Synthesis, Biological Activity, and Molecular Modeling Studies of Selective 5-HT$_{2C/2B}$ Receptor Antagonists

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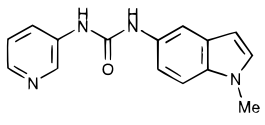
The synthesis and biological activity are reported for a series of analogues of the previously published indole urea **2** (SB-206553), designed to probe the 5-HT$_{2C}$ receptor binding site. Small molecule modeling studies have been used to define a region in space which is allowed at the 5-HT$_{2C}$ receptor but disallowed at the 5-HT$_{2A}$ receptor. In a complementary approach, docking of **2** into our model of the 5-HT$_{2C}$ receptor has allowed us to propose a novel primary binding interaction for this series of diaryl ureas, involving a potential double hydrogen-bonding interaction between the urea carbonyl oxygen of the ligand and two serine residues in the receptor. The difference of two valine residues in the 5-HT$_{2C}$ receptor for leucine residues in the 5-HT$_{2A}$ receptor is believed to account for the observed 5-HT$_{2C}$/5-HT$_{2A}$ selectivity with **2**.

5-Hydroxytryptamine (5-HT, serotonin) is an important neurotransmitter in the central nervous system (CNS).[1] Dysfunction of the 5-HT system has been implicated in various psychiatric and other CNS disorders such as anxiety, depression, panic attacks, and migraine, and these conditions can be treated by pharmacological intervention with modulators of 5-HT receptor function. The study of 5-HT receptors has been revolutionized in recent years by molecular biological techniques, with seven classes of receptors now identified (5-HT$_1$−5-HT$_7$) and numerous subclasses.[2] The 5-HT$_2$ family of receptors consists of three subtypes, namely, 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$, which have been grouped together on the basis of molecular sequence, secondary-messenger system, and operational profile.[3] Sequence analysis indicates approximately 80% amino acid identity in the transmembrane regions of these three subtypes, and it is 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.

We have recently reported the syntheses of pyridylurea **1** (SB-200646A)[4] and the more potent conformationally restricted analogue **2** (SB-206553)[5] as the first 5-HT$_{2C/2B}$ receptor antagonists with selectivity over the closely related 5-HT$_{2A}$ site. Our interest in the 5-HT$_{2C}$



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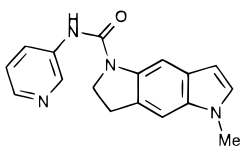

2

receptor developed from literature reports that the selective 5-HT$_{2C/2B}$ receptor agonist (*m*-chlorophenyl)-piperazine causes anxiety both in animal models[6] and in humans.[7] This has been attributed to stimulation of 5-HT$_{2C/2B}$ receptors and implies that selective 5-HT$_{2C/2B}$ receptor antagonists might be useful anxiolytic agents.[8] Indeed, compound **2** exhibits significant anxiolytic activity in three animal models of anxiety, which strengthens our hypothesis that blockade of 5-HT$_{2C/2B}$ receptors causes anxiolysis.[9] Our previous work[4] on modifications to structure **1** established that the optimum position of attachment of the urea group was at the 5-position of the indole ring and at the 3-position of the pyridine. We now report the synthesis and structure-activity relationships (SAR) of a number of analogues of **2** designed to probe the size and shape of the receptor binding pocket, along with our receptor modeling studies.

Chemistry

The indolyl ureas **2** and **3** were prepared as previously reported.[5] Compounds **4** and **5** were prepared as shown in Scheme 1. 1-Acetyl-6-aminoindoline (**6**) was alkylated with bromoacetaldehyde diethyl acetal to give **7** which was then cyclized in refluxing TFAA/TFA[5] to afford a 4:1 mixture of **8** and **9**. These compounds were separated by chromatography, and each was subjected to the sequence of hydrolysis, N-methylation, and hydrolysis, as detailed in Scheme 1, to give the tricyclic intermediates **10** and **11**. Conversion to the ureas **4** and **5** was achieved by treatment with 3-pyridyl isocyanate. The indolyl urea **12** was prepared as shown in Scheme 2. 1-Methyl-6-nitroindole (**13**) was reacted with (4-chlorophenoxy)acetonitrile[10] to afford regioselectively the 7-cyanomethyl derivative **14** which was converted to the corresponding methyl ester **15**. Treatment of **15** with $LiAlH_4$ afforded the alcohol **16** which was converted to its mesylate **17**. Hydrogenation of **17** effected reduction of the nitro group and concomitant cyclization to the tricyclic **18**. Treatment of **18** with 3-pyridyl isocyanate provided the urea **12**.

N-Alkylated analogues of **2** were prepared by either of two routes. In the first approach (Scheme 3), alkylation of the tricyclic intermediate **19**[5] afforded the *N*-alkyl derivatives **20** which were deprotected to give the indolines **21**. Reaction with 3-pyridyl isocyanate afforded the desired ureas **22**−**24**. Alternatively, the *N*-acetyl intermediate **19** was hydrolyzed to the unsubstituted tricycle **25** (Scheme 4) which was reacted with

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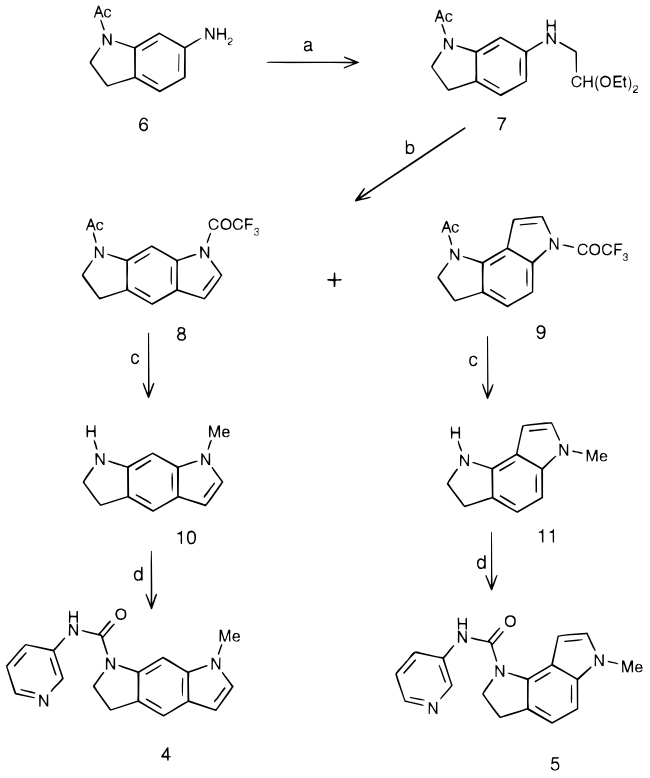
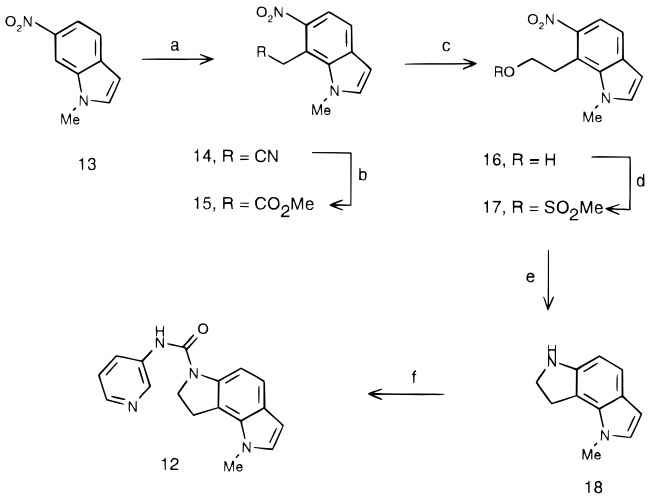
Scheme 1. Synthesis of *N*-Methylindoles **4** and **5**[a]



[a] Reagents: (a) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF, 100 °C, 18 h (40%); (b) TFAA, TFA, reflux, 66 h; (c) (i) K_2CO_3, MeOH, 1 h, (ii) NaH, MeI, DMF, 2 h, (iii) 10% aqueous NaOH, EtOH, reflux, 2 h; (d) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 1 h.

Scheme 2. Synthesis of *N*-Methylindole **12**[a]

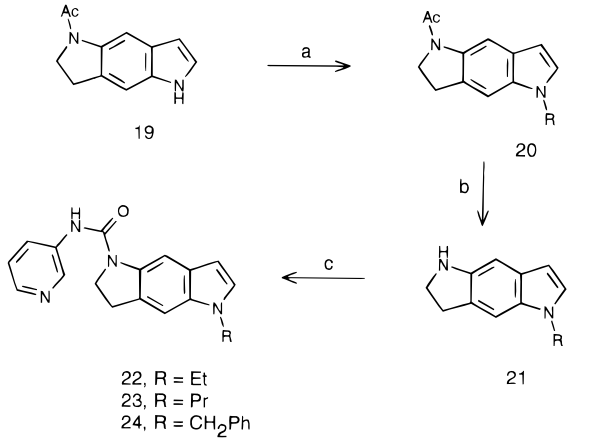


[a] Reagents: (a) 4-ClPhOCH$_2$CN, KO^{t}Bu, DMF, 0 °C, 15 min (78%); (b) (i) $SOCl_2$, MeOH, reflux, 100 h, (ii) 10% aqueous NaOH, EtOH, 3 h, (iii) $SOCl_2$, MeOH, reflux, 2 h (42% overall); (c) $LiAlH_4$, THF, 10 min (47%); (d) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 30 min (64%); (e) EtOH, H_2, 5% Pd−C, 2 h (85%); (f) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 1 h (57%).

3-pyridyl isocyanate to give the urea **26**. Regioselective alkylation at the 5-position was achieved by treatment with excess sodium hydride and 2-iodopropane to afford **27**.

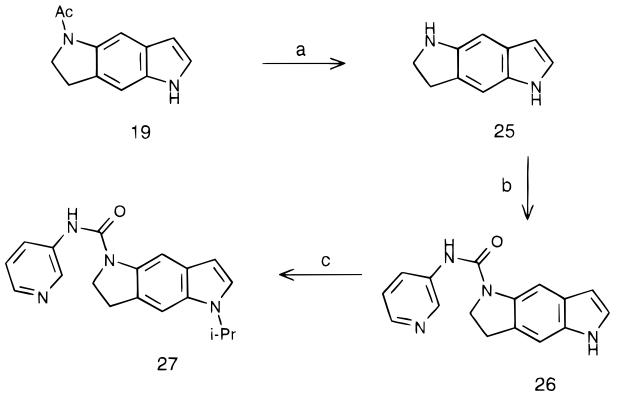
Synthesis of the 5,6-dimethyl analogue **33** was achieved as shown in Scheme 5. 1-Acetyl-5-aminoindoline (**28**) was alkylated with 2,3-dichloroprop-1-ene to give **29**, which was then reductively alkylated with formaldehyde to **30**. Thermal rearrangement[11] of **30**

Scheme 3. Synthesis of N-Alkylated Indoles **22**−**24**[a]



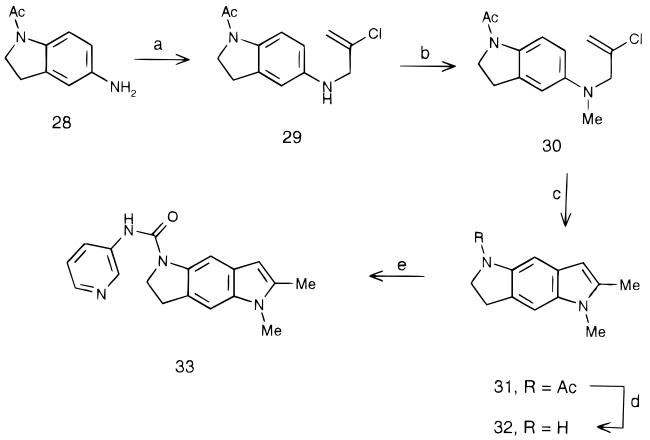
[a] Reagents: (a) NaH, RBr or RI, DMF, 1−18 h (79−99%); (b) 10% aqueous NaOH, EtOH, reflux, 8 h (68−98%); (c) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (70−83%).

Scheme 4. Synthesis of Indoles **26** and **27**[a]



[a] Reagents: (a) 10% aqueous NaOH, EtOH, reflux, 8 h (89%); (b) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (80%); (c) NaH, ^{i}PrI, DMF, 24 h (35%).

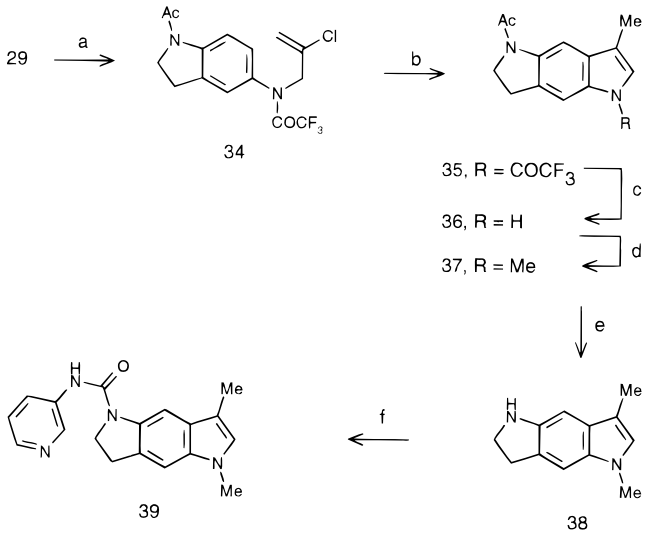
Scheme 5. Synthesis of Indole **33**[a]



[a] Reagents: (a) $ClCH_2C(Cl)=CH_2$, K_2CO_3, DMF, 70 °C, 16 h (92%); (b) CH_2O, $NaBH_4$, THF, <20 °C, 15 min (100%); (c) polyphosphoric acid, 140 °C, 24 h (12%); (d) 10% aqueous NaOH, EtOH, reflux, 8 h (60%); (e) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (39%).

followed by intramolecular electrophilic cyclization afforded the linear tricyclic ring system **31**, albeit in low yield. Hydrolysis of the *N*-acetyl group in **31** to **32** followed by treatment with 3-pyridyl isocyanate afforded the desired product **33**.

Scheme 6. Synthesis of Indole **39**[a]



[a] Reagents: (a) TFAA, CH_2Cl_2, NEt_3, 1 h (95%); (b) polyphosphoric acid, 140 °C, 1.5 h (7%); (c) K_2CO_3, MeOH, 30 min (91%); (d) NaH, MeI, DMF, 24 h (79%); (e) 10% aqueous NaOH, EtOH, reflux, 8 h (60%); (f) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (42%).

Synthesis of the 5,7-dimethyl derivative **39** (Scheme 6) started with the intermediate **29**. Conversion of **29** to the trifluoroacetamide **34** followed by electrophilic cyclization[12] gave the tricyclic system of **35**. Hydrolysis of **35** to **36** and subsequent *N*-methylation provided the intermediate **37**. Deacetylation of **37** gave the indoline **38** which was reacted with 3-pyridyl isocyanate to give the urea **39**.

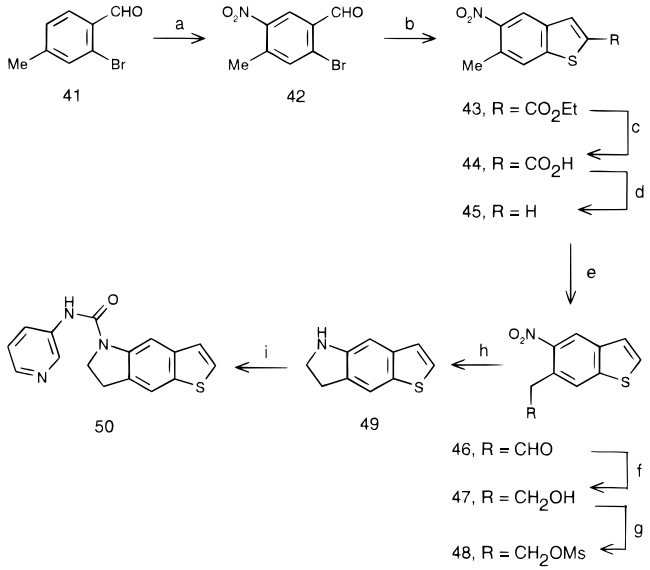
Compounds in Table 3 were prepared by several different methods. Reduction of **2** with sodium cyanoborohydride afforded the reduced indoline **40**. The preparation of the benzothiophene **50** is summarized in Scheme 7. Nitration of the aldehyde **41** gave a mixture of nitrated products from which **42** was isolated by recrystallization. Reaction of **42** with ethyl thioglycolate under basic conditions[13] afforded the benzothiophene **43**, which was converted to **45** via decarboxylation of the corresponding carboxylic acid **44**. Enamine formation from **45** using Leimgruber's conditions[14] followed by acid hydrolysis provided the aldehyde **46**, which was reduced to the alcohol **47** and converted to the mesylate **48**. Reduction of the nitro group in **48** with concomitant cyclization afforded the desired tricyclic intermediate **49** which was converted to the urea **50** by treatment with 3-pyridyl isocyanate.

The synthesis of the furan **58** is shown in Scheme 8. 6-Nitroindoline (**51**) was converted to the trifluoroacetamide **52**, which was then reduced to the aniline **53**. Diazotization of **53** followed by treatment with aqueous acid afforded the phenol **54**. Alkylation of **54** with chloroacetone provided the ether **55** which was cyclized to the tricyclic intermediate **56** by treatment with concentrated sulfuric acid.[15] Hydrolysis of **56** to **57** followed by reaction with 3-pyridyl isocyanate afforded the desired product **58**.

Results and Discussion

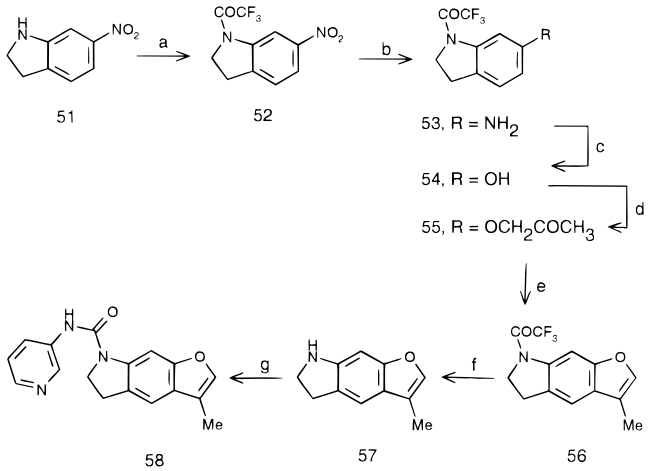
The affinity of compounds for the 5-HT_{2A} receptor was determined in rat frontal cortex preparations using [^{3}H]-ketanserin as radioligand in binding studies, for the 5-HT_{2B} receptor from the inhibition of 5-HT-induced

Scheme 7. Synthesis of Benzothiophene **50**[a]



[a] Reagents: (a) concentrated H_2SO_4, concentrated HNO_3, <15 °C (63%); (b) $HSCH_2CO_2Et$, NaOEt, EtOH, reflux, 3 h (96%); (c) NaOH, EtOH, reflux, 3 h (96%); (d) quinoline, Cu, 190 °C, 3 h (89%); (e) (i) DMFDMA, DMF, pyrrolidine, (ii) 5 M HCl, reflux, 30 min (78%); (f) $NaBH_4$, EtOH, 1 h (98%); (g) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 1 h (88%); (h) EtOAc, H_2, 10% Pd−C, Et_3N, 1.5 h (100%); (i) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (83%).

Scheme 8. Synthesis of Benzofuran **58**[a]

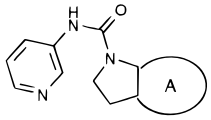


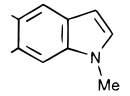
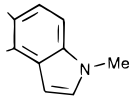
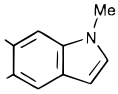
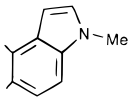
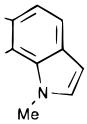
[a] Reagents: (a) TFAA, CH_2Cl_2, NEt_3, 1 h (93%); (b) EtOH, H_2, 5% Pd−C, 4 h (99%); (c) concentrated H_2SO_4, $NaNO_2$, aqueous $CuSO_4$, reflux, 5 min (67%); (d) K_2CO_3, $ClCH_2COCH_3$, DMF, 64 h (97%); (e) concentrated H_2SO_4, 0 °C, 15 min (21%); (f) NaOH, EtOH, 15 min (96%); (g) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (59%).

contractions of the rat stomach fundus, and for the 5-HT_{2C} receptor using binding to rat cloned 5-HT_{2C} receptors expressed in HEK 293 cells and [^{3}H]mesulergine as the radioligand.[4] It should be noted that the 5-HT_{2B} receptor affinities are based on functional data, and caution should be exercised when making comparisons with data from the receptor binding assays (5-HT_{2A} and 5-HT_{2C}).

We have previously reported compound **2** (SB-206553) as a selective 5-$HT_{2C/2B}$ receptor antagonist with ≥100-fold selectivity over the closely related 5-HT_{2A} receptor.[5] The angular indole isomer **3** was also found to possess reasonable affinity at the 5-HT_{2C} and 5-HT_{2B} receptors. Encouraged by these results, we have extended our initial study with the synthesis of a range of pyrrole ring

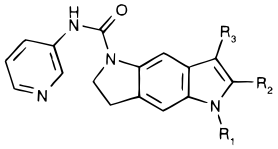
Table 1. 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptor Binding Affinities of Indole Analogues[a]



compound	A	pK$_i$, 5-HT$_{2A}$[b]	pA$_2$, 5-HT$_{2B}$[c]	pK$_i$, 5-HT$_{2C}$[d]	sel 5-HT$_{2C/2A}$
2		6.3	8.5	8.3	100
3		5.7	7.8	7.6	80
4		-	-	5.9	-
5		-	-	6.7	-
12		5.5	-	7.2	50

[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 (rat frontal cortex, [^{3}H]ketanserin). [c] Binding affinity (rat stomach fundus, inhibition of 5-HT). [d] Binding affinity (rat clones expressed in HEK 293 cells, [^{3}H]mesulergine).

Table 2. 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptor Binding Affinities of Indole Analogues[a]



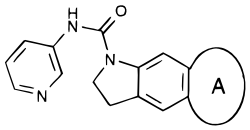
compd	R$_1$	R$_2$	R$_3$	pK_i, 5-HT$_{2A}$[b]	pA_2, 5-HT$_{2B}$[c]	pK_i, 5-HT$_{2C}$[d]	sel 5-HT$_{2C/2A}$
2	Me	H	H	6.3	8.5	8.3	100
26	H	H	H	5.8	7.5	6.9	13
22	Et	H	H	5.9	8.0	8.1	160
23	Pr	H	H	5.5	8.1	7.9	250
27	^{i}Pr	H	H	5.4	8.2	8.0	400
24	CH_2Ph	H	H	<5.2	6.7	7.3	>130
33	Me	Me	H	5.5	7.7	7.4	80
39	Me	H	Me	5.5	8.2	6.9	25

[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 (rat frontal cortex, [^{3}H]ketanserin). [c] Binding affinity (rat stomach fundus, inhibition of 5-HT). [d] Binding affinity (rat clones expressed in HEK 293 cells, [^{3}H]mesulergine).

isomers (Table 1) designed to investigate the tolerance of steric bulk at various positions around the rigid aromatic ring system and also the effects of altering the electrostatic potential orientation around the indole ring. From Table 1, it can be seen that the [2,3-*f*] isomer **2** is the most potent in this series and has 100-fold 5-HT$_{2C}$/5-HT$_{2A}$ selectivity. The [3,2-*e*], [2,3-*g*], and [2,3-*e*] isomers **3**, **5**, and **12** all possess weaker affinity at the 5-HT$_{2C}$ receptor having pK_i's between 0.7 and 1.6 log units less than **2**. In contrast, the linear [3,2-*f*] isomer **4** is over 100-fold less potent at the 5-HT$_{2C}$ receptor compared with **2**.

Since the linear [2,3-*f*] isomer **2** is the most potent and most selective analogue, we decided to further explore the structure−affinity relationships in this specific isomeric series, with respect to the substitution on the pyrrole ring. Removal of the *N*-methyl group in **2** to give **26** (Table 2) led to significant loss in 5-HT$_{2C}$ and 5-HT$_{2B}$ receptor affinity, suggesting the presence of a lipophilic pocket in these receptors accommodating the *N*-methyl substituent. Alternatively, the presence of the polar indole NH may be detrimental to binding. The *N*-ethyl, *N*-propyl, and *N*-isopropyl analogues **22, 23**, and **27** all retained a similar 5-HT$_{2C}$ receptor affinity to that for **2**, with a trend toward increasing 5-HT$_{2C}$/5-HT$_{2A}$ selectivity as size increases. The *N*-benzyl analogue **24** however showed a reduction in affinity at the 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors and more noticeably at the 5-HT$_{2B}$ receptor indicating a limit to the size of this binding pocket in these receptors. We have further probed the size of this lipophilic pocket with the synthesis of the 5,6- and 5,7-dimethyl analogues **33** and **39**. In both cases, a drop in 5-HT$_{2C}$ receptor affinity and selectivity was observed which was more apparent

Table 3. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} Receptor Binding Affinities of Indole Isosteres[a]



compound	A	pK_i, 5-HT_{2A}[b]	pA_2, 5-HT_{2B}[c]	pK_i, 5-HT_{2C}[d]	sel 5-$HT_{2C/2A}$
40		5.3	7.9	7.2	80
50		6.6	8.0	8.1	30
58		6.4	8.9	8.6	160

[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 (rat frontal cortex, [^{3}H]ketanserin). [c] Binding affinity (rat stomach fundus, inhibition of 5-HT). [d] Binding affinity (rat clones expressed in HEK 293 cells, [^{3}H]mesulergine).

with **39**. However it is interesting to note that the 5-HT_{2B} receptor affinity of **39** is relatively unaffected by this variation. Clearly, these results indicate subtle differences between the 5-HT_{2C} and 5-HT_{2B} receptors.

Compound **2** has been shown to have anxiolytic activity in three animal models of anxiety.[9] However, **2** undergoes metabolic *N*-demethylation in the rat to afford **26** as the principal metabolite. Unfortunately **26** is less potent and less selective than **2**, and there was evidence that **26** was present in significant quantities in the brain.[16] In order to obviate this problem, we undertook the synthesis of several indole isosteres lacking a pyrrole *N*-methyl group (Table 3) as potentially metabolically stable analogues of **2**.

The reduced indole **40** was found to be less potent at the 5-HT_{2C} receptor than **2** by a factor of 10, perhaps due to the presence of the more polar indoline nitrogen. Of more interest was the benzothiophene **50** which retained high affinity at the 5-HT_{2C} and 5-HT_{2B} receptors but unfortunately had increased affinity at the 5-HT_{2A} receptor resulting in only 30-fold 5-HT_{2C}/5-HT_{2A} selectivity. This confirms the earlier results, with compound **26** and others, that steric bulk around the indole nitrogen in **2** is important for enhanced 5-HT_{2C}/5-HT_{2A} selectivity (see modeling section later). Accordingly, we synthesized the inverted furan **58** which possesses a potentially metabolically more stable *C*-methyl substituent in the same area as the *N*-methyl substituent in **2**. As predicted, **58** demonstrated both high 5-HT_{2C} and 5-HT_{2B} receptor affinity, along with 160-fold selectivity over the 5-HT_{2A} receptor.

***In Vivo* Evaluation.** We have previously reported the ID_{50} of **2** (5.5 mg/kg po) in an *in vivo*, centrally mediated assay of 5-HT_{2C} receptor function, the reversal of *m*-CPP-induced hypolocomotion in the rat.[5] Compounds **22** and **27,** which retained good *in vitro* activity, were slightly less potent with ID_{50}'s of 15 and 11 mg/kg po, respectively. However, metabolic dealkylation of **22** and **27** remained a problem[16] despite the increased steric hindrance in **27**. The benzothiophene **50** had an ID_{50} of 1.5 mg/kg po representing the most potent compound *in vivo* in this series. Rather disappointingly, it was found that the more selective benzofuran **58** possessed an ID_{50} of 17 mg/kg po. However, after iv administration, **58** was significantly more potent with an ID_{50} of 0.1 mg/kg, which compares favorably with an ID_{50} of 0.3 mg/kg iv for compound **2**, suggesting that the poor oral bioavailability of **58** may be due to lack of efficient gut absorption or extensive first-pass metabolism.

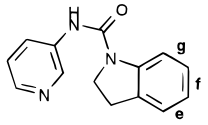


Figure 1. Pharmacophore for 5-$HT_{2C/2B}$ receptor affinity.

Molecular Modeling Studies. Our aim in the ligand modeling studies was to use the "active analogue approach" developed by Marshall[17] and to overlap common structural features of both active and inactive analogues to gain information about the steric requirements at the 5-HT_{2C} receptor. Compounds were overlapped by superimposing the urea functional group in all compounds and using low-energy conformations where appropriate. Our working hypothesis is based on the assumption that weakly active compounds have substituents in sterically disallowed areas. Data from Table 1 indicate that with respect to 5-HT_{2C} receptor affinity, pyrrole ring fusion is tolerated across the *e* bond of the indoline ring system in both orientations and across the *f* bond in only one of the two possible orientations (Figure 1). From the compounds reported in Tables 1−3, along with other published derivatives,[18] we were able to define an allowed volume at the 5-HT_{2C} receptor (Figure 2; shown in green) by overlapping structures with a p$K_i \geq 7.5$. The pyridine ring has been excluded from this calculation because of a large number of low-energy conformations. This allowed volume should be similar to the size and shape of the binding pocket. By also modeling compounds with a low 5-HT_{2A} receptor affinity (p$K_i < 5.5$), we were able to define on the surface of the 5-HT_{2C} allowed volume a disallowed area at the 5-HT_{2A} receptor (Figure 2, shown in pink). The use of this model in the design of potent and selective 5-HT_{2C} receptor antagonists will be the subject of a future publication. In a complementary approach, we sought to confirm these results by considering in more detail how our series of diaryl ureas may be interacting at the molecular level with the 5-HT_{2C} and 5-HT_{2A} receptors.

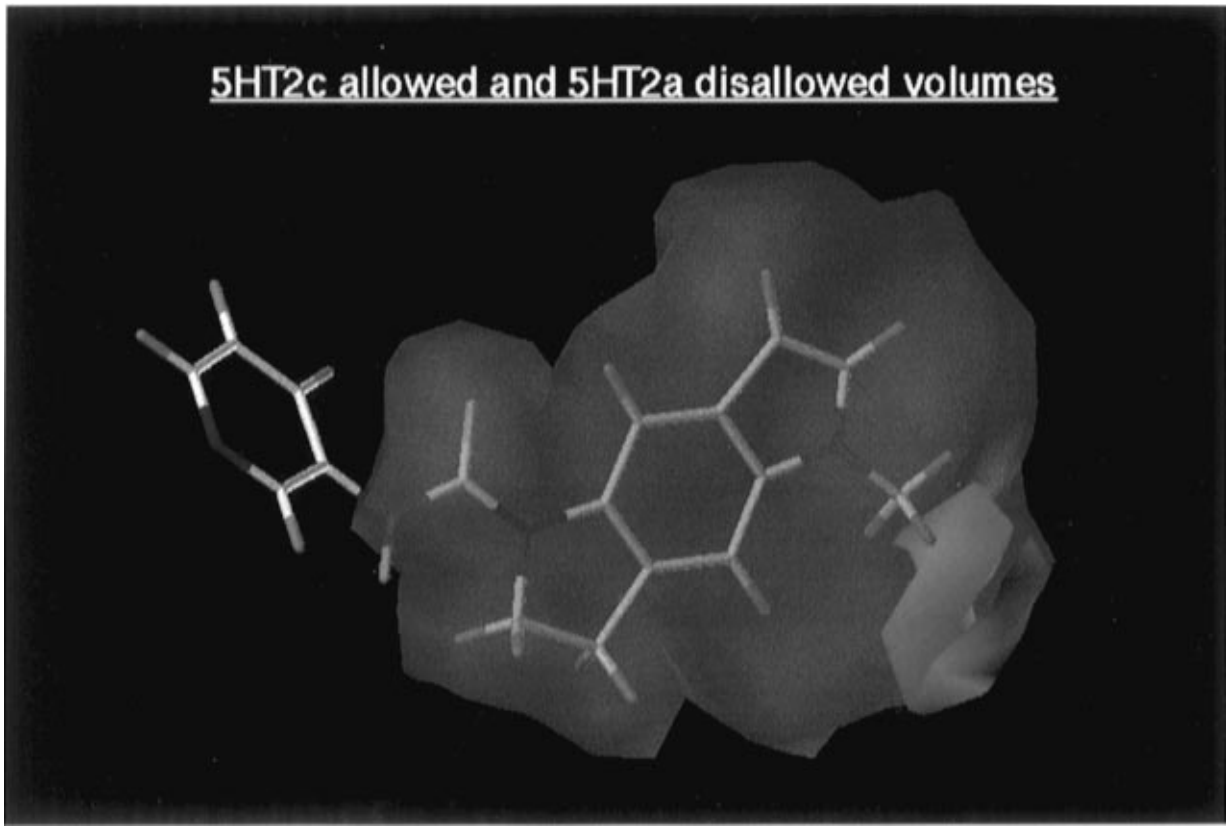


Figure 2. 5-HT$_{2C}$ allowed (green) and 5-HT$_{2A}$ disallowed (pink) volumes viewed around the structure of compound **2**.

Construction of the 5-HT$_{2C}$ Receptor Model. The serotonin 5-HT$_{2C}$ receptor sequence[19] was obtained from the Swissprot database using the GCG software. A combination of hydropathic analysis using Kyte−Doolittle parameters and sequence alignments with other related 5-HT receptors was used to identify the putative transmembrane regions. The receptor model was generated with the transmembrane regions only, using the GPCR_Builder program[20] with its built-in standard cationic neurotransmitter template. This template is based very loosely on the conformation of the helix bundle of bacteriorhodopsin. The inward faces of the helices were determined by a Fourier transform of the periodicity of conservation taken from a multiple-sequence alignment (Clustal W[21]) of all mammalian 5-HT receptors. This procedure has been described in detail by Donnelly et al.[22] The ends of each helix were capped with *N*-methyl amides at the C-termini and acetamido groups at the *N*-termini. The backbone dihedrals of this model were constrained to the conformation of an "idealized" α-helix[23] in a hydrophobic environment but using weaker (10%) constraints on the proline ϕ angles. Minimization was performed with 5000 steps of conjugate gradient and 5000 ABNR using the CHARMm[24] program. The dihedral constraints were gradually weakened with continuous minimization, and eventually these were completely removed. The resulting model showed a completely acceptable backbone ϕ-ψ plot, and as expected, "kinks" were observed in the regions of the prolines.

Docking of Compound 2 (SB-206553) into the 5-HT$_{2C}$ Receptor. It is generally accepted[25,26] that the standard agonists and antagonists at 5-HT receptors bind their protonated amino sites to the highly conserved aspartate on transmembrane helix 3 (TM3). Compound **2** however does not have a strongly basic nitrogen (pK_a = 4.9), and an alternative binding mode was therefore sought. Although *ab initio* quantum calculations have shown that some rotation is allowed around the urea bonds, the molecule is essentially rigid, and its dimensions are such that it cannot fit in the "agonist" cavity between TM3 and TM5. Other modes of binding were examined, and on steric grounds, it seemed likely that **2** is aligned along the axes of the TM helices. SAR studies have shown that one essential feature of this series of compounds is the carbonyl group of the urea, and the receptor model was therefore examined for possible hydrogen bond donors. TM3 contains two serine residues on its interior face, one and two helical turns, respectively, below the conserved aspartate. Within 5-HT receptors, the former of these is only found in the 5-HT$_2$ subtypes and is one of the features that distinguishes the 5-HT$_2$ family from other 5-HT sequences.[27] As no binding has been observed of **2** to 5-HT$_1$ cloned receptors, it seemed likely that this serine (Ser-312[28]) might be a likely candidate as a hydrogen bond donor. Positioning the urea carbonyl in this pocket, it is possible to form two H-bonds with the serines, Ser-312 and Ser-315 (see Figure 3). The two aromatic regions of the molecule can now reside in well-defined hydrophobic pockets. The first of these is formed by a number of highly conserved aromatic residues on helices 5 and 6, in the general vicinity of Asp-308. These are Phe-508, Phe-616, Phe-617, and Trp-613. The second hydrophobic pocket is a long cavity bounded by His-318, Phe-609, Val-212, and Val-608. It was not possible at first to decide which aromatic system of **2** would dock into which pocket in the receptor. The ligand was therefore initially positioned in both orientations and energy minimized using the CHARMm pro-

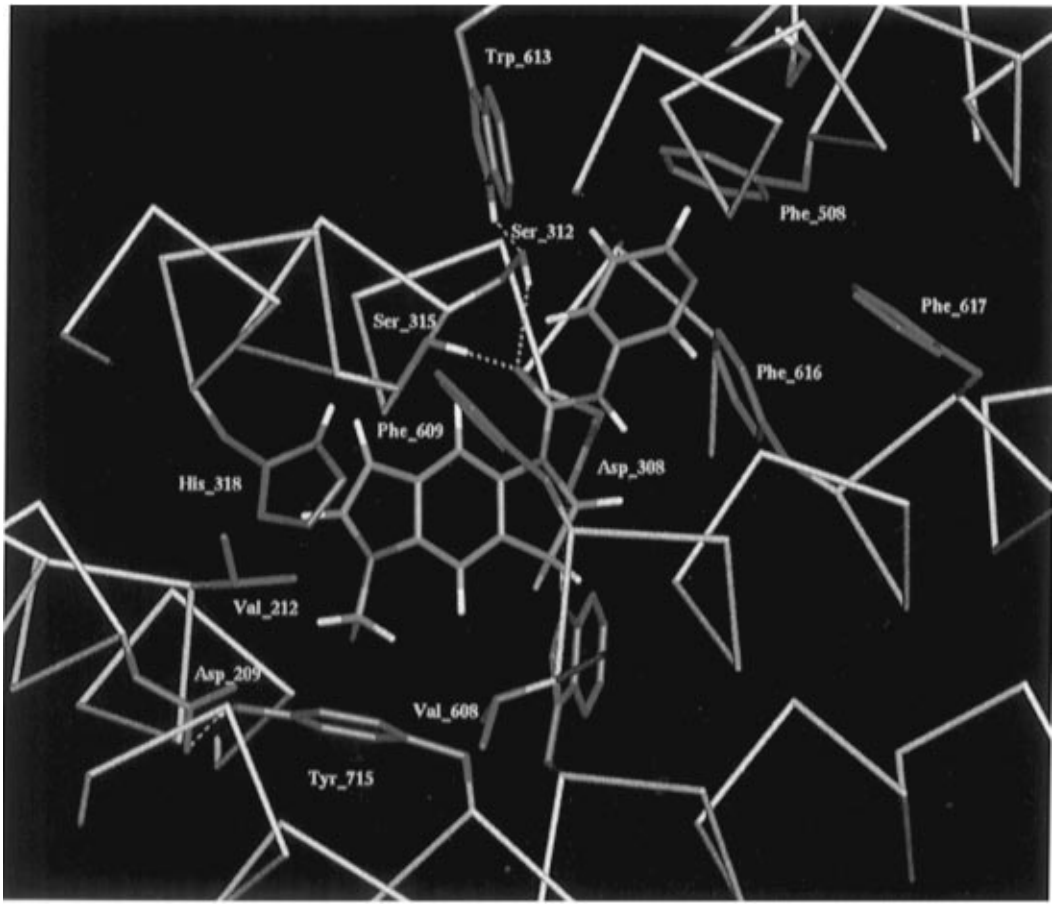


Figure 3. Structure **2** docked into the model of the 5-HT_{2C} receptor.

gram. From the resulting interaction energies, it was evident that **2** preferred to orient itself with the pyridine ring in the upper (first) hydrophobic pocket. This places the indole between the two valines on helices 2 and 6 (Val-212 and Val-608, see Figure 3). A study of the sequences of the mammalian 5-HT_2 receptors shows that these two residues are among the principal differences between 5-HT_{2A} and 5-HT_{2C}. Both residues are leucines in the 5-HT_{2A} sequence, thus constricting the pocket in this receptor. Binding is therefore less favorable in the 5-HT_{2A} receptor compared to the 5-HT_{2C} receptor, and these valine−leucine differences are therefore postulated as being the major reason for the observed selectivity. This result closely parallels the result from our small molecule modeling studies (above).

Summary

In conclusion, we report the synthesis and biological activity of a series of analogues of the previous lead indole urea **2**, designed to probe the 5-HT_{2C} receptor binding site. We have used small molecule modeling studies to define a region in space which is allowed at the 5-HT_{2C} receptor but disallowed at the 5-HT_{2A} receptor. Docking of **2** into our model of the 5-HT_{2C} receptor has allowed us to propose a novel primary binding interaction for this series of diaryl ureas, involving a double hydrogen-bonding interaction between the urea carbonyl oxygen of the ligand and two serine residues in the receptor. The difference of two valine residues in the 5-HT_{2C} receptor for leucine residues in the 5-HT_{2A} receptor is believed to account for the observed 5-HT_{2C}/5-HT_{2A} selectivity with **2**. Use of this model to design more potent and more selective antagonists for the 5-HT_{2C} receptor will be the subject of a future publication.

Experimental Section

NMR spectra were determined using Bruker AC-200 or AC-250 spectrometers. Electron impact mass spectra were determined using a Fisons VG 302 single quadrupole mass spectrometer. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. 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. Organic extracts were dried over anhydrous sodium sulfate before evaporation at reduced pressure. Chromatography was performed on Merck Art. 7734 silica gel or Fluka silica gel 60 (60739).

***N*-(1-Acetyl-6-indolinyl)-2,2-diethoxyethylamine (7).** A mixture of 1-acetyl-6-aminoindoline (**6**) (9.5 g, 54 mmol), bromoacetaldehyde diethyl acetal (8.9 mL, 59 mmol), and potassium carbonate (11.1 g) in DMF (100 mL) was heated at 100 °C for 18 h. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, and evaporated to give a gray solid. Chromatography on silica gel using 0−100% ethyl acetate/chloroform followed by 4% methanol/ethyl acetate afforded **7** (6.1 g, 39%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.26 (6H, t, J = 9 Hz), 2.21 (3H, s), 3.09 (2H, t, J = 9 Hz), 3.26 (2H, d, J = 8 Hz), 3.5−3.8 (4H, m), 4.03 (2H, d, J = 9 Hz), 4.68 (1H, t, J = 8 Hz), 6.32 (1H, m), 6.97 (1H, d, J = 9 Hz), 7.68 (1H, m).

1-Acetyl-7-(trifluoroacetyl)-1,2,3,7-tetrahydropyrrolo-[3,2-*f*]indole (8) and 1-Acetyl-6-(trifluoroacetyl)-1,2,3,6-tetrahydropyrrolo[2,3-*g*]indole (9). The acetal **7** (7.1 g, 24

mmol) was added to a mixture of trifluoroacetic anhydride (35 mL) and trifluoroacetic acid (85 mL) and heated under reflux for 66 h. After cooling, the solution was evaporated to dryness and chromatographed on silica gel eluting with 0−60% ethyl acetate/chloroform to give as a faster running band the angular isomer **9** (1.3 g, 18%) as an impure product (MS *m/e* 296 (M^+)), which was used without further purification, and as a slower running band the linear isomer **8** (5.1 g, 71%): ^{1}H NMR (DMSO-d_6) δ 2.32 (3H, s), 3.28 (2H, t, J = 9 Hz), 4.20 (2H, t, J = 9 Hz), 7.30 (1H, d, J = 9 Hz), 7.47 (1H, m), 7.76 (1H, m), 8.21 (1H, d, J = 9 Hz); MS *m/e* 296 (M^+).

7-Methyl-1,2,3,7-tetrahydropyrrolo[3,2-*f*]indole (10). The linear isomer **8** (5.1 g, 17 mmol) was stirred in methanol (50 mL) containing potassium carbonate (3.6 g) for 1 h. The mixture was diluted with water (500 mL) and the crude product filtered off. The solid was resuspended in ethanol (20 mL) and stirred as 10% aqueous sodium hydroxide (3 mL) was added. After 1 h, the mixture was diluted with water (200 mL), and the solid was filtered and dried to afford 1-acetyl-1,2,3,7-tetrahydropyrrolo[3,2-*f*]indole (1.6 g, 45%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.15 (3H, s), 3.18 (2H, t, J = 9 Hz), 4.10 (2H, t, J = 9 Hz), 6.28 (1H, m), 7.20 (1H, m), 7.31 (1H, s), 8.18 (1H, s), 10.92 (1H, s).

This material was added to a stirred suspension of 80% sodium hydride (0.31 g, 10.3 mmol) in DMF (20 mL) under argon. After stirring for 30 min, methyl iodide (0.73 mL, 11.7 mmol) was added dropwise. The mixture was stirred for 1 h and then diluted with water (200 mL). The resultant solid was filtered off and dried to afford 1-acetyl-7-methyl-1,2,3,7-tetrahydropyrrolo[3,2-*f*]indole (1.5 g, 91%): ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s), 3.27 (2H, t, J = 9 Hz), 3.78 (3H, s), 4.11 (2H, t, J = 9 Hz), 6.37 (1H, d, J = 3 Hz), 6.98 (1H, d, J = 3 Hz), 7.35 (1H, s), 8.29 (1H, s); MS *m/e* 214 (M^+).

This material (0.82 g, 3.8 mmol) was added to a mixture of ethanol (5 mL) and 10% aqueous sodium hydroxide (20 mL), and the solution was heated under reflux for 32 h. After cooling, the solution was diluted with water (50 mL) and extracted with ethyl acetate. The organic layer was dried and evaporated to afford **10** (0.6 g, 90%) as a black oil: ^{1}H NMR ($CDCl_3$) δ 3.10 (2H, t, J = 9 Hz), 3.59 (2H, t, J = 9 Hz), 3.67 (3H, s), 6.31 (1H, d, J = 3 Hz), 6.57 (1H, s), 6.82 (1H, d, J = 3 Hz), 7.31 (1H, s).

7-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,7-tetrahydropyrrolo[3,2-*f*]indole (4). Nicotinoyl azide[4] (**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 quantities of nitrogen are rapidly evolved. Appropriate precautions for the storage and utilization of this reagent are strongly advised.) (0.57 g, 3.9 mmol) in dry toluene (10 mL) was heated under reflux for 1 h and allowed to cool to room temperature. This solution was added to a stirred solution of the amine **10** (0.60 g, 3.5 mmol) in dichloromethane (10 mL). After stirring for 1 h, the precipitate was filtered off and dried to afford **4** (0.40 g, 43%) as a light pink solid: mp 207−211 °C; ^{1}H NMR (DMSO-d_6) δ 3.31 (2H, t, J = 9 Hz), 3.77 (3H, s), 4.25 (2H, t, J = 9 Hz), 6.33 (1H, d, J = 3 Hz), 7.22 (1H, d, J = 3 Hz), 7.40 (2H, m), 8.00 (1H, s), 8.10 (1H, m), 8.29 (1H, m), 8.75 (1H, s), 8.84 (1H, d, J = 2 Hz); MS *m/e* 292 (M^+). Anal. ($C_{17}H_{16}N_4O$) C, H, N.

6-Methyl-1,2,3,6-tetrahydropyrrolo[2,3-*g*]indole (11). The crude linear isomer **9** (1.3 g, 4.4 mmol) was stirred in methanol (20 mL) containing potassium carbonate (0.92 g) for 1 h. The mixture was diluted with water (200 mL) and the crude product filtered off to afford 1-acetyl-1,2,3,6-tetrahydropyrrolo[2,3-*g*]indole (0.5 g, 60%) as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.21 (3H, s), 3.12 (2H, t, J = 9 Hz), 4.11 (2H, t, J = 9 Hz), 6.84 (1H, m), 6.95 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 9 Hz), 7.18 (1H, m); MS *m/e* 200 (M^+).

This material was added to a stirred suspension of 80% sodium hydride (0.11 g, 3.7 mmol) in DMF (10 mL) under argon. After stirring for 30 min, methyl iodide (0.25 mL, 4.0 mmol) was added dropwise. The mixture was stirred for 1 h and then diluted with water (50 mL). The resultant solid was filtered off and dried to afford 1-acetyl-6-methyl-1,2,3,6-tetrahydropyrrolo[2,3-*g*]indole (0.41 g, 71%): ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 3.22 (2H, t, J = 9 Hz), 3.78 (3H, s), 4.16 (2H, t, J = 9 Hz), 6.95−7.10 (4H, m); MS *m/e* 214 (M^+).

This material was added to a mixture of ethanol (5 mL) and 10% aqueous sodium hydroxide (20 mL) and the solution heated under reflux for 2 h. After cooling, the solution was diluted with water (50 mL) and extracted with ethyl acetate. The organic layer was dried and evaporated to afford **11** (0.31 g, 91%) as a brown oily solid: ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, t, J = 9 Hz), 3.69 (2H, t, J = 9 Hz), 3.74 (3H, s), 6.29 (1H, d, J = 3 Hz), 6.74 (1H, d, J = 9 Hz), 6.93 (1H, d, J = 3 Hz), 7.07 (1H, d, J = 9 Hz).

6-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,6-tetrahydropyrrolo[2,3-*g*]indole (5). The title compound was prepared in 62% yield from nicotinoyl azide (0.29 g, 1.9 mmol) and the amine **11** (0.31 g, 1.8 mmol) using a procedure similar to that for the preparation of **4**: mp 197−199 °C; ^{1}H NMR (DMSO-d_6) δ 3.20 (2H, t, J = 9 Hz), 3.75 (3H, s), 4.20 (2H, t, J = 9 Hz), 6.58 (1H, d, J = 3 Hz), 7.05 (2H, m), 7.18 (1H, d, J = 2 Hz), 7.32 (1H, m), 8.00 (1H, m), 8.21 (1H, m), 8.73 (1H, d, J = 2 Hz), 8.98 (1H, s); MS *m/e* 292 (M^+). Anal. ($C_{17}H_{16}N_4O$) C, H, N.

7-(Cyanomethyl)-1-methyl-6-nitroindole (14). 1-Methyl-6-nitroindole (**13**) (1.1 g, 6.0 mmol) and (4-chlorophenoxy)-acetonitrile (1.2 g, 7.2 mmol) were stirred in DMF (20 mL) at 0 °C, and potassium *tert*-butoxide (2.0 g, 17.9 mmol) was added portionwise. After 15 min, the solution was diluted with water (100 mL) and acidified with 5 M hydrochloric acid. The resultant solid was filtered off and chromatographed on silica gel using 0−20% ethyl acetate/dichloromethane as eluant to afford **14** (1.0 g, 78%) as a yellow solid: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 4.06 (3H, s), 4.25 (2H, s), 6.40 (1H, d, J = 3 Hz), 7.14 (1H, d, J = 3 Hz), 7.47 (1H, d, J = 9 Hz), 7.51 (1H, d, J = 9 Hz); MS *m/e* 215 (M^+).

Methyl (1-Methyl-6-nitro-7-indolyl)acetate (15). The nitrile **14** (0.88 g, 4.1 mmol) was stirred in methanol (100 mL) and thionyl chloride (10 mL) added dropwise. The mixture was then heated under reflux for 110 h. After cooling, the mixture was evaporated to dryness and partitioned between water and chloroform. The organic layer was dried and evaporated to give a brown solid (1.1 g). This solid was suspended in ethanol (10 mL) containing 10% aqueous sodium hydroxide (1.5 mL) and stirred for 3 h. The mixture was then diluted with water (100 mL) and washed with chloroform. The aqueous layer was acidified and extracted with ethyl acetate to afford a brown solid (0.4 g) which was dissolved in methanol (25 mL) and stirred as thionyl chloride (2 mL) was added. The mixture was heated under reflux for 2 h and then evaporated to dryness to afford the methyl ester **15** (0.43 g, 41%) as a brown solid: ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 4.07 (3H, s), 4.38 (2H, s), 6.54 (1H, d, J = 3 Hz), 7.20 (1H, d, J = 3 Hz), 7.57 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 9 Hz).

2-(1-Methyl-6-nitro-7-indolyl)ethanol (16). The ester **15** (0.43 g, 1.7 mmol) was dissolved in THF (20 mL) under argon and lithium aluminum hydride (0.16 g, 4.2 mmol) added portionwise. After 30 min, the reaction was carefully quenched with water; then the mixture was diluted with water (100 mL), acidified with 5 M hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to afford the alcohol **16** (0.18 g, 47%) as a dark gum: ^{1}H NMR (MeOH-d_4) δ 3.40 (2H, t, J = 10 Hz), 3.90 (2H, t, J = 10 Hz), 4.12 (3H, s), 4.93 (1H, s), 6.46 (1H, d, J = 3 Hz), 7.30 (1H, d, J = 3 Hz), 7.44 (2H, s).

2-(1-Methyl-6-nitro-7-indolyl)ethyl Methanesulfonate (17). The alcohol **16** (0.18 g, 0.82 mmol), triethylamine (0.14 mL), and methanesulfonyl chloride (0.08 mL, 1.0 mmol) were added to dichloromethane (10 mL) with stirring. After 30 min, water was added and the mixture acidified with 5 M hydrochloric acid. The aqueous layer was extracted with chloroform, and the combined organic layers were dried and evaporated. Chromatography on silica gel using dichloromethane as eluant afforded **17** (0.16 g, 64%) as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 2.91 (3H, s), 3.76 (2H, t, J = 10 Hz), 4.16 (3H, s), 4.63 (2H, t, J = 10 Hz), 6.52 (1H, d, J = 3 Hz), 7.21 (1H, d, J = 3 Hz), 7.53 (1H, d, J = 9 Hz), 7.67 (1H, d, J = 9 Hz).

4-Methyl-1,2,3,4-tetrahydropyrrolo[2,3-*e*]indole (18). The mesylate **17** (0.16 g, 0.54 mmol) was dissolved in ethanol

(25 mL) and hydrogenated over 5% palladium on charcoal (0.23 g) at 50 psi for 2 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The residue was partitioned between chloroform and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated to afford **18** (0.08 g, 85%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 3.41 (2H, t, J = 9 Hz), 3.61 (2H, t, J = 9 Hz), 3.86 (3H, s), 6.36 (1H, d, J = 3 Hz), 6.60 (1H, d, J = 9 Hz), 6.79 (1H, d, J = 3 Hz), 7.29 (1H, d, J = 3 Hz).

4-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,4-tetrahydropyrrolo[2,3-*e*]indole (12). The title compound was prepared in 57% yield from nicotinoyl azide (0.08 g, 0.6 mmol) and the amine **18** (0.08 g, 0.47 mmol) using a procedure similar to that for the preparation of **4**: mp 225 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.69 (2H, d, J = 9 Hz), 3.91 (3H, s), 4.25 (2H, d, J = 9 Hz), 6.33 (1H, d, J = 3 Hz), 7.13 (1H, d, J = 3 Hz), 7.32 (2H, m), 7.78 (1H, d, J = 8 Hz), 7.99 (1H, m), 8.21 (1H, m), 8.64 (1H, s), 8.75 (1H, d, J = 2 Hz); MS m/e 292 (M^+). Anal. ($C_{17}H_{16}N_4O$) C, H, N.

1-Acetyl-5-ethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (20, R = Et). To a stirred suspension of 80% sodium hydride (0.42 g, 15 mmol) in DMF (20 mL) under argon was added dropwise a solution of 1-acetyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (**19**)[5] (2.9 g, 15 mmol in DMF (10 mL)). After stirring for 30 min, iodoethane (1.2 mL, 14.5 mmol) was added and stirring continued for 18 h. The suspension was poured onto water and extracted with ethyl acetate. The organic layer was dried and evaporated to dryness to afford **20** (R = Et) as a yellow oil (3.1 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 8 Hz), 2.23 (3H, s), 3.29 (2H, t, J = 10 Hz), 4.0−4.25 (4H, m), 6.43 (1H, d, J = 3 Hz), 7.03 (1H, d, J = 3 Hz), 7.10 (1H, s), 8.48 (1H, s); MS m/e 228 (M^+).

1-Acetyl-5-propyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (20, R = Pr). The title compound was prepared in 98% yield from 1-acetyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (**19**),[5] sodium hydride, and iodopropane using a similar procedure to that for **20** (R = Et): ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 8 Hz), 1.86 (2H, m), 2.29 (3H, s), 3.30 (2H, t, J = 8 Hz), 4.0−4.15 (4H, m), 6.47 (1H, d, J = 3 Hz), 7.03 (1H, d, J = 3 Hz), 7.12 (1H, s), 8.48 (1H, s); MS m/e 242 (M^+).

1-Acetyl-5-(phenylmethyl)-1,2,3,5-tetrahydropyrrolo-[2,3-*f*]indole (20, R = CH_2Ph). The title compound was prepared in 79% yield from 1-acetyl-1,2,3,5-tetrahydropyrrolo-[2,3-*f*]indole (**19**),[5] sodium hydride, and benzyl bromide using a similar procedure to that for **20** (R = Et): ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s), 3.24 (2H, t, J = 8 Hz), 4.08 (2H, t, J = 8 Hz), 5.29 (2H, s), 6.51 (1H, d, J = 3 Hz), 7.00 (1H, s), 7.06 (3H, m), 7.28 (3H, m), 8.50 (1H, s); MS m/e 290 (M^+).

5-Ethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (21, R = Et). To a solution of the *N*-acetyl derivative **20** (R = Et) (3.1 g, 14 mmol) in ethanol (60 mL) was added 10% aqueous sodium hydroxide (60 mL) along with sodium hydroxide pellets (6 g) under argon. The mixture was heated under reflux for 8 h, allowed to cool, and poured onto water. The aqueous solution was extracted with dichloromethane, and the organic layer was dried and evaporated to give **21** (R = Et) as a dark solid (2.5 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 8 Hz), 3.12 (2H, t, J = 10 Hz), 3.58 (2H, t, J = 10 Hz), 4.08 (2H, q, J = 8 Hz), 6.26 (1H, d, J = 3 Hz), 6.84 (1H, s), 6.97 (1H, d, J = 3 Hz), 7.12 (1H, s); MS m/e 186 (M^+).

5-Propyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (21, R = Pr). The title compound was prepared in 60% yield from **20** (R = Pr) and aqueous sodium hydroxide using a procedure similar to that for **21** (R = Et): ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 8 Hz), 1.87 (2H, m), 3.12 (2H, t, J = 8 Hz), 3.59 (2H, t, J = 8 Hz), 4.03 (2H, t, J = 8 Hz), 6.29 (1H, d, J = 3 Hz), 6.87 (1H, s), 6.98 (1H, d, J = 3 Hz), 7.28 (1H, s); MS m/e 200 (M^+).

5-(Phenylmethyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (21, R = CH_2Ph). The title compound was prepared in 96% yield from **20** (R = CH_2Ph) and aqueous sodium hydroxide using a procedure similar to that for **21** (R = Et): ^{1}H NMR ($CDCl_3$) δ 3.08 (2H, t, J = 8 Hz), 3.57 (2H, t, J = 8 Hz), 5.28 (2H, s), 6.35 (1H, d, J = 3 Hz), 6.88 (1H, s), 7.02 (2H, m), 7.10 (2H, m), 7.29 (3H, m); MS m/e 248 (M^+).

5-Ethyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (22). The title compound was prepared in 83% yield from nicotinoyl azide (2.2 g, 12 mmol) and the amine **21** (R = Et) (2.2 g, 12 mmol) using a procedure similar to that for the preparation of **4**. Chromatography of the product on silica gel using 2% methanol/dichloromethane as eluant afforded **22** (3.0 g, 83%) as a white solid: mp 202−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 8 Hz), 3.28 (2H, t, J = 10 Hz), 4.16 (4H, m), 6.31 (1H, d, J = 3 Hz), 7.24 (1H, d, J = 3 Hz), 7.30 (1H, s), 7.32 (1H, m), 8.00 (1H, m), 8.03 (1H, s), 8.22 (1H, m), 8.65 (1H, s), 8.77 (1H, s); MS m/e 306 (M^+). Anal. ($C_{18}H_{18}N_4O$) C, H, N.

5-Propyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (23). The title compound was prepared in 70% yield from nicotinoyl azide and the amine **21** (R = Pr) using a procedure similar to that for the preparation of **4**: mp 175−176 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 8 Hz), 1.88 (2H, m), 3.32 (2H, t, J = 8 Hz), 4.04 (2H, t, J = 8 Hz), 4.18 (2H, t, J = 8 Hz), 6.46 (1H, d, J = 3 Hz), 6.91 (1H, s), 7.07 (1H, d, J = 3 Hz), 7.30 (2H, m), 7.94 (1H, s), 8.15 (1H, m), 8.34 (1H, m), 8.52 (1H, s); MS m/e 320 (M^+). Anal. ($C_{19}H_{20}N_4O$) C, H, N.

5-(Phenylmethyl)-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (24). The title compound was prepared in 80% yield from nicotinoyl azide and the amine **21** (R = CH2Ph) using a procedure similar to that for the preparation of **4**: mp 199−200 °C; ^{1}H NMR (DMSO-d_6) δ 3.21 (2H, t, J = 8 Hz), 4.13 (2H, t, J = 8 Hz), 5.38 (2H, s), 6.40 (1H, d, J = 3 Hz), 7.1−7.4 (8H, m), 8.00 (1H, m), 8.05 (1H, m), 8.21 (1H, d, J = 6 Hz), 8.62 (1H, s), 8.77 (1H, d, J = 3 Hz); MS m/e 368 (M^+). Anal. ($C_{23}H_{20}N_4O$) C, H, N.

1,2,3,5-Tetrahydropyrrolo[2,3-*f*]indole (25). The title compound was prepared in 89% yield from 1-acetyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (**19**)[5] and aqueous sodium hydroxide using a procedure similar to that for the preparation of **21** (R = Et): ^{1}H NMR (DMSO-d_6) δ 2.89 (2H, t, J = 10 Hz), 3.35 (2H, t, J = 10 Hz), 6.08 (1H, m), 6.52 (1H, s), 7.00 (2H, m); MS m/e 158 (M^+).

1-(3-Pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (26). The title compound was prepared in 80% yield from nicotinoyl azide and the amine **25** using a procedure similar to that for the preparation of **4**: mp 205−206 °C; ^{1}H NMR (DMSO-d_6) δ 3.21 (2H, t, J = 10 Hz), 4.15 (2H, t, J = 10 Hz), 6.31 (1H, m), 7.20 (1H, m), 7.31 (1H, m), 8.03 (2H, m), 8.21 (1H, m), 8.64 (1H, bs), 8.79 (1H, m), 10.88 (1H, bs); MS m/e 278 (M^+). Anal. ($C_{16}H_{14}N_4O$) C, H, N.

5-Isopropyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (27). The indolyl urea **26** (0.38 g, 1.4 mmol) was dissolved in DMF (10 mL) at 0 °C and treated with 80% sodium hydride (0.09 g, 2.9 mmol). After 15 min, 2-iodopropane (0.14 mL, 1.5 mmol) was added, and the mixture was allowed to warm to room temperature. After 4 h, additional sodium hydride (0.05 g) and 2-iodopropane (0.07 mL) were added, and the mixture was stirred for 18 h. The mixture was evaporated to dryness and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated. Chromatography of the residue on silica gel using 0−5% methanol/dichloromethane afforded **27** (0.15 g, 35%): mp 182−183 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (6H, d, J = 7 Hz), 3.29 (2H, t, J = 8 Hz), 4.17 (2H, t, J = 8 Hz), 4.60 (1H, m, J = 7 Hz), 6.47 (1H, d, J = 3 Hz), 6.90 (1H, s), 7.2−7.3 (3H, m), 7.95 (1H, s), 8.11 (1H, m), 8.30 (1H, d, J = 6 Hz), 8.53 (1H, d, J = 3 Hz); MS m/e 320 (M^+). Anal. ($C_{19}H_{20}N_4O$) C, H, N.

***N*-(1-Acetyl-5-indolinyl)-2-chloroallylamine (29)**. 1-Acetyl-5-aminoindoline (**28**) (4.36 g, 24.8 mmol), potassium carbonate (5.1 g, 37 mmol), and 2,3-dichloro-1-propene (4.5 mL, 49 mmol) were stirred in DMF (50 mL) at 70 °C for 16 h. The mixture was then diluted with water (500 mL) and stirred for 10 min. The precipitate was filtered off and dried to afford **29** (5.7 g, 92%) as a dark olive solid: ^{1}H NMR ($CDCl_3$) δ 2.19 (3H, s), 3.13 (2H, t, J = 8 Hz), 3.9−4.2 (5H, m), 5.32 (1H, m), 5.41 (1H, m), 6.4−6.6 (2H, m), 8.05 (1H, d, J = 9 Hz).

***N*-(1-Acetyl-5-indolinyl)-2-chloro-*N*-methylallylamine (30).** To a mixture of 40% aqueous formaldehyde (2.8 mL, 36 mmol) and 3 M sulfuric acid (5 mL) was added portionwise, with cooling, a suspension of sodium borohydride (1.7 g, 44 mmol) and the amine **29** (3.1 g, 12 mmol) in tetrahydrofuran (60 mL). The mixture was stirred at room

temperature for 15 min and then basified with excess solid sodium hydroxide. The mixture was extracted with ethyl acetate and the combined organic solution dried and evaporated to afford **30** (3.8 g) as a brown solid which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 2.20 (3H, s), 3.00 (3H, s), 3.16 (2H, t, J = 7 Hz), 3.95−4.20 (4H, m), 5.22 (1H, m), 5.30 (1H, m), 6.56 (2H, m), 8.08 (1H, d, J = 8 Hz).

1-Acetyl-5,6-dimethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (31). The allylamine **30** (2.1 g, 7.9 mmol) was stirred in polyphosphoric acid (44 g) at 140 °C for 24 h, cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give a pink solid. Chromatography on silica gel eluting with 0−20% ethyl acetate/dichloromethane afforded, *inter alia*, the linear tricyclic **31** (0.21 g, 12%) as a white solid: ^{1}H NMR ($CDCl_3$) δ (major rotamer) 2.25 (3H, s), 2.39 (3H, s), 3.29 (2H, t, J = 7 Hz), 3.62 (3H, s), 4.10 (2H, t, J = 7 Hz), 6.22 (1H, s), 7.03 (1H, s), 8.38 (1H, s).

5,6-Dimethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (32). The title compound was prepared in 60% yield from the acetamide **31** and aqueous sodium hydroxide using a procedure similar to that for **21** (R = Et): ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 3.12 (2H, t, J = 7 Hz), 3.56 (2H, t, J = 7 Hz), 3.58 (3H, s), 6.06 (1H, s), 6.78 (1H, s), 7.03 (1H, s).

5,6-Dimethyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (33). The title compound was prepared in 39% yield from nicotinoyl azide and the amine **32** using a procedure similar to that for the preparation of **4**: mp 225 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.36 (3H, s), 3.26 (2H, t, J = 8 Hz), 3.60 (3H, s), 4.17 (2H, t, J = 8 Hz), 6.11 (1H, s), 7.21 (1H, s), 7.32 (1H, dd, J = 7, 4 Hz), 7.93 (1H, s), 8.00 (1H, d, J = 7 Hz), 8.21 (1H, d, J = 4 Hz), 8.63 (1H, s), 8.75 (1H, d, J = 2 Hz); MS m/e 306 (M^+). Anal. ($C_{18}H_{18}N_4O$) C, H, N.

***N*-(1-Acetyl-5-indolinyl)-2-chloro-*N*-(trifluoroacetyl)-allylamine (34)**. The amine **29** (5.7 g, 25 mmol) and triethylamine (3.3 mL, 27 mmol) in chloroform (100 mL) were stirred during the addition of trifluoroacetic anhydride (3.8 mL, 27 mmol) dropwise. The mixture was stirred for 1 h and then diluted with water (100 mL). The organic layer was dried and evaporated to give **34** (7.5 g, 95%) as a dark oil: ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.24 (2H, t, J = 8 Hz), 4.16 (2H, t, J = 8 Hz), 4.52 (2H, s), 5.23 (1H, s), 5.36 (1H, s), 7.1 (2H, m), 8.23 (1H, d, J = 8 Hz).

1-Acetyl-7-methyl-5-(trifluoroacetyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (35). The trifluoroacetamide **34** (7.6 g, 22 mmol) was stirred in polyphosphoric acid (38 g) at 140 °C for 1.5 h. The mixture was cooled, diluted with water (200 mL), and then extracted with ethyl acetate. The organic layer was filtered through Kieselguhr, dried, and evaporated to give a dark oil. Chromatography on silica gel eluting with 0−20% ethyl acetate/chloroform gave **35** (0.5 g, 7%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s), 2.33 (3H, s), 3.36 (2H, t, J = 8 Hz), 4.18 (2H, t, J = 8 Hz), 7.19 (1H, s), 8.24 (1H, s), 8.36 (1H, s).

1-Acetyl-7-methyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (36). The title compound was prepared in 91% yield from the trifluoroacetamide **35** using potassium carbonate in methanol as in the preparation of **11**: ^{1}H NMR (DMSO-d_6) δ 2.15 (3H, s), 2.18 (3H, s), 3.17 (2H, t, J = 8 Hz), 4.09 (2H, t, J = 8 Hz), 7.00 (1H, s), 7.14 (1H, s), 8.16 (1H, s), 10.55 (1H, bs).

1-Acetyl-5,7-dimethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (37). The title compound was prepared in 79% yield from the indole **36**, sodium hydride, and methyl iodide using a procedure similar to that for **20** (R = Et): ^{1}H NMR ($CDCl_3$) δ (major rotamer) 2.27 (3H, s), 2.30 (3H, s), 3.30 (2H, t, J = 8 Hz), 3.68 (3H, s), 4.10 (2H, t, J = 8 Hz), 6.76 (1H, s), 7.05 (1H, s), 8.42 (1H, s).

5,7-Dimethyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (38). The title compound was prepared in ∼60% yield from the acetamide **37** and aqueous sodium hydroxide using a procedure similar to that for **21** (R = Et). Some starting material remained in the crude product which was used in the next step without further purification.

5,7-Dimethyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (39). The title compound was prepared in 42% yield from nicotinoyl azide and the amine **38** using a procedure similar to that for the preparation of **4**: mp 224−227 °C; ^{1}H NMR (DMSO-d_6) δ 2.19 (3H, s), 3.27 (2H, t, J = 8 Hz), 3.67 (3H, s), 4.18 (2H, t, J = 8 Hz), 6.96 (1H, s), 7.21 (1H, s), 7.32 (1H, dd, J = 7, 4 Hz), 8.00 (1H, s), 8.02 (1H, dd, J = 7, 2 Hz), 8.22 (1H, dd, J = 4, 2Hz), 8.62 (1H, s), 8.77 (1H, s); MS m/e 306 (M^+). Anal. ($C_{18}H_{18}N_4O$) C, H, N.

5-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,5,6,7-hexahydropyrrolo[2,3-*f*]indole (40). The indole **2**[5] (0.80 g, 2.7 mmol) was treated with sodium cyanoborohydride (0.90 g, 14 mmol) in acetic acid at room temperature for 4 h. Water was added, and the mixture was basified with 10% aqueous sodium hydroxide and extracted with dichloromethane. The organic layer was washed with brine, dried, and evaporated to give a solid which was recrystallized from methanol/60−80 °C petroleum ether ether to give **40** (0.40 g, 53%) as a white solid: mp 153−155 °C; ^{1}H NMR (DMSO-d_6) δ 2.62 (3H, s), 2.80 (2H, t, J = 8 Hz), 3.05 (2H, t, J = 8 Hz), 3.17 (2H, t, J = 8 Hz), 4.10 (2H, t, J = 8 Hz), 6.40 (1H, s), 7.30 (1H, q, J = 4 Hz), 7.65 (1H, s), 7.91−7.98 (1H, m), 8.19 (1H, d, J = 4 Hz), 8.55 (1H, s), 8.72 (1H, d, J = 4 Hz); MS m/e 294 (M^+). Anal. ($C_{17}H_{18}N_4O$) C, H, N.

2-Bromo-4-methyl-5-nitrobenzaldehyde (42). 2-Bromo-4-methylbenzaldehyde (**41**) (57.0 g, 286 mmol) was added dropwise as a melt to concentrated sulfuric acid (300 mL) with stirring and ice cooling. Concentrated nitric acid (36 mL, 570 mmol) was then added dropwise keeping the temperature below 15 °C. After the addition was completed, stirring was continued for 20 min; then the mixture was poured onto ice/water (2.5 L) with vigorous stirring. The resultant precipitate was filtered off, extracted with 5% methanol/chloroform, washed with saturated sodium hydrogen carbonate solution followed by brine, and then evaporated to dryness. Recrystallization from ethyl acetate/60−80 °C petroleum ether gave **42** (44.2 g, 63%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 7.70 (1H, s), 8.50 (1H, s), 9.80 (1H, s); MS m/e 243, 245 (M^+).

Ethyl 6-Methyl-5-nitrobenzothiophene-2-carboxylate (43). Sodium (4.3 g, 180 mmol) was added portionwise to dry ethanol (250 mL) over 30 min. The solution was then cooled in an ice bath, and ethyl 2-mercaptoacetate (20 mL, 180 mmol) was added. The mixture was stirred at 5 °C for 20 min and then diluted with ethanol (300 mL). The aldehyde **42** (44.2 g, 180 mmol) was then added portionwise over 10 min. Additional ethanol (200 mL) was added and the mixture heated under reflux for 3 h. The mixture was then cooled and the ethanol evaporated. The residue was partitioned between water and dichloromethane, and the organic layer was washed with brine, dried, and evaporated to give **43** (46 g, 96%): ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 8 Hz), 2.75 (3H, s), 4.43 (2H, q, J = 8 Hz), 7.70 (1H, s), 8.10 (1H, s), 8.53 (1H, s); MS m/e 265 (M^+).

6-Methyl-5-nitrobenzothiophene-2-carboxylic Acid (44). The ester **43** (46 g, 170 mmol) was heated under reflux in ethanol (500 mL), water (300 mL), and sodium hydroxide (27 g, 680 mmol) for 3 h. The mixture was allowed to cool and most of the ethanol removed under reduced pressure. The residue was poured into a mixture of 5 M HCl (250 mL) and ice/water (1 L) with vigorous stirring. The precipitate was filtered off and dried at 80 °C to give **44** (41 g, 100%) as a brown solid: ^{1}H NMR (DMSO-d_6) δ 2.62 (3H, s), 8.20 (1H, s), 8.26 (1H, s), 8.75 (1H, s), 13.7 (1H, bs); MS m/e 237 (M^+).

6-Methyl-5-nitrobenzothiophene (45). The acid **44** (41 g, 170 mmol), in quinoline (300 mL) containing copper powder (25 g), was heated to 190 °C for 3 h. The mixture was cooled and diluted with diethyl ether (1 L). The mixture was filtered through Kieselguhr, then washed with 5 M HCl (3 × 500 mL), water, and brine, dried, and evaporated to give **45** (29.6 g, 89%): ^{1}H NMR ($CDCl_3$) δ 2.72 (3H, s), 7.40 (1H, d, J = 6 Hz), 7.55 (1H, d, J = 6 Hz), 7.80 (1H, s), 8.51 (1H, s); MS m/e 193 (M^+).

5-Nitrobenzothiophene-6-acetaldehyde (46). 6-Methyl-5-nitrobenzothiophene (**45**) (29.6 g, 153 mmol) in DMF (300 mL) was treated with DMF dimethyl acetal (61 mL, 460 mmol) and pyrrolidine (25.7 mL, 300 mmol) at 150 °C for 3 h under argon. The mixture was cooled and concentrated under reduced pressure. Toluene (600 mL), 5 M HCl (300 mL), and

water (800 mL) were added to the residue, which was heated under reflux for 30 min. The mixture was cooled, extracted with ethyl acetate, washed with water, dried, and evaporated. Chromatography on silica gel eluting with dichloromethane afforded **46** (26.4 g, 78%): ^{1}H NMR ($CDCl_3$) δ 4.22 (2H, s), 7.48 (1H, d, J = 6 Hz), 7.64 (1H, d, J = 6 Hz), 7.81 (1H, s), 8.67 (1H, s), 9.91 (1H, s); MS m/e 221 (M^+).

2-(5-Nitro-6-benzothienyl)ethanol (47). The aldehyde **46** (25.3 g, 114 mmol) in ethanol (300 mL) was treated portionwise with sodium borohydride (8.7 g, 130 mmol), with stirring at room temperature for 1 h. The solution was then concentrated under reduced pressure, and water (500 mL) was added. The mixture was carefully acidified with 5 M HCl, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and evaporated to give **47** (25.0 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.78 (1H, bs), 3.29 (2H, t, J = 8 Hz), 4.12 (2H, t, J = 8 Hz), 7.41 (1H, d, J = 6 Hz), 7.59 (1H, d, J = 6 Hz), 7.89 (1H, s), 8.45 (1H, s); MS m/e 223 (M^+).

2-(5-Nitro-6-benzothienyl)ethyl Methanesulfonate (48). The alcohol **47** (25.0 g, 112 mmol) was dissolved in dry dichloromethane (500 mL) and treated with triethylamine (16.4 mL, 118 mmol), and methanesulfonyl chloride (9.2 mL, 120 mmol) was added dropwise over 15 min. The mixture was stirred at room temperature for 1 h, then washed with saturated aqueous sodium hydrogen carbonate, and brine, dried, and evaporated to afford **48** (29.6 g, 88%): ^{1}H NMR ($CDCl_3$) δ 2.96 (3H, s), 3.48 (2H, t, J = 8 Hz), 4.60 (2H, t, J = 8 Hz), 7.46 (1H, d, J = 7 Hz), 7.55 (1H, d, J = 7 Hz), 7.90 (1H, s), 8.56 (1H, s); MS m/e 301 (M^+).

6,7-Dihydro-5*H*-thieno[2,3-*f*]indole (49). The mesylate **48** (10.3 g, 34.0 mmol) in ethyl acetate (500 mL) containing triethylamine (10 mL) and 10% palladium on carbon (1 g) was hydrogenated at atmospheric pressure at 50 °C for 1.5 h. The reaction mixture was then filtered through Kieselguhr, washed with water, and evaporated to dryness to afford **49** (6.0 g, 100%): ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, t, J = 8 Hz), 3.54 (1H, bs), 3.65 (2H, t, J = 8 Hz), 7.02 (1H, s), 7.15 (1H, d, J = 7 Hz), 7.30 (1H, d, J = 7 Hz), 7.57 (1H, s); MS m/e 175 (M^+).

6,7-Dihydro-5-(3-pyridylcarbamoyl)-5*H*-thieno[2,3-*f*]-indole (50). The title compound was prepared in 83% yield from the amine **49** (17.7 g, 101 mmol) and nicotinoyl azide (16.0 g, 108 mmol) using the same procedure as for **4**: mp 189−190 °C; ^{1}H NMR (DMSO-d_6) δ 3.35 (2H, t, J = 8 Hz), 4.19 (2H, t, J = 8 Hz), 6.67 (1H, s), 7.2−7.4 (3H, m), 7.63 (1H, m), 8.12 (1H, m), 8.32 (2H, m), 8.53 (1H, m); MS m/e 295 (M^+). Anal. ($C_{16}H_{13}N_3OS$) C, H, N.

6-Nitro-1-(trifluoroacetyl)indoline (52). 6-Nitroindoline (**51**) (6.5 g, 40 mmol) and triethylamine (6.6 mL, 47 mmol) were stirred in dichloromethane (65 mL) as trifluoroacetic anhydride (6.6 mL, 47 mmol) was added dropwise. This mixture was stirred for 45 min; then water (100 mL) was added. After stirring for 10 min, the mixture was acidified with 5 M HCl. The organic layer was washed with brine, dried, and evaporated to give **52** (9.6 g, 93%) as a yellow-brown solid: ^{1}H NMR ($CDCl_3$) δ 3.40 (2H, t, J = 8 Hz), 4.40 (2H, t, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 8, 2 Hz), 9.05 (1H, d, J = 2 Hz).

6-Amino-1-(trifluoroacetyl)indoline (53). The nitroindoline **52** (4.1 g, 16 mmol) in ethanol (200 mL) was hydrogenated over 5% palladium on carbon (60% aqueous paste, 1 g) for 4 h. The catalyst was removed by filtration and the filtrate evaporated to afford **53** (3.6 g, 99%) as a light brown solid: ^{1}H NMR ($CDCl_3$) δ 3.15 (2H, t, J = 8 Hz), 3.35 (2H, bs), 4.25 (2H, t, J = 8 Hz), 6.50 (1H, dd, J = 8 Hz, 2 Hz), 7.00 (1H, d, J = 8 Hz), 7.65 (1H, d, J = 2 Hz).

6-Hydroxy-1-(trifluoroacetyl)indoline (54). The aniline **53** (3.0 g, 13 mmol) was stirred in water (30 mL) as concentrated sulfuric acid (3 mL) was added dropwise. The solution was cooled to 0 °C, and a solution of sodium nitrite (0.98 g, 14 mmol) in water (10 mL) was added dropwise, maintaining the temperature ≤ 0 °C. The mixture was stirred for 5 min and then transferred to a boiling solution of copper sulfate (13.0 g, 52 mmol) in water (50 mL). The mixture was boiled for 5 min and cooled, and the black solid was filtered off and dried. Chromatography on silica gel eluting with 0−5% methanol in chloroform gave **54** (1.0 g, 67%) as a dark brown solid: ^{1}H NMR (DMSO-d_6) δ 3.10 (2H, t, J = 8 Hz), 4.25 (2H, t, J = 8 Hz), 6.60 (1H, dd, J = 8, 2 Hz), 7.10 (1H, d, J = 8 Hz), 7.60 (1H, d, J = 2 Hz), 9.05 (1H, bs).

6-(2-Oxopropoxy)-1-(trifluoroacetyl)indoline (55). A mixture of the phenol **54** (2.0 g, 8.7 mmol), potassium carbonate (1.8 g, 13.0 mmol), and chloroacetone (0.8 mL, 10 mmol) were stirred in dry DMF (20 mL) for 64 h. The mixture was diluted with ethyl acetate (200 mL), filtered, washed with water, dried, and evaporated to give **55** (2.4 g, 97%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s), 3.20 (2H, t, J = 8 Hz), 4.30 (2H, t, J = 8 Hz), 4.60 (2H, s), 6.75 (1H, dd, J = 8, 2 Hz), 7.15 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 2 Hz).

5,6-Dihydro-3-methyl-7-(trifluoroacetyl)furo[3,2-*f*]indole (56). Concentrated sulfuric acid (25 mL) was added at 0 °C to the ketone **55** (2.4 g, 8.4 mmol). The dark mixture was stirred at room temperature for 15 min and poured onto ice. The crude product was extracted into ethyl acetate, washed with water and brine, dried, and evaporated to dryness. Chromatography on silica gel eluting with chloroform gave **56** (0.5 g, 21%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.35 (2H, t, J = 8 Hz), 4.35 (2H, t, J = 8 Hz), 7.35 (1H, s), 7.45 (1H, s), 8.35 (1H, s); MS m/e 263 (M^+).

5,6-Dihydro-3-methylfuro[3,2-*f*]indole (57). The trifluoroacetamide **56** (0.50 g, 1.8 mmol) was stirred in ethanol (10 mL) as 2.5 M aqueous sodium hydroxide (1 mL) was added. The mixture was stirred for 15 min, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give **57** (0.30 g, 96%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 2.20 (3H, s), 3.10 (2H, t, J = 8 Hz), 3.30 (1H, bs), 3.60 (2H, t, J = 8 Hz), 6.70 (1H, s), 7.20 (2H, m); MS m/e 173 (M^+).

5,6-Dihydro-3-methyl-7-(3-pyridylcarbamoyl)furo[3,2-*f*]indole (58). The title compound was prepared in 59% yield from the amine **57** (0.15 g, 0.87 mmol) and nicotinoyl azide (0.14 g, 0.94 mmol) using the same procedure as for **4**: mp 227−228 °C; ^{1}H NMR (DMSO-d_6) δ 2.17 (3H, s), 3.27 (2H, t, J = 8 Hz), 4.24 (2H, t, J = 8 Hz), 7.35 (2H, m), 7.62 (1H, d, J = 2 Hz), 8.01 (2H, m), 8.24 (1H, m), 8.76 (2H, s); MS m/e 293.1162 (M^+). $C_{17}H_{15}N_3O_2$ requires 293.1164.

Computational Studies and Molecular Modeling. Molecular mechanics and dynamics calculations on the protein structures with and without bound ligands were performed using the CHARMm program. Geometries for the ligands were generated by optimization with the COSMIC molecular mechanics force field or, where parameters were unavailable, with the semiempirical molecular orbital program VAMP, using the AM1 Hamiltonian. Natural atomic orbital charges were used for the docking calculations, and these were generated from single-point Hartree−Fock calculations using the Spartan suite of programs (Wavefunction Inc.) with a 3-21G basis set. The results for the CHARMm calculations were visualized using the program QUANTA (Molecular Simulations, Inc.). The allowed−disallowed volume and overlap studies on the ligands were carried out using the SYBYL program (Tripos Assoc.). All calculations were performed on either a Silicon Graphics 4D-380 Powerserver or a DEC alpha 2100 workstation and the results visualized on a Silicon Graphics Indigo-2 Extreme workstation.

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