Biarylcarbamoylindolines Are Novel and Selective 5-HT$_{2C}$ Receptor Inverse Agonists: Identification of 5-Methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a Potential Antidepressant/Anxiolytic Agent

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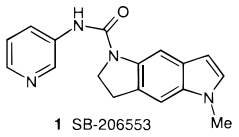
The evolution, synthesis, and biological activity of a novel series of 5-HT$_{2C}$ receptor inverse agonists are reported. Biarylcarbamoylindolines have been identified with excellent 5-HT$_{2C}$ affinity and selectivity over 5-HT$_{2A}$ receptors. In addition, (pyridyloxypyridyl)carbamoylindolines have been discovered with additional selectivity over the closely related 5-HT$_{2B}$ receptor. Compounds from this series are inverse agonists at the human cloned 5-HT$_{2C}$ receptor, completely abolishing basal activity in a functional assay. The new series have reduced P450 inhibitory liability compared to a previously described series of 1-(3-pyridylcarbamoyl)indolines (Bromidge et al. *J. Med. Chem.* **1998**, *41*, 1598) from which they evolved. Compounds from this series showed excellent oral activity in a rat mCPP hypolocomotion model and in animal models of anxiety. On the basis of their favorable biological profile, **32** (SB-228357) and **40** (SB-243213) have been selected for further evaluation to determine their therapeutic potential for the treatment of CNS disorders such as depression and anxiety.

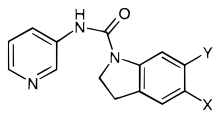
Introduction

The 5-HT$_2$ receptor family is a member of the seven-transmembrane-spanning G-protein-coupled receptor superfamily and constitutes one of the 7 classes of 5-HT receptors (5-HT$_1$ to 5-HT$_7$) which are currently subdivided into 14 recognized human receptors.[1] The 5-HT$_2$ receptor family consists of 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors, which have been grouped together on the basis of primary structure, secondary-messenger system, and pharmacological profile.[2] Sequence analysis indicates approximately 80% amino acid identity in the predicted seven-transmembrane domains of the 5-HT$_2$ receptors although there are distinct differences in distribution. The 5-HT$_{2A}$ receptor is widely distributed in peripheral tissues and also present in the CNS. The 5-HT$_{2B}$ receptor is principally located in the periphery and only sparsely in the CNS. In contrast, the 5-HT$_{2C}$ receptor has been found only in the CNS, being highly expressed in many regions of the mammalian brain including the choroid plexus and the limbic and basal ganglia structures.[1] There remains a paucity of selective ligands to more fully elucidate the functional role of the different 5-HT$_2$ receptors.

Our interest in the 5-HT$_{2C}$ receptor goes back over several years. The observation that the moderately selective 5-HT$_{2C/2B}$ agonist, *m*-chlorophenylpiperazine (mCPP), caused behavioral indications of anxiety in both animal models and humans[3] led us to speculate that selective 5-HT$_{2C/2B}$ antagonists might be useful anxiolytic agents. Subsequently, we developed a number of selective 5-HT$_{2C/B}$ receptor antagonists, such as **1** (SB-206553) and **2** (SB-221284), which block the centrally mediated mCPP-induced hypolocomotion in rats. These compounds also exhibited significant anxiolytic activity in several different animal models, lending strong support to our original hypothesis.[4−6] More recently, an accumulating body of published data[7−10] has suggested that 5-HT$_{2C}$ antagonism may also offer significant therapeutic opportunities for the treatment of other CNS disorders such as depression,[7,8] schizophrenia,[8] migraine,[9] and Parkinson's disease.[10]



1 SB-206553



2 X = SMe Y = CF_3

3 X = OMe Y = CF_3

4 X = Me Y = Cl

Recently we reported the synthesis and biological activity of a series of substituted 1-(3-pyridylcarbamoyl)-indolines such as **2**−**4** which remain the most potent and selective 5-HT$_{2C/2B}$ receptor antagonists yet reported.[5] Compound **2** was selected on the basis of its overall biological profile for further evaluation of its

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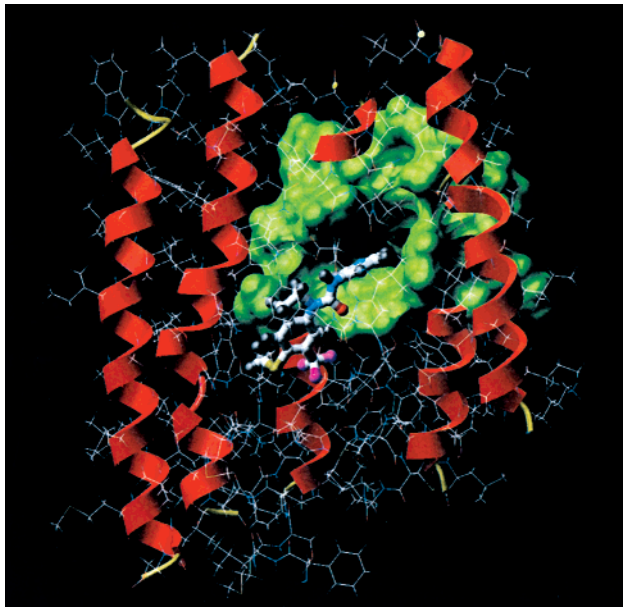


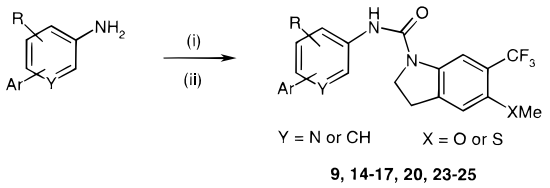
Figure 1. Structure **2** docked into the model of the 5-HT_{2C} receptor. TM2 and TM3 have been removed for clarity. The molecular surface (green) has been placed around the residues on the extracellular side of TM5 and TM6 and shows the deep aromatic cavity which accommodates the pyridyl ring of **2** at its mouth.

therapeutic potential. Unfortunately, **2** and related analogues were found to be potent inhibitors of a number of human cytochrome P450 enzymes, in particular the CYP1A2 isoform, which precluded further development.[11] Subsequent structural modification of the 3-amidopyridyl ring of **2** by the introduction of steric hindrance around the pyridine nitrogen has revealed that the unhindered nitrogen is responsible for the P450 inhibitory activity.

In conjunction with this work, ligand docking studies were carried out using a model of the 5-HT_{2C} receptor which had been constructed as previously described.[12] In the proposed binding mode a double hydrogen bond between the urea carbonyl oxygen of **2** and the hydroxyl side chains of the two serines in helix 3 (residues 138 and 141) was invoked.[5] The 3-pyridyl ring occupies a lipophilic pocket defined by the side chains of the aromatic residues Phe-223, Trp-324, Phe-327, and Phe-328 and is able to form both $\pi-\pi$ stacking and edge-to-face aromatic interactions with several of these residues. Closer examination of this lipophilic pocket revealed that it was quite deep, extending back to Phe-220 and Phe-224, and that this might be exploited by substitution of the pyridyl ring with suitable aryl groups (Figure 1).

Since the introduction of further steric bulk into the molecules might also be expected to reduce the cytochrome P450 inhibitory liability, in addition to any beneficial effects on 5-HT_{2C} activity, a program of work was undertaken initially investigating substitution of the pyridyl ring with a variety of aryl groups. As substituent changes on the indoline ring did not significantly affect the level of P450 inhibition, this work was carried out with our two previously[5] optimized indolines: 5-methylthio-6-trifluoromethylindoline or 5-methoxy-6-trifluoromethylindoline. These particular substituents were hypothesized to afford the desired selectivity by occupying a region of space which is

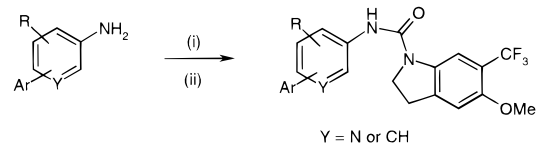
Scheme 1[a]



9, 14-17, 20, 23-25

[a] Reagents: (i) CDI, DCM, rt, 2 h; (ii) 5-methylthio-6-trifluoromethylindoline or 5-methoxy-6-trifluoromethylindoline, DMF, 100 °C, 1 h.

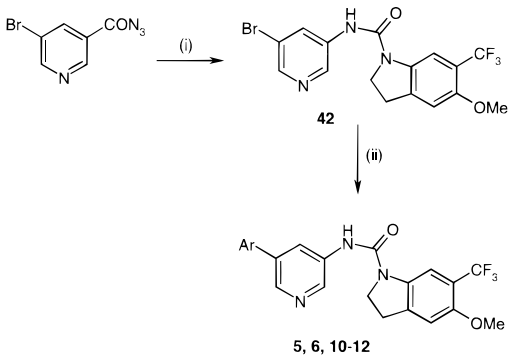
Scheme 2[a]



13, 18-19, 21-22, 26-37

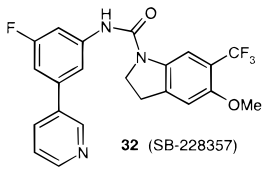
[a] Reagents: (i) PhOCOCl/NEt_3, DCM, −20 °C, 1 h; (ii) 5-methoxy-6-trifluoromethylindoline, NEt_3/DMF, 100 °C, 1 h.

Scheme 3[a]

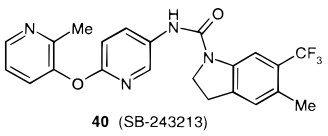


[a] Reagents: (i) toluene, reflux, 1 h, 5-methoxy-6-trifluoromethylindoline, DCM, rt, 18 h; (ii) $ArB(OH)_2/Na_2CO_3/Pd(PPh_3)_4$, DME/$H_2O$, reflux, 10 h.

"allowed" in the 5-HT_{2C} receptor but "disallowed" in the 5-HT_{2A} receptor due to steric differences between the structures of the two binding sites.[5] The work described in this paper has culminated in the identification of **32** (SB-228357) and **40** (SB-243213) which have been selected for evaluation as novel nonsedating antidepressant/anxiolytic agents. The bispyridyl ether **40** is currently in clinical development.



32 (SB-228357)



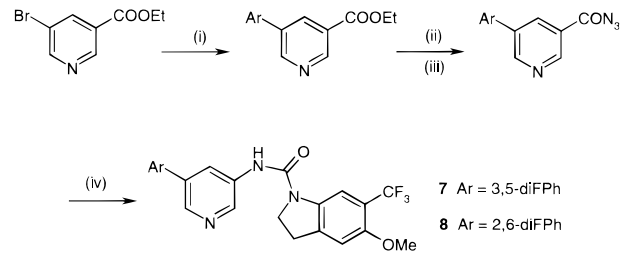
40 (SB-243213)

Chemistry

The synthetic methods used in the preparation of compounds **5**−**41** are shown in Schemes1−6.

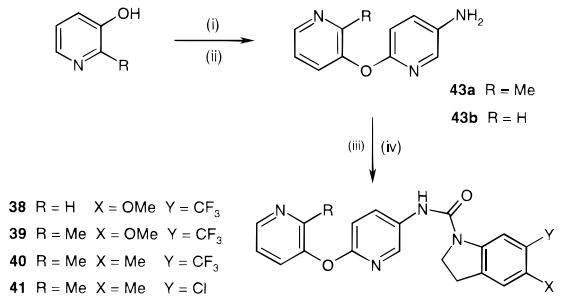
Compounds **9** and **13**−**37** were prepared by coupling biarylanilines with 5-methylthio-6-trifluoromethylindoline or 5-methoxy-6-trifluoromethylindoline using 1,1-carbonyldiimidazole (Scheme 1). Alternatively, the biarylanilines were converted to the corresponding phenyl carbamates, by treatment with phenyl chloroformate, which were then coupled with the indoline (Scheme 2).[13]

Scheme 4[a]



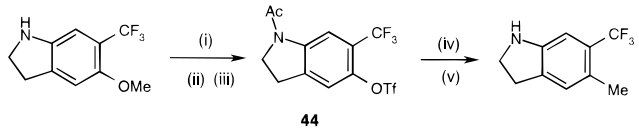
[a] Reagents: (i) (2,6- or 3,5-diFPh)Bu_3Sn/Pd(PPh_3)$_4$, xylene, reflux, 24 h; (ii) $NH_2NH_2 \cdot H_2O$, MeOH, reflux, 18 h; (iii) $NaNO_2$, aq HCl, −5 °C, 0.5 h; (iv) toluene, reflux, 1 h, 5-methoxy-6-trifluoromethylindoline, DCM, rt, 18 h.

Scheme 5[a]



[a] Reagents: (i) NaH, DMF/2-chloro-5-nitropyridine, 0 °C−rt, 18 h; (ii) $SnCl_2$, EtOH/concd HCl, 50 °C, 1 h; (iii) PhOCOCl/NEt_3, DCM, −20 °C, 1 h; (iv) 5-X-6-Y-indoline, NEt_3/DMF, 100 °C, 1 h.

Scheme 6[a]



44

[a] Reagents: (i) TMSI, $CDCl_3$, reflux, 65 h; (ii) Ac_2O, DCM, rt, 1 h; (iii) Tf_2O, pyridine, 0 °C−rt, 18 h; (iv) $SnMe_4$/Pd(PPh_3)$_2Cl_2$/LiCl, DMF, 110 °C, 3 h; (v) aq NaOH, EtOH, reflux, 18 h.

The biarylanilines were either commercially available, known, or prepared by Suzuki[14] methodology.

Compounds **5**, **6**, and **10**−**12** were prepared by reaction of 1-[(5-bromo-3-pyridyl)carbamoyl]-5-methoxy-6-trifluoromethylindoline **(42)** with the appropriate arylboronic acid under Suzuki conditions (Scheme 3).[14] **42** was itself prepared by reacting 5-bromo-3-pyridyl isocyanate, generated in situ from the corresponding 5-bromonicotinic acid azide,[15] with 5-methoxy-6-trifluoromethylindoline.[5] Compounds **7** and **8** were prepared by an analogous procedure by coupling (3,5-difluorophenyl)tributyltin or (2,6-difluorophenyl)tributyltin, respectively, with ethyl 5-bromonicotinate under Stille[14,16] conditions (Scheme 4). The resultant biaryl ester was then converted to the isocyanate, via the azide, and coupled with 5-methoxy-6-trifluoromethylindoline.

The bispyridyl ethers **39**−**41** were prepared by coupling the bispyridyl ether amine **43a** with 5-methoxy-6-trifluoromethylindoline,[5] 6-chloro-5-methylindoline,[5] or 5-methyl-6-trifluoromethylindoline, respectively, via the phenyl carbamate (Scheme 5).[13,17] **43a** was itself prepared by treating the anion of 3-hydroxy-2-methylpyridine with 2-chloro-5-nitropyridine followed by reduction of the resultant nitrobispyridyl ether.[11] 5-Methyl-6-trifluoromethylindoline was prepared from 5-methoxy-6-trifluoromethylindoline[5] by demethylation followed by N-protection and conversion of the resultant phenol to the triflate **44**. Palladium coupling[18] of **44** with tetramethyltin completed the synthesis (Scheme 6). The bispyridyl ether **38** was prepared similarly from 5-methoxy-6-trifluoromethylindoline[5] and 5-amino-2-(3-pyridyloxy)pyridine[19] **(43b)** (Scheme 5).

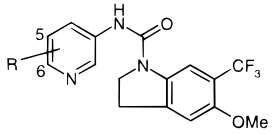
Results and Discussion

The affinities of the compounds were measured by means of radioligand binding studies conducted with human cloned 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors expressed in HEK 293 cells using [^{3}H]ketanserin, [^{3}H]5-HT, and [^{3}H]mesulergine, respectively, as radioligands.[4] The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP1A2 as has been previously described[20] [caffeine N3-demethylation (500 μM)]. Compounds which satisfied in vitro criteria were evaluated in vivo in a centrally mediated model of 5-HT$_{2C}$ receptor function by measuring their ability to block the hypoactivity in rats produced by a standard dose of the moderately selective 5-HT$_{2C}$ agonist mCPP.[4] This mCPP-induced hypoactivity is absent in mutant mice lacking the 5-HT$_{2C}$ receptor.[21]

Phenylpyridylcarbamoylindolines (Table 1). We were encouraged to find that in the 5-methoxy-6-trifluoromethylindoline series incorporating a 5-phenyl substituent into the 3-pyridyl ring of **3** to give **5** slightly increased 5-HT$_{2C}$ affinity and selectivity over 5-HT$_{2A}$ (Table 1). In addition the CYP1A2 inhibitory activity was reduced by 100-fold (target IC$_{50}$ > 10 μM). Unfortunately, **5** was found to have low oral activity in the rat hypolocomotion model. We reasoned that this may be due to metabolism of the relatively electron-rich 5-phenyl ring so fluoro groups were introduced in an attempt to block metabolism and improve oral activity. Unfortunately, these compounds **6**−**8** showed either reduced 5-HT$_{2C}$ affinity (**7** and **8**) or selectivity over 5-HT$_{2A}$ receptors (**6** and **7**). However, the modest oral activity of 4-fluorophenyl analogue **6** in the rat hypolocomotion model was moderately encouraging. It is possible that the poor oral bioavailability of these compounds may be related to their poor aqueous solubility, and in fact the corresponding 6-phenyl-substituted analogue **9** proved too insoluble to obtain receptor binding data.

Bispyridylcarbamoylindolines (Table 1). In an attempt to increase water solubility and metabolic stability, the 5-phenyl substituent of **5** was replaced by pyridyl. Both the 5-substituted 4-pyridyl **(10)** and 3-pyridyl **(11)** analogues demonstrated almost 10-fold improved 5-HT$_{2C}$ affinity relative to **5**, suggesting an additional binding interaction between the terminal pyridyl and the 5-HT$_{2C}$ receptor. However, both compounds showed a larger increase in affinity at the 5-HT$_{2A}$ receptor resulting in reduced selectivity, although this was still around 100-fold. Compound **12** containing a 4-methyl substituent in the terminal 3-pyridyl, which would have the effect of twisting the pyridyl rings out of plane, was found to have slightly increased 5-HT$_{2C}$ affinity, whereas the 5-HT$_{2A}$ affinity was reduced and consequently selectivity was restored. Compound **12** also demonstrated moderate oral activity in the hypolocomotion model. The 5-substituted pyridyl

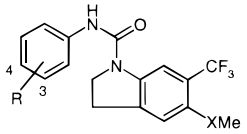
Table 1. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} Receptor Binding Affinities,[a] Human CYP1A2 Inhibitory Potential,[e] and in Vivo Activity[f] of 1-(Aryl-3-pyridylcarbamoyl)indolines **5**−**13**



			pK_i			selectivity			
compd	R5	R6	5-HT_{2A}[b]	5-HT_{2B}[c]	5-HT_{2C}[d]	5-$HT_{2C/2A}$	5-$HT_{2C/2B}$	IC_{50}[e] (μM) CYP1A2	ID_{50}[f] (mg/kg po)
3[5]	H	H	6.0	-	8.0	120	-	0.02	0.8
5	Ph	H	5.8	7.6	8.3	320	5	2.6	>20
6	4-FPh	H	6.6	7.2	8.2	40	10	-	10
7	3,5-diFPh	H	5.9	6.3	7.1	15	6	-	-
8	2,6-diFPh	H	<5	7.0	7.6	>420	4	-	-
9	H	Ph	insol	insol	insol	-	-	-	-
10	4-Py	H	7.2	8.0	9.2	100	16	50%	-
11	3-Py	H	7.2	8.0	9.1	80	12	77%	-
12	4-Me-3-Py	H	7.0	8.2	9.4	250	15	0.2	5
13	H	3-Py	<5.0	8.0	8.3	>2000	2	7%	IA

[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]ketanserin). [c] Binding affinity (human cloned receptors, HEK 293 cells, [^{3}H]5-HT). [d] Binding affinity (human cloned receptors, HEK 293 cells, [^{3}H]mesulergine). [e] The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP1A2 as has been previously described[20] [caffeine N3-demethylation (500 μM)]. These values are the mean of duplicate determinations which did not vary by more than 10% and are expressed as IC_{50} (μM) or percentage reversal at 1 μM. [f] Dose of compound required to reverse mCPP (7 mg/kg ip administered 30 min pretest) induced hypolocomotion by 50%.

Table 2. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} Receptor Binding Affinities,[a] Human CYP1A2 Inhibitory Potential,[e] and in Vivo Activity[f] of 1-(Arylphenylcarbamoyl)indolines **14**−**24**



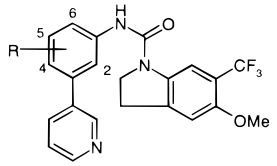
				pK_i			selectivity			
compd	R3	R4	X	5-HT_{2A}[b]	5-HT_{2B}[c]	5-HT_{2C}[d]	5-$HT_{2C/2A}$	5-$HT_{2C/2B}$	IC_{50}[e] (μM) CYP1A2	ID_{50}[f] (mg/kg po)
14	4-Py	H	S	6.8	7.6	8.5	50	8	-	-
15	3-Py	H	S	7.1	8.1	8.8	50	5	-	-
16	2-Py	H	O	6.3	-	7.7	25	-	3%	-
17	3-Py	H	O	6.7	8.1	9.0	200	8	4	0.6
18	4-Me-3-Py	H	O	6.6	-	9.2	400	-	8%	5
19	2-Me-3-Py	H	O	6.3	7.8	8.3	100	3	2%	>10
20	2,4-diMe-3-Py	H	O	6.7	7.9	8.6	80	5	-	-
21	4-Me-3-Py	Me	O	<5.2	8.4	9.5	>20000	12	>100	1.4
22	4-Me-3-Py	Cl	O	<6.0	-	9.2	>1500	-	11%	1.4
23	H	3-Py	O	5.4	8.0	7.8	250	0.6	0%	>10
24	H	4-Py	O	<5.0	7.9	8.3	>2000	3	-	IA

[a] −*f*See corresponding footnotes in Table 1.

analogues **10**−**12** still showed unacceptable CYP1A2 activity although this was considerably reduced relative to **3**. This activity is presumably due to the relatively unhindered nature of the central 3-amidopyridyl ring, and therefore compounds of this type were not pursued further. Moving the 3-pyridyl group from the 5- to 6-position of the 3-amidopyridyl to increase steric crowding of the central pyridine nitrogen gave **13**. Although this compound showed reduced 5-HT_{2C} affinity, it achieved over 2000-fold selectivity over 5-HT_{2A} receptors with low CYP1A2 inhibition but was unfortunately orally inactive (10 mg/kg po).

Pyridylphenylcarbamoylindolines (Table 2). As the exposed nitrogen of the 1-(3-pyridylcarbamoyl)-indolines such as **1**−**4** was apparently responsible for high inhibitory CYP1A2 activity, we investigated the replacement of this ring with phenyl substituted with pyridyl to retain solubility and probe for beneficial interactions with the 5-HT_{2C} receptor. As hoped, these compounds (**14**−**24**) generally retained good 5-HT_{2C} affinity and selectivity over 5-HT_{2A} receptors combined with reduced P450 liability. In combination with the 5-thiomethyl-6-trifluoromethylindoline, both the 3-substituted 4-pyridyl (**14**) and 3-pyridyl (**15**) analogues demonstrated good 5-HT_{2C} affinity but relatively modest selectivity over 5-HT_{2A} receptors. However, incorporating the 5-methoxy-6-trifluoromethylindoline led to improved selectivity with the 3-substituted 3-pyridyl analogue **17** exhibiting nanomolar 5-HT_{2C} affinity combined with good selectivity over 5-HT_{2A}. **17** also demonstrated potent oral activity in the rat hypolocomotion model (ID_{50} = 0.6 mg/kg), but unfortunately moderate CYP1A2 inhibition was still evident (IC_{50} = 4 μM). As previously, increasing the torsion angle between the two aromatic rings by introduction of a 4-methyl into the pyridyl ring *ortho* to the biaryl bond **(18)** increased selectivity over 5-HT_{2A} receptors. In contrast, the 2-methyl analogue **19** and the 2,4-dimethyl analogue **20** demonstrated reduced

Table 3. 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptor Binding Affinities,[a] Human CYP1A2 Inhibitory Potential,[e] and in Vivo Activity[f] of 1-[3-(3-Pyridyl)phenylcarbamoyl]indolines **25**−**37**



		pK_i			selectivity			
compd	R	5-HT$_{2A}$[b]	5-HT$_{2B}$[c]	5-HT$_{2C}$[d]	5-HT$_{2C/2A}$	5-HT$_{2C/2B}$	IC$_{50}$[e] (μM) CYP1A2	ID$_{50}$[f] (mg/kg po)
25	6-F	5.1	5.7	5.7	4	1	-	-
26	2-Me	6.4	-	7.6	16	-	-	-
27	2-Cl	6.6	8.3	8.0	25	0.5	-	-
28	4-Me	5.3	8.3	9.0	5000	5	7%	1.6
29	4-t-Bu	6.0	7.4	8.5	320	13	-	IA
30	4-Cl	5.9	7.6	8.3	250	5	73	5.5
31	4-MeO	6.7	7.8	9.3	400	30	3%	1.2
32	5-F	6.9	8.0	9.0	130	10	28	0.7
33	5-Br	<6.0	7.7	8.7	>500	10	7%	5
34	5-Et	6.7	8.0	9.2	320	16	6%	1.2
35	5-Ph	6.2	7.8	8.6	250	6	0%	>5
36	4-Me-5-F	5.8	8.1	9.2	1600	13	-	>5
37	4,5-OCH$_2$CH$_2$	6.6	8.1	9.3	500	16	2%	2.0

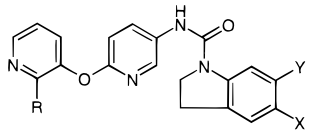
[a−f] See corresponding footnotes in Table 1.

5-HT$_{2C}$ activity and selectivity. Combining a 4-methyl-3-pyridyl at the 3-position of the phenyl with a 4-methyl to give **21**, which modeling showed would result in an almost orthogonal relationship of the two aryl rings, gave sub-nanomolar 5-HT$_{2C}$ affinity while effectively abolishing 5-HT$_{2A}$ activity and thus affording spectacular selectivity of >20 000. The corresponding 4-chlorophenyl analogue **22** had a similar profile confirming this trend. Unfortunately, although **18, 19**, and **22** showed good oral activity in the rat hypolocomotion model and low CYP1A2 inhibitory activity, on screening at other P450 enzymes significant inhibition of the CYP2D6 isoform (IC$_{50}$ < 1 μM) was apparent. The 2-pyridyl analogue **16** showed considerably reduced 5-HT$_{2C}$ affinity and selectivity relative to **17**. The 4-substituted pyridyl analogues **23** and **24** demonstrated reduced but still reasonable 5-HT$_{2C}$ affinity with good selectivity over 5-HT$_{2A}$ receptors and low CYP1A2 inhibitory liability. Unfortunately, both these compounds displayed poor oral activity.

Pyridyl-Substituted Phenylcarbamoylindolines (Table 3). From the work described above, the 3-(3-pyridyl)phenylcarbamoylindoline **17** emerged with the best overall in vitro profile, combined with high potency in the hypolocomotion model. However, time course studies revealed that the duration of activity in this model following oral dosing at 3 × ID$_{50}$ was less than 1 h. We hypothesized that this short duration of action may be due to metabolism of the relatively electron-rich phenyl ring. Therefore, a series of analogues was prepared containing additional substituents in the phenyl ring to explore binding and P450 SAR and with the additional aim of blocking putative metabolism. Introducing substituents into the 2- and 6-positions **(25**−**27)** resulted in a significant drop in 5-HT$_{2C}$ affinity and selectivity relative to **17**. This effect was dramatic in the case of the 6-fluoro analogue **25** presumably due to an unfavorable effect on the relative conformation of the aromatic ring and the carbamoyl moiety. In contrast, a variety of both electron-withdrawing and electron-donating substituents were well-tolerated at both the 4- (**28**−**31**) and 5-positions (**32**−**35**), affording good to excellent 5-HT$_{2C}$ affinity and selectivity over 5-HT$_{2A}$. The good activity of the triaryl analogue **35** indicates considerable space in the receptor binding pocket. In general, the 4-substituted analogues **28**−**31** demonstrated increased selectivity over 5-HT$_{2A}$, relative to **17**, which is consistent with the finding that an out-of-plane conformation of the aryl rings disfavors 5-HT$_{2A}$ activity. Incorporating 4,5-disubstitution as in **36** and **37** produced an additive effect on activity leading to some of the highest 5-HT$_{2C}$ affinities and selectivities over 5-HT$_{2A}$ so far seen. In addition to excellent binding profiles, all the compounds tested in this series demonstrated low inhibition of CYP1A2. Several compounds, in particular **28**, **31**, **32**, **34,** and **37**, also demonstrated potent oral activity in the rat hypolocomotion model. These compounds were further profiled in time course studies in this model to determine if our aim of increasing metabolic stability relative to **17** had been achieved. In the case of **32** a 6-h duration of effect was observed following oral dosing at 3 × ID$_{50}$, and this compound was therefore selected for further evaluation.

(3-Pyridyloxy)pyridylcarbamoylindolines (Table 4). Although many of the compounds described above demonstrated excellent 5-HT$_{2C}$ affinity and selectivity over 5-HT$_{2A}$, selectivity over the 5-HT$_{2B}$ receptor was absent or at best modest. The high affinity of the triaryl analogue **35**, together with further receptor−ligand modeling work, suggested that the lipophilic pocket within the 5-HT$_{2C}$ receptor was still not fully exploited. The model suggested that introducing a linker group between the aromatic rings would more optimally occupy these hydrophobic regions (Figure 2). Consequently, the bispyridyl ether **38** was prepared and found to have excellent 5-HT$_{2C}$ affinity and almost 100-fold selectivity over 5-HT$_{2A}$. As previously, increasing the torsion angle between the two aryl rings by introduction of a 2-methyl substituent into the terminal pyridyl ring to give **39** afforded a beneficial effect on 5-HT$_{2C}$ affinity and a 10-fold increase in selectivity over 5-HT$_{2A}$. In addition, we were very excited to discover that 80-fold

Table 4. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} Receptor Binding Affinities,[a] Human CYP1A2 Inhibitory Potential,[e] and in Vivo Activity[f] of [(3-Pyridyl)oxy]-5-pyridylcarbamoylindolines **38**−**41**



				pK_i			selectivity			
compd	R	X	Y	5-HT_{2A}[b]	5-HT_{2B}[c]	5-HT_{2C}[d]	5-$HT_{2C/2A}$	5-$HT_{2C/2B}$	IC_{50}[e] (μM) CYP1A2	ID_{50}[f] (mg/kg po)
38	H	OMe	CF_3	7.0	7.7	8.9	80	16	4%	0.7
39	Me	OMe	CF_3	6.1	7.3	9.2	1300	80	>100	2.8
40	Me	Me	CF_3	6.8	7.0	9.0	160	100	>100	0.7
41	Me	Me	Cl	6.8	7.0	9.0	160	100	>100	2.0

[a] −[f]See corresponding footnotes in Table 1.

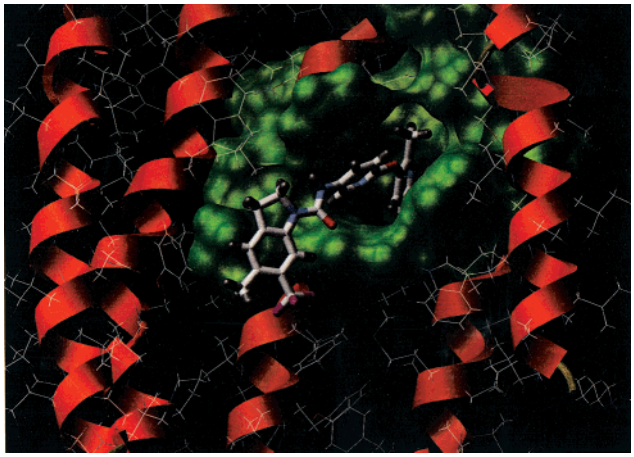


Figure 2. Structure **40** docked into the model of the 5-HT_{2C} receptor (TM2 and TM3 removed for clarity) showing the 2-methyl-3-pyridyloxy group extending deep into the cavity.

selectivity over the 5-HT_{2B} receptor was now apparent. Compounds **38** and **39** also demonstrated low CYP1A2 inhibitory liability and good in vivo activity in the rat hypolocomotion model. Although **39** showed an excellent overall profile we had concerns that the 5-methoxyindoline substituent may be metabolically labile.[22] In the previous 1-(3-pyridylcarbamoyl)indoline series we identified a number of other indoline substitution patterns, such as the 6-chloro-5-methylindoline **4**, which had good 5-HT_{2C} affinity and reduced but still moderate selectivity but which promised to be potentially more metabolically stable.[5] Incorporating the 6-chloro-5-methylindoline into the bispyridyl ether series afforded **41** (SB-242084) which maintained both 5-HT_{2C} affinity and 100-fold selectivity over both 5-HT_{2A} and 5-HT_{2B}, although selectivity over 5-HT_{2A} was reduced 7-fold relative to **39**.[11] This compound also demonstrated potent oral activity (ID_{50} = 2.0 mg/kg) in the rat hypolocomotion model. Replacing the 6-chloro substituent of **41** with trifluoromethyl gave **40** with an identical 5-HT_2 binding profile but somewhat improved oral activity (ID_{50} = 0.7 mg/kg) combined with a good duration of action (6 h). In addition both **40** and **41** showed negligible CYP1A2 inhibitory activity (Table 5).

From the work described above compounds **32** and **40** were selected for detailed preclinical evaluation based on their overall biological profile. On further cross-screening **32** and **40** were found to have >100-fold selectivity over more than 50 other receptor, ion-channel, and enzyme binding sites. In a 5-HT-stimulated phosphoinositol (PI) hydrolysis model of 5-HT_{2C} receptor function,[6] using human cloned receptors expressed in HEK 293 cells, **32** and **40** were found to display negative efficacy and completely abolished the basal effector activity which is a feature of this cloned system. Hence, they are inverse agonists with pK_B's of 9.3 and 9.5, respectively, which are consistent with their binding affinities. This phenomenon may be a result of optimization of the ligand-independent receptor activity due to overexpression in this cloned system,[23] although there is evidence that constitutively active 5-HT_{2C} receptors may be biologically significant.[24] The P450 inhibitory activity of **32** and **40** across a range of human isoforms is shown in Table 5 together with that of **2** for comparison. These compounds, in particular **40**, have generally low inhibitory activity indicating that they are unlikely to invoke undesirable drug−drug interactions in a clinical setting.

Table 5. Human Cytochrome P450 Inhibitory Potential[a] of Compounds **2**, **32**, **40,** and **41**

	IC_{50} (μM)				
compd	1A2	2C9	2C19	2D6	3A4
2	0.013	>100	>100	0.11	>100
32	28	82	>100	21	9
40	>100	23	>100	>100	>100
41	>100	>100	>100	>100	>100

[a] The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. IC_{50}'s were determined at the substrate K_m as has been previously described[20] [CYP1A2: caffeine N3-demethylation (500 μM), CYP2C9: tobutamide methylhydroxylation (100 μM), CYP2C19: *S*-mephenytoin 4-hydroxylation (100 μM), CYP2D6: bufuralol 1′-hydroxylation (10 μM), and CYP3A4: total cyclosporin oxidation (1 μM)]. These values are the mean of duplicate determinations which did not vary by more than 10%.

Compounds **32** and **40** were then further evaluated in two different rat models of anxiety, namely the Geller Seifter conflict test and the social interaction test.[3,4] Significant anxiolytic activity was observed at doses (0.2−5 mg/kg po) similar to those that antagonized mCPP-induced hypolocomotion with no evidence of sedative effects.[25] The observation of marked anxiolytic activity with both a mixed 5-$HT_{2C/2B}$ antagonist (**32**) and a selective 5-HT_{2C} antagonist (**40**) at similar doses provides compelling evidence that this effect is 5-HT_{2C} mediated. Significantly, acute administration of **32** or **40** showed no evidence of proconvulsant activity in the rat maximal electroshock threshold test (up to 30 mg/kg po) while chronic administration (up to 30 mg/kg po

b.i.d. × 14 days) produced no evidence of hyperphagic properties. Both these activities are characteristic of mutant mice lacking the 5-HT$_{2C}$ receptor.[21] In addition there was no evidence of increased sensitivity to 5-HT$_{2C}$ agonist-induced effects after chronic dosing, indicating no effects on receptor density or sensitivity. On the basis of their overall biological profile **32** and **40** were selected for development as novel nonsedating antidepressant/anxiolytic agents. The bispyridyl ether **40** is currently in phase 1 clinical development.

Conclusion

In summary, a series of biarylcarbamoylindolines has been identified with excellent 5-HT$_{2C}$ affinity and selectivity over the 5-HT$_{2A}$ receptor. In addition, bispyridyl ether carbamoylindolines have been identified with additional selectivity over the closely related 5-HT$_{2B}$ receptor. These compounds are inverse agonists at the human cloned 5-HT$_{2C}$ receptor completely abolishing basal activity in a functional PI assay. This series has reduced P450 inhibitory liability compared to a previously described series of 1-(3-pyridylcarbamoyl)indolines[5] from which they evolved. Some analogues demonstrated excellent oral activity in a rat pharmacodynamic model and in animal models of anxiety. On the basis of their favorable biological profile **32** and **40** have been selected for further development to determine their therapeutic potential for the treatment of CNS disorders such as depression and anxiety.

Experimental Section

Chemistry. Melting points are uncorrected. The elemental analyses were within 0.4% of the theoretical values. HPLC analysis of test compounds was carried out on a Gilson 712 HPLC system, using a model 231 sample injector, 306 pump with 806 manomeric module detector. A Hypersil BDS C18 3-μm (100 × 3 mm i.d.) column was used with elution under the following conditions: eluant A 0.1% TFA/H_2O v/v, eluant B 0.1% TFA/CH_3CN v/v; flow rate 0.7 mL/min. The elution gradient was 0% B held for 0.5 min, then linearly increased to 75% B over 24.5 min, then held for 5 min. The UV detection wavelength was 218 nm. Final compounds were greater than 95% pure as judged by area under the curve apart from **9**, **10**, **23**, **30,** and **36** which were 90−95% pure. NMR spectra were recorded on a Bruker AC-200, AC-250, or AM-400 spectrometer using Me_4Si as internal standard. Electron impact mass spectra were determined using a Fisons VG 302 single quadrupole mass spectrometer. *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were of commercial grade and dried over 4 Å molecular sieves before use. Other solvents and reagents were of commercial grade and used without purification. Petroleum ether refers to the fraction with bp 60−80 °C. All reactions were carried out under argon. All evaporations of solvents were carried out under reduced pressure, and organic solutions were dried over Na_2SO_4. Chromatography was performed on Merck Art. 7734 silica gel or Fluka silica gel 60 (60739).

Compounds **9**, **14**−**17**, **20**, and **23**−**25** were prepared by coupling biarylamines with 5-methoxy-6-trifluoromethylindoline[5] using 1,1-carbonyldiimidazole (Scheme 1). The biarylamines were generally prepared by Suzuki palladium coupling methodology.[14] The synthesis of **17** is illustrative:

5-Methoxy-1-[[3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (17). A mixture of 3-bromopyridine (2.9 mL, 30 mmol), 3-aminophenylboronic acid (4.6 g, 30 mmol), sodium carbonate (10 g, 90 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.9 g) in 1,2-dimethoxyethane (150 mL) and water (50 mL) was heated under reflux for 12 h. The cooled reaction mixture was concentrated, then partitioned between dilute brine (200 mL) and ethyl acetate (3 × 150 mL). The combined organic extracts were dried and evaporated to afford a brown gum (6 g). Chromatography on silica gel eluting with 50% ethyl acetate/petroleum ether then 100% ethyl acetate afforded 3-(3-pyridyl)aniline as a yellow crystalline solid (4.8 g, 95%). NMR ($CDCl_3$) δ: 3.8 (2H, br s), 6.70 (1H, m), 6.85 (1H, m), 6.95 (1H, m), 7.25 (1H, m), 7.35 (1H, m) 7.85 (1H, m), 8.60 (1H, m), 8.85 (1H, m). 3-(3-Pyridyl)-aniline (0.27 g, 1.6 mmol) in dichloromethane (5 mL) was added dropwise over 5 min to a solution of 1,1-carbonyldiimidazole (0.28 g, 1.7 mmol) in dichloromethane (5 mL). After 2 h at room temperature the mixture was evaporated to dryness and the residue dissolved in *N*,*N*-dimethylformamide (20 mL). 5-Methoxy-6-trifluoromethylindoline[5] (0.35 g, 1.6 mmol) was added and the mixture heated to 100 °C for 1 h. After cooling, water (30 mL) was added and the mixture was set aside in the fridge for 1 h. Filtration and drying afforded a brown solid (0.59 g). Chromatography on silica gel, eluting with a gradient of 0−3% methanol in dichloromethane, afforded the title compound as a white solid (0.56 g, 85%), mp 193−194 °C. NMR (DMSO-d_6) δ: 3.25 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz) 7.20 (1H, s), 7.35−7.55 (3H, m), 7.67 (1H, d, J = 7 Hz), 7.90 (1H, s), 8.05 (1H, m), 8.15 (1H, s), 8.60 (1H, m), 8.70 (1H, s), 8.86 (1H, s). MS: *m*/*e* 414 (M^+). Purity was determined as 100.0% by HPLC, retention time 21.48 min.

The following examples were prepared in a similar manner:

5-Methylthio-1-[[3-(4-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (14). 3-(4-Pyridyl)aniline, prepared as described above in 72% yield using 4-bromopyridine instead of 3-bromopyridine, was coupled with 5-methylthio-6-trifluoromethylindoline[5] using 1,1-carbonyldiimidazole as above to give the title compound as a white crystalline solid (47%). NMR (DMSO-d_6) δ: 2.52 (3H, s), 3.30 (2H, t, J = 8 Hz), 4.25 (2H, t, J = 8 Hz), 7.50 (3H, m), 7.70 (3H, m), 8.02 (1H, s), 8.25 (1H, s), 8.70 (2H, m), 8.80 (1H, s). MS: *m*/*e* 429 (M^+). Purity was determined as 97.0% by HPLC, retention time 23.75 min.

5-Methoxy-1-[(6-phenyl-3-pyridyl)carbamoyl]-6-trifluoromethylindoline (9). Palladium coupling of 2-bromo-5-nitropyridine and phenylboronic acid gave 5-nitro-2-phenylpyridine (90%) which was reduced to the corresponding aniline using catalytic hydrogenation (81%). Treatment with 1,1-carbonyldiimidazole and 5-methoxy-6-trifluoromethylindoline[5] as above afforded the title compound as a white crystalline solid (89%), mp 204−207 °C. NMR (DMSO-d_6) δ: 3.31 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.22 (2H, t, J = 8 Hz) 7.22 (1H, s), 7.36−7.52 (3H, m), 7.92 (1H, d, J = 8 Hz), 8.01−8.16 (4H, m), 8.82 (1H, m), 8.87 (1H, s). MS: *m*/*e* 414 (M^+). Purity was determined as 93.1% by HPLC, retention time 26.27 min.

5-Methylthio-1-[[3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (15). 3-(3-Pyridyl)aniline, prepared as described for **17**, was coupled with 5-methylthio-6-trifluoromethylindoline[5] using 1,1-carbonyldiimidazole as above to afford the title compound as white solid (42%), mp 208−210 °C. NMR (DMSO-d_6) δ: 2.50 (3H, s), 3.30 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 7.40 (3H, m), 7.50 (1H, dd, J = 5, 7 Hz), 7.65 (1H, dm, J = 7 Hz), 7.90 (1H, s), 8.10 (1H, dm, J = 7 Hz), 8.20 (1H, s), 8.60 (1H, m), 8.80 (1H, s), 8.90 (1H, m, J = 5 Hz). MS: *m*/*e* 429 (M^+). Purity was determined as 98.6% by HPLC, retention time 23.38 min.

5-Methoxy-1-[[3-(2-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (16). 3-(2-Pyridyl)aniline, prepared by palladium coupling of 2-bromopyridine and 3-aminophenylboronic acid in 44% yield, was coupled with 1,1-carbonyldiimidazole and 5-methylthio-6-trifluoromethylindoline[5] as above to afford the title compound as a white crystalline solid (40%), mp 220−225 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.40 (2H, m), 7.70 (2H, m), 7.90 (2H, m), 8.15 (1H, s), 8.35 (1H, s), 8.65 (1H, m), 8.70 (1H, s). MS: *m*/*e* 414 (M^+). Purity was determined as 98.1% by HPLC, retention time 23.15 min.

5-Methoxy-1-[[4-(3-pyridyl)phenyl]carbamoyl]-6-trifluromethylindoline (23). 4-(3-Pyridyl)aniline, prepared by palladium coupling of 3-bromopyridine and 4-aminophenylboronic acid in 27% yield, was coupled with 1,1-carbonyldi-

imidazole and 5-methylthio-6-trifluoromethylindoline[5] as above to afford the title compound as a white crystalline solid (85%), mp >230 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.45 (1H, m), 7.70 (4H, m), 8.05 (1H, m), 8.15 (1H, s), 8.55 (1H, m), 8.70 (1H, s), 8.90 (1H, m). MS: m/e 414 (MH^+). Purity was determined as 91.9% by HPLC, retention time 22.39 min.

5-Methoxy-1-[[4-(4-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (24). 4-(4-Pyridyl)aniline, prepared by palladium coupling of 4-bromoaniline and 4-pyridylboronic acid in 31% yield, was coupled with 1,1-carbonyldiimidazole and 5-methylthio-6-trifluoromethylindoline[5] as above to afford the title compound as a white crystalline solid (5%), mp >210 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.70 (2H, d), 7.75 (4H, m), 8.15 (1H, s), 8.60 (2H, d), 8.85 (1H, s). MS: m/e 413 (M^+). Purity was determined as 100.0% by HPLC, retention time 22.10 min.

5-Methoxy-1-[[3-(2,4-dimethyl-3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (20). 3-(2,4-Dimethyl-3-pyridyl)aniline, prepared by palladium coupling of 2,4-dimethyl-3-trifluoromethylsulfonyloxypyridine and 3-aminophenylboronic acid in 31% yield,[26] was coupled with 1,1-carbonyldiimidazole and 5-methylthio-6-trifluoromethylindoline[5] as above to afford the title compound as a white crystalline solid (17%), mp 202−204 °C. NMR (DMSO-d_6) δ: 2.03 (3H, s), 2.20 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 6.87 (1H, d, J = 7 Hz), 7.18 (1H, d, J = 5 Hz), 7.20 (1H, s), 7.41 (2H, m), 7.51 (1H, d, J = 8 Hz), 8.10 (1H, s), 8.32 (1H, d, J = 5 Hz), 8.64 (1H, s). MS: m/e 442 (MH^+). Purity was determined as 99.9% by HPLC, retention time 16.60 min.

1-[[2-Fluoro-5-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (25). 2-Fluoro-5-(3-pyridyl)aniline, prepared in 74% overall yield by palladium coupling of 2-fluoro-5-bromonitrobenzene and 3-pyridylboronic acid followed by reduction using stannous chloride in aqueous HCl, was coupled with 1,1-carbonyldiimidazole and 5-methylthio-6-trifluoromethylindoline[5] as above to afford the title compound as a white crystalline solid (10%), mp 233 °C dec. NMR (DMSO-d_6) δ: 3.20 (2H, t, J = 8 Hz), 3.82 (3H, s), 3.94 (2H, t, J = 8 Hz), 7.13−7.28 (2H, m), 7.38−7.58 (3H, m), 7.87 (1H, m), 7.98 (1H, s), 8.35 (1H, s), 8.55 (1H, dd), 8.64 (1H, d). MS: m/e 432 (MH^+).

The following examples **13**, **18**, **19**, **21**, **22**, and **26**−**37** were prepared from biarylamines via the phenyl carbamate (Scheme 2). The synthesis of **32** is illustrative:

1-[[3-Fluoro-5-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (32). 3-Fluoro-5-(3-pyridyl)aniline was prepared in 55% overall yield by palladium coupling of 3-fluoro-5-iodonitrobenzene and 3-pyridylboronic acid followed by reduction using stannous chloride in aqueous HCl. The aniline (1.0 g, 0.50 mmol) in dry dichloromethane (20 mL) was treated with triethylamine (1.1 mL, 0.80 mmol) followed dropwise by phenyl chloroformate (0.97 mL, 0.77 mmol) and stirred at ambient temperature for 18 h. The reaction mixture was washed with water (2 × 20 mL), dried and evaporated in vacuo to afford phenyl *N*-[3-fluoro-5-(3-pyridyl)phenyl]carbamate (1.1 g, 71%) as an off-white solid. NMR (DMSO-d_6) δ: 7.20−7.49 (3H, m), 7.49−7.59 (5H, m), 7.63 (1H, d), 8.07 (1H, m), 8.63 (1H, d), 8.87 (1H, s), 10.61 (1H, s). Phenyl *N*-[3-fluoro-5-(3-pyridyl)phenyl]carbamate in dry dimethylformamide was treated with 5-methoxy-6-trifluoromethylindoline[5] and triethylamine as in the preparation of **40**, followed by chromatography on silica gel, eluting with a gradient of 0−3% methanol in dichloromethane to afford the title compound as a white solid in 26% yield, mp 220−223 °C. NMR (DMSO-d_6) δ: 3.29 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.21 (2H, t, J = 8 Hz), 7.23 (1H, s), 7.30 (1H, d, J = 8 Hz), 7.54 (1H, dd, J = 5, 7 Hz), 7.65 (1H, dm, J = 10 Hz), 7.76 (1H, s), 8.09 (1H, dm, J = 7 Hz), 8.15 (1H, s), 8.62 (1H, m), 8.78−9.00 (2H, m). MS: m/e 432 (MH^+). Anal. ($C_{22}H_{17}N_3O_2F_4$) C, H, N. Purity was determined as 100.0% by HPLC, retention time 17.68 min.

The following examples were prepared similarly:

5-Methoxy-1-[[6-(3-pyridyl)-3-pyridyl]carbamoyl]-6-trifluoromethylindoline (13). 3-Amino-6-(3-pyridyl)pyridine, prepared in 69% overall yield by palladium coupling of 2-bromo-5-nitropyridine and 3-pyridylboronic acid followed by reduction using catalytic hydrogenation, was converted to the phenyl carbamate (100%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (78%), mp >270 °C. NMR (DMSO-d_6) δ: 3.32 (2H, t, J = 8 Hz), 3.88 (3H, s), 4.23 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.45−7.55 (1H, m), 7.98−8.18 (3H, m), 8.35−8.43 (1H, m), 8.55−8.60 (1H, m), 8.85 (1H, d, J = 4 Hz), 8.91 (1H, s), 9.23 (1H, s). MS: m/e 415 (MH^+). Purity was determined as 96.5% by HPLC, retention time 21.82 min.

5-Methoxy-1-[[3-(4-methyl-3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (18). 3-(4-Methyl-3-pyridyl)aniline, prepared in 91% overall yield by palladium coupling of 3-bromo-4-methylpyridine and 3-nitrophenylboronic acid followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (100%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (34%), mp 178−180 °C. NMR (DMSO-d_6) δ: 2.29 (3H, s), 3.29 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.19 (2H, t, J = 8 Hz), 7.01 (1H, d, J = 6 Hz), 7.20 (1H, s), 7.31−7.43 (2H, m), 7.55−7.62 (2H, m), 8.10 (1H, s), 8.32 (1H, s), 8.40 (1H, d, J = 6 Hz), 8.62 (1H, s). MS: m/e 428 (MH^+). Purity was determined as 95.2% by HPLC, retention time 16.82 min.

5-Methoxy-1-[[3-(2-methyl-3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (19). 3-(2-Methyl-3-pyridyl)aniline, prepared in 63% overall yield by palladium coupling of 3-bromo-2-methylpyridine and 3-nitrophenylboronic acid followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (90%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound as an off-white solid (53%), mp 179−180 °C. NMR ($CDCl_3$) δ: 2.50 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.12 (2H, t, J = 8 Hz), 6.56 (1H, s), 6.86 (1H, s), 7.03 (1H, m), 7.18 (1H, dd, J = 6, 8 Hz), 7.32−7.47 (3H, m), 7.51 (1H, dd, J = 2, 8 Hz) 8.22 (1H, s), 8.50 (1H, m). MS: m/e 428 (MH^+). Purity was determined as 99.4% by HPLC, retention time 16.10 min.

1-[[5-Bromo-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (33). 5-Bromo-3-(3-pyridyl)aniline, prepared in 53% overall yield by palladium coupling of 3-pyridylboronic acid and 3,5-dibromonitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (24%). NMR ($CDCl_3$) δ: 3.25 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.15 (2H, t, J = 8 Hz), 6.82 (1H, s), 7.32−7.44 (3H, m), 7.60 (1H, m), 7.74 (1H, m), 7.88 (1H, d, J = 7 Hz), 8.19 (1H, s), 8.54 (1H, m, J = 5 Hz), 8.74 (1H, m). Purity was determined as 100.0% by HPLC, retention time 18.73 min.

1-[[5-Ethyl-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (34). 5-Bromo-3-(3-pyridyl)nitrobenzene, prepared as described above for **33**, was coupled with tributylethenylstannane and reduced using catalytic hydrogenation to give 5-ethyl-3-(3-pyridyl)aniline in 77% overall yield. Conversion to the phenyl carbamate (100%) and reaction with 5-methoxy-6-trifluoromethylindoline[5] as above afforded the title compound (40%) as a tan powder, mp 205−207 °C. NMR ($CDCl_3$) δ: 1.3 (3H, t, J = 7 Hz), 2.60 (2H, q, J = 7 Hz), 3.28 (2H, t, J = 8 Hz), 3.88 (3H, s), 4.12 (2H, t, J = 8 Hz), 6.52 (1H, s), 6.85 (1H, s), 7.12 (1H, s), 7.32 (2H, m), 7.48 (1H, s), 7.88 (1H, m, J = 7 Hz), 8.22 (1H, s), 8.58 (1H, m, J = 5 Hz), 8.81 (1H, m). MS: m/e 442 (MH^+). Purity was determined as 98.7% by HPLC, retention time 18.45 min.

5-Methoxy-1-[[5-phenyl-3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (35). 5-Bromo-3-(3-pyridyl)nitrobenzene, prepared as above for **33**, was coupled with phenylboronic acid and reduced using stannous chloride in aqueous HCl to give 5-phenyl-3-(3-pyridyl)aniline in 43% yield.

Conversion to the phenyl carbamate (99%) and reaction with 5-methoxy-6-trifluoromethylindoline[5] as above afforded the title compound (47%) as an off-white solid, mp 150−151 °C. NMR ($CDCl_3$) δ: 3.28 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.12 (2H, t, J = 8 Hz), 6.65 (1H, br s), 6.85 (1H, s), 7.30−7.50 (5H, m), 7.55−7.70 (4H, m), 7.90 (1H, m, J = 7 Hz), 8.24 (1H, s), 8.60 (1H, m, J = 5 Hz), 8.87 (1H, m). Purity was determined as 95.5% by HPLC, retention time 20.09 min.

5-Methoxy-1-[[5-fluoro-4-methyl-3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (36). 5-Fluoro-4-methyl-3-(3-pyridyl)aniline, prepared in 77% overall yield by palladium coupling of 3-pyridylboronic acid and 3-fluoro-5-iodo-4-methylnitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (96%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound as an off-white solid (93%), mp 244−247 °C. NMR (DMSO-d_6) δ: 2.08 (3H, d, J = 2 Hz), 3.27 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.16 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.33 (1H, br s), 7.52 (1H, dd, J = 6, 8 Hz), 7.59 (1H, dd, J = 2, 12 Hz), 7.82 (1H, m), 8.10 (1H, s), 8.59 (1H, m), 8.62 (1H, dd, J = 2, 6 Hz), 8.72 (1H, s). MS: m/e 446 (MH^+). Purity was determined as 91.0% by HPLC, retention time 17.45 min.

1-[[2,3-Dihydro-7-(3-pyridyl)benzofuran-5-yl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (37). 2,3-Dihydro-7-iodo-5-nitrobenzofuran, prepared in 26% yield from 2,3-dihydro-7-iodobenzofuran by treatment with copper nitrate in acetic anhydride, was coupled with 3-pyridylboronic acid, as described generally above, in 30% yield. Reduction using stannous chloride in aqueous HCl followed by conversion to the phenyl carbamate (80% overall) and reaction with 5-methoxy-6-trifluoromethylindoline[5] as above afforded the title compound (26%) as a beige solid. NMR (DMSO-d_6) δ: 3.12−3.49 (4H, m), 3.85 (3H, s), 4.15 (2H, t, J = 8 Hz), 4.61 (2H, t, J = 8 Hz), 7.21 (1H, s), 7.40−7.58 (3H, m), 8.07 (1H, dd, J = 1, 7 Hz), 8.13 (1H, s), 8.43−8.60 (2H, m), 8.88 (1H, d, J = 1 Hz). MS: m/e 456 (MH^+). Purity was determined as 98.7% by HPLC, retention time 16.29 min.

5-Methoxy-1-[[4-methyl-3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (28). 4-Methyl-3-(3-pyridyl)-aniline, prepared in 87% overall yield by palladium coupling of 3-pyridylboronic acid and 3-bromo-4-methylnitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (93%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (26%) as a white solid, mp 211−212 °C. NMR (DMSO-d_6) δ: 2.20 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.11 (2H, t, J = 8 Hz), 6.44 (1H, s), 6.85 (1H, s), 7.18−7.45 (4H, m), 7.59−7.72 (1H, m), 8.22 (1H, s), 8.49−8.69 (2H, m). MS: m/e 427 (M^+). Purity was determined as 100.0% by HPLC, retention time 16.33 min.

1-[[4-*tert*-Butyl-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (29). 4-*tert*-Butyl-3-(3-pyridyl)aniline, prepared in 39% overall yield by palladium coupling of 3-pyridylboronic acid and 3-bromo-4-*tert*-butylnitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (68%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (23%). NMR ($CDCl_3$) δ: 1.25 (9H, s), 3.27 (2H, t, J = 9 Hz), 3.85 (3H, s), 4.09 (2H, t, J = 9 Hz), 6.43 (1H, s), 6.85 (1H, s), 7.00 (1H, d, J = 1 Hz), 7.18−7.35 (1H, m), 7.39−7.69 (3H, m), 8.20 (1H, s), 8.42−8.69 (2H, m). MS: m/e 470 (MH^+). Purity was determined as 98.7% by HPLC, retention time 26.47 min.

1-[[4-Chloro-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (30). 4-Chloro-3-(3-pyridyl)-aniline, prepared in 14% overall yield by palladium coupling of 3-pyridylboronic acid and 4-chloro-3-iodonitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (95%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (36%) as an off-white solid, mp 210−213 °C. NMR ($CDCl_3$) δ: 3.30 (2H, t, J = 9 Hz), 3.87 (3H, s), 4.12 (2H, t, J = 9 Hz), 6.56 (1H, s), 6.87 (1H, s), 7.29−7.58 (4H, m), 7.81 (1H, d, J = 8 Hz), 8.21 (1H, s), 8.60 (1H, d, J = 5 Hz), 8.69 (1H, d, J = 3 Hz). MS: m/e 447 (M^+). Purity was determined as 93.5% by HPLC, retention time 23.72 min.

1-[[4-Methoxy-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (31). 4-Methoxy-3-(3-pyridyl)aniline, prepared in 47% overall yield by palladium coupling of 3-pyridylboronic acid and 3-bromo-4-methoxynitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (75%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound (32%). NMR (DMSO-d_6) δ: 3.26 (2H, t, J = 9 Hz), 3.76 (3H, s), 3.83 (3H, s), 4.14 (2H, t, J = 9 Hz), 7.10 (1H, d, J = 7 Hz), 7.19 (1H, s), 7.45 (1H, dd, J = 1, 5 Hz), 7.54 (1H, s), 7.59 (1H, d, J = 3 Hz), 7.87 (1H, dd, J = 1, 5 Hz), 8.10 (1H, s), 8.47−8.55 (2H, m), 8.67 (1H, d, J = 3 Hz). MS: m/e 444 (MH^+). Purity was determined as 99.0% by HPLC, retention time 22.37 min.

5-Methoxy-1-[[2-methyl-3-(3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (26). 2-Methyl-3-(3-pyridyl)-aniline, prepared in 53% overall yield by palladium coupling of 3-pyridylboronic acid and 3-bromo-2-methylnitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (87%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound as an off-white solid (56%), mp 192−193 °C. NMR (DMSO-d_6) δ: 2.11 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.13 (1H, d, J = 8 Hz), 7.22 (1H, s), 7.27−7.42 (2H, m), 7.51 (1H, dd, J = 6, 8 Hz), 7.78 (1H, m), 8.10 (1H, s), 8.37 (1H, s), 8.55 (1H, m), 8.61 (1H, m). MS: m/e 428 (MH^+). Purity was determined as 99.5% by HPLC, retention time 21.52 min.

1-[[2-Chloro-3-(3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (27). 3-Bromo-2-chloronitrobenzene was coupled with 3-pyridylboronic acid under the usual conditions and the resulting nitroarylpyridine reduced using stannous chloride in aqueous HCl to give 2-chloro-3-(3-pyridyl)-aniline (57% overall). Conversion to the phenyl carbamate (100%) and reaction with 5-methoxy-6-trifluoromethylindoline[5] as above afforded the title compound as an off-white solid (45%), mp 214−216 °C. NMR ($CDCl_3$) δ: 3.33 (2H, t, J = 8 Hz), 3.88 (3H, s), 4.21 (2H, t, J = 8 Hz), 6.89 (1H, s), 7.05 (1H, dd, J = 2, 7 Hz), 7.22 (1H, s), 7.34−7.43 (2H, m), 7.76 (1H, m), 8.28 (1H, s), 8.40 (1H, dd, J = 2, 8 Hz), 8.62−8.69 (2H, m). MS: m/e 448 (MH^+). Purity was determined as 99.6% by HPLC, retention time 22.63 min.

5-Methoxy-1-[[4-methyl-3-(4-methyl-3-pyridyl)phenyl]carbamoyl]-6-trifluoromethylindoline (21). 4-Methyl-3-(4-methyl-3-pyridyl)aniline, prepared in 74% overall yield by palladium coupling of 4-methyl-3-pyridylboronic acid and 3-bromo-4-methylnitrobenzene followed by reduction using stannous chloride in aqueous HCl, was converted to the phenyl carbamate (97%) and reacted with 5-methoxy-6-trifluoromethylindoline[5] as above to afford the title compound as an off-white solid (47%), mp 153−155 °C. NMR ($CDCl_3$) δ: 2.00 (3H, s), 2.10 (3H, s), 3.27 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.12 (2H, t, J = 8 Hz), 6.64 (1H, s), 6.85 (1H, s), 7.12−7.28 (3H, m), 7.43 (1H, dd, J = 7, 2 Hz), 8.22 (1H, s), 8.30 (1H, s), 8.44 (1H, d, J = 6 Hz). MS: m/e 442 (MH^+). Purity was determined as 96.2% by HPLC, retention time 17.29 min.

1-[[4-Chloro-3-(4-methyl-3-pyridyl)phenyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (22). Palladium coupling of 3-bromo-4-chloronitrobenzene and 4-methyl-3-pyridylboronic acid gave 4-chloro-3-(4-methyl-3-pyridyl)nitrobenzene in 33% yield which was reduced in 95% yield by stannous chloride in aqueous HCl to 4-chloro-3-(4-methyl-3-pyridyl)-aniline. Conversion to the phenyl carbamate (98%) in the usual manner and then treatment with 5-methoxy-6-trifluoromethylindoline[5] gave the title compound (49%), mp 140−141 °C. NMR ($CDCl_3$) δ: 2.19 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.82 (3H, s), 4.15 (2H, t, J = 8 Hz), 6.81 (1H, s), 7.09 (1H, s), 7.20 (1H, d, J = 6 Hz), 7.25 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.52−7.59 (1H, m), 8.20 (1H, s), 8.30 (1H, s), 8.45 (1H, d, J = 6 Hz). MS: m/e 462 (MH^+). Purity was determined as 97.0% by HPLC, retention time 17.15 min.

Compounds **5**, **6**, and **10**−**12** were prepared by reaction of 1-[(5-bromo-3-pyridyl)carbamoyl]-5-methoxy-6-trifluoromethylindoline **(42)** with the appropriate arylboronic acid under Suzuki conditions (Scheme 3).[14] The synthesis of **5** is illustrative:

1-[(5-Bromo-3-pyridyl)carbamoyl]-5-methoxy-6-trifluoromethylindoline (42). A solution of (5-bromo-3-pyridyl)-carbonyl azide[15] (3.16 g, 13.9 mmol) in toluene (500 mL) was heated to reflux for 1 h [**CAUTION!** Heating this material in the absence of solvent can lead to explosive decomposition. Larger-scale (ca. 20 g or above) preparations following this procedure may be noticeably exothermic on reaching 70−80 °C, and copious volumes of nitrogen are rapidly evolved. Appropriate precautions for the storage and utilization of this reagent are strongly advised.] The solution was allowed to cool to room temperature then added to a solution of 5-methoxy-6-trifluoromethylindoline[5] (2.7 g, 13 mmol) in dichloromethane (200 mL). The mixture was set aside in the refrigerator for 1 h and then the precipitate was collected and dried to afford the title compound **42** as a white solid (4.62 g, 89%), mp 220−222 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.19 (2H, t, J = 8 Hz), 7.20 (1H, s), 8.10 (1H, s), 8.30−8.35 (2H, m), 8.73 (1H, s), 8.94 (1H, s).

5-Methoxy-1-[(5-phenyl-3-pyridyl)carbamoyl]-6-trifluoromethylindoline (5). A mixture of 1-[(5-bromo-3-pyridyl)carbamoyl]-5-methoxy-6-trifluoromethylindoline **(42)** (0.21 g, 0.50 mmol), phenylboronic acid (0.30 g, 2.4 mmol), sodium carbonate (0.32 g, 3.0 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.03 g) in a mixture of dimethoxyethane (5 mL) and water (1 mL) was heated to reflux for 10 h. The cooled reaction mixture was partitioned between brine (20 mL) and ethyl acetate (3 × 30 mL). The combined organic extract was dried and evaporated to give a brown solid (0.14 g). Column chromatography on silica gel, eluting with a gradient of 0−5% methanol in ethyl acetate, afforded the title compound as a white crystalline solid (0.10 g, 48%), mp 162−164 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.50 (3H, m), 7.70 (2H, m), 8.10 (1H, s), 8.30 (1H, m), 8.55 (1H, m), 8.75 (1H, m), 8.85 (1H, s). MS: m/e 414 (MH^+). Purity was determined as 98.1% by HPLC, retention time 25.51 min.

The following examples were prepared in a similar manner from **42** and known arylboronic acids:

5-Methoxy-1-[[5-(4-fluorophenyl)-3-pyridyl]carbamoyl]-6-trifluoromethylindoline (6). Isolated as a white crystalline solid (30%), mp >200 °C. NMR (DMSO-d_6) δ: 3.31 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.22 (2H, t, J = 8 Hz), 7.22 (1H, s), 7.37 (2H, m), 7.76 (2H, dd, J = 6, 8 Hz), 8.13 (1H, s), 8.28 (1H, m), 8.54 (1H, s), 8.75 (1H, d), 8.87 (1H, s). MS: m/e 431 (M^+). Purity was determined as 99.9% by HPLC, retention time 25.21 min.

5-Methoxy-1-[[5-(4-pyridyl)-3-pyridyl]carbamoyl]-6-trifluoromethylindoline (10). Isolated as a white crystalline solid (71%), mp 230−234 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.75 (2H, m) 8.15 (1H, s), 8.40 (1H, t, J = 2 Hz), 8.65 (1H, d, J = 2 Hz), 8.70 (2H, m), 8.85 (1H, m), 8.98 (1H, br s). MS: m/e 414 (M^+). Purity was determined as 93.9% by HPLC, retention time 18.43 min.

5-Methoxy-1-[[5-(3-pyridyl)-3-pyridyl]carbamoyl]-6-trifluoromethylindoline (11). Isolated as a white crystalline solid (29%), mp 113−114 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.20 (1H, s), 7.55 (1H, m), 8.10 (1H, m), 8.15 (1H, s), 8.30 (1H, m), 8.60−8.65 (2H, m), 8.80 (1H, m), 8.95 (2H, m). Purity was determined as 99.5% by HPLC, retention time 18.90 min.

5-Methoxy-1-[[5-(4-methyl-3-pyridyl)-3-pyridyl]carbamoyl]-6-trifluoromethylindoline (12). Isolated as a white crystalline solid (65%), mp 125−128 °C. NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.32 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.18 (2H, t, J = 8 Hz), 6.90 (2H, s), 7.21 (1H, d, J = 4 Hz), 8.10 (1H, s), 8.18 (1H, s), 8.27 (1H, s), 8.40 (1H, s), 8.45−8.53 (2H, m). MS: m/e 429 (M^+). Purity was determined as 100.0% by HPLC, retention time 19.15 min.

Compounds **7** and **8** were prepared by an analogous procedure to that described above by coupling ethyl 5-bromonicotinate with the appropriate arylstannane under Stille conditions (Scheme 4).[16] The synthesis of **8** is illustrative:

1-[[5-(2,6-Difluorophenyl)-3-pyridyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (8). A mixture of (2,6-difluorophenyl)tributyltin[27] (1.18 g, 2.9 mmol), ethyl 5-bromonicotinate (0.69 g, 3.0 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.10 g) in xylene (10 mL) was heated under reflux for 24 h, then cooled, filtered and evaporated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate/petroleum ether to give ethyl 5-(2,6-difluorophenyl)nicotinate (0.64 g, 84%) as a white solid. NMR ($CDCl_3$) δ: 1.43 (3H, t, J = 7 Hz), 4.44 (2H, q, J = 7 Hz), 7.06 (2H, t, J = 7 Hz), 7.39 (1H, m), 8.42 (1H, s), 8.88 (1H, s), 9.23 (1H, s). MS: m/e 264 (MH^+). A mixture of this ester (0.64 g, 2.4 mmol) and 98% hydrazine hydrate (1 mL) in methanol (10 mL) was heated under reflux overnight and then cooled in ice and the resultant precipitate collected. The filtrate was evaporated and the residue was triturated with water before combining with the initial precipitate. The crude product was washed with ether and dried in vacuo to give 5-(2,6-difluorophenyl)nicotinoyl hydrazide (0.50 g, 84%) as a solid which was used without further purification. NMR (DMSO-d_6) δ: 4.60 (2H, s), 7.29 (2H, t, J = 7 Hz), 7.57 (1H, m), 8.28 (1H, s), 8.80 (1H, s), 9.03 (1H, s), 10.05 (1H, s). MS: m/e 250 (MH^+). To a suspension of the hydrazide (0.50 g, 2.0 mmol) in concentrated hydrochloric acid (3 mL) and water (2 mL) at −5 °C was added dropwise a solution of sodium nitrite (0.14 g, 2.0 mmol) in water (2 mL). The mixture was stirred at −5 °C for 0.5 h, then a solution of potassium carbonate (2.3 g) in water (25 mL) was added cautiously. The precipitate was collected, washed with water and dried in vacuo at room temperature to give 5-(2,6-difluorophenyl)nicotinoyl azide (0.48 g, 93%) as a solid. NMR ($CDCl_3$) δ: 7.05 (2H, t, J = 7 Hz), 7.40 (1H, m, J = 7 Hz), 8.41 (1H, s), 8.93 (1H, s), 9.22 (1H, s). MS: m/e 261 (MH^+), 233 ($MH^+ - N_2$). A solution of 5-(2,6-difluorophenyl)nicotinoyl azide (0.46 g, 1.8 mmol) in toluene (10 mL) was heated under reflux for 2 h. After cooling, a solution of 5-methoxy-6-trifluoromethylindoline[5] (0.40 g, 1.8 mmol) in dichloromethane (10 mL) was added and the mixture was stirred overnight at room temperature. The precipitate was collected and washed with petrol. The crude product was recrystallized from dichloromethane/petroleum ether to give the title compound (0.66 g, 82%), mp 217−219 °C. NMR (DMSO-d_6) δ: 3.29 (2H, t, J = 8 Hz), 3.84 (3H, s), 4.21 (2H, t, J = 8 Hz), 7.22 (1H, s), 7.29 (2H, t, J = 7 Hz), 7.56 (1H, m, J = 7 Hz), 8.11 (1H, s), 8.15 (1H, s), 8.32 (1H, s), 8.80 (1H, s), 8.93 (1H, s). MS: m/e 450 (MH^+). Anal. ($C_{22}H_{16}N_3O_2F_5$) C, H, N. Purity was determined as 100.0% by HPLC, retention time 18.71 min.

1-[[5-(3,5-Difluorophenyl)-3-pyridyl]carbamoyl]-5-methoxy-6-trifluoromethylindoline (7). The title compound was similarly prepared, via coupling of ethyl 5-bromonicotinate and the corresponding arylstannane in 70% yield, as a white crystalline solid (52%), mp 226−229 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 3.87 (3H, s), 4.25 (2H, t, J = 8 Hz), 7.20−7.34 (2H, m), 7.48 (2H, m), 8.18 (1H, s), 8.33 (1H, s), 8.61 (1H, m), 8.87 (1H, m), 8.90 (1H, br s). MS: m/e 450 (MH^+). Purity was determined as 99.6% by HPLC, retention time 19.34 min.

The bispyridyl ethers **39**−**41** were prepared by coupling the aniline **43a** with 5-methoxy-6-trifluoromethylindoline, 6-chloro-5-methylindoline, and 5-methyl-6-trifluoromethylindoline, respectively, via the phenyl carbamate (Scheme 5).[13,17] **38** was prepared similarly from 5-amino-2-(3-pyridyloxy)pyridine **(43b)**.[19] 5-Methyl-6-trifluoromethylindoline was prepared according to Scheme 6.

5-Methyl-6-trifluoromethylindoline. A mixture of 5-methoxy-6-trifluoromethylindoline[5] (7.50 g, 34.3 mmol) and iodotrimethylsilane (12.5 mL, 89.3 mmol) in dry chloroform (70 mL) was heated under reflux for 65 h. The mixture was cooled and methanol (5 mL) was cautiously added with stirring. The solvent was removed in vacuo and the residue treated with aqueous sodium bicarbonate solution until basic and then

extracted with a 3:1 mixture of dichloromethane and methanol (4 × 100 mL). The combined organic extracts were washed with brine (250 mL), dried and evaporated. The residue was extracted with ether in a Soxhlet apparatus, and concentration of the resultant solution gave 5-hydroxy-6-trifluoromethylindoline in three crops (total 2.9 g, 41%), mp > 180 °C dec. NMR ($CDCl_3$/CD_3OD) δ: 3.02 (2H, t, J = 8 Hz), 3.52 (2H, t, J = 8 Hz), 4.00 (2H, s), 6.77 (1H, s), 6.83 (1H, s). A mixture of this indoline (2.8 g, 14 mmol) and acetic anhydride (1.3 mL, 14 mmol) in dry dichloromethane (50 mL) was stirred at room temperature for 3 h, then evaporated. The residue was treated cautiously with saturated aqueous sodium bicarbonate solution, then the solid product was filtered off, washed with water and dried to give 1-acetyl-5-hydroxy-6-trifluoromethylindoline (3.3 g, 96%), mp 244−247 °C. NMR (DMSO-d_6) δ: 2.10 (3H, s), 3.11 (2H, t, J = 8 Hz), 4.06 (2H, t, J = 8 Hz), 6.88 (1H, s), 8.18 (1H, s). To a solution of the acetylindoline (1.2 g, 4.9 mmol) in dry pyridine (10 mL) at 0 °C was added trifluoromethanesulfonic anhydride (1.5 g, 5.4 mmol). The mixture was then stirred overnight, while slowly warming to room temperature. The mixture was partially evaporated, the residual liquor was diluted with water and the precipitate was collected. The crude material was dissolved in dichloromethane (150 mL) and the solution was washed with 1 N hydrochloric acid (50 mL) and brine (50 mL), dried and evaporated to give 1-acetyl-6-trifluoromethyl-5-trifluoromethylsulfonyloxyindoline **(44)** (1.8 g, 96%). NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.32 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 7.29 (1H, s), 8.60 (1H, s). MS: m/e 378 (MH^+). To a mixture of **44** (1.8 g, 4.7 mmol), lithium chloride (0.60 g, 14 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.10 g, 0.14 mmol) in dry dimethylformamide (15 mL) was added tetramethyltin (0.72 mL, 5.2 mmol). The mixture was heated at 110 °C for 3.5 h, then cooled and evaporated. The residue was partitioned between dichloromethane (3 × 100 mL) and water (75 mL), and the combined organic phases washed with brine (100 mL), dried and evaporated. A mixture of this crude product, ethanol (30 mL), 10% aqueous sodium hydroxide solution (7.5 mL) and solid sodium hydroxide (1 g) was heated under reflux overnight. Ethanol was removed in vacuo, and the residue was diluted with water (20 mL) and extracted with dichloromethane (3 × 50 mL). The organic extracts were washed with brine (50 mL), dried and evaporated and the residue was chromatographed on silica gel, eluting with 2:1 ether/petroleum ether to give the title compound (0.70 g, 74%), mp 43−44 °C. NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.02 (2H, t, J = 8), 3.57 (2H, t, J = 8), 3.78 (1H, broad), 6.85 (1H, s), 7.00 (1H, s).

5-Methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (40). Sodium hydride (11 g of an 80% dispersion in oil, 0.37 mol) was added portionwise to a solution of 3-hydroxy-2-methylpyridine (40 g, 0.37 mol) in dry DMF (1.3 L) at 0 °C. The resultant mixture was stirred at 0 °C for 15 min and then room temperature for 3 h before 2-chloro-5-nitropyridine (59 g, 0.37 mol) was added portionwise. The reaction mixture was stirred for 18 h at room temperature then water (50 mL) was added dropwise and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (400 mL), washed with 10% aqueous sodium hydroxide (200 mL), and water (200 mL), dried and evaporated in vacuo to afford 2-[(2-methyl-3-pyridyl)oxy]-5-nitropyridine (81 g, 95%) as a yellow solid. NMR ($CDCl_3$) δ: 2.22 (3H, s), 6.93 (1H, d, J = 8 Hz), 7.00−7.13 (1H, m), 7.23 (1H, dd, J = 1, 8 Hz), 8.25 (1H, dd, J = 1, 5 Hz), 8.32 (1H, dd, J = 3, 8 Hz), 8.79 (1H, d, J = 3 Hz). 2-[(2-Methyl-3-pyridyl)oxy]-5-nitropyridine (81 g, 0.35 mol) in ethanol (2 L) was treated with tin(II) chloride (232 g, 1.23 mol) in concentrated hydrochloric acid (500 mL) and heated to 50 °C for 1 h. After cooling to ambient temperature, the mixture was basified with 40% aqueous sodium hydroxide solution, extracted into ethyl acetate (300 mL), dried and evaporated in vacuo to afford 5-amino-2-[(2-methyl-3-pyridyl)oxy]pyridine **(43a)** (60 g, 86%) as a brown solid. NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.40 (2H, br s), 6.56 (1H, d, J = 9 Hz), 6.81−6.97 (2H, m), 7.08 (1H, dd, J = 1, 5 Hz), 7.43 (1H, d, J = 3 Hz), 8.09 (1H, dd, J = 1, 4 Hz). Phenyl chloroformate (41 mL, 0.33 mol) was added dropwise to a stirred solution of **43a** (60 g, 0.30 mol) and triethylamine (46 mL, 0.33 mol) in dry dichloromethane (2.5 L) at −20 °C. The mixture was stirred at −20 °C for 1 h then warmed to ambient temperature and washed with dilute aqueous $NaHCO_3$ (2 × 500 mL), dried and evaporated in vacuo. The residue was recrystallized from ethyl acetate/petroleum ether to afford phenyl *N*-[[2-(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamate (54 g, 56%) as a pink solid. NMR ($CDCl_3$) δ: 2.44 (3H, s), 6.94 (1H, d, J = 7 Hz), 7.08−7.29 (4H, m), 7.33−7.45 (3H, m), 7.90 (1H, br s), 7.98−8.13 (2H, m), 8.39 (1H, d, J = 5 Hz). A mixture of phenyl *N*-[[2-(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamate (32 g, 100 mmol) and triethylamine (14 mL, 100 mmol) was treated with 5-methyl-6-trifluoromethylindoline (20 g, 100 mmol) in dry dimethylformamide (1 L) at 95−105 °C for 1 h. After cooling the reaction mixture was evaporated in vacuo and the residue diluted with dichloromethane (500 mL) and washed with 10% aqueous sodium hydroxide (200 mL), with addition of methanol (100 mL) to keep the product in organic solution. The organic phase was then washed with water (200 mL) and brine (200 mL), dried and evaporated. The crude product was recrystallized from dichloromethane to give the title compound (33 g, 76%), mp 112−114 °C. NMR (DMSO-d_6) δ: 2.32 (3H, s), 2.38 (3H, s), 3.22 (2H, t, J = 8 Hz), 4.16 (2H, t, J = 8 Hz), 7.09 (1H, d, J = 8 Hz), 7.25 (1H, s), 7.30 (1H, dd, J = 5, 8 Hz), 7.49 (1H, d, J = 8 Hz), 8.06 (1H, dd, J = 2, 8 Hz), 8.16 (1H, s), 8.20 (1H, d, J = 2 Hz), 8.31 (1H, d, J = 5 Hz), 8.78 (1H, s). The hydrochloride salt was isolated from methanol/ether as a white solid, mp 241−246 °C. NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.58 (3H, s), 3.23 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 7.24 (1H, d, J = 8 Hz), 7.26 (1H, s), 7.83 (1H, dd, J = 5, 8 Hz), 8.15 (1H, s), 8.18 (1H, m), 8.21 (1H, d, J = 8 Hz), 8.32 (1H, d, J = 2 Hz), 8.51 (1H, d, J = 8 Hz), 9.00 (1H, s). Anal. ($C_{22}H_{19}N_4O_2F_3$·HCl) C, H, N. Purity was determined as 99.0% by HPLC, retention time 17.72 min.

Compounds **38**, **39,** and **41** were similarly prepared:

6-Chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]indoline (41). Phenyl *N*-[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamate was reacted with 6-chloro-5-methylindoline,[5] as described above for **40**, to afford the title compound as a white crystalline solid (71%), mp 181−183 °C. NMR (DMSO-d_6) δ: 2.25 (3H, s), 2.31 (3H, s), 3.13 (2H, t, J = 8 Hz), 4.13 (2H, t, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.17 (1H, s), 7.30 (1H, dd, J = 5, 8 Hz), 7.48 (1H, d, J = 6 Hz), 7.87 (1H, s), 8.03 (1H, dd, J = 2, 8 Hz), 8.21 (1H, d, J = 2 Hz), 8.32 (1H, d, J = 5 Hz), 8.74 (1H, s). MS: m/e 395 (MH^+). Anal. ($C_{21}H_{19}N_4O_2Cl$·1.1HCl) C, H, N.

5-Methoxy-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]-carbamoyl]-6-trifluoromethylindoline (39). Phenyl *N*-[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamate was reacted with 5-methoxy-6-trifluoromethylindoline,[5] as described above for **40**, to afford the title compound as a white crystalline solid (71%), mp 227−230 °C. NMR (DMSO-d_6) δ: 2.32 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.85 (3H, s), 4.15 (2H, t, J = 8 Hz), 7.09 (1H, d, J = 8 Hz), 7.21 (1H, s), 7.30 (1H, dd, J = 8, 5 Hz), 7.49 (1H, d, J = 8 Hz), 8.04 (1H, dd, J = 8, 2 Hz), 8.10 (1H, s) 8.20 (1H, d, J = 2 Hz), 8.32 (1H, d, J = 5 Hz), 8.72 (1H, s). MS: m/e 445 (MH^+). Purity was determined as 100.0% by HPLC, retention time 15.33 min.

5-Methoxy-1-[[2-[(3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (38). Phenyl *N*-[2-[(3-pyridyl)-oxy]-5-pyridyl]carbamate, prepared as described above for **40** but using 5-amino-2-(3-pyridyl)oxypyridine **(43b)**,[19] was treated with 5-methoxy-6-trifluoromethylindoline[5] as above to give the title compound as a white crystalline solid (74%), mp 202−204 °C. NMR (DMSO-d_6) δ: 3.28 (2H, t, J = 8 Hz), 3.86 (3H, s), 4.18 (2H, t, J = 8 Hz), 7.12 (1H, d, J = 9 Hz), 7.22 (1H, s), 7.47 (1H, dd, J = 7, 5 Hz), 7.51 (1H, m, J = 7 Hz), 8.08 (1H, dd, J = 8, 2 Hz), 8.10 (1H, s), 8.27 (1H, d, J = 2 Hz), 8.40−8.47 (2H, m), 8.78 (1H, s). MS: m/e 431 (MH^+). Purity was determined as 100.0% by HPLC, retention time 21.38 min.

References

(1) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine. *Pharmacol. Rev.* **1994**, *46*, 157−203.

(2) (a) Humphrey, P. P. A.; Hartig, P.; Hoyer, D. A Proposed New Nomenclature of 5-HT Receptors. *Trends Pharmacol. Sci.* **1993**, *14*, 233−236. (b) Nelson, D. L. The 5-HT_2 Subfamily of Receptors: Pharmacological Challenges. *Med. Chem. Res.* **1993**, *3*, 306−316. (c) Baxter, G.; Kennett, G. A.; Blaney, F.; Blackburn, T. 5-HT_2 Receptor Subtypes: A Family Re-united? *Trends Pharmacol. Sci.* **1995**, *16*, 105−110.

(3) (a) Kahn, R. S.; Wetzler, S. mCPP as a Probe of Serotonin Function. *Biol. Psychiat.* **1991**, *30*, 1139−1166. (b) Kennett, G. A. 5-HT_{1C} Receptor Antagonists have Anxiolytic-like Actions in the Rat Social Interaction Model. *Psychopharmacology* **1992**, *107*, 379. (c) Kennett, G. A. 5-HT_{1C} receptors and their therapeutic relevance. *Curr. Opin. Invest. Drugs* **1993**, *2*, 317−362 and references therein. (d) Kennett, G. A.; Pittaway, K.; Blackburn, T. P. Evidence that 5-HT_{1C} Receptor Antagonists are Anxiolytic in the Geller-Seifter Model of Anxiety. *Psychopharmacology* **1994**, *114*, 90−96. (e) Kennett, G. A.; Wood, M. D.; Glen, A.; Grewal, S.; Forbes, I. T.; Gadre, A.; Blackburn, T. P. In Vivo Properties of SB-200646, a 5-$HT_{2C/2B}$ Receptor Antagonist. *Br. J. Pharmacol.* **1994**, *111*, 797−802.

(4) Kennett, G. A.; Wood, M. D.; Bright, F.; Cilia, J.; Piper, D. C.; Gager, T.; Thomas, D.; Baxter, G. S.; Forbes. I. T.; Ham, P.; Blackburn, T. P. In Vitro and In Vivo Profile of SB-206553, A potent 5-HT_{2C}/5-HT_{2B} receptor antagonist with anxiolytic-like properties. *Br. J. Pharmacol.* **1996**, *117*, 427−434.

(5) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders: D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. Novel and selective 5-$HT_{2C/2B}$ receptor antagonists as potential anxiolytic agents: synthesis, quantitative structure−activity relationships, and molecular modelling of substituted 1-(3-pyridylcarbamoyl)indolines. *J. Med. Chem.* **1998**, *41*, 1598−1612.

(6) Kennett, G. A.; Wood, M. D.; Bright, F.; Trail, B.; Riley, G.; Holland, V.; Avenell, K. Y.; Stean, T.; Upton, N.; Bromidge S. M.; Forbes, I. T.; Brown, A. M.; Middlemiss, D. N.; Blackburn, T. P. SB-242084, A Selective and Brain Penetrant 5-HT_{2C} Receptor Antagonist. *Neuropharmacology* **1997**, *36*, 609−620.

(7) (a) Kennett, G. A.; Lightowler, S.; De Biasi, V.; Stevens, N. C.; Wood, M. D.; Tulloch, I. F.; Blackburn, T. P. Effect of chronic administration of selective 5-hydroxytryptamine and noradrenaline uptake inhibitors on a putative index of 5-HT2C/2B receptor function. *Neuropharmacology* **1994**, *33*, 1581−1588. (b) Palvimaki, E. P.; Roth, B. L.; Majasuo, H.; Laakso, A.; Kuoppamaki, M.; Syvalahti, E.; Hietala, J. Interactions of selective serotonin reuptake inhibitors with the serotonin 5-HT2C receptor. *Psychopharmacology* **1996**, *126*, 234−240. (c) Ni, Y. G.; Miledi, R. Blockage of 5-HT_{2C} serotonin receptors by fluoxetine (Prozac). *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2036−2040. (d) Quested, D. J.; Sargent, P. A.; Cowen, P. J. SSRI treatment decreases prolactin and hyperthermic responses to mCPP. *Psychopharmacology* **1997**, *133*, 305−308. (e) Kennaway, D. J.; Moyer, R. W. Serotonin 5-HT_{2C} agonists mimic the effect of light pulses on circadian rhythms. *Brain Res.* **1998**, *806*, 257−270. (f) Moreau, J.-L.; Bos, M.; Jenck, F.; Martin, J. R.; Mortas, P.; Wichmann, J. 5-HT_{2C} receptor agonists exhibit antidepressant-like properties in the anhedonia model of depression. *Eur. Neuropsychopharmacol.* **1996**, *6*, 169−175.

(8) (a) Di Giovanni, G.; De Deurwaerdere, P.; Di Mascio, M.; Di Matteo, V.; Esposito, E.; Spampinato, U. Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: A *combined in vivo* electrophysiological and microdialysis study. *Neuroscience* **1999**, *91*, 587−597. (b) Dimatteo, V.; Digiovanni, G.; Dimascio, M.; Esposito, E. Selective blockade of serotonin(2C/2B) receptors enhances dopamine release in the rat nucleus accumbens. *Neuropharmacology* **1998**, *37*, 265−272. (c) Millan, M. J.; Dekeyne, A.; Gobert, A. Serotonin 5-HT_{2C} receptors tonically inhibit dopamine and noradrenaline, but not 5-HT, release in the frontal cortex in vivo. *Neuropharmacology* **1998**, *37*, 953−955. (d) Reavill, C.; Kettle, A.; Holland, V.; Riley, G.; Blackburn, T. P. Attenuation of haloperidol-induced catalepsy by a 5-HT_{2C} receptor antagonist. *Br. J. Pharmacol.* **1999**, *126*, 572−574.

(9) Kalkman, H. O. Is migraine prophylactic activity caused by 5-HT_{2B} or 5-HT_{2C} receptor blockade. *Life Sci.* **1994**, *54*, 641−644.

(10) Fox, S. H.; Moser, B.; Brotchie, J. M. Behavioural effects of 5-HT_{2C} receptor antagonism in the substantia nigra zona reticulata of the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. *Exp. Neurol.* **1998**, *151*, 35−49.

(11) Bromidge, S. M.; Duckworth, M.; Forbes, I. T.; Ham, P.; King, F. D.; Thewlis, K. M.; Blaney, F. E.; Naylor, C. B.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D.; Clarke, S. E. 6-Chloro-5-methyl-1-[2-(2-methyl-3-pyridyloxy)-5-pyridylcarbamoyl]indoline (SB-242084): The First Selective and Brain Penetrant 5-HT_{2C} Receptor Antagonist. *J. Med. Chem.* **1997**, *40*, 3494−3496.

(12) Forbes, I. T.; Dabbs, S.; Duckworth, D. M.; Ham, P.; Jones, G. E.; King, F. D.; Saunders: D. V.; Blaney, F. E.; Naylor, C. B.; Baxter, G. S.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D. Synthesis, Biological Activity, and Molecular Modeling Studies of Selective 5-$HT_{2C/2B}$ Receptor Antagonists. *J. Med. Chem.* **1996**, *39*, 4966−4977.

(13) Gaster, L. M.; Wyman, P. A.; Mulholland, K. R.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Jones, G. E. WO Patent 96/23,-783, Aug 8, 1996.

(14) Stanforth, S. P. Catalytic cross-coupling reactions in biaryl synthesis. *Tetrahedron* **1998**, *54*, 263−303.

(15) Kuznetsova, E. A.; Voronina, T. A.; Khromova, I. V.; Garibova, T. L.; Tosina, E. K.; Stolyarova, L. G.; Troitskaya, V. S.; Smirnov, L. D. Amino acid derivatives of nicotinic acids: synthesis and pharmacological activity. *Khim.-Farm. Zh.* **1989**, *23*, 1425−1431.

(16) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille reaction. *Org. React.* **1997**, *50*, 1−652.

(17) Bromidge, S. M.; Forbes, I. T. WO Patent 97/48,699, Oct 16, 1997.

(18) Echavarren, A. M.; Stille, J. K. Palladium Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109*, 5478−86.

(19) Friedman, H. L.; Braitberg, L. D.; Tolstoouhov, A. V.; Tisza, E. T. Tuberculostatic compounds. I. Ethers of 2-hydroxy-5-aminopyridine. *J. Am. Chem. Soc.* **1947**, *69*, 1204−1206.

(20) Baldwin, S. J.; Bloomer, J. C.; Smith, G. J.; Ayrton, A. D.; Clarke, S. E.; Chenery, R. J. Ketoconazole and Sulfaphenazole as the respective selective inhibitors of P450 3A and 2C9. *Xenobiotica* **1995**, *25*, 261−270.

(21) (a) Das, S.; Tecott, L. Diminished Anxiety-Like Responses in 5-HT_{2C} Receptor Mutant Mice. *Am. Soc. Neurosci.* **1996**, *22* (Abstr.), 811.2. (b) Tecott, L. H.; Sun, L. M.; Akana, S. F.; Strack, A. M.; Lowenstein, D. H.; Dallman, M. F.; Julius, D. Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. *Nature* **1995**, *374*, 542−546.

(22) Unpublished results from the Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham.

(23) Berg, K. A.; Stout, B. D.; Cropper, J. D.; Maayani, S.; Clarke, W. P. Novel actions of inverse agonists on 5-HT_{2C} receptor systems. *Mol. Pharmacol.* **1999**, *55*, 863−872.

(24) Jenk, F.; Bös, M.; Wichmann, J.; Stadler, H.; Martin, J. R.; Moreau, J. L. The role of 5-HT_{2C} receptors in affective disorders. *Exp. Opin. Invest. Drugs* **1998**, *7*, 1587−1599.

(25) Detailed in vivo biological results will be published elsewhere.

(26) Mangutova, Y. S.; Mal'tseva, L. S.; Kamaev, F. G.; Leont′ev, V. B.; Mukhamedkhanova, S.; Otroshchenko, O. S.; Sadykov, A. S. Stereochemistry and electronic structure in a series of dipyridyls. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, *7*, 1510−1517.

(27) Suzuki, F.; Nakasato, Y.; Tumuki, H.; Sato, S.; Tamura, T.; Nakajima, H. Preparation of novel tetracyclic condensed quinoline derivatives as immunosuppressants. WO Patent 95/09,153, Apr 6, 1995.

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