Novel and Selective 5-HT$_{2C/2B}$ Receptor Antagonists as Potential Anxiolytic Agents: Synthesis, Quantitative Structure−Activity Relationships, and Molecular Modeling of Substituted 1-(3-Pyridylcarbamoyl)indolines

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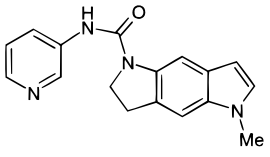
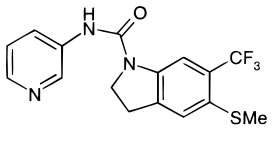
The synthesis, biological activity, and molecular modeling of a novel series of substituted 1-(3-pyridylcarbamoyl)indolines are reported. These compounds are isosteres of the previously published indole urea **1** (SB-206553) and illustrate the use of aromatic disubstitution as a replacement for fused five-membered rings in the context of 5-HT$_{2C/2B}$ receptor antagonists. By targeting a region of space previously identified as sterically allowed at the 5-HT$_{2C}$ receptor but disallowed at the 5-HT$_{2A}$ receptor, we have identified a number of compounds which are the most potent and selective 5-HT$_{2C/2B}$ receptor antagonists yet reported. **46** (SB-221284) was selected on the basis of its overall biological profile for further evaluation as a novel, potential nonsedating anxiolytic agent. A CoMFA analysis of these compounds produced a model with good predictive value and in addition good qualitative agreement with both our 5-HT$_{2C}$ receptor model and our proposed binding mode for this class of ligands within that model.

The explosive growth of the 5-hydroxytryptamine (5-HT, serotonin) superfamily of receptors has continued to provide pharmaceutical research with new opportunities for drug discovery.[1] Advances in molecular biological techniques have so far led to the identification of 7 classes of receptor (5-HT$_1$ to 5-HT$_7$) and 14 acknowledged human subclasses.[2] The 5-HT$_2$ family of receptors is comprised of 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ subtypes which have been grouped together on the basis of primary structure, secondary messenger system, and operational profile.[3] All 3 subtypes are G-protein-coupled, activate phospholipase C as a principal transduction mechanism, and contain a predicted seven-transmembrane domain structure. Sequence analysis indicates approximately 80% amino acid identity in these regions, and it is therefore not surprising that many compounds once thought to be selective for the 5-HT$_{2A}$ (classical 5-HT$_2$) receptor also bind with high affinity to the 5-HT$_{2B}$ and 5-HT$_{2C}$ sites. Consequently there remains a need to identify more selective ligands to fully elucidate the functional role of the different subtypes. There are distinct differences in the distribution of the three 5-HT$_2$ subtypes. In contrast to the 5-HT$_{2B}$ receptor which is principally located in the periphery and only sparsely in the central nervous system (CNS), 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. This pattern of CNS distribution is different and more widespread than that of the 5-HT$_{2A}$ receptor which is also widely distributed in peripheral tissues.[2]

Our interest in the 5-HT$_{2C}$ receptor originally stemmed from the finding that the moderately selective 5-HT$_{2C/2B}$ agonist *m*-chlorophenylpiperazine (mCPP) causes behavioral indications of anxiety in both animal models and humans, implying that selective 5-HT$_{2C/2B}$ antagonists might be useful anxiolytic agents.[4] Recent evidence suggests that 5-HT$_{2C}$ receptor ligands may also have antidepressant properties.[5] We have recently reported the synthesis and biological activity of the pyridylurea **1** (SB-206553) which is a potent 5-HT$_{2C/2B}$ receptor antagonist (pK_i 8.0) with 160-fold selectivity over the closely related 5-HT$_{2A}$ site.[6] This compound



1 (SB-206553)



46 (SB-221284)

blocked the hypolocomotion in rats produced by mCPP which is a model of central 5-HT$_{2C}$ receptor function that can be elicited by direct infusion of mCPP into the cerebral ventricles[7] and is absent in mutant mice lacking the 5-HT$_{2C}$ receptor.[8] Thus, **1** demonstrates oral activity in a centrally mediated model of 5-HT$_{2C}$ function. It also exhibited significant anxiolytic activity in several different animal models of anxiety, providing strong support for our original hypothesis.[9] Unfortunately, the 1-methylindole moiety of **1** was subject to a metabolic demethylation to a less selective compound which precluded its development as a potential anxi-

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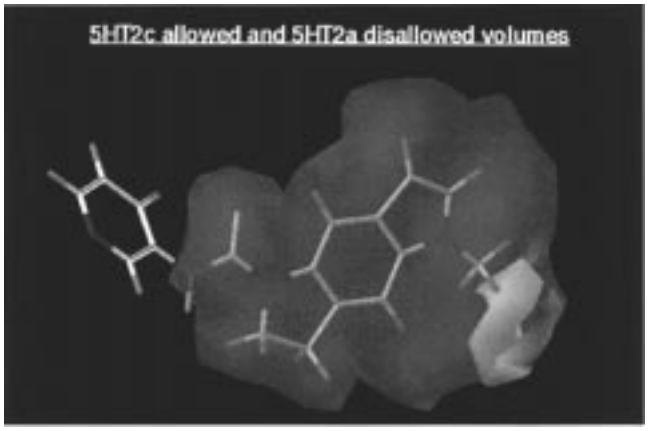
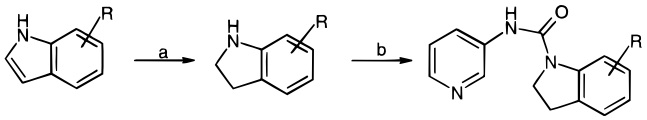


Figure 1. 5-HT$_{2C}$-allowed (green) and 5-HT$_{2A}$-disallowed (pink) volumes viewed around the structure of compound **1**.[9]

olytic agent.[10] Recently the 5-HT$_{2C}$ knockout mouse has been shown to have a diminished anxiety-like response[8] and to be associated with proconvulsant and hyperphagic behavior.[11]

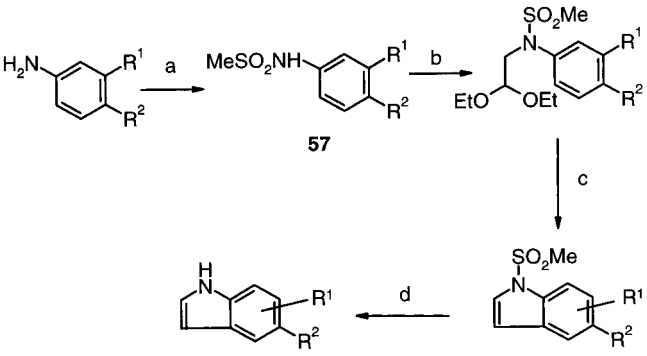
We also recently reported[12] the synthesis and activity of a number of other tricyclic analogues of **1** in addition to a full range of isomeric N-substituted pyrrolo analogues in which the pyrrole ring was fused across each of the 4−5, 5−6, and 6−7 bonds of the indoline. By use of the "active analogue approach" developed by Marshall[13] to overlap common structural features of compounds of varying activity, we were able to define an allowed volume for 5-HT$_{2C}$ receptor affinity which included a volume that was disallowed at the 5-HT$_{2A}$ receptor (Figure 1). This finding was rationalized by considering key differences in the sequences of the 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors in a region adjacent to the indole *N*-methyl group in the proposed binding mode of the compound in our model of the 5-HT$_{2C}$ receptor. This mode invokes hydrogen bonding between the urea carbonyl oxygen and Ser-312 and Ser-315 as the primary interaction, placing the indole *N*-methyl group in a lipophilic pocket adjacent to valines-212 and -608. In the 5-HT$_{2A}$ receptor the corresponding receptor residues which define this pocket are both leucine. These sequence differences would be expected to give rise to a smaller binding pocket which can less easily accommodate the indole *N*-methyl group of **1** thus leading to the observed selectivity. We now report the use of this information to design a novel series of substituted 1-(3-pyridylcarbamoyl)indolines, incorporating monocyclic isosteres of the *N*-methylindole of **1**, which are potent and selective 5-HT$_{2C/2B}$ receptor antagonists.[14] This approach has culminated in the identification of **46** (SB-221284) which has improved in vitro and in vivo properties compared to **1**. Significantly, **46** showed no evidence of either proconvulsant or hyperphagic properties which are characteristic of mutant mice lacking the 5-HT$_{2C}$ receptor.[11] A quantitative structure−activity relationship (QSAR) analysis of these indolinylureas has been undertaken as a means of testing the validity of our 5-HT$_{2C}$ receptor model and also our proposed ligand docking mode using the comparative molecular field analysis (CoMFA)[15] module within the Sybyl[16] molecular modeling environment.

Scheme 1[a]



[a] Reagents: (a) $NaCNBH_3$, AcOH, rt, 3 h (75−95%); (b) nicotinic acid azide, toluene, reflux, 0.5 h (50−90%).

Scheme 2[a]



[a] Reagents: (a) $MeSO_2Cl$, pyridine, CH_2Cl_2, 0 °C−rt, 2 h; (b) NaH, DMF, 0 °C, $(EtO)_2CHCH_2OTf$; (c) $TiCl_4$, toluene, 0 °C, rt, reflux, 1−2 h; (d) aq NaOH, EtOH, reflux, 0.5 h (overall yields 20−30%).

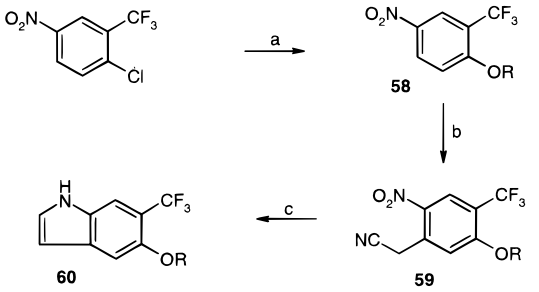
Chemistry

Compounds **2**−**56** were prepared by reacting the appropriately substituted indoline with 3-pyridyl isocyanate which was prepared in situ from the acyl azide (Scheme 1). Compounds **2**−**4, 6, 7, 9, 10, 12, 13, 20, 24,** and **44** were prepared from known or commercially available indolines or via indolines accessed by sodium cyanoborohydride/acetic acid reduction of indoles,[17] which were themselves either commercially available or known.

The following compounds were similarly obtained via reduction of indoles which were themselves prepared by a variety of routes based on literature methods. Indoles leading to **5, 8, 15**−**18, 22, 23, 26**−**30, 33**−**37,** and **39**−**41** were prepared from the corresponding protected anilines **57** by alkylation with either 2,2-dimethoxyacetaldehyde or $(EtO)_2CHCH_2OTf$ followed by cyclization under either Nordlander[18] or, more satisfactorily, Sundberg[19] conditions (Scheme 2). In the case of unsymmetrical substituted anilines, mixtures of indole isomers were obtained which were separated by fractional crystallization or chromatography following deprotection of the indole nitrogen. Alternatively, the mixture of indoles was carried through to give a mixture of final compounds which were then separated by preparative HPLC. Indoles leading to **21, 25, 38,** and **42** were prepared from the appropriate 2-methylnitrobenzene by the Leimgrüber procedure.[20]

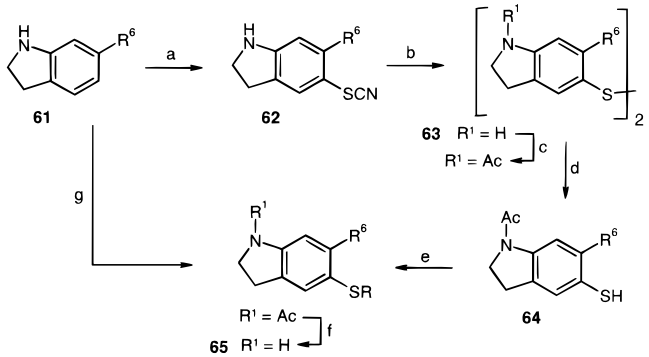
The 5-alkoxy-6-(trifluoromethyl)indoles **60**, which were the necessary precursors to **51**−**55**, were synthesized from the corresponding 1-alkoxy-2-(fluoroalkyl)-4-nitrobenzenes **58** by "vicarious" nucleophilic substitution[21] with 4-chlorophenoxyacetonitrile using KO^{t}Bu in DMF to give the 5-acetonitrile 1-alkoxy-2-(fluoroalkyl)-4-nitrobenzenes **59** which were hydrogenated to afford the desired indoles **60** (Scheme 3).[22]

Scheme 3[a]



[a] Reagents: (a) NaOR, ROH, reflux, 3 h (99%); (b) 4-chlorophenoxyacetonitrile, KO^{t}Bu, DMF, −10 °C, 1 h (78%); (c) H_2/10% Pd−C, 50 psi, AcOH, EtOH/H_2O, rt, 0.5 h (96%).

Scheme 4[a]

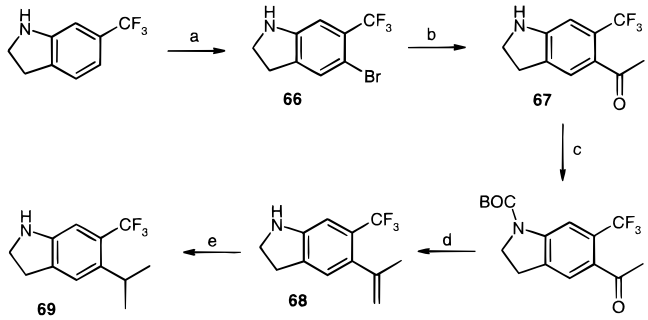


[a] Reagents: (a) KSCN/Br_2, MeOH, 0 °C, 0.5 h (72%); (b) aq NH_3, 90 °C, 1 h (100%); (c) Ac_2O/NEt_3, CH_2Cl_2, 1 h (94%); (d) PPh_3, HCl, dioxane/H_2O, reflux, 1 h (91%); (e) RI, K_2CO_3, DMF, 80 °C, 1 h (97%); (f) NaOH, H_2O, EtOH, reflux, 1.5 h (99%); (g) (i) KSCN/Br_2, MeOH, 0 °C−rt, 4 h; (ii) aq NaOH, 45 °C, 0.5 h, (iii) MeI, 12 °C−rt, 1.5 h (approximately 60% overall yield).

Compounds **11, 32, 43**, **45**−**49,** and **56** were obtained from indolines prepared by the following routes. The 5-(thioalkyl)indolines **65** leading to **11, 43,** and **45**−**49** were prepared by the route shown in Scheme 4. Treatment of the corresponding 5-unsubstituted indoline **61** with bromine and KSCN gave the thiocyanate[23] **62** which on treatment with aqueous ammonia gave the disulfide **63**.[24] Acylation of the indoline nitrogen followed by reduction using PPh_3/HCl gave the sulfide **64** which was alkylated and N-deprotected to give the required indoline **65**.[25] A convenient one-pot variation of this procedure was developed for 5-(thiomethyl)-6-(trifluoromethyl)indoline directly from 6-(trifluoromethyl)indoline which avoided the need to protect the indole nitrogen.[26] The 6-cyano-5-(trifluoromethyl) analogue **32** was prepared from the corresponding 6-iodo compound **45** by copper-catalyzed cyanide exchange.[27] The 6-(pentafluoroethyl) derivative **56** was also prepared by copper-catalyzed exchange of 1-acetyl-6-bromo-5-(methylthio)indoline with sodium pentafluoropropionate.[28]

Compounds **14** and **19** were prepared via lithium aluminum hydride reduction of the corresponding isatins.[29] Compounds **31** and **50** were prepared by the route shown in Scheme 5. Reaction of 5-bromo-6-(trifluoromethyl)indoline (**66**) with (1-ethoxyvinyl)tributyl tin[30] in the presence of palladium(0) afforded 5-acetyl-6-(trifluoromethyl)indoline (**67**) which was converted to **31**. N-Protection of 5-acetyl-6-(trifluoromethyl)indoline followed by addition of methyl magnesium bromide and dehydration/deprotection afforded 5-isopropenyl-6-(trifluoromethyl)indoline (**68**) which was hydrogenated to **69** and then coupled in the usual manner to give **50** (Scheme 5).

Scheme 5[a]



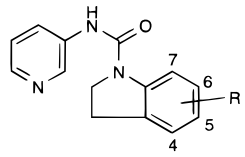
[a] Reagents: (a) NBS, DMF, −5 °C, 1 h (35%); (b) (1-ethoxyvinyl)tributyl tin/$Pd^0(Ph_3P)_3$, toluene, reflux, 28 h (58%); (c) $(BOC)_2O$/NEt_3, toluene, reflux, 4 h (58%); (d) (i) MeMgBr, ether, 0 °C, 1.5 h, (ii) TFAA, rt, 1 h (40%); (e) H_2/10% Pd−C, EtOH, rt, 2 h (80%).

Results and Discussion

The affinities of the compounds were measured by means of radioligand binding studies conducted with 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.[9]

We have previously reported **1** to be a selective 5-$HT_{2C/2B}$ receptor antagonist with 160-fold selectivity over the closely related 5-HT_{2A} receptor.[9] In an attempt to circumvent the metabolic demethylation of **1** to the unselective NH-indole,[10] we investigated the replacement of the pyrroloindole of **1** with simple substituted indolines as in **2**−**30**. The rapid synthesis of 1-(3-pyridylcarbamoyl)indolines containing a wide range of substituents around the indoline ring was undertaken to define SAR and optimize activity in this series, and these results are shown in Table 1. The unsubstituted indoline **2** had weak activity for 5-HT_{2C} receptors (pK_i 5.9). However, introduction of a range of electron-withdrawing or electron-donating substituents at either the 5- or 6-position (**4**−**13**) led to modest increases in 5-HT_{2C} affinity giving pK_i's in the range 6.5−7.5. Substitution at the 7-position (**19, 20**) appeared to have a detrimental effect on affinity. The 4-chloroindoline **3** was slightly more active than **2**, and the 4,5-disubstituted compounds **14**−**18** generally showed a modest increase in potency relative to the corresponding 5-monosubstituted analogues **4**−**11**. 5,6-Disubstitution (**21**−**28**) was even more beneficial conveying an additive effect on 5-HT_{2C} activity and resulting in compounds with pK_i's greater than 8 and moderate selectivity over 5-HT_{2A} receptor affinity. Analysis of the SAR revealed a correlation between increasing 5-HT_{2C} affinity and increasing lipophilicity of the 5-substituent and that an electron-withdrawing group at the 6-position was optimal. Although many of these compounds possess modest selectivity over the 5-HT_{2A} receptor, the 5-thiomethyl analogue **11** was exceptional demonstrating over 100-fold selectivity. The 4,5,6-trisubstituted analogues **29** and **30** maintained good affinity over 5-HT_{2C} but had reduced selectivity.

Table 1. 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptor Binding Affinities[a] of Substituted 1-(3-Pyridylcarbamoyl)indolines



compd	R4	R5	R6	R7	pK_i 5-HT$_{2A}$[b]	pK_i 5-HT$_{2C}$[c]	selectivity 5-HT$_{2C/2A}$
2	H	H	H	H		5.9	
3	Cl	H	H	H	5.4	6.3	9
4	H	Cl	H	H	5.6	7.1	32
5	H	CF_3	H	H	5.9	7.5	40
6	H	NO_2	H	H	<5.2	6.5	>20
7	H	Me	H	H	5.3	6.8	30
8	H	^{i}Pr	H	H	5.7	7.1	27
9	H	Ph	H	H	5.3	6.9	46
10	H	NMe_2	H	H	<5.2	6.5	20
11	H	SMe	H	H	5.4	7.4	110
12	H	H	CF_3	H	6.3	7.3	12
13	H	H	Cl	H	6.1	7.3	13
14	Cl	Cl	H	H	6.2	7.6	24
15	Br	Me	H	H	6.9	8.1	17
16	I	Me	H	H	5.6	7.6	100
17	Cl	^{t}Bu	H	H	6.2	7.4	20
18	Cl	SMe	H	H	5.3	7.2	80
19	H	H	Cl	Cl	5.3	6.1	7
20	H	Br	H	NO_2	5.4	6.5	12
21	H	Cl	Cl	H	6.6	8.1	32
22	H	I	Cl	H	7.0	8.5	35
23	H	Cl	CF_3	H	6.8	8.2	27
24	H	Br	SMe	H	5.6	7.3	45
25	H	Cl	Me	H	6.4	8.0	45
26	H	Me	Cl	H	6.8	8.2	26
27	H	Me	Br	H	7.2	8.4	19
28	H	Me	I	H	7.2	8.5	23
29	Cl	Me	Cl	H	7.5	8.4	7
30	Cl	SMe	Cl	H	7.2	8.6	26

[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]mesulergine).

Although many of the initial 5,6-disubstituted analogues such as **26** showed good affinity at the 5-HT$_{2C}$ receptor, demonstrating that they could serve as indole isosteres in this context, the selectivity of the compounds over the 5-HT$_{2A}$ receptor was generally modest. In an attempt to increase the selectivity, a series of further 5,6-disubstituted analogues **31**−**56** was prepared containing a variety of 5-substituents in combination with small, lipophilic, electron-withdrawing 6-substituents. The size and shape of the 5-substituent was varied in order to probe the crucial 5-HT$_{2C}$-allowed/5-HT$_{2A}$-disallowed region previously identified,[12] and results are shown in Table 2. In the 5-alkyl-6-chloro series **26**−**37**, increasing the size of the 5-alkyl group produced a modest increase in selectivity although this was accompanied by a slight reduction in 5-HT$_{2C}$ affinity. The 5-^{i}Pr-6-Cl-indoline **37** (pK_i 7.7) was the most selective compound of this series demonstrating 110-fold selectivity over 5-HT$_{2A}$ receptor.

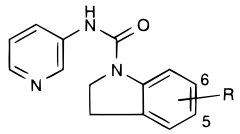
The approach was more successful in the case of the 5-alkylthio- and 5-alkyloxy-disubstituted series. Several of these compounds combine high 5-HT$_{2C}$ affinity (pK_i ≥ 8) with selectivities over 5-HT$_{2A}$ of >100-fold and in some cases >1000-fold and so represent the most potent and selective 5-HT$_{2C/2B}$ receptor antagonists reported to date. In the 5-methylthio (**32, 33, 39, 43, 45, 46, 56**)- and 5-methoxy (**44, 51, 55**)-disubstituted series, all the analogues have good affinity and >100-fold selectivity with the order of affinity for the different 6-substituents being C_2F_5 = CF_3 = I = Br > Cl > CN = OCF_3. The selectivities of these analogues are similar, although the C_2F_5 substituent (**55, 56**) imparts enhanced selectivity. Focusing on the 5-(alkylthio)-6-CF_3 (**46**−**49**) and the 5-alkoxy-6-CF_3 (**51**−**54**) series, one can see that the size and shape of the 5-substituent are clearly crucial to the selectivity of the compounds with the optimal size of the thioalkyl group being ethyl (**47**) or *n*-propyl (**48**) and that of the alkyloxy group being ^{i}Pr (**53**). Increasing the size of the substituents further (**49, 54**) leads to a fall-off in affinity and selectivity.

A small number of compounds were also evaluated at the cloned 5-HT$_{2B}$ receptor, and although affinities were reduced at this receptor, the observed selectivities were modest (<10-fold). Additionally, **46** was evaluated on a number of other receptor systems and found to have negligible affinity on a total of 57 different binding sites. **46** was also found to be a competitive antagonist with a pK_B of 9.8 in the 5-HT-stimulated phosphoinositol (PI) hydrolysis model of 5-HT$_{2C}$ receptor activation,[9] using human cloned receptors in HEK 293 cells.

In Vivo Evaluation. Compounds which satisfied our 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 activity is absent in mutant mice lacking the 5-HT$_{2C}$ receptor (see introductory section).[8] Several of the compounds (**26, 43**−**47, 51**−**53**) tested have extremely potent oral activity in this model with ID$_{50}$'s of around 1 mg/kg po (Table 2), which compare very favorably with that of **1** (5.5 mg/kg). Whereas all the 5-alkoxy-6-CF_3 analogues **51**−**53** demonstrate potent oral activity, increasing the size of the alkyl group of the 5-(alkylthio)-6-CF_3 analogues **46**−**48** led to reduction or loss of in vivo activity. The corresponding 6-halo-disubstituted analogues **39**−**41** and **43**−**45** also generally have reduced in vivo activity compared to the corresponding 6-CF_3 compounds **46** and **51**−**53**. The 6-C_2F_5 analogues **55** and **56**, which have similar in vitro profiles to the 6-CF_3 compounds **51** and **46**, also show reduced oral activity. The 5-monosubstituted analogues **9**−**11** possess no oral activity in this model. The reason for the observed differences in oral activity between such close analogues is not obvious but likely to be the overall result of variation in a number of complex factors including absorption, metabolism, and brain penetration.

The most potent compounds were further evaluated in two different models of anxiety,[4] namely, the Geller−Seifter Conflict Test and the Social Interaction Test, in the rat and found to have significant anxiolytic activity with no evidence of sedative effects at doses (0.2−5 mg/kg po) similar to those that antagonized mCPP-induced hypolocomotion. The Geller−Seifter results for compounds **43**, **46**, **51,** and **52** are shown in Table 3. In trained rats, these compounds markedly increased footshock punished responding (lever presses for a food reward) with minimum effective doses of 0.2−1 mg/kg po but had little effect on unpunished responding. This

Table 2. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} Receptor Binding Affinities[a] and in Vivo Activity of 5,6-Disubstituted 1-(3-Pyridylcarbamoyl)indolines



compd	R5	R6	pK_i 5-HT_{2A}[b]	pK_i 5-HT_{2B}[c]	pK_i 5-HT_{2C}[d]	selectivity 5-$HT_{2C/2A}$	ID_{50}[e] (mg/kg po)
1	*N*-methylpyrrolo		5.7	7.6	7.9	160	5.5
31	COMe	CF_3	5.5		7.3	60	
32	SMe	CN	5.6		7.8	140	37%
33	SMe	OCF_3	5.5		7.6	130	14%
26	Me	Cl	6.8		8.2	26	0.6
34	Et	Cl	6.4		8.3	76	60%
35	^{n}Pr	Cl	5.9		7.7	62	
36	^{t}Bu	Cl	6.2	6.8	7.7	27	
37	^{i}Pr	Cl	5.7		7.7	110	33%
38	Ph	Cl	5.4		6.9	28	
39	SMe	Cl	5.6		8.2	420	10
40	OEt	Cl	5.4		7.6	150	3.4
41	O^{i}Pr	Cl	<5.2		7.8	400	4
42	CO_2Me	Cl	5.2		7.5	190	16
43	SMe	Br	6.3		8.7	210	3
44	OMe	Br	5.8		7.9	140	1.8
45	SMe	I	6.3		8.7	250	3.2
46	SMe	CF_3	6.4	7.9	8.6	160	1.2
47	SEt	CF_3	5.5	8.0	8.5	1000	4.4
48	S^{n}Pr	CF_3	<5.2	7.8	8.2	>1000	10%
49	S^{i}Pr	CF_3	5.3		7.5	220	87%
50	^{i}Pr	CF_3	<5.2		7.6	240	20%
51	OMe	CF_3	6.0		8.0	120	0.8
52	OEt	CF_3	5.8		8.2	275	1
53	O^{i}Pr	CF_3	5.8	8.4	8.5	470	1.4
54	$OCH_2{}^c$Pr	CF_3	5.4		7.7	200	
55	OMe	C_2F_5	5.4		7.9	330	54%
56	SMe	C_2F_5	5.6	7.5	8.4	600	5

[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] Dose of compound required to reverse mCPP (7 mg/kg ip adminstration 30 min pretest)-induced hypolocomotion by 50% or percentage reversal at 10 mg/kg (in the case of **49** at 5 mg/kg).

profile is consistent with the compounds having anxiolytic-like properties.[42] Significantly, acute administration of **46** 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.[11] In addition there was no evidence of increased sensitivity to 5-HT_{2C} agonist-induced effects after chronic dosing of **46**, indicating that there were no effects on receptor density or sensitivity. Based on its overall biological profile, **46** was selected for further evaluation as a novel, nonsedating anxiolytic agent.

Molecular Modeling Studies on 46. Molecular modeling reveals that these substituents optimally interact/occupy the crucial 5-HT_{2C}-allowed/5-HT_{2A}-disallowed volume previously identified[12] (Figure 1). The introduction of a 6-substituent also has the added beneficial effect of restricting the rotation of the 5-substituent to favor those conformations in which the alkyl group occupies the crucial region. This may account for the finding that the 6-chloro-5-(trifluoromethyl)indoline **39** is more potent and selective than the 5-(trifluoromethyl) analogue **11** which is in turn more selective than the 4-chloro-5-(trifluoromethyl) analogue **18**.

Compound **46** was manually docked into a model of the 5-HT_{2C} receptor which was constructed based on the structure of bacteriorhodopsin and the ligand−receptor complex minimized. The proposed binding mode (Figure 2) is very similar to that previously proposed[12] for **1** with the urea carbonyl oxygen double-hydrogen-bonding to the hydroxyl side chains of Ser-312 and Ser-315.[31] Furthermore, the indole −NH of Trp-613 is also close enough to interact with the oxygen of the urea carbonyl, although the hydrogen-bonding geometry is nonideal. In the minimized receptor-bound conformation, both the 3-pyridyl ring and the methylthio group are twisted out of plane and are almost perpendicular to the indoline ring.

The 3-pyridyl ring occupies a lipophilic pocket defined by the side chains of the aromatic residues Phe-508, Trp-613, Phe-616, and Phe-617. Within this pocket the 3-pyridyl ring is able to form both $\pi-\pi$ stacking and edge-to-face aromatic interactions with several of the aromatic residues lining the pocket. These interactions probably contribute significantly to the overall binding of these ligands to the receptor.

The substituted indoline is placed in another pocket, the boundary of which is defined by residues Val-212, Phe-311, Val-608, Phe-609, Met-612, and Tyr-715. This pocket is also very lipophilic in nature, although less aromatic than the 3-pyridyl binding pocket. In this

Table 3. Effect of Compounds **43**, **46**, **51**, and **52** on Rat Responses in the Geller−Seifter Conflict Test[42]

compd	treatment (mg/kg po 1 h pretest)	percentage change in no. of lever presses from mean score on 2 preceding days after vehicle treatment[a] unpunished (VI)	punished (FR)
43	0.5	0	0
	1	+2	+24***
	2	+5*	+29***
	5	+4	+28***
	10	+3	+38***
	20	+6**	+53***
46	0.5	+3	+6
	1	+10**	+30***
	2	+4*	+36***
	5	+2	+38**
	10	−2	+46***
	20	0	+76***
51	0.1	+8*	−8
	0.2	+2	+26***
	0.5	+2	+36***
	1	−2	+28***
	2	+3	+34***
	5	+8**	+37***
	10	0	+63***
	20	−1	+62***
52	0.2	−3	−5
	0.5	+3	+31***
	1	+4	+33***
	2	+1	+24***
	5	0	+31***
diazepam	5	−19*	70***

[a] All data cited as means of groups that contain 6−8 rats. Significance of the difference from lever presses on each of 2 preceding test days after vehicle treatment indicated by: *,**,***p < 0.05, 0.01, 0.001, by two-way ANOVA of square-root-transformed data.

binding pocket the two residues Val-212 and Val-608 are seen to make the closest contacts with the −SMe and $-CF_3$ substituents around the indoline ring. In the 5-HT$_{2B}$ receptor sequence the corresponding 608 residue is Leu, and in the 5-HT$_{2A}$ receptor sequence both the 212 and 608 residues are Leu. These differences would be expected to lead to binding pockets of reduced size, and it is proposed that these steric differences in the receptors may also account for the observed 5-HT$_{2C}$ selectivity.

QSAR Analysis: CoMFA Studies. As a possible means of testing the validity of our 5-HT$_{2C}$ receptor model, and also our proposed ligand docking mode, the set of 55 indolinylureas **2**−**56** shown in Tables 1 and 2 were selected for QSAR analysis using the CoMFA[32] module within the Sybyl[33] molecular modeling environment. All compounds were docked into the 5-HT$_{2C}$ receptor model in a manner analogous to that described for **46** above. Each receptor−ligand complex was then subjected to brief energy minimization in order to remove any bad steric contacts that may have arisen during the docking procedure. The individual ligands were then extracted from their respective receptor complexes (after any necessary realignment of the backbone atoms of the receptor) and subjected to CoMFA analysis. For this purpose a subset of 8 compounds was chosen at random to serve as a test set for predictions from the analysis, leaving a set of 47 compounds on which the analysis was actually performed.

The set of 47 aligned ligands were loaded into a Sybyl database and from there imported into a Sybyl Molecular Spreadsheet. An Autocomfa analysis using all of the default CoMFA options was then performed. This yielded a model whose statistical details are listed in Table 4. The predicted activities for the 47 compounds versus their actual activities are plotted in Figure 3.

From the residual plot in Figure 3, and from the fitted r^2 value of 0.877 from Table 4, it is clear that the CoMFA model explains the variance in the biological data for the 47 compounds used in the derivation of the model reasonably well. Also, the fact that ∼80% of the variance in the model is explained by the steric fields surrounding the molecules and only ∼20% is electrostatic in origin is in good agreement with the proposed

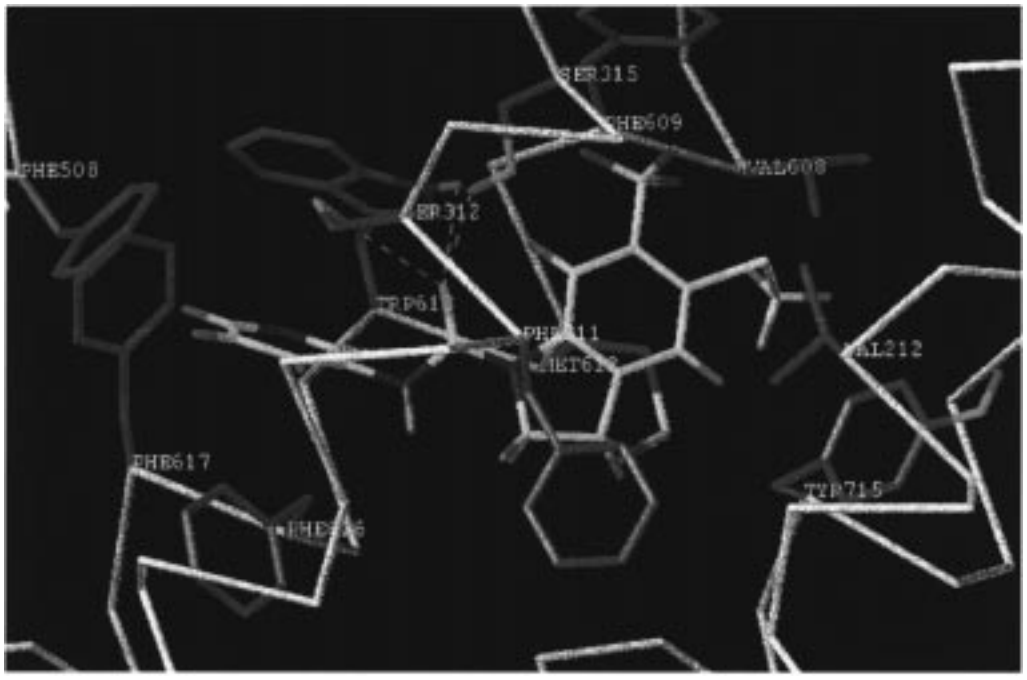


Figure 2. Structure **46** docked into the model of the 5-HT$_{2C}$ receptor.

Table 4. Statistical Details of the Derived CoMFA Model

maximum no. of PLS components	5
no. of cross-validation groups	5
optimal no. of PLS components	4
r^2	0.877
standard error of estimate	0.268
F values ($n_1 = 4$, $n_2 = 45$)	75.00
probability of $r^2 = 0$	0
q^2	0.656
no. of PLS variables	770
relative contribution of steric variables to final model	79.0%
relative contribution of electrostatic variables to final model	21.0%

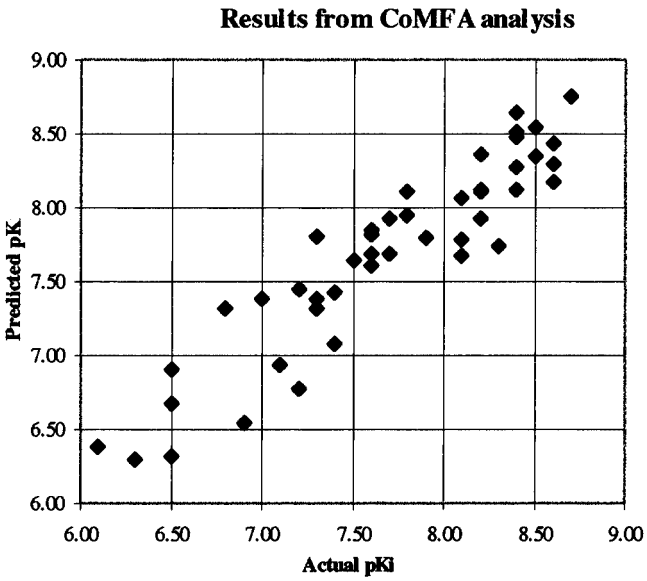


Figure 3. Plot of actual vs predicted 5-HT_{2C} pK_i values for the 50 compounds used in the derivation of the CoMFA model.

Table 5. Predictions for the Eight Test Compounds Not Used in the Derivation of the CoMFA Model

	5-HT_{2C} (pK_i)		
compd	actual	predicted	residual
13	7.30	6.92	0.38
14	7.60	7.14	0.46
25	8.00	7.94	0.06
35	7.70	7.64	0.06
41	7.80	7.52	0.28
43	8.70	8.13	0.57
44	7.90	7.85	0.05
49	7.50	8.46	−0.96

binding mode which hypothesizes that both "ends" of the structures are bound in lipophilic binding pockets. Furthermore, the q^2 (cross-validated r^2) figure of 0.656 suggests that the model should have good predictivity for similar molecules not present within the original training set. Accordingly, the eight test compounds that were originally kept aside were each placed into the model in turn and their activities predicted. The results of these predictions are shown in Table 5. This shows that in six of the eight cases, the CoMFA prediction of the activity is within 0.5 log unit of the actual value and in many cases significantly better than this figure. The remaining two cases have predictions between 0.5 and 1.0 log unit away from the true value, namely, 0.57 for **43** and −0.96 for **49**. However, these differences are accounted for by the statistical variation within the biological data itself. These results therefore suggest

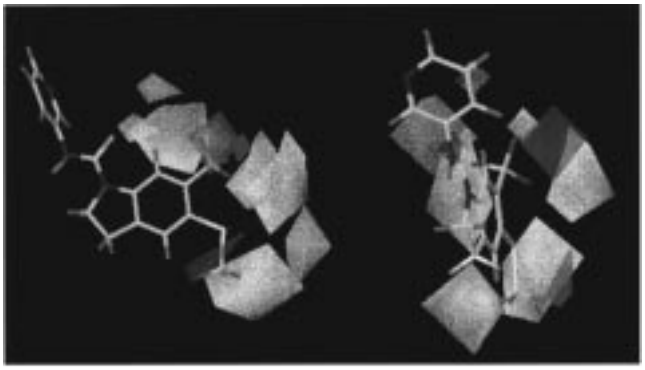


Figure 4. Orthogonal views of **46** embedded in color-coded regions deemed by the CoMFA model to be important for activity. Green regions are where more steric bulk is predicted to be beneficial for activity; yellow regions are where less steric bulk is predicted to be beneficial for activity.

that the obtained CoMFA model not only is robust but also has good predictivity for similar molecules not used in its derivation.

Lastly, in relation to the CoMFA model, we used the graphical capabilities within the Sybyl/CoMFA modeling environment to display those regions of space around our ligands that the CoMFA model suggested were important for explaining the observed biological activities. The resulting color-coded surfaces are shown in Figure 4, around **46** for reference. Since the CoMFA model had limited contributions from the electrostatic variables, only the steric field terms were contoured and displayed. The yellow surfaces define regions where the model suggests that extra steric bulk would be detrimental to the observed biological activity. The green surfaces define regions where extra steric bulk would be beneficial for increased biological activity. The predominance of yellow regions in Figure 4 suggests that the indoline ring and its substituents fit into a very tight binding pocket with very limited scope for additional or larger substituents. This is particularly true around the 5-position of the indoline. In our proposed binding model substituents at this position, and to a lesser extent at the 6- and 7-positions, are seen to make close steric contacts with the residues Val-212 and Val-608 of the receptor, as described earlier. These two residues are thought to play a key role in the observed 5-HT_{2C} selectivity of these ligands over the 5-HT_{2B} and 5-HT_{2A} subtypes where one or both of these residues respectively are replaced by leucines. Thus the CoMFA model is in good qualitative agreement both with our 5-HT_{2C} receptor model and with our proposed binding mode for this class of ligands within that model.

Conclusion

In conclusion, we report the synthesis and biological activity of a series of substituted 1-(3-pyridylcarbamoyl)-indolines which illustrates the use of 5,6-disubstituted monocyclic rings as *N*-methylindole isosteres in the context of 5-$HT_{2C/2B}$ receptor antagonists. By targeting a region of space previously identified as allowed at the 5-HT_{2C} receptor but disallowed at the 5-HT_{2A} receptor, due to steric differences in the receptor, we have identified a number of metabolically stable compounds which are the most potent and selective 5-$HT_{2C/2B}$ receptor antagonists yet reported. Compound **46** was

selected on the basis of its overall biological profile for further evaluation as a potential, novel, nonsedating anxiolytic agent. Unfortunately, **46** and related compounds were found to be potent inhibitors of a number of human cytochrome P450 enzymes which precluded their further development.[41] A CoMFA analysis of these compounds produced a model with good predictive value and in addition good qualitative agreement both with our 5-HT_{2C} receptor model and with our proposed binding mode for this class of ligands within that model.

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 and 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. All final compounds were greater than 95% pure as judged by area under the curve. 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. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere before use. *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 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).

The following compounds were prepared from commercially available or known indolines.

5-Nitro-1-(3-pyridylcarbamoyl)indoline Hydrochloride (6). A solution of nicotinic acid azide (0.43 g, 2.9 mmol) [**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 are 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.] in toluene (20 mL) was heated at reflux for 0.5 h to form 3-pyridyl isocyanate and then cooled to room temperature. A solution of 5-nitroindoline (0.38 g, 2.3 mmol) in dichloromethane (20 mL) was then added, and the mixture was stirred overnight at room temperature. The resulting precipitate was treated with excess HCl in ether to give the title compound **6** (0.64 g, 76%) as a light-yellow powder, mp 244−247 °C dec. NMR (DMSO-d_6) δ: 3.32 (2H, t, J = 8 Hz), 4.35 (2H, t, J = 8 Hz), 7.8−8.2 (4H, m), 8.5−8.65 (2H, m), 9.14 (1H, d, J = 2 Hz), 9.78 (1H, s). MS: m/e 284.0894 (M^+), $C_{14}H_{12}N_4O_3$ requires 284.0909.

1-(3-Pyridylcarbamoyl)indoline (2). Indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **2** as a white solid (98%), mp 206−208 °C. NMR (DMSO-d_6) δ: 3.29 (2H, t, J = 8 Hz), 4.24 (2H, t, J = 8 Hz), 7.03 (1H, dd, J = 6 Hz), 7.19−7.36 (2H, m), 7.44 (1H, dd, J = 5, 7 Hz), 7.98 (1H, d, J = 7 Hz), 8.09 (1H, m) 8.33 (1H, m), 8.83 (1H, m). MS: m/e 239 (M^+). Anal. ($C_{14}H_{13}N_3O$) C, H, N.

6-Chloro-1-(3-pyridylcarbamoyl)indoline (13). The title compound was prepared as in the preparation of **6** from 3-pyridyl isocyanate and 6-chloroindoline to give the title compound **13** (1.54 g, 73%), mp 204−205 °C. NMR (DMSO-d_6-) δ: 3.19 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 6.93−6.99 (1H, m), 7.23 (1H, d, J = 8 Hz), 7.31−7.38 (1H, m), 7.88 (1H, s), 7.94−8.02 (1H, m), 8.24 (1H, d, J = 6 Hz), 8.72 (1H, s), 8.82 (1H, s). Anal. ($C_{14}H_{12}N_3OCl$) C, H, N.

5-Bromo-7-nitro-1-(3-pyridylcarbamoyl)indoline (20). 5-Bromo-7-nitro-1-indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **20** as a yellow solid (19%), mp 185−186 °C (EtOH). NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 4.30 (2H, t, J = 8 Hz), 7.35 (1H, m), 7.79−7.96 (3H, m), 8.26 (1H, m), 8.65 (1H, m), 9.69 (1H, s). Anal. ($C_{14}H_{11}N_4O_3Br$) C, H, N.

5-(*N*,*N*-Dimethylamino)-1-(3-pyridylcarbamoyl)indoline (10). A mixture of 1-acetyl-5-nitroindoline (0.9 g, 4.37 mmol), 37% aqueous formaldehyde (1 mL), and 10% Pd−C (0.1 g) in ethanol (15 mL) was hydrogenated at 45 psi at room temperature overnight. The reaction mixture was filtered through Celite and evaporated to afford 1-acetyl-5-(*N*,*N*-dimethylamino)indoline (0.89 g, 100%). NMR ($CDCl_3$) δ: 2.20 (3H, s), 2.92 (6H, s), 3.18 (3H, m,), 4.02 (2H, J = 8 Hz), 6.61 (2H, m), 8.08 (1H, m). Without further purification this material (0.6 g, 2.94 mmol) was heated on a steam bath with concentrated HCl (10 mL) for 45 min, cooled, and then partitioned between aqueous K_2CO_3 (50 mL) and $CHCl_3$ (50 mL). The organic phase was dried (Na_2SO_4), evaporated to dryness, and purified by chromatography on silica gel eluting with 5−10% MeOH in EtOAc to afford 5-(*N*,*N*-dimethylamino)-indoline (0.29 g, 61%) which was immediately treated with 3-pyridyl isocyanate as in the preparation of **6** to afford the title compound **10** (550 mg, 99%) as an off-white solid, mp 135−137 °C. NMR (DMSO-d_6) δ: 2.82 (6H, s), 3.14 (2H, t, J = 8 Hz), 4.08 (2H, t, J = 8 Hz), 6.53 (1H, m), 6.68 (1H, d), 7.70 (1H, d), 7.98 (1H, dd), 8.20 (1H, m), 8.58 (1H, s), 8.72 (1H, d). MS: m/e 282 (M^+). Anal. ($C_{16}H_{18}N_4O \cdot 0.75H_2O$) C, H, N.

The following compounds were prepared from indolines obtained via reduction of commercially available or known indoles.

1-(3-Pyridylcarbamoyl)-6-(trifluoromethyl)indoline (12). 6-(Trifluoromethyl)indole[32] (5.27 g, 28.5 mmol) in glacial acetic acid (50 mL) was treated with sodium cyanoborohydride (3.60 g, 57.0 mmol) portionwise at room temperature with stirring. After 3 h at room temperature the reaction mixture was diluted with water (100 mL) and basified with 40% aqueous NaOH with cooling. The mixture was then extracted with dichloromethane (3 × 150 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to give 6-(trifluoromethyl)indoline (4.83 g, 91%) as a brown solid which was used without further purification. NMR ($CDCl_3$) δ: 3.07 (2H, t, J = 8 Hz), 3.62 (2H, t, J = 8 Hz), 6.80 (1H, s), 6.92 (1H, d, J = 8 Hz), 6.92 (1H, d, J = 8 Hz), 7.15 (1H, d, J = 8 Hz). The 6-(trifluoromethyl)indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **12** as a white solid (88%), mp 225−228 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 4.22 (2H, t, J = 8 Hz), 7.25−7.50 (2H, m), 8.02 (1H, m), 8.19 (1H, s), 8.28 (1H, m), 8.76 (1H, m) 8.89 (1H, s). MS: m/e 307.0949 (M^+), $C_{15}H_{12}N_3OF_3$ requires 307.0932.

5-Chloro-1-(3-pyridylcarbamoyl)indoline (4). 5-Chloroindoline was prepared by reduction of 5-chloroindole as above and converted to the title compound **4** (82%) as in the preparation of **6** to afford a white solid, mp 204−205 °C. NMR (DMSO-d_6) δ: 3.18 (2H, t, J = 8 Hz), 4.15 (2H, t, J = 8 Hz), 7.15−7.18 (1H, m), 7.25 (1H, s), 7.27−7.35 (1H, m), 7.85 (1H, d, J = 8 Hz), 7.93−8.00 (1H, m), 8.19−8.24 (1H, m), 8.70−8.80 (2H, m). MS: m/e 273.0668 (M^+), $C_{14}H_{12}N_3OCl$ requires 273.0669.

5-Methyl-1-(3-pyridylcarbamoyl)indoline (7). 5-Methylindole was treated with sodium cyanoborohydride as for **12** and the resulting indoline reacted with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **7** as a white solid (78%), mp 205−206 °C (MeOH/CH_2Cl_2). NMR (DMSO-d_6) δ: 2.30 (3H, s), 3.25 (2H, t, J = 8 Hz), 4.22 (2H, t, J = 8 Hz), 7.05 (1H, d, J = 8 Hz), 7.15 (1H, s), 7.40−7.47 (1H, m), 7.82 (1H, d, J = 8 Hz), 8.10 (1H, m), 8.30 (1H, m), 8.78 (1H, s), 8.86 (1H, s). Anal. ($C_{15}H_{15}N_3O$) C, H, N.

4-Chloro-1-(3-pyridylcarbamoyl)indoline (3). 4-Chloroindole was treated with sodium cyanoborohydride as for **12**. The resulting indoline was reacted with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **3** as a white solid (76%), mp 203−205 °C ($MeOH/CH_2Cl_2$). NMR (DMSO-d_6) δ: 3.21 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 6.99 (1H, d, J = 8 Hz), 7.18 (1H, dd, J = 8 Hz), 7.35 (1H, m), 7.81 (1H, d, J = 8 Hz), 8.00 (1H, m), 8.24 (1H, m), 8.75 (1H, s), 8.80 (1H, s). MS: m/e 273.0670 (M^+), $C_{14}H_{12}N_3OCl$ requires 273.0669. Anal. ($C_{14}H_{12}N_3ClO$) C, H, N.

5-Phenyl-1-(3-pyridylcarbamoyl)indoline (9). 5-Phenylindole[33] was reduced to 5-phenylindoline as described for **12** and treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **9** as a white solid (52%), mp 241−242 °C. NMR (DMSO-d_6) δ: 3.25 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 7.23−7.69 (8H, m), 7.89−8.03 (2H, m), 8.11 (1H, m), 8.75−8.80 (2H, m). MS: m/e 315.1371 (M^+), $C_{20}H_{17}N_3O$ requires 315.1372.

The following compounds were prepared by the Nordlander[18] synthesis or, more satisfactorily, by the Sundberg modification[19] of the Nordlander synthesis.

5-(2-Propyl)indole. A mixture of 4-(2-propyl)aniline (20.4 g, 151 mmol) and 2,2-dimethoxyethanal (49.8 g, 196 mmol) in ethanol (400 mL) was stirred with 5% palladium on charcoal (5 g) under hydrogen (1 atm) for 18 h. The mixture was then filtered through Kieselgühr and evaporated. The residue was dissolved in ethyl acetate and washed with brine. The organic solution was dried and evaporated to give *N*-[(2,2-dimethoxyethyl)amino]-4-(2-propyl)aniline (33.69 g, 100%) as a red oil. NMR ($CDCl_3$) δ: 1.20 (6H, d, J = 6 Hz), 2.81 (1H, m, J = 6 Hz), 3.22 (2H, d, J = 5 Hz), 3.40 (6H, s), 3.75 (1H, broad), 4.58 (1H, t, J = 5 Hz), 6.59 (2H, d, J = 8 Hz), 7.05 (2H, d, J = 8 Hz). The acetal (1.02 g, 4.55 mmol) was heated in trifluoroacetic acid/trifluoroacetic anhydride according to the method of Nordlander.[18] The crude product was chromatographed on silica gel eluting with 1:1 dichloromethane/petroleum ether to give 5-(2-propyl)-1-(trifluoroacetyl)indole (0.25 g, 22%). NMR ($CDCl_3$) δ: 1.29 (6H, d, J = 7 Hz), 3.00 (1H, m, J = 7 Hz), 6.68 (1H, d, J = 5 Hz), 7.27 (1H, d, J = 7 Hz), 7.42 (2H, s), 8.32 (1H, d, J = 7 Hz). The (trifluoroacetyl)indole (0.25 g, 0.99 mmol) was stirred with potassium carbonate (0.20 g, 1.5 mmol) in methanol (7.5 mL) at 55 °C for 1.5 h. Solvent was evaporated, and the residue was partitioned between water and dichloromethane. The organic extract was dried and evaporated to give the title compound (0.14 g, 86%). NMR ($CDCl_3$) δ: 1.30 (6H, d, J = 7 Hz), 3.00 (1H, m, J = 7 Hz), 6.48 (1H, m), 7.01 (1H, m), 7.09 (1H, d, J = 8 Hz), 7.20 (1H, d, J = 8 Hz), 7.49 (1H, s), 7.71 (1H, broad).

5-(2-Propyl)-1-(3-pyridylcarbamoyl)indoline (8). 5-(2-Propyl)indole was treated with sodium cyanoborohydride as for **12** to give 5-(2-propyl)indoline (84%). NMR ($CDCl_3$) δ: 1.23 (6H, d, J = 7 Hz), 2.81 (1H, m, J = 7 Hz), 2.91 (2H, t, J = 8 Hz), 3.38 (2H, t, J = 8 Hz), 3.59 (1H, s), 6.47 (1H, d, J = 8 Hz), 6.85 (1H, d, J = 8 Hz), 6.98 (1H, s). Treatment of the indoline with 3-pyridyl isocyanate as in the preparation of **6** gave the title compound **8** as a white solid (45%), mp 163−165 °C. NMR (DMSO-d_6) δ: 1.18 (6H, d, J = 7 Hz), 2.83 (1H, m, J = 7 Hz), 3.18 (2H, t, J = 8 Hz), 4.13 (2H, t, J = 8 Hz), 7.00 (1H, d, J = 7 Hz), 7.10 (1H, s), 7.32 (1H, dd, J = 7, 5 Hz), 7.77 (1H, d, J = 7 Hz), 7.99 (1H, dm, J = 7 Hz), 8.22 (1H, d, J = 5 Hz), 8.69 (1H, s), 8.74 (1H, d, J = 2 Hz). Anal. ($C_{17}H_{19}N_3O$) C, H, N.

6-Chloro-5-*tert*-butylindole and 4-Chloro-5-*tert*-butylindole. 3-Chloro-4-*tert*-butylaniline[34] was converted to a 5:4 mixture of the title compounds by the method developed by Sundberg[19] in an overall yield of 37%. The isomers were separated by column chromatography on silica gel using 5% ethyl acetate in petroleum ether (60−80 °C) to give in order of elution 6-chloro-5-*tert*-butylindole [NMR ($CDCl_3$) δ: 1.54 (9H, s), 6.50 (1H, m), 7.17 (1H, m), 7.41 (1H, s), 7.69 (1H, s), 8.02 (1H, bs)] and 4-chloro-5-*tert*-butylindole [NMR ($CDCl_3$) δ: 1.55 (9H, s), 6.70 (1H, m), 7.15−7.28 (3H, m)].

6-Chloro-5-*tert*-butyl-1-(3-pyridylcarbamoyl)indoline (36). 6-Chloro-5-*tert*-butylindole was reduced with sodium cyanoborohydride as for **12** to give 6-chloro-5-*tert*-butylindoline as a yellow oil. NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.89 (2H, t, J = 8 Hz), 3.46 (2H, t, J = 8 Hz), 3.60 (1H, bs), 6.53 (1H, s), 7.09 (1H, s). The indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **36** (35%) as a white crystalline solid, mp 200 °C (ethanol/diethyl ether). NMR (DMSO-d_6) δ: 1.40 (9H, s), 3.15 (2H, t, J = 8 Hz), 4.15 (2H, t, J = 8 Hz), 7.30 (1H, s), 7.33 (1H, m), 7.85 (1H, s), 7.98 (1H, d, J = 9 Hz), 8.22 (1H, d, J = 5 Hz), 8.73 (1H, m), 8.78 (1H, s). Anal. ($C_{18}H_{20}N_3OCl$) C, H, N.

4-Chloro-5-*tert*-butyl-1-(3-pyridylcarbamoyl)indoline (17). 4-Chloro-5-*tert*-butylindole was treated with sodium cyanoborohydride as for **12** to give 4-chloro-5-*tert*-butylindoline as a yellow oil. NMR ($CDCl_3$) δ: 1.44 (9H, s), 3.09 (2H, t, J = 8 Hz), 3.58 (2H, b, J = 8 Hz), 3.76 (1H, b), 6.47 (1H, d), 7.07 (1H, d). The indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **17** (58%) as a white crystalline solid, mp 174−176 °C (ethanol/diethyl ether). NMR (DMSO-d_6) δ: 1.42 (9H, s), 3.21 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 7.25 (1H, d, J =7 Hz), 7.33 (1H, m), 7.70 (1H, d, J = 7 Hz), 7.99 (1H, d, J = 9 Hz), 8.22 (1H, d, 5 Hz), 8.77 (2H, m). Anal. ($C_{18}H_{20}N_3OCl$) C, H, N.

The following compounds were prepared according to the general procedures described above employing the appropriate 3-chloro-4-alkylanilines (themselves prepared by the general procedure described by Lampooy[34]).

6-Chloro-5-isopropyl-1-(3-pyridylcarbamoyl)indoline (37): recrystallized from ethanol/diethyl ether as a white crystalline solid (57%), mp 183−185 °C. NMR (DMSO-d_6) δ: 1.19 (6H, d, J = 8 Hz), 2.18 (2H, t, J = 8 Hz), 3.23 (1H, m, J = 8 Hz), 4.15 (2H, t, J = 8 Hz), 7.24 (1H, s), 7.33 (1H, m), 7.86 (1H, s), 7.98 (1H, d, J = 9 Hz), 8.22 (1H, d, J = 5 Hz), 8.73 (1H, m), 8.78 (1H, s). Anal. ($C_{17}H_{18}N_3OCl$) C, H, N.

6-Chloro-5-methyl-l-(3-pyridylcarbamoyl)indoline (26): obtained as a white powder (62%), mp 221−223 °C. NMR (DMSO-d_6) δ: 2.25 (3H, s), 3.15 (2H, t, J = 8 Hz), 4.16 (2H, t, J = 8 Hz), 7.17 (1H, s), 7.33 (1H, dd, J = 8, 4 Hz), 7.88 (1H, s), 7.98 (1H, m), 8.23 (1H, dd, J = 5, 2 Hz), 8.75 (2H, m). MS: m/e 287.289 (M^+), requires 287.289. Anal. ($C_{15}H_{14}ClN_3O$) C, H, N.

6-Chloro-5-ethyl-1-(3-pyridylcarbamoyl)indoline (34): recrystallized from ethanol/diethyl ether as a white crystalline solid (59%), mp 227 °C. NMR (DMSO-d_6) δ: 1.13 (3H, t, J = 8 Hz), 2.62 (2H, q, J = 8 Hz), 3.17 (2H, t, J = 8 Hz), 4.16 (2H, t, J = 8 Hz), 7.18 (1H, s), 7.33 (1H, m), 7.87 (1H, s), 7.99 (1H, d, J = 9 Hz), 8.23 (1H, d, J = 5 Hz), 8.73 (1H, m), 8.79 (1H, s). Anal. ($C_{16}H_{16}N_3ClO$) C, H, N.

6-Chloro-5-propyl-1-(3-pyridylcarbamoyl)indoline (35): recrystallized from ethanol/diethyl ether as a white crystalline solid (58%), mp 218−220 °C. NMR (DMSO-d_6) δ: 1.00 (3H, t, J = 8 Hz), 1.66 (2H, q, J = 8 Hz), 2.70 (2H, t, J = 8 Hz), 3.27 (2H, t, J = 8 Hz), 4.26 (2H, t, J = 8 Hz), 7.25 (1H, s), 7.42 (1H, m), 7.98 (1H, s), 8.08 (1H, d, J = 8 Hz), 8.32 (1H, d, J = 5 Hz), 8.83 (1H, m), 8.89 (1H, s). MS: m/e 315.1143 (M^+), $C_{17}H_{18}N_3OCl$ requires 315.1138.

4,6-Dichloro-5-methyl-1-(3-pyridylcarbamoyl)indoline (29). Starting with 3,5-dichloro-4-methylaniline and following the general procedures described above, the title compound was prepared as a white solid (27%), mp 234−235 °C (dichloromethane/ethanol). NMR (DMSO-d_6) δ: 8.82 (1H, s), 8.7 (1H, m), 8.25 (1H, d, J = 5 Hz), 7.95 (1H, m), 7.32 (1H, m), 4.20 (2H, t, J = 8 Hz), 3.17 (2H, t, J = 8 Hz), 2.32 (3H, s). Anal. ($C_{15}H_{13}N_3Cl_2O$) C, H, N.

The following compounds were prepared according to the general procedures described above starting from the appropriate 3-halo-4-methylaniline.

6-Iodo-5-methyl-1-(3-pyridylcarbamoyl)indoline (28) and 4-Iodo-5-methyl-1-(3-pyridylcarbamoyl)indoline (16). 6-Iodo-5-methylindoline and 4-iodo-5-methylindoline were prepared as a 4:1 mixture starting from 3-iodo-4-methylaniline. Treatment of this mixture with 3-pyridyl isocyanate as in the preparation of **6** gave the title compounds as a mixture (4:1, 38% combined yield), a portion of which was separated by preparative HPLC.

6-Iodo-5-methyl-1-(3-pyridylcarbamoyl)indoline (28): obtained as a white solid, mp 252−254 °C. NMR (DMSO-d_6) δ: 2.32 (3H, s), 3.13 (2H, t, J = 9 Hz), 4.15 (2H, t, J = 9 Hz), 7.19 (1H, s), 7.33 (1H, m), 7.98 (1H, m), 8.23 (1H, m), 8.34 (1H, s), 8.73 (1H, m). MS: m/e 379.0188 (M^+), $C_{15}H_{14}N_3OI$ requires 379.0182.

4-Iodo-5-methyl-1-(3-pyridylcarbamoyl)indoline (16): obtained as a white solid, mp 222−224 °C. NMR (DMSO-d_6) δ: 2.33 (3H, s), 3.11 (2H, t, J = 9 Hz), 4.17 (2H, t, J = 9 Hz), 7.09 (1H, d, J = 8 Hz), 7.34 (1H, m), 7.76 (1H, d, J = 8 Hz), 7.97 (1H, m), 8.23 (1H, m), 8.71 (1H, s), 8.74 (1H, m). MS: m/e 379.0183 (M^+), $C_{15}H_{14}N_3OI$ requires 379.0182.

6-Bromo-5-methyl-1-(3-pyridylcarbamoyl)indoline (27) and 4-Bromo-5-methyl-1-(3-pyridylcarbamoyl)indoline (15). 6-Bromo-5-methylindoline and 4-bromo-5-methylindoline were prepared as a 3:1 mixture starting from 3-bromo-4-methylaniline. Treatment with 3-pyridyl isocyanate as in the preparation of **6** gave the title compounds as a mixture (3:1, 52%), a portion of which was separated by preparative HPLC.

6-Bromo-5-methyl-1-(3-pyridylcarbamoyl)indoline (27): obtained as a white solid, mp 246−247 °C. NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.20 (2H, t, J = 9 Hz), 4.12 (2H, t, J = 9 Hz), 6.42 (1H, bs), 7.04 (1H, s), 7.27 (1H, m), 8.11 (1H, m), 8.16 (1H, s), 8.35 (1H, m), 8.50 (1H, s). MS: m/e 331.0331 (M^+), $C_{15}H_{14}N_3OBr$ requires 331.0320.

4-Bromo-5-methyl-1-(3-pyridylcarbamoyl)indoline (15): obtained as a white solid, mp 211−213 °C. NMR ($CDCl_3$) δ: 2.36 (3H, s), 3.27 (2H, t, J = 9 Hz), 4.15 (2H, t, J = 9 Hz), 6.45 (1H, b s), 7.09 (1H, d, J = 8 Hz), 7.28 (1H, m), 7.75 (1H, d, J = 8 Hz), 8.09 (1H, m), 8.32 (1H, m), 8.50 (1H, s). MS: m/e 331.0323 (M^+), $C_{15}H_{14}N_3OBr$ requires 331.0320.

The following compounds were prepared in analogous ways starting from the appropriate anilines.

5-(Trifluoromethyl)-1-(3-pyridylcarbamoyl)indoline (5): recrystallized from ethanol/diethyl ether as a white crystalline solid (38%), mp 188−189 °C. NMR (DMSO-d_6) δ: 3.28 (2H, t, J = 8 Hz), 4.22 (2H, t, J = 8 Hz), 7.31−7.37 (1H, m), 7.47−7.57 (2H, m), 7.95−8.03 (2H, m), 8.24 (1H, d, J = 6 Hz), 8.75 (1H, s), 8.90 (1H, s). MS: m/e 307.0923 (M^+), $C_{15}H_{12}N_3OF_3$ requires 307.0932.

6-Chloro-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (39): recrystallized from ethanol/diethyl ether as a white crystalline solid (81%), mp 241−242 °C. NMR (DMSO-d_6) δ: 2.48 (3H, s), 3.22 (2H, t, J = 8 Hz), 4.18 (2H, t, J = 8 Hz), 7.22 (1H, s), 7.33 (1H, dd, J = 9, 5 Hz), 7.91 (1H, s), 7.98 (1H, d, J = 9 Hz), 8.23 (1H, d, J = 5 Hz), 8.74 (1H, m), 8.80 (1H, s). Anal. ($C_{15}H_{14}N_3OSCl$) C, H, N.

4-Chloro-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (18): recrystallized from ethanol as a white crystalline solid (84%), mp 237−241 °C. NMR (DMSO-d_6) δ: 2.43 (3H, s), 3.20 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 7.14 (1H, d, J = 7 Hz), 7.34 (1H, dd, J = 9, 5 Hz), 7.83 (1H, d, J = 7 Hz), 7.98 (1H, d, J = 7 Hz), 8.24 (1H, d, J = 5 Hz), 8.73 (1H, m), 8.78 (1H, s). Anal. ($C_{15}H_{14}N_3OSCl$) C, H, N.

6-Chloro-5-iodo-1-(3-pyridylcarbamoyl)indoline (22): obtained as a white crystalline solid, mp >200 °C. NMR (DMSO-d_6) δ: 3.15 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 7.35 (1H, m), 7.75 (1H, s), 7.95 (1H, m), 8.00 (1H, s), 8.25 (1H, m), 8.70 (1H, m), 8.85 (1H, s). MS: m/e 399 (M^+).

6-Chloro-5-ethoxy-1-(3-pyridylcarbamoyl)indoline (40): isolated as a white crystalline solid (72%), mp 219 °C. NMR (DMSO-d_6) δ: 1.33 (3H, t, J = 7 Hz), 3.20 (2H, t, J = 8 Hz), 4.07 (2H, t, J = 7 Hz), 4.18 (2H, t, J = 8 Hz), 7.08 (1H, s), 7.33 (1H, dd, J = 7, 5 Hz), 7.90 (1H, s), 7.99 (1H, dd, J = 7, 2 Hz), 8.22 (1H, dd, J = 7, 2 Hz), 8.72 (2H, m). MS: m/e 317.0948 (M^+), $C_{16}H_{16}N_3O_2Cl$ requires 317.0931.

6-Chloro-5-isopropoxy-1-(3-pyridylcarbamoyl)indoline (41): prepared as a white crystalline solid (80%), mp 169−171 °C. ^{1}H NMR (DMSO-d_6) δ: 1.28 (6H, d, J = 7 Hz), 3.19 (2H, t, J = 8 Hz), 4.17 (2H, t, J = 7 Hz), 4.42−4.60 (1H, m), 7.10 (1H, s), 7.32 (2H, m, J = 5, 7 Hz), 7.88 (1H, s), 7.98 (1H, dd, J = 2, 7 Hz), 8.22 (1H, dd, J = 2, 5 Hz), 8.72 (1H, d, J = 2 Hz). ^{13}C NMR (D_6-DMSO) δ: 21.8, 27.3, 47.6, 72.0, 113.9, 115.7, 120.8, 123.1, 127.2, 131.2, 136.2, 137.7, 141.9, 142.5, 148.0, 152.2. MS: m/e 331.1096 (M^+), $C_{17}H_{18}ClN_3O_2$ requires 331.1102.

5-Chloro-6-(trifluoromethyl)-1-(3-pyridylcarbamoyl)-indoline (23): obtained as a white solid (86%), mp >220 °C. NMR (DMSO-d_6) δ: 3.30 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 7.35 (1H, m), 7.55 (1H, s), 8.00 (1H, m), 8.25 (1H, m), 8.30 (1H, s), 8.75 (1H, m) 8.90 (1H, s). MS: m/e 341.0530 (M^+), $C_{15}H_{11}N_3OClF_3$ requires 341.0543.

4,6-Dichloro-5-(methylthio)-1-(3-pyridylcarbamoyl)-indoline (30). The title compound was prepared from 3,5-dichloro-4-(methylthio)aniline[26] as a white crystalline solid (67%), mp 199−200 °C (EtOAc/CH_2Cl_2). NMR (DMSO-d_6) δ: 2.32 (3H, s), 3.20 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 7 Hz), 7.34 (1H, m), 8.98 (2H, m), 8.27 (1H, m), 8.71 (1H, d), 8.91 (1H, s). MS: m/e 321.0430 (M^+), $C_{15}H_{13}N_3OCl_2$ requires 321.0436.

Starting with the appropriate *o*-nitrotoluene, the following compounds (**21, 25, 38, 42**) were prepared by the Leimgruber[20] procedure.

5,6-Dichloro-1-(3-pyridylcarbamoyl)indoline (21). 2-Nitro-4,5-dichlorotoluene[35] was treated with *N*,*N*-dimethylformamide dimethyl acetal followed by $TiCl_3$ according to the general method described by Leimgruber[20] to give 5,6-dichloroindole (1.3 g, 72%). NMR ($CDCl_3$) δ: 6.48−6.52 (1H, m), 7.22−7.25 (1H, m), 7.50 (1H, s), 7.73 (1H, s), 8.01−8.31 (1H, br s). 5,6-Dichloroindole was then reduced as for **12** with sodium cyanoborohydride in acetic acid to give 5,6-dichloroindoline NMR ($CDCl_3$) δ: 3.01 (2H, t, J = 8 Hz), 3.63 (1H, t, J = 8 Hz), 3.75−3.91 (1H, br s), 6.70 (1H, s), 7.15 (1H, s). Treatment with 3-pyridyl isocyanate as in the preparation of **6** gave the title compound **21** as a white solid (1.27 g, 65%), mp 236−238 °C. NMR (DMSO-d_6) δ: 3.18 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 7.28−7.35 (1H, m), 7.47 (1H, s), 7.92−7.99 (1H, m), 8.00 (1H, s), 8.23 (1H, d, J = 6 Hz), 8.70 (1H, s), 8.83 (1H, s). Anal. ($C_{14}H_{11}N_3OCl_2$) C, H, N.

5-Chloro-6-methyl-1-(3-pyridylcarbamoyl)indoline (25). Starting with 2-chloro-5-nitro-*p*-xylene, the title compound was obtained as a white solid (73%), mp 217−218 °C (ethanol/dichloromethane). NMR (DMSO-d_6) δ: 2.27 (3H, s), 3.13 (2H, t, J = 8 Hz), 4.13 (2H, t, J = 8 Hz), 7.21 (1H, s), 7.29−7.37 (1H, m), 7.82 (1H, s), 7.93−7.99 (1H, m), 8.22 (1H, d, J = 6 Hz), 8.73 (1H, s). Anal. ($C_{15}H_{14}N_3OCl$) C, H, N.

6-Chloro-5-phenyl-1-(3-pyridylcarbamoyl)indoline (38). To a stirred solution of 2-chloro-5-methyl-4-nitrophenol[36] (5 g, 26.6 mmol) and pyridine (2.4 mL, 30 mmol) in dichloromethane (100 mL) at −5 °C (ice/salt) was added a solution of trifluoroacetic anhydride (5 mL, 30 mmol) in dichloromethane (5 mL) dropwise. The mixture was warmed to room temperature and washed with 2 N aqueous HCl (50 mL) and water (50 mL). The organic phase was dried and evaporated to give trifluoromethanesulfonic acid 2-chloro-5-methyl-4-nitrophenyl ester (8.2 g, 96%) as an oil. NMR ($CDCl_3$) δ: 2.68 (3H, s), 7.40 (1H, s), 8.20 (1H, s). The crude triflate (8.2 g, 25.6 mmol) was taken up in dioxane (100 mL) together with phenyltrimethyltin (4.9 mL, 26.9 mmol), tetrakis(triphenylphosphine)palladium (0.6 g, 0.5 mmol), and lithium chloride (3.2 g, 76.1 mmol) and heated at reflux for 2 h.[37] After cooling the reaction mixture was treated with a solution of KF (1.78 g, 30.7 mmol) in water (10 mL), and the resulting solution was filtered and partitioned between ether (3 × 100 mL) and water (100 mL). The combined organics were washed with water (100 mL), dried, and evaporated to give an oily residue which was purified by chromatography on silica gel eluting with 2% EtOAc/petroleum ether to give 4-chloro-2-nitro-5-phenyltoluene (3.3 g, 52%) as a pale-yellow oil. NMR ($CDCl_3$) δ: 2.61 (3H, s), 7.33 (1H, s), 7.35−7.50 (5H, m), 8.16 (1H, s). Without further purification this toluene was converted to 6-chloro-5-phenylindole by the method of Liemgruber[20] as described for **21** to give a brown oil (93%). NMR ($CDCl_3$) δ: 6.60 (1H, m), 7.25 (1H, m), 7.34−7.60 (7H, m), 8.20 (1H, br s). The indole was reduced as for **12** to give 6-chloro-5-phenylindoline. NMR ($CDCl_3$) δ: 3.02 (2H, t, J = 8 Hz), 3.61 (1H, t, J = 8 Hz), 3.87 (1H, br s), 6.70 (1H, s), 7.09 (1H, s), 7.25−7.50 (5H, m). Treatment with 3-pyridyl isocyanate as in the preparation of

6 gave the title compound **38** as a white solid (57%), mp 214−215 °C (ethanol/dichloromethane). NMR (DMSO-d_6) δ: 3.23 (2H, t, J = 8 Hz), 4.22 (2H, t, J = 8 Hz), 7.25 (1H, s), 7.12−7.50 (6H, m), 7.96−8.04 (2H, m), 8.26 (1H, m), 8.76 (1H, d, J = 2 Hz), 8.87 (1H, s). Anal. ($C_{20}H_{16}N_3OCl$) C, H, N.

Methyl 6-Chloro-1-(3-pyridylcarbamoyl)indoline-5-carboxylate (42). A solution of trifluoromethanesulfonic acid 2-chloro-5-methyl-4-nitrophenyl ester (4.6 g, 14.4 mmol) and vinyltributyltin (6 g, 19.2 mmol) in dioxane (50 mL) was treated with lithium chloride (1.8 g, 42.6 mmol), tetrakis-(triphenylphosphine)palladium (0.33 g, 0.3 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (10 mg).[37] The mixture was heated at reflux overnight (~17 h). After cooling the mixture was added to a mixture of ether (100 mL) and aqueous KF (100 mL) with vigorous swirling. The mixture was filtered and the organic phase separated, dried, and evaporated to give a brown solid which was chromatographed on silica gel eluting with 0−5% EtOAc in petroleum ether to give 4-chloro-2-nitro-5-vinyltoluene (2.2 g, 79%) as a yellow crystalline solid. NMR ($CDCl_3$) δ: 2.63 (3H, s), 5.58 (1H, d, J = 13 Hz), 5.90 (1H, d, J = 20 Hz), 7.08 (1H, dd, J = 20, 13 Hz), 7.51 (1H, s), 8.06 (1H, s). A solution of the crude olefin (2.2 g, 11.1 mmol) in dichloromethane (100 mL) was ozonolyzed for 1 h at −78 °C. Oxygen was then bubbled through the solution for 0.5 h followed by argon for 0.5 h. Triphenylphosphine (3.05 g, 11.6 mmol) was then added, and the mixture was allowed to warm to room temperature. After 2 h silica gel was added, and the solvents were evaporated. Chromatography on silica gel, eluting with 0−10% EtOAc in petroleum ether, afforded 2-chloro-5-methyl-4-nitrobenzaldehyde (1.72 g, 77%) as a yellow crystalline solid. NMR ($CDCl_3$) δ: 2.63 (3H, s), 7.91 (1H, s), 8.06 (1H, s), 10.48 (1H, s). The crude aldehyde (1.72 g, 8.6 mmol) in acetic acid (20 mL) was treated with sodium perborate (3.96 g, 25.8 mmol) at 80 °C for 0.75 h. After cooling the reaction mixture was partitioned between EtOAc (150 mL) and brine (100 mL). The organic phase was separated, washed with brine (2 × 100 mL), dried, and evaporated to afford 2-chloro-5-methyl-4-nitrobenzoic acid (1.43 g, 77%) as a white solid. NMR ($CDCl_3$) δ: 2.50 (3H, s), 2.70−4.00 (1H, br s), 7.89 (1H, s), 8.17 (1H, s). Without further purification this acid was subjected to the procedures described above for **21** to give methyl 6-chloroindole-5-carboxylate as a white solid (40%). NMR ($CDCl_3$) δ: 3.96 (3H, s) 6.60 (1H, m), 7.27 (1H, m), 7.49 (1H, s), 8.23 (1H, s), 8.42 (1H, br s). The indole was reduced with sodium cyanoborohydride in acetic acid as described for **12** to give methyl 6-chloroindoline-5-carboxylate. NMR ($CDCl_3$) δ: 3.03 (2H, t, J = 8 Hz), 3.67 (1H, t, J = 8 Hz), 3.88 (3H, s), 6.58 (1H, s), 7.68 (1H, s). Treatment with 3-pyridyl isocyanate as in the preparation of **6** gave the title compound **42** as a white solid (57%), mp 210 °C (methanol). NMR (DMSO-d_6) δ: 3.23 (2H, t, J = 8 Hz), 3.81 (3H, s), 4.24 (2H, t, J = 8 Hz), 7.35 (1H, dd, J = 8, 6 Hz), 7.72 (1H, s), 7.95−8.05 (2H, m), 8.27 (1H, m, J = 6 Hz), 8.76 (1H, m), 8.95 (1H, s). Anal. ($C_{15}H_{14}N_3OCl$) C, H, N.

The following compounds (**51**−**55**) were prepared via vicarious nucleophilic substitution using 4-chlorophenoxyacetonitrile.[21]

Preparation of 5-Methoxy-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (51). 1-Methoxy-4-nitro-2-(trifluoromethyl)benzene. Sodium (11.8 g, 0.512 mol) was dissolved in dry methanol (1 L), and to the resulting solution was added a solution of 1-chloro-4-nitro-2-(trifluoromethyl)-benzene (96.2 g, 0.427 mol) in methanol (100 mL). The reaction mixture was refluxed for 3 h, then cooled, and evaporated in vacuo. The residue was partitioned between water (500 mL) and dichloromethane (3 × 400 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (93.8 g, 99%) as a white solid. NMR ($CDCl_3$) δ: 4.05 (3H, s), 7.12 (1H, d, J = 9 Hz), 8.45 (1H, dd, J = 3, 9 Hz), 8.52 (1H, d, J = 3 Hz).

[5-Methoxy-2-nitro-4-(trifluoromethyl)phenyl]acetonitrile. A mixture of 1-methoxy-4-nitro-2-(trifluoromethyl)-benzene (93.0 g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.6 g, 0.463 mol) in dry DMF (500 mL) was added dropwise over 0.75 h to a stirred solution of KO^{t}Bu (103.9 g, 0.927 mol) in dry DMF (400 mL) at −10 °C.[21] After complete addition the resulting purple solution was maintained at −10 °C for 1 h and then poured into a mixture of ice/water (1.5 L) and 5 M aqueous HCl (1.5 L). The resulting mixture was extracted with dichloromethane (3 × 1 L). The combined extracts were washed with water (3 L), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel using 10−40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallized from ethyl acetate/petroleum ether to afford the title compound (85.1 g, 78%) as a white solid, mp 103−104 °C. NMR ($CDCl_3$) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

5-Methoxy-6-(trifluoromethyl)indole. [5-Methoxy-2-nitro-4-(trifluoromethyl)phenyl]aceonitrile (85.0 g, 0.327 mol) in ethanol/water (9:1, 1.6 L) and glacial acetic acid (16 mL) were hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature.[22] The reaction mixture was filtered and evaporated in vacuo. The residue was partitioned between aqueous K_2CO_3 (1 L) and dichloromethane (2 × 1 L), and the combined organic extract was dried (Na_2SO_4) and evaporated to afford the title indole (67.6 g, 96%) as a gray solid, mp 104 °C. NMR ($CDCl_3$) δ: 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

5-Methoxy-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)-indoline (51). The indole (67.6 g, 0.637 mol) was treated with sodium cyanoborohydride (40 g, 0.637 mol) in glacial acetic acid (500 mL) as in the method described for **12** to afford 5-methoxy-6-(trifluoromethyl)indoline (67.7 g, 99%) as an off-white solid, mp 83 °C. NMR ($CDCl_3$) δ: 3.07 (2H, t, J = 8 Hz), 3.58 (2H, t, J = 8 Hz), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s). This indoline (67.7 g, 0.312 mol) was treated with 3-pyridyl isocyanate according to the general method described for **6** and the crude product was recrystallized from ethanol/dichloromethane to give the title compound **51** (67.2 g, 64%) as a white crystalline solid, mp 265−267 °C. On partial evaporation of the mother liquors, a second crop (12 g, 11%) was obtained, mp 263−265 °C. NMR (DMSO-d_6) δ: 3.29 (2H, t, J = 8 Hz), 3.87 (3H, s), 4.20 (2H, t, J = 8 Hz), 7.23 (1H, s), 7.34 (1H, dd, J = 4, 7 Hz), 8.00 (1H, d, J = 7 Hz), 8.13 (1H, s), 8.24 (1H, d, J = 4 Hz), 8.73 (1H, m), 8.78 (1H, s). Anal. ($C_{16}H_{14}F_3N_3O_2$) C, H, N.

Reacting 1-chloro-4-nitro-2-(trifluoromethyl)benzene with the appropriate alkoxide salt and following the same procedures as detailed for **51**, the following compounds were prepared.

5-Ethoxy-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)-indoline (52): recrystallized from ethanol as a white crystalline solid (81%), mp 258−259 °C. NMR (DMSO-d_6) δ: 1.32 (3H, t, J = 7 Hz), 3.26 (2H, t, J = 8 Hz), 4.11 (2H, q, J = 7 Hz), 4.18 (2H, t, J = 8 Hz), 7.21 (1H, s), 7.34 (1H, dd, J = 4, 7 Hz), 7.99 (1H, d, J = 7 Hz), 8.12 (1H, s), 8.24 (1H, d, J = 4 Hz), 8.72 (1H, m), 8.76 (1H, s). Anal. ($C_{17}H_{16}N_3O_2F_3$) C, H, N.

5-Isopropoxy-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (53): recrystallized from ethanol/diethyl ether as a white crystalline solid (58%), mp 237 °C. NMR (DMSO-d_6) δ: 1.27 (6H, d, J = 7 Hz), 3.26 (2H, t, J = 8 Hz), 4.18 (2H, t, J = 8 Hz), 4.69 (1H, sept, J = 7 Hz), 7.23 (1H, s), 7.32 (1H, dd, J = 4, 7 Hz), 7.98 (1H, d, J = 7 Hz), 8.08 (1H, s), 8.22 (1H, d, J = 4 Hz), 8.72 (1H, m), 8.77 (1H, s). Anal. ($C_{18}H_{18}F_3N_3O_2$) C, H, N.

5-(Cyclopropylmethoxy)-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (54): recrystallized from methanol/diethyl ether as a white solid (33%), mp 224−225 °C. NMR ($CDCl_3$) δ: 0.32−0.48 (2H, m), 0.55−0.64 (2H, m), 1.20−1.33 (1H, m), 3.28 (2H, t, J = 7 Hz), 3.85 (2H, d, J = 7 Hz), 4.12 (2H, t, J = 7 Hz), 6.51 (1H, s), 6.82 (1H, s), 7.21−7.30 (1H, m), 8.02−8.11 (1H, m), 8.20 (1H, s), 8.28−8.32 (1H, m), 8.43−8.48 (1H, m). MS: m/e 377.1362 (M^+), $C_{19}H_{18}N_3O_2F_3$ requires 377.1351.

5-Methoxy-6-(pentafluoroethyl)-1-(3-pyridylcarbamoyl)-indoline (55). 2-Bromo-4-nitroanisole (3.5 g, 0.015 mol) was treated with sodium pentafluoropropionate[28] (5.2 g, 0.028 mol)

and copper(I) iodide (5.7 g, 0.030 mol) in dry DMF (70 mL) and toluene (25 mL) at 120 °C with removal of the toluene by means of a Dean−Stark trap.[24] The reaction mixture was then heated to 155 °C for 6 h. After cooling to ambient temperature, the mixture was poured into H_2O (100 mL) and diethyl ether (100 mL) and filtered through Kieselguhr. The filtrate was separated and the organic layer washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to leave a brown oil which was purified by flash column chromatography on silica gel to afford 1-methoxy-4-nitro-2-(pentafluoroethyl)benzene (1.9 g, 47%) as a yellow oil. NMR ($CDCl_3$) δ: 4.02 (3H, s), 7.14 (1H, d, $J = 9$ Hz), 8.44 (1H, d, $J = 8$ Hz), 8.47 (1H, s). This anisole was subjected to the same procedures as detailed for the preparation of **51** to give the title compound **55** which was recrystallized from ethanol/dichloromethane as a white crystalline solid (47%), mp 255 °C dec. NMR (DMSO-d_6) δ: 3.28 (2H, t, $J = 9$ Hz), 3.83 (3H, s), 4.20 (2H, t, $J = 9$ Hz), 7.26 (1H, s), 7.35 (1H, q, $J = 4$, 8 Hz), 7.98 (1H, m), 8.10 (1H, s), 8.25 (1H, dd, $J = 3$, 5 Hz), 8.73 (1H, d, $J = 3$ Hz), 8.79 (1H, s). MS: m/e 387.0988 (M^+), $C_{17}H_{14}N_3O_2F_5$ requires 387.1006.

The following 5-thioalkyl compounds were prepared via thiocyanation of the appropriately substituted indoline.

Preparation of 5-(Methylthio)-6-(trifluoromethyl)-indoline. Method a. 5-(Thiocyanato)-6-(trifluoromethyl)indoline. A mixture of 6-(trifluoromethyl)indoline[32] (9.7 g, 52 mmol) and potassium thiocyanate (10.09 g, 104 mmol) in methanol (200 mL) was treated with a solution of bromine (2.82 mL, 55 mmol) in methanol (35 mL) dropwise over 0.5 h at −5−0 °C.[23] The reaction mixture was allowed to warm to room temperature, stirred overnight, and then evaporated to dryness. The residue was partitioned between aqueous K_2CO_3 (100 mL) and dichloromethane (3 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel using 2−30% ethyl acetate/petroleum ether as eluant to afford the title compound (9.1 g, 72%) as a yellow solid. NMR ($CDCl_3$) δ: 3.12 (2H, t, $J = 8$ Hz), 3.72 (3H, t, $J = 8$ Hz), 4.23 (1H, br s), 6.89 (1H, s), 7.50 (1H, s).

Bis[5-[6-(trifluoromethyl)indolinyl]] Disulfide. The thiocyanate (28.5 g, 0.116 mol) in dioxane (200 mL) and water (100 mL) was treated with aqueous ammonia (880, 200 mL) at 90 °C for 1 h.[24] The mixture was cooled and evaporated to give a residue which was partitioned between water (300 mL) and dichloromethane (4 × 300 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give the title compound (25.5 g, 100%) as a yellow solid. NMR ($CDCl_3$) δ: 3.03 (2H, t, $J = 8$ Hz), 3.67 (2H, t, $J = 8$ Hz), 4.00 (1H, br s), 6.80 (1H, s), 7.49 (1H, s).

Bis[5-[1-Acetyl-6-(trifluoromethyl)indolinyl]] Disulfide. The disulfide (26 g, 0.119 mol) in dichloromethane (300 mL) and triethylamine (47.3 mL, 0.339 mol) was treated dropwise with a solution of acetic anhydride (22.5 mL, 0.238 mol) in dichloromethane (50 mL) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 1 h, and then poured into 2.5 M aqueous HCl (400 mL). The organic layer was separated, and the aqueous was further extracted with dichloromethane (200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (29.1 g, 94%) as a yellow solid. NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.21 (2H, t, $J = 8$ Hz), 4.10 (2H, t, $J = 8$ Hz), 7.68 (1H, s), 8.47 (1H, s).

1-Acetyl-5-mercapto-6-(trifluoromethyl)indoline. A mixture of the diacetyl disulfide (28.5 g, 54.8 mmol), triphenylphosphine (20.9 g, 79.5 mmol), and concentrated aqueous HCl (1 mL) in dioxane (300 mL) and water (75 mL) was heated at reflux for 1.5 h.[25] The reaction mixture was cooled and evaporated to a residue which was partitioned between dichloromethane (300 mL) and 1% aqueous NaOH (300 mL). The organic phase was further extracted with 1% aqueous NaOH (200 mL), and the combined aqueous fractions were carefully acidified and extracted with dichloromethane (3 × 300 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the title compound (26 g, 91%) as a yellow solid. NMR ($CDCl_3$) δ: 2.24 (3H, s), 3.20 (2H, t, $J = 8$ Hz), 3.68 (1H, m), 4.11 (2H, t, $J = 8$ Hz), 7.22 (1H, s), 8.51 (1H, s).

1-Acetyl-5-(methylthio)-6-(trifluoromethyl)indoline. A mixture of the thiol (26 g, 99 mmol), anhydrous K_2CO_3 (15.1 g,109 mmol), and iodomethane (18.6 mL, 300 mmol) in dry DMF (500 mL) was heated at 80 °C for 1 h. The reaction mixture was cooled, evaporated in vacuo, and partitioned between water (200 mL) and dichloromethane (3 × 200 mL). The combined organics were washed with water (400 mL), dried (Na_2SO_4), and evaporated to yield the title compound (26.3 g, 97%) as a yellow oil. NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.49 (3H, s), 3.24 (2H, t, $J = 8$ Hz), 4.12 (2H, t, $J = 8$ Hz), 7.23 (1H, s), 8.51 (1H, s).

5-(Methylthio)-6-(trifluoromethyl)indoline. The acetylindoline (26.3 g, 95 mmol) was treated with NaOH (30 g, 750 mL) in water (150 mL) and ethanol (200 mL) at reflux for 1.5 h. The reaction mixture was cooled and diluted with water (200 mL) and most of the ethanol evaporated in vacuo. The remaining aqueous mixture was extracted with dichloromethane (3 × 200 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to afford the title compound (21.9 g, 99%) as a yellow oil. NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.07 (2H, t, $J = 8$ Hz), 3.63 (2H, t, $J = 8$ Hz), 3.90 (1H, br s), 6.88 (1H, s), 7.30 (1H, s).

Preparation of 5-(Methylthio)-6-(trifluoromethyl)-indoline. Method b. A stirred solution of potassium thiocyanate (38.6 g, 0.39 mol) in methanol (470 mL) at −2 °C under argon was treated dropwise over 10 min with bromine (10.3 mL, 0.195 mol) giving a yellow precipitate. The reaction mixture was stirred at 0 °C for a further 15 min, then treated with a solution of 6-(trifluoromethyl)indoline (33.2 g, 0.177 mol) in methanol (320 mL), and allowed to warm to room temperature and stir for 4 h. A solution of potassium hydroxide (49.5 g, 0.88 mol) in water (300 mL) was added in one portion, causing the temperature to rise to 43 °C and a brown solution to be produced. The mixture was stirred at 43−45 °C for 25 min, then cooled to 12 °C, and treated with iodomethane (10.9 mL, 0.177 mol). The resulting mixture was allowed to warm to room temperature, stirred for 1.5 h, and then concentrated in vacuo to ca. 350 mL volume. The residual aqueous mixture was extracted with dichloromethane (2 × 400 mL) and the combined extract dried (Na_2SO_4) and concentrated in vacuo to give a brown oil (43 g), which was chromatographed on silica gel eluting with dichloromethane to afford the title compound as a light-brown low-melting solid (25.3 g, 61%) with spectral properties identical to those described above.

5-(Methylthio)-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (46). A solution of nicotinic acid azide (15.3 g, 103 mmol) [**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 are 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.] in toluene (300 mL) was heated at reflux for 0.5 h to form 3-pyridyl isocyanate, then cooled to room temperature, and treated with the indoline (21.9 g, 0.4 mmol) as in the preparation of **6**. The resulting precipitate was filtered off and recrystallized from methanol/dichloromethane to afford the title compound **46** (27.2 g, 82%) as a white solid, mp 262−264 °C. NMR (DMSO-d_6) δ: 2.50 (3H, s), 3.28 (2H, t, $J = 8$ Hz), 4.21 (2H, t, $J = 8$ Hz), 7.33 (1H, dd, $J = 4$, 7 Hz), 7.47 (1H, s), 7.98 (1H, d, $J = 7$ Hz), 8.21 (1H, s), 8.24 (1H, d, $J = 4$ Hz), 8.73 (1H, m), 8.84 (1H, s). MS: m/e 353 (M^+). Anal. ($C_{16}H_{14}F_3N_3OS$) C, H, N.

By reacting 1-acetyl-5-mercapto-6-(trifluoromethyl)indoline with the appropriate alkyl halide according to the same procedures as detailed for **46**, the following final compounds were prepared.

5-(Ethylthio)-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (47): recrystallized from ethanol/diethyl ether as a white crystalline solid (68%), mp 246−247 °C. NMR (DMSO-d_6) δ: 1.20 (3H, t, $J = 7$ Hz), 2.99 (2H, q, $J = 7$ Hz), 3.28 (2H, t, $J = 8$ Hz), 4.22 (2H, t, $J = 8$ Hz), 7.34 (1H, dd, $J = 4$, 7 Hz),

7.55 (1H, s), 7.99 (1H, d, J = 7 Hz), 8.23 (1H, s), 8.24 (1H, d, J = 4 Hz), 8.73 (1H, m), 8.87 (1H, s). Anal. ($C_{17}H_{16}F_3N_3SO$) C, H, N.

5-(Propylthio)-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (48): recrystallized from ethanol/diethyl ether as a white crystalline solid (56%), mp 240−243 °C. NMR (DMSO-d_6) δ: 0.96 (3H, t, J = 7 Hz), 1.57 (2H, m, J = 7 Hz), 2.96 (2H, t, J = 7 Hz), 3.29 (2H, t, J = 8 Hz), 4.22 (2H, t, J = 8 Hz), 7.33 (1H, dd, J = 4, 7 Hz), 7.55 (1H, s), 7.99 (1H, d, J = 7 Hz), 8.22 (1H, s), 8.25 (1H, d, J = 4 Hz), 8.73 (1H, m), 8.86 (1H, s). Anal. ($C_{18}H_{18}N_3F_3SO$) C, H, N.

5-(Isopropylthio)-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (49): recrystallized from ethanol/diethyl ether to yield a white crystalline solid (60%), mp 234−237 °C. NMR (DMSO-d_6) δ: 1.22 (6H, d, J = 7 Hz), 3.28 (2H, t, J = 8 Hz), 3.47 (1H, m, J = 7 Hz), 4.23 (2H, t, J = 8 Hz), 7.33 (1H, dd, J = 4, 7 Hz), 7.60 (1H, s), 7.99 (1H, d, J = 7 Hz), 8.23 (1H, s), 8.24 (1H, d, J = 4 Hz), 8.73 (1H, m), 8.86 (1H, s). Anal. ($C_{18}H_{18}N_3F_3SO$) C, H, N.

Starting from 6-bromoindoline or 6-iodoindoline and following the same procedures as described for **46**, the following final compounds were prepared.

6-Bromo-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (43): recrystallized from ethanol to afford a white crystalline solid (71%), mp 242−244 °C. NMR (DMSO-d_6) δ: 2.47 (3H, s), 3.19 (2H, t, J = 8 Hz), 4.18 (2H, t, J = 8 Hz), 7.19 (1H, s), 7.34 (1H, dd, J = 4, 7 Hz), 7.97 (1H, d, J = 7 Hz), 8.09 (1H, s), 8.24 (1H, d, J = 4 Hz), 8.73 (1H, m), 8.81 (1H, s). MS: m/e 363.0020 (M^+), $C_{15}H_{14}N_3OBrS$ requires 363.0041.

6-Iodo-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (45): recrystallized from ethanol to afford a white crystalline solid (53%), mp 235−237 °C. NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.18 (2H, t, J = 8 Hz), 4.13 (2H, t, J = 8 Hz), 7.15 (1H, s), 7.32 (1H, dd, J = 4, 7 Hz), 7.97 (1H, d, J = 7 Hz), 8.24 (1H, d, J = 4 Hz), 8.42 (1H, s), 8.70 (1H, m), 8.78 (1H, s). MS: m/e 410.9912 (M^+), $C_{15}H_{14}N_3OIS$ requires 410.9902.

6-Cyano-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (32). 6-Iodo-5-(methylthio)-1-(3-pyridylcarbamoyl)indoline (**45**) (0.19 g, 0.46 mmol) and copper(I) cyanide (0.086 g, 0.96 mmol) were heated together in DMF (10 mL) at 150 °C for 1 h.[27] The mixture was cooled, poured into 2 N aqueous ammonium hydroxide (100 mL), and extracted with EtOAc (3 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give a residue which was purified by chromatography to affford a white crystalline solid (14%), mp 228−229 °C. NMR (DMSO-d_6) δ: 2.49 (3H, s), 3.31 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 7.35 (1H, m), 7.45 (1H, s), 8.00 (1H, m), 8.08 (1H, s), 8.26 (1H, d), 8.74 (1H, m), 8.90 (1H, s). MS: m/e 311 (MH^+).

5-(Methylthio)-6-(pentafluoroethyl)-1-(3-pyridylcarbamoyl)indoline (56). 1-Acetyl-6-bromo-5-(methylthio)indoline (2.5 g, 0.0087 mol) was dissolved in dry DMF (40 mL) and toluene (15 mL) under argon. Sodium pentafluoropropionate (3.0 g, 0.016 mol) and copper(I) iodide (3.3 g, 0.017 mol) were added, and the mixture was heated to 120 °C with removal of the toluene by means of a Dean−Stark trap.[24] The reaction mixture was then heated to 155 °C for 6 h. After cooling to ambient temperature, the mixture was poured into H_2O (100 mL) and diethyl ether (100 mL) and filtered through Kieselgühr. The filtrate was separated and the organic layer washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to leave an orange solid. This was purified by flash column chromatography on silica gel eluting with 2% methanol in dichloromethane to give 1-acetyl-5-(methylthio)-6-(pentafluoroethyl)indoline (0.62 g, 22%) as a pale-yellow solid. NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.46 (3H, s), 3.26 (2H, t, J = 8 Hz), 4.11 (2H, t, J = 8 Hz), 7.22 (1H, s), 8.44 (1H, s). The indoline was converted to the title compound according to the procedures detailed for **46** to give the title compound **56** as a white solid (74%), mp 227 °C dec. NMR (DMSO-d_6) δ: 2.50 (3H, s), 3.30 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 7.32 (1H, dd, J = 4, 7 Hz), 7.56 (1H, s), 8.00 (1H, d, J = 7 Hz), 8.13 (1H, s), 8.23 (1H, d, J = 4 Hz), 8.71 (1H, m), 8.75−8.99 (1H, br s). MS: m/e 403.0790 (M^+), $C_{17}H_{14}F_5N_3OS$ requires 403.0778.

5-(Methylthio)-1-(3-pyridylcarbamoyl)-6-(trifluoromethoxy)indoline (33). 3-(Trifluoromethoxy)aniline was converted to 6-(trifluoromethoxy)indoline by the Norlander procedure[18] as described for **8** followed by sodium cyanoborohydride reduction as described for **12**. Treatment of this indoline with potassium thiocyanate and bromine followed with aqueous potassium hydroxide and methyl iodide as in the procedure described for the preparation of **46** (method b) afforded 5-(methylthio)-6-(trifluoromethoxy)indoline which was converted to the title compound **33** as in the preparation of **6** to give a white solid (39%), mp 264−267 °C (Et_2O/CH_2Cl_2). NMR (DMSO-d_6) δ: 2.46 (3H, s), 3.22 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 7.25−7.39 (2H, m), 7.89 (1H, d, J = 2 Hz), 8.00 (1H, dd, J = 2, 7 Hz), 8.26 (1H, dd, J = 2, 5 Hz), 8.73 (1H, d, J = 2 Hz), 8.83 (1H, s). Anal. ($C_{16}H_{14}F_3N_3O_2S$) C, H, N.

5-(Methylthio)-1-(3-pyridylcarbamoyl)indoline (11). Starting with indoline and following the same procedures as described for **46**, the title compound **11** was prepared (77%) as a white solid, mp 160−162 °C (50% aqueous ethanol). NMR (DMSO-d_6) δ 2.44 (3H, s), 3.18 (2H, t, J = 8 Hz), 4.15 (2H, t, J = 8 Hz), 7.08 (1H, d, J = 7 Hz), 7.19 (1H, s), 7.33 (1H, dd, J = 7, 5 Hz), 7.82 (1H, d, J = 7 Hz), 7.98 (1H, d, J = 7 Hz), 8.22 (1H, d, J = 5 Hz), 8.74 (1H, s). Anal. ($C_{15}H_{15}N_3OS$) C, H, N.

The following compounds were prepared by alkylation of the corresponding thiol or alcohol.

5-Bromo-6-(methylthio)-1-(3-pyridylcarbamoyl)indoline (24). 1-Acetyl-6-mercaptoindoline[38] was alkylated with methyl iodide as in the preparation of **46**. The resulting 1-acetyl-6-(methylthio)indoline (2.4 mmol) was taken up in $CHCl_3$ (50 mL) and treated with bromine (2.6 mmol) in $CHCl_3$ (1 mL) at 0 °C. After complete addition the reaction mixture was heated to reflux for 4 h, then cooled, and poured into aqueous Na_2SO_3. The organics were separated to give, after drying and removal of solvent, 1-acetyl-5-bromo-6-(methylthio)indoline (98%). Heating with aqueous sodium hydroxide hydrolyzed the acetyl group to afford the indoline which was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **24** as a white solid (72%), mp >220 °C. NMR (DMSO-d_6) δ: 2.4 (3H, s), 3.2 (2H, t, J = 8 Hz), 4.2 (2H, t, J = 8 Hz), 7.3 (1H, m), 7.4 (1H, s), 7.9 (1H, s), 8.0 (1H, m), 8.2 (1H, m), 8.7 (1H, m) 8.8 (1H, s). MS: m/e 363.0033 (M^+), $C_{15}H_{14}N_3OBrS$ requires 363.0041.

6-Bromo-5-methoxy-1-(3-pyridylcarbamoyl)indoline (44). 1-Acetyl-6-bromo-5-hydroxyindoline[39] was alkylated with sodium hydride and methyl iodide as in the preparation of **46**. Hydrolysis of the acetyl group and treatment of the resultant indoline with 3-pyridyl isocyanate as in the preparation of **6** gave the title compound **44** as a white solid (43%), mp 238−240 °C. ^{1}H NMR (DMSO-d_6) δ: 3.18 (2H, t, J = 8 Hz), 3.80 (3H, s), 4.15 (2H, t, J = 8 Hz), 7.07 (1H, s), 7.32 (1H, dd, J = 2, 7 Hz), 7.96 (1H, dd, J = 2, 7 Hz), 8.06 (1H, s), 8.22 (1H, d, J = 5 Hz), 8.72 (2H, m). ^{13}C NMR (DMSO-d_6) δ: 27.5, 47.6, 56.3, 107.9, 109.7, 118.5, 123.1, 127.2, 132.0, 136.2, 137.7, 141.9, 143.4, 150.6, 152.2. MS: m/e 348/350 (MH^+). MS: m/e 347.0274 (M^+), $C_{15}H_{14}N_3O_2Br$ requires 347.0269.

The following compounds (**14, 19**) were prepared via reduction of the corresponding isatins.[29]

4,5-Dichloro-1-(3-pyridylcarbamoyl)indoline (14). 4,5-Dichloroisatin (8.4 g, 0.039 mol)[40] was treated with lithium aluminum hydride (15.0 g, 0.390 mol) in THF (500 mL) under reflux. Aqueous workup and treatment of the intermediate hydroxyindoline compound with *p*-toluenesulfonic acid in toluene gave 4,5-dichloroindole (1.34 g, 19%). NMR ($CDCl_3$) δ: 6.60−6.70 (1H, m), 7.19−7.35 (3H, m), 8.10−8.45 (1H, br s). This was reduced to the indoline using sodium cyanoborohydride as for **12.** NMR ($CDCl_3$) δ: 3.10 (2H, t, J = 8 Hz), 3.61 (2H, t, J = 8 Hz), 3.76−3.91 (1H, br s), 6.41 (1H, d, J = 10 Hz), 7.10 (1H, d, J = 10 Hz). This indoline was converted directly to the title compound **14** as in the preparation of **6** to give a white solid (25%), mp >240 °C. NMR (DMSO-d_6) δ:

3.28 (2H, t, J = 8 Hz), 4.21 (2H, t, J = 8 Hz), 7.30−7.42 (2H, m), 7.80 (1H, d, J = 8 Hz), 7.92−7.98 (1H, m), 8.20−8.24 (1H, m), 8.72 (1H, s), 8.82 (1H, s). MS: m/e 307.0275 (M^+), $C_{14}H_{11}N_3OCl_2$ requires 307.0279.

6,7-Dichloro-1-(3-pyridylcarbamoyl)indoline (19): prepared from 6,7-dichloroisatin[40] following the procedures described above for **14** as a white solid (46% from indoline, 19% overall), mp 178−180 °C. NMR (DMSO-d_6) δ: 3.11 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 7.21−7.35 (3H, m), 7.89−7.94 (1H, m), 8.09−8.12 (1H, m), 8.70 (1H, s), 9.68 (1H, s). MS: m/e 307.0274 (M^+), $C_{14}H_{11}N_3OCl_2$ requires 307.0279.

The following compounds (**31, 50**) were prepared via bromination and Stille coupling of 6-(trifluoromethyl)indoline with (1-ethoxyvinyl)tributyl tin.

5-Bromo-6-(trifluoromethyl)indoline. A stirred solution of 6-(trifluoromethyl)indoline (3.0 g, 0.016 mol) in dry DMF (30 mL) at −5 °C under argon was treated dropwise over 30 min with a solution of freshly recrystallized *N*-bromosuccinimide (3.03 g, 0.017 mol) in dry DMF (15 mL). After complete addition the reaction mixture was stirred at 0 °C for a further 20 min, then poured into cold 10% aqueous Na_2CO_3 solution (100 mL), and extracted with ethyl acetate (100 mL). The extract was washed with water (3 × 100 mL) to remove any DMF, then dried, and concentrated under vacuum to leave a brown oil which was chromatographed on silica gel eluting with 40% ether/60−80 petroleum ether. The first product to elute was 7-bromo-6-(trifluoromethyl)indoline (1.0 g), followed by the title compound (1.5 g, 35%) as a brown oil. NMR ($CDCl_3$) δ: 3.07 (2H, t, J = 8 Hz), 3.63 (2H, t, J = 8 Hz), 6.88 (s, 1H), 7.35 (s, 1H).

5-Acetyl-6-(trifluoromethyl)indoline. A stirred solution of 5-bromo-6-(trifluoromethyl)indoline (1.5 g, 5.6 mmol) in toluene (70 mL) under argon was treated with (1-ethoxyvinyl)-tributyl tin (2.0 g, 5.6 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (120 mg).[30] The mixture was then heated under reflux for 28 h, then cooled, diluted with ether (70 mL), washed with 1% Na_2CO_3 solution, then dried, and concentrated under vacuum. The residue was treated with a mixture of 2 M HCl acid (10 mL) and THF (30 mL) and stirred vigorously at room temperature for 1 h. The reaction mixture was concentrated to remove the THF and the residual acid solution diluted with water (30 mL), then basified with K_2CO_3, and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried and concentrated and the residue chromatographed on silica gel eluting with 1:1 ether/60−80 petroleum ether to afford the required product (0.75 g, 58%) as a light-brown solid. NMR ($CDCl_3$) δ: 2.52 (3H, s), 3.10 (2H, t, J = 8 Hz), 3.70 (2H, t, J = 8 Hz), 4.20 (1H, br s), 6.84 (1H, s), 7.33 (1H, s).

5-Isopropenyl-6-(trifluoromethyl)indoline. A mixture of 5-acetyl-6-(trifluoromethyl)indoline (0.36 g, 1.6 mmol), triethylamine (0.25 mL, 1.8 mmol), and di-*tert*-butyl dicarbonate (0.37 g, 1.7 mmol) in toluene (10 mL) was heated under reflux for 4 h. The cooled solution was treated with 10% aqueous Na_2CO_3 solution (25 mL) and extracted with ethyl acetate (50 mL). The extract was dried and concentrated and the residue chromatographed on silica gel eluting with 1:1 ether/60−80 petroleum ether to give the *N*-Boc-5-acetyl-6-(trifluoromethyl)-indoline (0.3 g, 58%) as a beige solid. NMR ($CDCl_3$) δ: 1.60 (9H, s), 2.55 (3H, s), 3.17 (2H, t, J = 8 Hz), 4.07 (2H, t, J = 8 Hz), 7.28 (1H, s), 8.20 (1H, br s). A stirred solution of the *N*-Boc-5-acetylindoline (0.36 g, 1.1 mmol) in dry ether (15 mL) at 0 °C under argon was treated with a 3 M solution of methylmagnesium bromide in ether (0.55 mL, 1.6 mmol). A yellow precipitate was immediately formed. The reaction mixture was allowed to warm to room temperature over 1.5 h and then added to excess 2 M HCl acid with efficient stirring. The aqueous mixture was basified with aqueous K_2CO_3 and extracted with ethyl acetate. The extract was dried and concentrated to leave a yellow oil, which was dissolved in dichloromethane (10 mL) and treated with trifluoroacetic acid (3 mL) for 1 h at room temperature. The reaction mixture was treated with excess 10% aqueous Na_2CO_3 solution and extracted with dichloromethane (100 mL). The extract was dried and concentrated to leave an orange solid which was chromatographed on silica gel eluting with 25% ether/60−80 petroleum ether to afford the title compound (0.1 g, 40%) as the first component to elute. NMR ($CDCl_3$) δ: 2.03 (3H, s), 3.04 (2H, t, J = 8 Hz), 3.30−3.75 (1H, br), 3.61 (2H, t, J = 8 Hz), 4.84 (1H, s), 5.14 (1H, s), 6.84 (1H, s), 6.97 (1H, s).

5-Isopropyl-6-(trifluoromethyl)indoline. A solution of 5-isopropenyl-6-(trifluoromethyl)indoline (0.1 g, 0.46 mmol) in ethanol (30 mL) was hydrogenated over 10% Pd−C (50 mg) at atmospheric temperature and pressure for 2 h. The catalyst was removed by filtration through Kieselgühr and the filtrate concentrated under vacuum to give a residue which was chromatographed on silica gel eluting with 25% ether/petroleum ether to yield the title compound (0.08 g, 80%) as a colorless oil. NMR ($CDCl_3$) δ: 1.21 (6H, d, J = 6 Hz), 3.05 (2H, t, J = 8 Hz), 3.24 (1H, septet, J = 6 Hz), 3.58 (2H, t, J = 8 Hz), 3.80 (1H, br s), 6.82 (1H, s), 7.20 (1H, s).

5-Isopropyl-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)indoline (50). 5-Isopropyl-6-(trifluoromethyl)indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **50** as a white solid (33%), mp 210−211 °C (ethyl acetate/petroleum ether). NMR ($CDCl_3$) δ: 1.23 (6H, d, J = 7 Hz), 3.30 (2H, t, J = 8 Hz), 3.32 (1H, m), 4.15 (2H, t, J = 8 Hz), 6.69 (1H, s), 7.27 (2H, m), 8.09 (1H, m), 8.21 (1H, s), 8.32 (1H, m), 8.48 (1H, m). MS: m/e 349 (M^+). Anal. ($C_{18}H_{18}N_3OF_3$) C, H, N.

5-Acetyl-1-(3-pyridylcarbamoyl)-6-(trifluoromethyl)-indoline (31). 5-Acetyl-6-(trifluoromethyl)indoline was treated with 3-pyridyl isocyanate as in the preparation of **6** to give the title compound **31** as a white solid (37%), mp 238−240 °C (chloroform). NMR ($CDCl_3$) δ: 2.57 (3H, s), 3.38 (2H, t, J = 8 Hz), 4.28 (2H, t, J = 8 Hz), 7.42 (1H, dd, J = 5, 7 Hz), 7.57 (1H, s), 8.08 (1H, m, J = 7 Hz), 8.27 (1H, m, J = 5 Hz), 8.34 (1H, s), 8.72 (1H, m). MS: m/e 349.1025 (M^+), $C_{17}H_{14}N_3O_2F_3$ requires 349.1038.

mCPP-Induced Hypolocomotion. Rats were placed in a room adjacent to the experimental room on the day of the procedure. They were dosed orally 1 h before the locomotion test with test compound or vehicle and injected ip 20 min before the test with mCPP or saline, in groups of 4. Rats were returned to their home cages after dosing. At 0 h, they were each placed in automated locomotor activity cages, made in black perspex with a clear perspex lid and sawdust-covered floor, under red light for 10 min. During this time, locomotion was recorded by means of consecutively breaking two photocell beams traversing opposite ends of the box (for full details, see ref 4).

Geller−Seifter Test. A colony of rats (male, Sprague−Dawley) were housed in pairs under a 12-h light/dark cycle and fed restricted diet to maintain their body weight to 80% of a free-feeding animal. The rats were trained initially in a typical operant box to associate pressing of a lever with a food pellet reward. As training progressed, the rats were introduced to a multiple schedule of reinforcement, i.e., five 3-min variable interval components (one reinforcement every 10−50 s (mean 30), VI30) alternating with five 3-min fixed ratio (one reinforcement every five lever presses, FR5) components. The FR component was signalled to the rat by a light above the lever, and in this component reinforcement was contingent with a footshock pulse width of 15 ms, at intervals of 200 ms for 1 s. The magnitude of the footshock was individually titrated for each rat up to a maximum of 0.75 mA, to give a lever-pressing rate of between two and seven reinforcements during each of the five, 3-min punished responding periods. Fully trained rats also had a high level of responding in the VI phases (typically 180 presses in 3 min) to detect nonspecific effects such as sedation or stimulant properties. Before use, all rats had met specific performance criteria and had shown a significant positive response to a reference anxiolytic drug (e.g., chlordiazepoxide). For full details, see ref 4d.

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