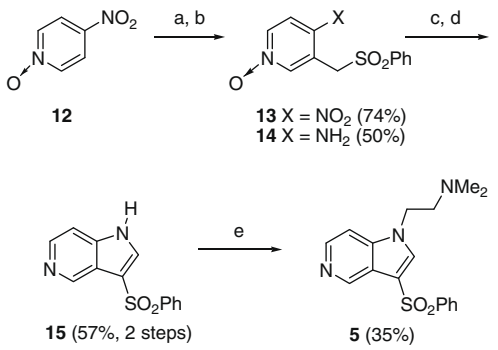
The most versatile route to 3-arylsulfonyl-1*H*-pyrrolopyridines relied heavily on the vicarious nucleophilic substitution (VNS) approach developed by Makosza.[6] To prepare **4**, we started with 2-chloro-5-nitropyridine (**7a**) which when reacted with $PhSO_2CH_2Cl$[7] in the presence of base provided a mixture of separable regioisomers **8** and **9a**, favoring the undesired 4-substitution product **9a** (Scheme 1).[8] Nonselective nitro reduction using prolonged hydrogenation of **8** gave aniline **10a** in which the 2-chloro substituent was cleaved from the pyridine ring.[9] An alternative reduction utilizing tin metal in acidic medium provided chloroaniline **10b**. Heating aniline **10a** with excess triethylorthoformate and *p*-TsOH in 1,2-dichloroethane gave an iminoether, which was treated with a slight excess of 1.0 M KO^{t}Bu in THF to afford **11a**. This one-pot approach to ring formation generally provided product in good yields. Alkylation with 2-(dimethylamino)ethyl chloride hydrochloride provided unsubstituted target **4a**. Application of the same sequence to **10b** provided additionally functionalized **4b**.

The regioisomeric pyrrolo[3,2-*c*]pyridine (**15**) was prepared by an analogous VNS route. Reaction of commercial **12** with $PhSO_2CH_2Cl$ in DMSO using KOH as base provided **13** (Scheme 2). The substitution product was reduced to aniline **14** on prolonged hydrogenation using ammonium formate as the hydrogen source. Cyclization to form **15** and subsequent alkylation completed the sequence to derivative **5**.

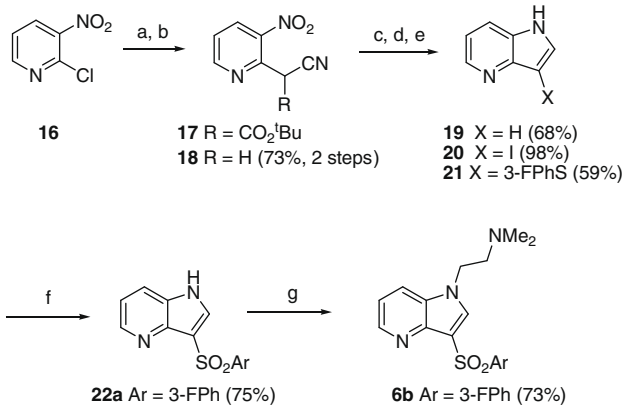
3-Arylsulfonyl-pyrrolo[3,2-*b*]pyridines **22** were produced by two different routes. The first began with the synthesis of pyrrolo[3,2-*b*]pyridine (**19**) from 2-chloro-3-nitropyridine **16** (Scheme 3). Katz



Scheme 1. Reagents and conditions: (a) $PhSO_2CH_2Cl$, THF, 1 M KO^{t}Bu in THF, −65 °C to 0 °C over 1.5 h, then AcOH; (b) Sn (4.4 equiv), 6 M aq HCl, MeOH, 45 °C, 4–6 h; (c) 10% palladium on carbon, hydrogen (55 psi), NaOAc, MeOH, 3 d; (d) $HC(OEt)_3$ (2–5 equiv), *p*-tolunesulfonic acid monohydrate (0.1 equiv), DCE, reflux, 7 h; (e) 1.0 M KO^{t}Bu in THF (1.3–1.5 equiv), THF, rt, 5–30 min; (f) $Me_2N(CH_2)_2Cl{\cdot}HCl$, (1.1 equiv), NaH (2.0 equiv), DMF (**11a**: 80 °C, overnight; **11b**: rt, 22 h, then 55 °C, 4 h).



Scheme 2. Reagents and conditions: (a) $PhSO_2CH_2Cl$, DMSO, KOH, 0 °C, 45 min; (b) 10% palladium on carbon, NH_4CO_2H (7 equiv), MeOH, 50 °C to reflux, 54 h; (c) $HC(OEt)_3$ (5 equiv), *p*-tolunesulfonic acid monohydrate (0.1 equiv), DCE, reflux, 7 h; (d) 1.0 M KO^{t}Bu in THF (1.3–1.5 equiv), THF, rt, 2 h; (e) $Me_2N(CH_2)_2Cl{\cdot}HCl$, NaH, DMF, rt, 24 h.



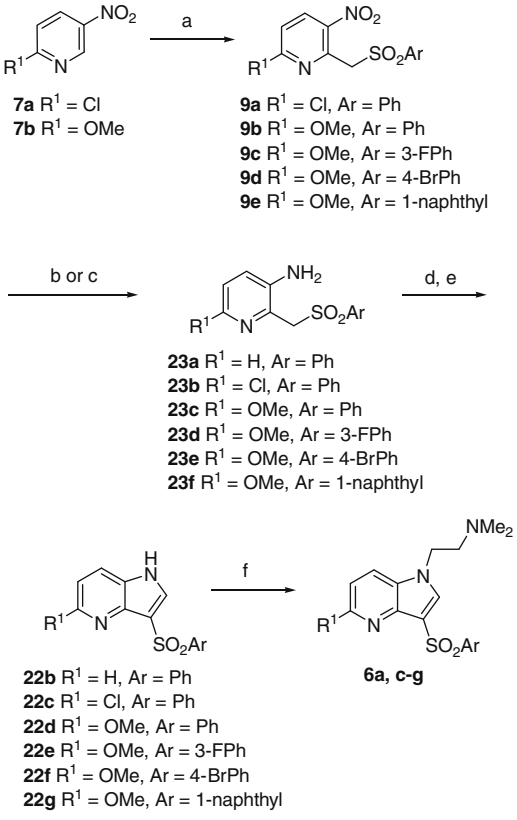
Scheme 3. Reagents and conditions: (a) $NCCH_2CO_2{}^tBu$, K_2CO_3, THF, reflux, 22 h; (b) *p*-TsOH hydrate (0.1 equiv), toluene, reflux, 2 h; (c) 10% Pd on carbon, AcOH, EtOH, hydrogen (55 psi), rt, 24 h; (d) I_2, KI, aq EtOH, rt, 4 h; (e) 3-FPhSH, $Pd(PPh_3)_4$, NaO^{t}Bu, EtOH, reflux, 17 h; (f) OXONE™, aq $NaHCO_3$, acetone, rt, 3 h; (g) $Me_2N(CH_2)_2Cl{\cdot}HCl$, NaH, DMF, rt, 24 h.

and Voyle described the introduction of *tert*-butyl cyanoacetate under basic conditions to give **17** followed by hydrolysis and decarboxylation to afford **18**.[10] Hydrogenation of **18** provided **19** for subsequent transformations. Direct iodination gave 3-iodopyrrolo[3,2-*b*]pyridine (**20**) which was converted to **21** by a palladium-mediated reaction using 3-fluorothiophenol. Oxidation[11] of **21** gave sulfone **22a**, which was in turn alkylated to final product **6b**.

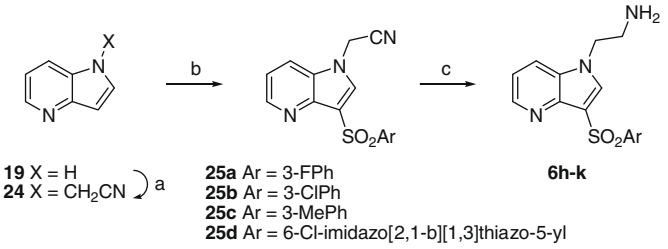
Alternatively, we utilized a VNS route to pyrrolo[3,2-*b*]pyridines **22**, allowing further substitution on the pyridyl ring (Scheme 4). Employing **7a** or **7b** as starting materials, VNS reaction with chloromethylarylsulfones provided **9a**–**e**. These sulfones were reduced to 3-aminopyridines **23a**–**f** and cyclized to pyrrolo[3,2-*b*]pyridines **22b**–**g** in a manner analogous to the previous syntheses. Alkylation gave the desired derivatives (**6a**, **6c**–**g**). The VNS approach utilized here allowed for variations in the arylsulfonyl based on the chloromethylarylsulfone employed. The chloromethylarylsulfones were conveniently prepared in one-pot from the corresponding arylsulfonyl chloride, as described previously.[7]

Preparation of primary amines **6** (R^1, R^2 = H) was accomplished by a three-step sequence, which used a nitrile as the amine precursor (Scheme 5).[5] Alkylation of **19** with bromoacetonitrile instead of 2-(dimethylamino)ethyl chloride provided **24**, which was subjected to arylsulfonylation in the presence of silver triflate to provide **25**.[5] Subsequent reduction of the nitrile with borane gave targeted primary amines **6h–k**.

Final compounds were tested for 5-HT_6 affinity in a radioligand binding assay[12] using human-cloned 5-HT_6 receptors (Table 1).



Scheme 4. Reagents and conditions: (a) $ArSO_2CH_2Cl$, THF, KO^{t}Bu, −65 °C to −20 °C over 1 h, then AcOH quench; (b) 10% Pd on carbon, H_2 (55 psi), NaOAc, MeOH, rt, 3 d (59%); (c) Sn (4.4 equiv), 6 M aq HCl, MeOH, 45 °C, 4–6 h; (d) $HC(OEt)_3$ (2–5 equiv), *p*-tolunesulfonic acid monohydrate (0.1 equiv), $ClCH_2CH_2Cl$, reflux, 6–24 h; (e) 1.0 M KO^{t}Bu in THF (1.3–1.5 equiv), THF, rt, 0.5–2 h; (f) $Me_2N(CH_2)_2Cl{\cdot}HCl$, NaH, DMF, rt, 18–24 h.

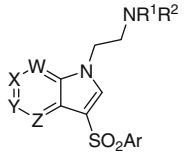


Scheme 5. Reagents and conditions: (a) NaH, $BrCH_2CN$, DMF, rt, 16 h; (b) $ArSO_2Cl$, AgOTf, $PhNO_2$, 100 °C, 3–5 h (28–52%); (c) BH_3 (1.0 equiv), THF, rt, 18–24 h, then 0 °C, 1 M aqueous HCl (51–71%).

Both **3a** and its 3-fluoro analog **3b** had good to excellent affinity for the target receptor with the 3-fluoro group increasing binding almost fivefold. Moving the nitrogen of pyridyl ring to the adjacent position on the ring provided derivatives **4a** and **4b**. Compound **4b** had little affinity for the target receptor. Similarly, shifting the nitrogen to the next position to afford **5** provided a compound with weak affinity for the 5-HT_6 receptor. It is plausible that differences in the basicity of **4b** and **5**, relative to **3**, were responsible for the reduced affinity.

The first example (**6a**) of the final regioisomers, arylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridines **6**, had modest affinity for the receptor but still had nearly 10-fold weaker binding compared to the comparably unsubstituted **3a** of the lead series. Encouragingly, introduction of a 3-fluoro group on the aryl ring modestly increased affinity, though the magnitude was less than the increase in affinity going from **3a** to **3b**. Similarly, a chloro substituent on the pyridyl ring improved affinity somewhat (compare **6a** to **6c**) and switching from a chloro substituent (**6c**) to a methoxy (**6d**) further improved affinity. Combining fluoro substitution on the arylsulfonyl ring with methoxy substitution on the pyridyl ring further increased affinity (**6e**) of this series. Replacement of the 3-fluorophenyl with 4-bromophenyl (**6f**) and then with 1-naphthyl (**6g**) continued the improve-

Table 1
5-HT_6 Binding and adenylyl cyclase activity of **3**, **4**, **5** and **6**[a]



Compd	W	X	Y	Z	R^1, R^2	Ar	5-HT_6 K_i (nM)	cAMP Assay for 5-HT_6	
								EC_{50} or IC_{50} (nM)	E_{max} or I_{max} (%)
3a	N	CH	CH	CH	Me, Me	Ph	23 (±2)	25 (±0.1) (ag)	94 (ag)
3b	N	CH	CH	CH	Me, Me	3-FPh	4.9 (±0.3)	7.3 (±1.6) (ag)	100 (ag)
4a	CH	N	CH	CH	Me, Me	Ph	No tested	—	—
4b	CH	N	CCl	CH	Me, Me	Ph	55% @ 1 μM	—	—
5	CH	CH	N	CH	Me, Me	Ph	39% @ 1 μM	—	—
6a	CH	CH	CH	N	Me, Me	Ph	368 (±23)	—	—
6b	CH	CH	CH	N	Me, Me	3-FPh	200 (±15)	—	—
6c	CH	CH	CCl	N	Me, Me	Ph	214 (±20)	—	—
6d	CH	CH	COMe	N	Me, Me	Ph	56 (±5.6)	—	—
6e	CH	CH	COMe	N	Me, Me	3-FPh	11.3 (±0.9)	41 (±34) (ant)	91 (ant)
6f	CH	CH	COMe	N	Me, Me	4-BrPh	3.9 (±0.3)	385 (±35) (ant)	100 (ant)
6g	CH	CH	COMe	N	Me, Me	1-Naphthyl	1.7 (±0.2)	295 (±46) (ant)	100 (ant)
6h	CH	CH	CH	N	H, H	3-FPh	76 (±1)	823 (±34) (ag)	51 (ag)
6i	CH	CH	CH	N	H, H	3-ClPh	35 (±8)	197 (±22) (ag)	56 (ag)
6j	CH	CH	CH	N	H, H	3-MePh	46 (±9)	—	—
6k	CH	CH	CH	N	H, H	6-Cl-imidazo[2,1-*b*][1,3]thiazo-5-yl	42 (±3)	—	—

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

ment to provide compounds with respectable K_i values at 5-HT_6 receptors (<10 nM). Compounds with a primary amine side chain (**6h–k**) in place of the *N*,*N*-dimethylamine were also examined. A modest increase in affinity was observed, comparing **6b** to **6h**, but this effect was relatively weak compared to the effect of introducing a methoxy group to the aryl ring. Incorporation of a 6-Cl-imidazo[2,1-*b*][1,3]thiazo-5-yl-sulfonyl group, which had provided a high affinity, potent 5-HT_6 agonist in the 1-arylsulfonyl-tryptamine series (**1**),[12] did not improve 5-HT_6 receptor affinity for **6k**.

Several compounds (**6e–i**) with good 5-HT_6 affinity were tested in an adenylyl cyclase assay to determine the ligands' ability to modulate 5-HT_6 function in vitro.[12] We expected these compounds, like regioisomeric analogs **3a–b**, to function as agonists in this assay. Instead, they proved to be only weak, full antagonists, with the exception of the primary amines **6h** and **6i**, which possessed weak agonist function.

Three regioisomeric series of 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-pyrrolopyridines, based on the high affinity 1-(aminoethyl)-3-(arylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridines **3**, were prepared using five synthetic routes. Three approaches incorporated a key VNS reaction, demonstrating the versatility of this approach. In contrast to pyrrolo[2,3-*b*]pyridines **3**, pyrrolo[2,3-*c*]pyridine **4b** and pyrrolo[3,2-*c*]pyridine **5** had significantly weaker affinity for 5-HT_6 receptors. More promising were pyrrolo[3,2-*b*]pyridines **6**, with optimized ligands possessing excellent affinity for the target receptors (e.g., **6f** and **6g** with 5-HT_6 binding K_i = 3.9 nM and 1.7 nM, respectively). However, these compounds were functionally weak agonists or antagonists as demonstrated in the adenylyl cyclase assay.

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