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1-[2-[(Heteroarylmethoxy)aryl]carbamoyl]indolines are Selective and Orally Active 5-HT_{2C} Receptor Inverse Agonists

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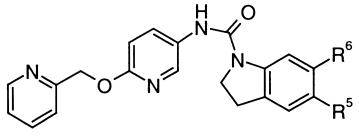
Abstract—Bisarylmethoxyethers have been identified with nanomolar 5-HT_{2C} affinity and selectivity over both 5-HT_{2A} and 5-HT_{2B} receptors. Compounds such as **1**, **2**, **8**, **12**, **14** and **18** have potent oral activity in a centrally mediated pharmacodynamic model of 5-HT_{2C} function and their therapeutic potential is currently under further investigation. © 2000 Elsevier Science Ltd. All rights reserved.

In our previous letter we described bisaryl ethers which are high affinity and selective 5-HT_{2C} receptor inverse agonists with excellent in vivo activity.[1] Such compounds are of considerable potential for the treatment of a range of CNS disorders, in particular anxiety and depression.[2] We now describe the discovery and SAR of a novel series of 1-[2-[(2-heteroarylylmethoxy)aryl]-carbamoyl]indolines such as **1** (SB-247853) and **2** which are also high affinity and selective 5-HT_{2C} receptor inverse agonists with potent oral activity in animal models.



1 R^5 = Me R^6 = CF_3 **(SB-247853)**
2 R^5 = CF_3 R^6 = H

Chemistry

The final compounds were prepared according to Schemes 1–4. **1**–**12**, **14** and **18**–**21** were obtained by treating the anion of the appropriately substituted hydroxymethyl-heteroaromatics with appropriately substituted 2-chloro-5-nitropyridines, or 4-fluoronitrobenzene in the case of **14**, to afford the nitrobisarylmethoxyethers in generally excellent yield (Scheme 1). Reduction to the corresponding amines and coupling with the appropriate substituted indolines,[3] via the phenyl carbamate, afforded the final compounds.[4] The hydroxymethylheteroaromatics and 2-chloro-5-nitropyridines were commercially available or known in the literature. Compound **17** was similarly prepared from 5-nitro-2-[2-(2-pyridinyl)ethoxy]pyridine,[5] itself prepared from 2-hydroxy-5-nitropyridine and 2-(2-hydroxyethyl)pyridine under Mitsunobu conditions. The pyridazine **13** was prepared by reacting 6-chloro-3-pyridazinecarboxylic acid ethyl ester with 2-(hydroxymethyl)pyridine under basic conditions to give the bisarylmethoxyether. The ester was then converted to the azide which was heated to generate the isocyanate and reacted in situ with 5-methyl-6-trifluoromethyl-indoline to afford **13** (Scheme 2). In an analogous procedure (Scheme 3), **16** was prepared by heating 2-hydroxypyridine and 6-(chloromethyl)-3-pyridinecarboxylic acid ethyl ester with silver carbonate in toluene in the dark to afford the bisarylmethoxyether which was then converted to **16** as in Scheme 2. The ethyl linked compound **15** was prepared by condensing 2-pyridinecarboxaldehyde with ethyl 2-methyl-5-pyridinecarboxylate in acetic anhydride followed by hydrogenation of the resulting ethylene linker (Scheme 4). The resulting ethyl linked bispyridyl ester was then converted to **15** as described in Scheme 2.

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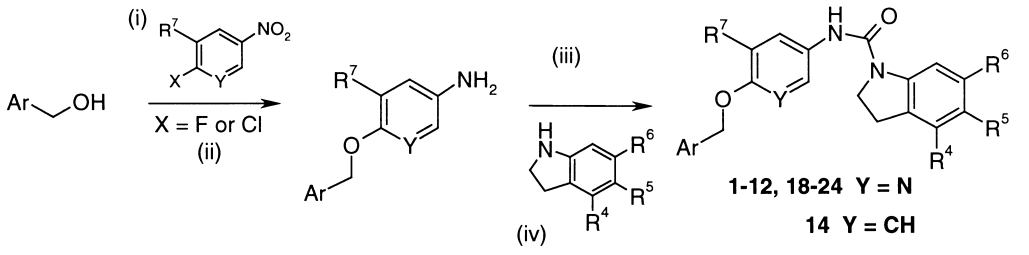
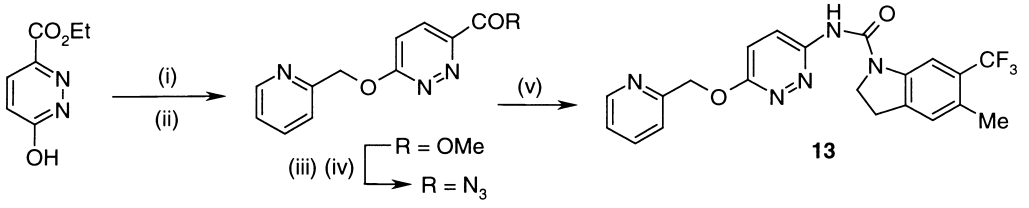
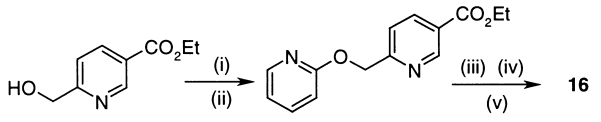


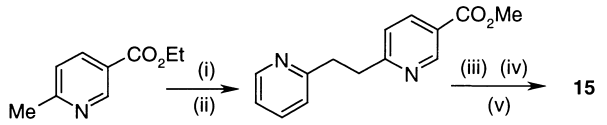
Scheme 1. Reagents and conditions: (i) NaH, DMF, −20 °C–rt, 18 h (31–91%); (ii) $SnCl_2$, EtOH/conc. HCl, 50 °C, 1 h (49–100%); (iii) PhOCOCl/NEt_3, CH_2Cl_2, −20 °C, 1 h; (iv) NEt_3/DMF, 100 °C, 1 h (35–85%).



Scheme 2. Reagents and conditions: (i) $POCl_3$, 100 °C, 2 h (74%); (ii) 2-pyridylmethanol/KO^{t}Bu, THF, −70 °C–rt, 18 h (22%); (iii) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, 4 h (81%); (iv) $NaNO_2$, aqueous HCl, 0 °C, 0.5 h (100%); (v) 5-methyl-6-trifluoromethylindoline, toluene, reflux, 1 h (45%).



Scheme 3. Reagents and conditions: (i) $SOCl_2$/pyridine, CH_2Cl_2, 0 °C, 4 h (30%); (ii) 2-hydroxypyridine/Ag_2CO_3, toluene, reflux (dark), 18 h (22%); (iii) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, 4 h (63%); (iv) $NaNO_2$, aqueous HCl, 0 °C, 0.5 h (53%); (v) 5-methyl-6-trifluoromethylindoline, toluene, reflux, 1 h (54%).



Scheme 4. Reagents and conditions: (i) 2-pyridinecarboxaldehyde, Ac_2O, reflux, 18 h (12%); (ii) H_2/ Pd/C, EtOH, rt, 4 h (66%); (iii) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, 4 h (83%); (iv) $NaNO_2$, aqueous HCl, 0 °C, 0.5 h (79%); (v) 5-methyl-6-trifluoromethylindoline, toluene, reflux, 1 h (59%).

Results and Discussion

Our original series of bispyridyl ethers was developed utilizing ligand docking studies into a model of the 5-HT_{2C} receptor.[2] In the proposed binding mode the bispyridyl ether moiety occupies a lipophilic pocket defined by side-chain aromatic residues on transmembrane helices 5 and 6. In order to further explore the size and shape of this binding pocket we prepared a range of analogues incorporating the longer methoxy linker group between the aromatic rings, initially in combination with the previously optimized 5-chloro- or 5-trifluoro- 6-methylindoline.

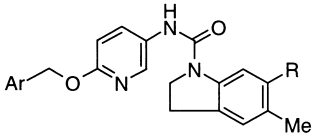
Heteroarylmethoxyethers (Table 1)

Preparation of all three possible terminal pyridyl isomers revealed that the position of the nitrogen atom was of key importance. The 3-pyridylmethoxy analogue **6** had relatively modest 5-HT_{2C} receptor affinity (reduced 25-fold relative to the corresponding bispyridyl ether SB-242084),[1] moderate selectivity over 5-HT_{2A} and no selectivity over 5-HT_{2B} receptors. The corresponding 4-pyridylmethoxy isomer **7** showed 10-fold increased 5-HT_{2C} affinity and somewhat improved, although still unimpressive, selectivity. However, the 2-pyridylmethoxy isomer **3** had similar target affinity to **7** combined with excellent selectivity and in addition this compound showed significant in vivo activity in the rat hypolocomotion model. In this centrally mediated pharmacodynamic model of 5-HT_{2C} function, the ability of compounds to block the hypolocomotion in rats produced by a standard dose of the moderately selective 5-HT_{2C} agonist *m*-chlorophenylpiperazine (mCPP) was measured.[6] The corresponding 5-trifluoro-6-methylindoline **1** showed an even better profile with sub-nanomolar 5-HT_{2C} affinity, further improved selectivity (1300-fold and 60-fold over 5-HT_{2A} and 5-HT_{2B}, respectively) and potent in vivo activity (ID_{50} 1 mg/kg p.o.). Interestingly, introduction of a 6-methyl group **4** or a 3-methyl group **5** into the terminal pyridine ring led to dramatic loss of selectivity and a 10-fold drop in 5-HT_{2C} affinity, suggesting that the unsubstituted 2-pyridyl side-chain optimally fills the lipophilic binding pocket. Introduction of an additional nitrogen gave the pyrazine **8** with a similar binding profile to **1**, although selectivity over 5-HT_{2B} and in vivo activity was somewhat reduced. A number of heteroaromatic five-membered rings were also investigated such as the imidazoles **9** and **10** and the thiazole **11**. Although these compounds had good 5-HT_{2C} affinity and reasonable selectivity over 5-HT_{2A}, selectivity over 5-HT_{2B} was low and **11** was inactive in vivo.

Variation of central ring and linker (Table 2)

Having established that the 2-pyridyl isomer **1** was optimal, a series of analogues was prepared investigating modifications to the central ring and the linker group. Considering the central ring, incorporation of a 5-methyl

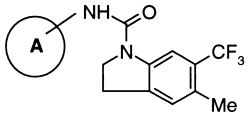
Table 1. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of 1-[2-[2-(heteroarylmethoxy)-5-pyridyl]carbamoyl]indolines **1** and **3**–**11**

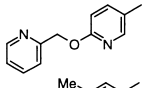
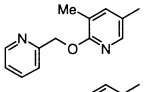
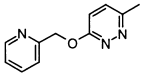
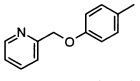
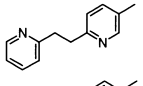
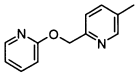
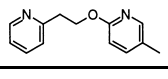


Compound	Ar	R	pK_i	pK_i (selectivity)		ID_{50}[e] (mg/kg p.o.)
			5-HT_{2C}[b]	5-HT_{2A}[c]	5-HT_{2B}[d]	
3	2-Pyridyl	Cl	8.6	< 6.1 (>320)	7.0 (40)	41%
1	2-Pyridyl	CF_3	9.3	6.2 (1300)	7.5 (60)	1.0
4	6-Methyl-2-pyridyl	CF_3	8.2	6.0 (160)	7.6 (4)	—
5	3-Methyl-2-pyridyl	CF_3	8.4	6.8 (40)	7.8 (4)	—
6	3-Pyridyl	Cl	7.6	< 6.1 (>30)	7.6 (1)	—
7	4-Pyridyl	Cl	8.9	7.1 (60)	8.1 (6)	—
8	2-Pyrazinyl	CF_3	9.3	6.5 (630)	8.0 (20)	58%
9	1-Methyl-2-imidazolyl	Cl	8.3	6.6 (50)	7.9 (2.5)	—
10	1-Methyl-5-imidazolyl	CF_3	8.4	7.0 (25)	8.2 (2)	—
11	2-Thiazolyl	Cl	8.3	< 6.1 (>160)	7.0 (20)	2%

[a]All values represent the mean of at least two determinations, with each determination lying within 0.2 log unit of the mean.
[b]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-mesulergine).[2]
[c]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-ketanserin).[2]
[d]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-5-HT).[2]
[e]Dose of compound required to reverse mCPP (7 mg/kg ip administered 30 min pretest) induced hypolocomotion by 50% or percentage reversal at 5 mg/kg.[2]

Table 2. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of 1-[[(2-pyridyl)linked aryl]carbamoyl]indolines **1** and **12**–**17**



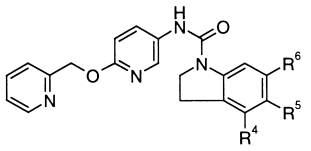
Compound	A	pK_i	pK_i (selectivity)		ID_{50}[e] (mg/kg p.o.)
		5-HT_{2C}[b]	5-HT_{2A}[c]	5-HT_{2B}[d]	
1		9.3	6.2 (1300)	7.5 (60)	1.0
12		9.4	7.4 (100)	8.1 (20)	0.3
13		8.3	6.6 (50)	7.1 (15)	—
14		8.6	6.4 (160)	7.6 (10)	84%
15		8.5	6.8 (50)	7.7 (6)	—
16		8.3	7.0 (20)	6.7 (40)	—
17		8.0	5.7 (200)	7.7 (2)	—

[a–e]See corresponding footnotes in Table 1.

group (compound **12**) retained affinity and gave the most potent in vivo activity yet achieved (ID_{50} 0.3 mg/kg) although selectivity was reduced relative to **1**. Replacement of the pyridine by pyridazine (compound **13**) resulted in a 10-fold drop in affinity and loss of selectivity.

The corresponding phenyl derivative **14** also showed reduced 5-HT_{2C} receptor affinity and selectivity, although over 100-fold selectivity over 5-HT_{2A} receptors and reasonable oral activity was maintained. The analogues incorporating an ethyl linker **15** and a reversed methoxy linker group **16** had disappointing in vitro profiles. The

Table 3. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of substituted 1-[[2-(2-pyridylmethoxy)-5-pyridyl]carbamoyl]indolines **1–3** and **18–21**



Compound	R^4	R^5	R^6	pK_i 5-HT_{2C}[b]	pK_i (selectivity)		ID_{50}[e] (mg/kg p.o.)
					5-HT_{2A}[c]	5-HT_{2B}[d]	
3	H	Me	Cl	8.6	< 6.1 (>320)	7.0 (40)	41%
1	H	Me	CF_3	9.3	6.2 (1300)	7.5 (60)	1.0
18	H	Br	H	7.8	5.6 (160)	6.3 (30)	2.4
2	H	CF_3	H	8.2	5.3 (800)	6.4 (60)	1.6
19	H	Cl	H	7.5	< 5.3 (>160)	6.0 (30)	—
20	Cl	H	H	7.1	5.3 (60)	6.0 (13)	—
21	H	H	CF_3	8.1	6.6 (30)	6.6 (30)	—

[a–e]See corresponding footnotes in Table 1.

three atom linked compound **17** showed a 10-fold reduction in affinity and selectivity relative to **1** suggesting that a two atom linker is optimal.

Optimization of indoline substitution (Table 3)

A limited programme of work to further investigate indoline substitution in the 2-pyridylmethoxy series was carried out. The 5-CF_3 indoline **2** and the 5-bromoindoline **18** had reduced but still reasonable 5-HT_{2C} receptor affinity and selectivity relative to **1** combined with potent oral activity. In contrast, the 5-chloro **19**, 4-chloro **20** and 6-trifluoromethyl **21** indolines had relatively modest affinity and selectivity.

Summary

A number of bisarylmethoxyethers have been identified with nanomolar 5-HT_{2C} affinity and selectivity over both 5-HT_{2A} and 5-HT_{2B} receptors. On further cross-screening these compounds were also found to be selective over a wide range of other monoamine receptors, including serotinergic and dopaminergic subtypes. In an in vivo human 5-HT_{2C} receptor functional assay they were found to be inverse agonists completely abolishing basal activity.[2] In addition **1**, **2**, **8**, **12**, **14** and **18** demonstrated potent oral activity in the rat hypolocomotion assay. Their activity in other animal models of anxiety will be reported elsewhere. Compound **1** (SB-247853) is currently in pre-clinical development.

References and Notes

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