Expedited Articles

5-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole: A Novel 5-HT_{2C}/5-HT_{2B} Receptor Antagonist with Improved Affinity, Selectivity, and Oral Activity

Ian T. Forbes,*,† Peter Ham,*,† Deborah H. Booth,† Roger T. Martin,† Mervyn Thompson,† Gordon S. Baxter,§ Thomas P. Blackburn,‡ Alison Glen,‡ Guy A. Kennett,‡ and Martyn D. Wood‡

SmithKline Beecham Pharmaceuticals, Discovery Research, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, England

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The preparation of a series of conformationally restricted analogues of indolylurea **1**, namely tetrahydropyrroloindoles and tetrahydropyrroloquinolines, is described. The binding affinities of these compounds at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors were determined. Of these compounds, the 1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole derivative, compound **11**, was found to have high affinity for the 5-HT_{2C} (pK_I 8.0) and 5-HT_{2B} receptors (pA_2 8.5), with excellent selectivity over the 5-HT_{2A} and various other receptors (pK_I <6). **11** is also considerably more active than **1** in both an *in vitro* functional model, 5-HT-stimulated phosphoinositol hydrolysis (pK_B 8.8), and an *in vivo* functional model, mCPP-induced hypolocomotion (ID_{50} 5.5 mg/kg po). **11** should therefore be of significant utility as a pharmacological tool to delineate the functional significance of blockade of 5-HT_{2B} and 5-HT_{2C} receptors.

The explosive growth of the 5-hydroxytryptamine (5-HT, serotonin) superfamily of G-protein coupled receptors has continued to provide pharmaceutical research with new opportunities for drug discovery. Currently, the 5-HT_2 division of receptors is comprised of three subtypes, namely 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}, which have been grouped in this same class on the basis of molecular structure, signal transduction characteristics, and pharmacology.[1] Sequence analysis indicates around 80% amino acid homology in the transmembrane domains of all three receptors,[2,3] 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_{2C} and 5-HT_{2B} sites. All three receptors are present in human brain, but to date only the 5-HT_{2A} and 5-HT_{2B} receptors have been demonstrated in the periphery.[3,4] In contrast to the 5-HT_1 family, 5-HT_2 receptors are coupled to phospholipase C, with receptor activation leading to stimulation of phosphatidylinositol (PI) metabolism and an increase in inositol trisphosphate (IP_3) production.[3,5,6]

Numerous classical 5-HT receptor antagonists, such as methysergide, metergoline, mianserin, and ritanserin, have similar affinities for the three 5-HT_2 receptor subtypes.[4,6] Several compounds, including ketanserin, MDL 100,907, and risperidone, exhibit selectivity for the 5-HT_{2A} site.[4,7] In contrast, there has been a paucity of antagonists selective for the 5-HT_{2C} receptor.[1] Our interest in the 5-HT_{2C} receptor developed from literature reports that the selective 5-$HT_{2C/2B}$ agonist *m*-chlorophenylpiperazine (mCPP) causes anxiety both in animal models[8] and in humans.[9] This has been attributed to stimulation of 5-$HT_{2C/2B}$ receptors and implies that selective 5-$HT_{2C/2B}$ antagonists might be useful antianxiety agents.[10]

We have previously reported the synthesis of the pyridylurea **1** (SB 200646A), the first selective 5-$HT_{2C/2B}$ antagonist,[11] which has been shown to have anxiolytic-like properties in animal models,[12] thus providing support for our hypothesis. Unfortunately, although **1** has provided an extremely useful tool for probing the functional role of 5-$HT_{2C/2B}$ receptors, it suffers from the drawback of possessing only modest affinity. A more recent publication reports 5-$HT_{2C/2B}$ activity of an indolonaphthyridine SDZ SER-082[13] of comparable potency, but this compound binds to a variety of other receptors with micromolar affinities and exhibits partial agonist activity. We now report the synthesis and biological evaluation of 5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole, a high-affinity 5-$HT_{2C/2B}$ antagonist with >100-fold selectivity over 5-HT_{2A} and other receptors.[14]

Chemistry

NMR studies of pyridylurea **1** indicated considerable conformational mobility around the four C–N single bonds of the urea linker group. We therefore wished to prepare analogues of **1** with lesser flexibility, expecting that appropriate conformational restraint would give rise to compounds with enhanced 5-HT_{2C} receptor affinity. We now report the synthesis, and 5-HT_2 receptor antagonist properties, of compounds in which rotation about the indole(C5)–urea bond has been

* Author to whom correspondence should be addressed.
† Department of Medicinal Chemistry.
‡ Department of Psychiatry Research.
§ Department of Neurology Research.
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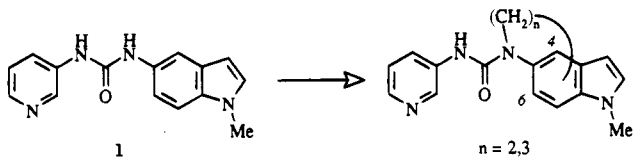
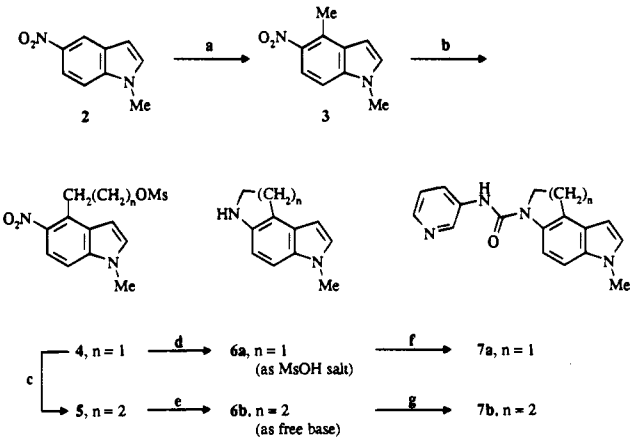


Figure 1. Introduction of conformational restraint.

Scheme 1. Synthesis of Compounds **7a** and **7b**[a]



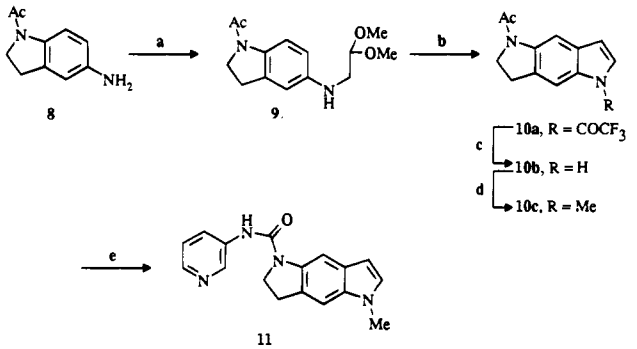
[a] Reagents: (a) MeMgBr, −10 °C, THF, 30 min; then DDQ, −10 °C to room temperature, 30 min (75%); (b) (i) $(CH_2O)_n$, KOH, DMSO−EtOH, 24 h (72%), (ii) MsCl, Et_3N, CH_2Cl_2, 10 min (79%); (c) (i) NaCN, DMSO, 100 °C, 5 h (94%), (ii) concentrated HCl, reflux, 7.5 h (59%), (iii) MeOH, $SOCl_2$, reflux, 2 h (58%), (iv) $LiAlH_4$, THF, 3 h (95%), (v) MsCl, Et_3N, CH_2Cl_2 (used crude); (d) 80 psi of H_2, Pd−C, DMF, 24 h (used crude); (e) 50 psi of H_2, Pd−C, EtOH, 6 h, then $NaHCO_3$ (65%); (f) 3-pyridyl isocyanate, Et_3N, CH_2Cl_2−PhMe, 24 h (46% from **4**); (g) 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 24 h (75%).

restricted by cyclization, *via* introduction of a methylene chain, onto the 4- or 6-position of the indole ring (see Figure 1).

The syntheses of these compounds are illustrated in Schemes 1−3. The compounds possessing angularly fused (i.e., indole *e*-, or quinoline *f*-fused) tricyclic ring systems were prepared (Scheme 1) *via* the regiospecific addition of methylmagnesium bromide[15] to 1-methyl-5-nitroindole **2**, followed by oxidation to give **3**. Hydroxymethylation of **3** with paraformaldehyde and catalytic potassium hydroxide in dimethyl sulfoxide (DMSO) gave the phenylethyl alcohol, which was converted to the mesylate **4** using standard conditions. Homologation of **4** *via* cyanide ion displacement, hydrolysis, and reduction gave the phenylpropyl alcohol, which was also mesylated to give **5**. Hydrogenation of **4** and **5** over palladium on charcoal, with concomitant cyclization, gave the parent tricyclics **6a** and **6b**, which reacted with 3-pyridyl isocyanate (prepared *in situ* from the acyl azide) to give the desired ureas **7a** and **7b**.

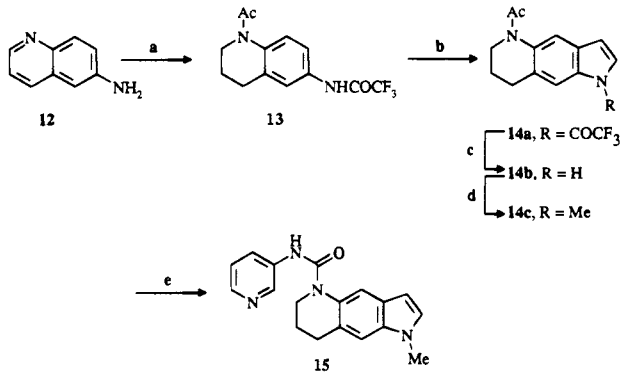
The linear isomers (*i.e.*, indole *f*-, or quinoline *g*-fused) required different methodology. The five-membered ring tricyclic **10** was prepared (Scheme 2) by reductive alkylation of 1-acetyl-5-aminoindoline **8** with 2,2-dimethoxyacetaldehyde,[16] giving **9**. This was cyclized under Nordlander's conditions[17] to the *N*-(trifluoroacetyl)indole **10a**. Hydrolysis, with anhydrous potassium carbonate in methanol, gave **10b**, which was cleanly methylated with sodium hydride and iodomethane in *N*,*N*-dimethylformamide (DMF). Sodium hydroxide hydrolysis of the acetyl group of **10c**, and

Scheme 2. Synthesis of Compound **11**[a]



[a] Reagents: (a) $(MeO)_2CHCHO$, H_2, Pd−C, EtOH, 3 days (93%); (b) TFAA, TFA, 0 °C, 30 min, then reflux, 64 h (89%); (c) K_2CO_3, MeOH, 30 min (80%); (d) NaH, MeI, DMF, 1 h (49%); (e) NaOH, reflux, 4 h, then 3-pyridyl isocyanate, CH_2Cl_2−PhMe, 2.5 h (63%).

Scheme 3. Synthesis of Compound **15**[a]



[a] Reagents: (a) (i) TFAA, Et_3N, $CHCl_3$, 1 h (80%), (ii) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 1.5 h (73%), (iii) AcCl, pyridine, CH_2Cl_2, 30 min (79%); (b) (i) NaOH, EtOH−H_2O, reflux, 30 min, then $(EtO)_2CHCH_2OTf$, $^iPr_2NEt$, DCE, reflux, 30 min (61%), (ii) TFAA, TFA, 0 °C, 30 min, then reflux, 90 h (73%); (c) K_2CO_3, MeOH, 1 h (73%); (d) NaH, MeI, DMF, 1 h (65%); (e) (i) NaOH, EtOH−H_2O, reflux, 23 h (81%), (ii) 3-pyridyl isocyanate, CH_2Cl_2−PhMe (53%).

reaction with 3-pyridyl isocyanate as before gave the urea **11**.

The linear tricyclic possessing a six-membered ring was prepared (Scheme 3) from 6-aminoquinoline **12**. Amino group protection as the trifluoroacetamide, pyridine ring reduction with nickel(II) chloride/sodium borohydride,[18] and differential protection of the newly formed secondary amine as the acetamide gave **13**. This was directly N-alkylated with triflate $(EtO)_2CHCH_2OTf$ (prepared from the alcohol with trifluoromethanesulfonic anhydride, CH_2Cl_2, −78 °C to ambient temperature) and then cyclized under Nordlander's conditions.[17] The remainder of the synthesis of **15** was accomplished by indole N-deprotection and methylation, followed by acylindoline hydrolysis and urea formation, in direct analogy with the procedure used for **11**.

In each case, the crude urea products precipitate from the reaction mixture (after evaporation of the CH_2Cl_2 in the case of **15**). Further purification can be achieved, if required, by recrystallization, *e.g.*, from EtOH.

Results and Discussion

The 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor binding affinities and 5-HT$_{2B}$ receptor inhibitory potency of the conformationally restricted analogues **7a**, **7b**, **11**, and **15** along with the parent indolylurea **1** are shown in Table 1. The

Table 1. 5-HT_{2A} and 5-HT_{2C} Receptor Binding Affinities and 5-HT_{2B} Inhibitory Potency of Pyridylureas[a]

compound	pK_I 5-HT_{2A}[b]	pK_I 5-HT_{2C}[c]	pA_2, 5-HT_{2B}[d]
1 (SB 200646A)	<5.2[e]	6.86 ± 0.07[e]	7.40 ± 0.06
7a	5.54 ± 0.04	7.18 ± 0.01	7.75 ± 0.12
7b	<5.2	<5.2	7.22 ± 0.16
11 (SB 206553)	5.79 ± 0.01	8.00 ± 0.02	8.48 ± 0.05
15	<5.2	5.39 ± 0.07	7.27 ± 0.07

[a] All values represent means ± SEM; $n \geq 3$ determinations. [b] Binding affinity (cloned human 5-HT_{2A} receptors expressed in 293 cells; [^{3}H]ketanserin). [c] Binding affinity (cloned human 5-HT_{2C} receptors expressed in 293 cells; [^{3}H]mesulergine). [d] Inhibitory potency (rat stomach fundus, 5-HT).[20] [e] Reference 11.

introduction of a six-membered ring (tetrahydroquinoline) as conformational restraint, as in **7b** and **15**, is clearly detrimental to 5-HT_{2C} receptor affinity. In marked contrast, however, the angular five-membered constrained system indoline **7a** retains the same level of affinity as the parent indole **1** at the 5-HT_{2C} receptor, whereas the corresponding linear isomer **11** is 1 order of magnitude more potent at this site.

We propose that the urea carbonyl group and the benzo ring of the bi- (**1**) or tricyclic (**7a, 7b**, **11**, and **15**) system participate in key binding interactions with the 5-HT_{2C} receptor and that their relative orientation is a crucial factor in determining the binding affinity. Molecular modeling[19] of these compounds suggests a clear difference between the indolines and tetrahydroquinolines. In the indoline **11**, the angle between the planes defined by (i) the urea NCON atoms and (ii) the 6 carbon atoms of the benzo group is low (*ca.* 9°). In distinct contrast, the angles between the complementary planes in the several minimum-energy conformers of the tetrahydroquinoline **15** are much larger (*ca.* 40°). Although this is tolerated at the 5-HT_{2B} receptor, we propose that the 5-HT_{2C} receptor imposes much more stringent geometrical requirements on these ligands.

This simple model also accounts for the activities (of different degree) of both indolines **7a** and **11**. Proposing the key interactions to lie with the carbonyl and benzo ring, the relative positions of the pyrrole ring (*i.e.*, *e*- or *f*-fusion) might then be expected to modulate activity, subject to the presence or absence of appropriate steric and/or electronic factors. Further studies to define the most favorable substituents and substitution pattern are ongoing and will be reported in due course.

The data in Table 1 also indicate that all the compounds in this series have very low affinity at the 5-HT_{2A} receptor, and so we have identified with compound **11** not only a high-affinity 5-HT_{2C} receptor antagonist, but one with high selectivity (120-fold) over the closely related 5-HT_{2A} site. As with the uncyclized indole **1**, compound **11** does not distinguish between the 5-HT_{2C} and 5-HT_{2B} sites.

It can also be seen from Table 1 that the analogues **7a**, **7b**, and **15** retain very similar affinity for the rat 5-HT_{2B} receptor, compared with the uncyclized parent **1**. Since the 5-HT_{2C} receptor affinity of the latter two compounds has decreased on cyclization, it is then apparent that **7b** and **15** represent lead compounds in the search for 5-HT_{2B} selective antagonists. It should be noted, however, that this selectivity is based on the comparison of data between a functional assay in the rat (5-HT_{2B}) and human receptor binding assays (5-HT_{2C} and 5-HT_{2A}), and it remains to be seen whether the affinity of the above compounds at the recently cloned human 5-HT_{2B} receptor parallels that seen in the rat stomach fundus.

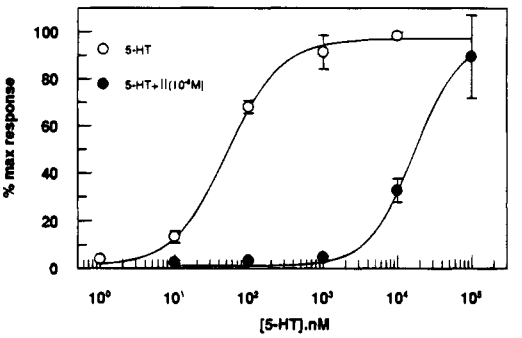


Figure 2. Effect of compound 11 on 5-HT_{2C}-mediated PI hydrolysis in pig choroid plexus.

Table 2. Receptor Binding Profile of Compound **11**[a]

receptor	species	affinity (pK_I)	receptor	species	affinity (pK_I)
5-HT_{1A}	rat	<5.0	D_2[c]	human	<5.0
5-HT_{1D}	guinea pig	<6.0	D_3[d]	human	<5.0
5-HT_{1E}[b]	human	<5.3	α_1	rat	<5.0
5-HT_3	rat	<5.0	H_1	guinea pig	<5.0
5-HT_4	rat	5.3	A_1	rat	<4.3

[a] Tissues and radioligands used in the binding assays are as used in ref 11 unless otherwise noted. [b] Cloned human 5-HT_{1E} receptors expressed in CHO cells; [^{3}H]-5-HT.[21] [c] Cloned human D_2 receptors expressed in CHO cells; [^{125}I]iodosulpiride.[22] [d] Cloned human D_3 receptors expressed in CHO cells; [^{125}I]iodosulpiride.[22]

Thus, through the effects of conformational restriction we have identified in **11** (SB 206553) a high-affinity 5-$HT_{2C/2B}$ receptor antagonist with 120-fold (5-HT_{2C}) and *ca.* 500-fold (5-HT_{2B}) selectivities over the closely related 5-HT_{2A} site, and this compound was progressed for further evaluation as indicated below.

Compound **11** was evaluated in the 5-HT-stimulated phosphoinositol hydrolysis model of 5-HT_{2C} receptor activation, using the procedure previously adopted.[11] As can be seen in Figure 2, the presence of **11** at 10^{-6} M (a concentration exhibiting no intrinsic activity) caused a pronounced parallel shift of the PI response to 5-HT, maximal response still being attainable with 10^{-4} M 5-HT. These effects of **11** on the PI response are consistent with competitive inhibition; the compound's calculated pK_B value (8.8), however, is slightly higher than its affinity for the 5-HT_{2C} receptor (8.0).

Compound **11** has been tested for affinity for other receptor sites (Table 2); of all the receptors tested, only the rat 5-HT_4 receptor showed any measurable affinity, and that only at a high concentration (pK_I 5.3).

Compound **11** was further evaluated in an *in vivo*, centrally mediated, functional assay, namely mCPP-induced hypolocomotion.[4,8] It was found that **11** blocked the hypolocomotion response to mCPP with an ID_{50} of 5.5 mg/kg po; this represents a 3–4-fold increase in potency over the previous lead compound **1**, which had an ID_{50} of 19.2 mg/kg po.[12]

In conclusion, we report the synthesis and biological profile of a series of conformationally restricted analogues of the previous lead indole urea **1**. With compound **11**, we have identified a novel 5-$HT_{2C/2B}$ receptor antagonist with high affinity and 120-fold (5-HT_{2C}) and

ca. 500-fold (5-HT$_{2B}$) selectivities over the closely related 5-HT$_{2A}$ and other receptors; this should prove to be a valuable tool in the investigation of the functional role of 5-HT$_{2C}$ receptors. We have also shown that **11** is orally active, having an ID$_{50}$ of 5.5 mg/kg po in the mCPP-induced hypolocomotion model. Based on earlier data with nonselective and moderately selective 5-HT$_{2C}$ receptor antagonists, we suggest that **11** (SB 206553), or related compounds, may have significant potential as novel anxiolytic agents. Further investigation of the biological properties of **11** will be reported in due course.

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 Büchi 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 were 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.

1,4-Dimethyl-5-nitroindole (3). 1-Methyl-5-nitroindole **2** (3.01 g, 17.1 mmol) was stirred under Ar in dry THF (100 mL) as MeMgBr (3 M in Et_2O, 8.5 mL, 25.5 mmol) was added, maintaining the temperature at −10 °C throughout. The mixture was stirred at −10 °C for 30 min, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (4.66 g, 20.5 mmol) was added, and the mixture was allowed to warm to ambient temperature over 30 min. It was then diluted with Et_2O, washed with $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography ($CHCl_3$) gave **3** (2.45 g, 75%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.83 (3H, s), 3.84 (3H, s), 6.70 (1H, d, J = 3 Hz), 7.20 (2H, m), 7.97 (1H, d, J = 9 Hz); MS *m/e* 190 (M^+).

2-(1-Methyl-5-nitro-4-indolyl)ethyl methanesulfonate (4). **3** (1.42 g, 7.5 mmol) and paraformaldehyde (0.22 g, 7.3 mmol) were stirred in dry DMSO (50 mL), and KOH (2.3 mL of an 18 mg/mL solution in EtOH, 0.7 mmol) was added. This mixture was stirred for 24 h, diluted with EtOAc, washed with water and brine, dried, and evaporated. Chromatography ($CHCl_3$ to elute residual **3**, then 0−50% EtOAc/CH_2Cl_2, gradient) gave **2-(1-methyl-5-nitro-4-indolyl)ethanol** (1.18 g, 72%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.85 (b), 3.51 (2H, t, J = 7 Hz), 3.84 (3H, s), 4.05 (2H, t, J = 7 Hz), 6.75 (1H, d, J = 3 Hz), 7.20 (2H, m), 7.94 (1H, d, J = 9 Hz); MS *m/e* 220 (M^+).

This material (0.50 g, 2.3 mmol) and Et_3N (0.38 mL, 2.7 mmol) were stirred in CH_2Cl_2 (10 mL), and $MeSO_2Cl$ (0.21 mL, 2.7 mmol) was added. The mixture was stirred for 10 min, when water (10 mL) was added, and then the resulting mixture was stirred vigorously for a further 10 min. After acidification with 5 M HCl and separation, the organic portion was dried and evaporated. Chromatography (0−100% CH_2Cl_2/$CHCl_3$, gradient) gave **4** (0.54 g, 79%) as an orange solid: ^{1}H NMR ($CDCl_3$) δ 2.93 (3H, s), 3.69 (2H, t, J = 7 Hz), 3.86 (3H, s), 4.64 (2H, t, J = 7 Hz), 6.80 (1H, d, J = 3 Hz), 7.24 (1H, d, J = 3 Hz), 7.29 (1H, d, J = 9 Hz), 8.00 (1H, d, J = 9 Hz); MS *m/e* 298 (M^+).

6-Methyl-1,2,3,6-tetrahydropyrrolo[3,2-*e*]indole Methanesulfonate Salt (6a). **4** (1.51 g, 1.3 mmol) was hydrogenated over 5% Pd/C (0.36 g) in dry DMF (20 mL) at 80 psi of H_2 for 4 h, when a further portion of catalyst (0.30 g) was added. Hydrogenation was continued for a further 24 h, when the mixture was diluted with EtOH (80 mL), filtered through kieselguhr, and evaporated to give crude **6a** as a black solid (1.52 g) containing residual DMF (NMR): ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 3.47 (2H, m), 3.82 (3H, s), 4.09 (2H, m), 6.44 (1H, d, J = 3 Hz), 7.18 (1H, d, J = 3 Hz), 7.2−7.5 (m), 10.85 (2H, b).

6-Methyl-3-(3-pyridylcarbamoyl)-1,2,3,6-tetrahydropyrrolo[3,2-*e*]indole (7a). Nicotinoyl azide (0.79 g, 5.3 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 quantities of nitrogen are rapidly evolved. Appropriate precautions for the storage and utilisation of this reagent are strongly advised.) was stirred at reflux under N_2 in dry toluene (10 mL) for 45 min, and cooled to ambient temperature. Et_3N (0.70 mL, 5.0 mmol) was added, followed by the crude **6a** (1.52 g) in CH_2Cl_2 (10 mL). The mixture was stirred for 20 h, with precipitation. The solid was then collected, washed with 1:1 CH_2Cl_2/toluene, and thoroughly dried. The crude material (0.87g) was recrystallized from EtOH, giving **7a** (0.68g, 46% from **4**) as a gray powder: mp 215 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.33 (2H, t, J = 8 Hz), 3.77 (3H, s), 4.22 (2H, t, J = 8 Hz), 6.28 (1H, d, J = 3 Hz), 7.23 (1H, d, J = 8 Hz), 7.3 (2H, m), 7.89 (1H, d, J = 8 Hz), 8.00 (1H, d, J = 8 Hz), 8.20 (1H, d, J = 5 Hz), 8.61 (1H, s), 8.75 (1H, d, J = 2 Hz); MS *m/e* 292 (M^+). Anal. ($C_{17}H_{16}N_4O\cdot H_2O$) C, H, N.

3-(1-Methyl-5-nitro-4-indolyl)-1-propyl methanesulfonate (5). **4** (1.60 g, 5.4 mmol) and NaCN (0.53 g, 10.8 mmol) were stirred in dry DMSO (15 mL) at 100 °C under Ar for 5 h. After cooling, the mixture was diluted with EtOAc (150 mL), washed with water, dried, and evaporated to give **3-(1-methyl-5-nitro-4-indolyl)propionitrile** (1.16 g, 94%) as a brown solid: ^{1}H NMR ($CDCl_3$) δ 2.93 (2H, t, J = 7 Hz), 3.60 (2H, t, J = 7 Hz), 3.87 (3H, s), 6.80 (1H, d, J = 3 Hz), 7.3 (2H, m), 8.05 (1H, d, J = 8 Hz); MS *m/e* 229 (M^+).

This nitrile (1.16 g, 5.1 mmol) was stirred at reflux in concentrated HCl (150 mL) for 7.5 h. After cooling, the dark mixture was extracted with EtOAc; the extract was dried and evaporated to give **3-(1-methyl-5-nitro-4-indolyl)propanoic acid** (0.74 g, 59%) as a brown solid: ^{1}H NMR ($CDCl_3$) δ 2.88 (2H, t, J = 7 Hz), 3.55 (2H, t, J = 7 Hz), 3.84 (3H, s), 6.76 (1H, d, J = 3 Hz), 7.21 (1H, d, J = 3 Hz), 7.25 (1H, d, J = 8 Hz), 7.98 (1H, d, J = 8 Hz); MS *m/e* 248 (M^+).

This acid (0.94 g, 3.8 mmol) was stirred in MeOH (10 mL) as $SOCl_2$ (1 mL) was added dropwise. The mixture was then stirred at reflux for 2 h and evaporated. Chromatography (CH_2Cl_2) gave **methyl 3-(1-methyl-5-nitro-4-indolyl)propanoate** (0.58 g, 58%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.81 (2H, t, J = 7 Hz), 3.55 (2H, t, J = 7 Hz), 3.70 (3H, s), 3.84 (3H, s), 6.73 (1H, d, J = 3 Hz), 7.20 (1H, d, J = 3 Hz), 7.24 (1H, d, J = 8 Hz), 7.97 (1H, d, J = 8 Hz); MS *m/e* 262 (M^+).

This ester (0.46 g, 1.8 mmol) was stirred under Ar in THF (25 mL) as $LiAlH_4$ (0.10 g, 2.6 mmol) was added portionwise. After 3 h, water (0.5 mL), 2.5 M NaOH solution (0.75 mL), and water (1.5 mL) were successively added. The mixture was then dried, filtered, and evaporated to a brown oil. Chromatography (0−20% EtOAc/CH_2Cl_2, gradient) gave **3-(1-methyl-5-nitro-4-indolyl)-1-propanol** (0.39 g, 95%) as an orange solid: ^{1}H NMR ($CDCl_3$) δ 2.05 (2H, m), 3.34 (2H, t, J = 7 Hz), 3.78 (2H, q, J = 6 Hz), 3.85 (4H, m), 6.77 (1H, d, J = 3 Hz), 7.18 (1H, d, J = 3 Hz), 7.22 (1H, d, J = 8 Hz), 7.96 (1H, d, J = 8 Hz).

This alcohol (0.39 g, 1.7 mmol) was mesylated as in the preparation of **4**. This gave **5** (0.54 g) as a brown oil, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 2.25 (2H, m), 3.05 (3H, s), 3.36 (2H, t, J = 7 Hz), 3.84 (3H, s), 4.37 (2H, t, J = 7 Hz), 6.73 (1H, d, J = 3 Hz), 7.21 (1H, d, J = 3 Hz), 7.25 (1H, d, J = 8 Hz), 7.98 (1H, d, J = 8 Hz).

3-Methyl-6,7,8,9-tetrahydro-3*H*-pyrrolo[3,2-*f*]quinoline (6b). **5** (0.54 g, 1.7 mmol) was hydrogenated over 5% Pd/C (0.5 g) in EtOH (50 mL) at 50 psi of H_2 for 6 h. The mixture was filtered through kieselguhr, evaporated, dissolved

in $CHCl_3$, washed with $NaHCO_3$ solution, dried, and evaporated again to **6b** (0.21 g, 65%), as a brown oil: ^1H NMR ($CDCl_3$) δ 2.05 (2H, m), 2.95 (2H, t, J = 6 Hz), 3.32 (2H, t, J = 6 Hz), 3.63 (1H, b), 3.73 (3H, s), 6.30 (1H, d, J = 3 Hz), 6.56 (1H, d, J = 8 Hz), 6.96 (1H, d, J = 3 Hz), 7.00 (1H, d, J = 8 Hz).

3-Methyl-*N*-(3-pyridyl)-6,7,8,9-tetrahydro-3*H*-pyrrolo-[3,2-*f*]quinoline-6-carboxamide (7b). This was prepared from **6b** (0.21 g, 1.1 mmol) and nicotinoyl azide (0.20 g, 1.3 mmol) as in the preparation of **7a** (**CAUTION!** See details concerning the potential hazard of this reagent, above), but omitting the addition of Et_3N. The reaction was worked up by evaporation to give a brown oil, which was chromatographed (0–10% MeOH/CH_2Cl_2, gradient). Recrystallization from EtOH/petroleum ether (bp 60–80 °C) gave **7b** (0.26 g, 75%) as a cream-colored solid: mp 174–5 °C, containing residual EtOH (NMR); ^1H NMR (DMSO-d_6) δ 1.98 (2H, m), 2.94 (2H, t, J = 7 Hz), 3.75 (5H, m), 6.41 (1H, d, J = 3 Hz), 7.13 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 8 Hz), 7.25–7.30 (2H, m), 7.89 (1H, m), 8.15 (1H, d, J = 3 Hz), 8.64 (1H, m) 8.77 (1H, s); MS *m/e* 306 (M^+). Anal. ($C_{18}H_{18}N_4O$·(0.14C_2H_6O)) C, H, N.

***N*-(1-Acetyl-5-indolinyl)-2,2-dimethoxyethylamine (9).** 1-Acetyl-5-aminoindoline **8** (28.26 g, 161 mmol) and 2,2-dimethoxyacetaldehyde (28.35 g, 273 mmol) were hydrogenated at atmospheric pressure over 5% Pd/C (15.0 g) in EtOH (800 mL) for 3 days. The mixture was filtered through kieselguhr, evaporated, dissolved in EtOAc (1000 mL), washed with water, dried, and evaporated to give **9** (39.62 g, 93%) as a white solid: ^1H NMR ($CDCl_3$) δ 2.19 (3H, s), 3.12 (2H, t, J = 8 Hz), 3.22 (2H, d, J = 5 Hz), 3.41 (6H, s), 3.45 (1H, b), 4.56 (1H, t, J = 5 Hz), 6.50 (2H, m), 8.03 (1H, d, J = 8 Hz); MS *m/e* 292 (M^+).

1-Acetyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (10b). **9** (6.51 g, 22 mmol) was added to an ice-cold, stirred mixture of CF_3CO_2H (25 mL) and $(CF_3CO)_2O$ (25 mL). The mixture was stirred at 0 °C under N_2 for 30 min, when further CF_3CO_2H (40 mL) was added. The mixture was then heated at reflux for 64 h, cooled, and evaporated to dryness. Chromatography (0–60% EtOAc/$CHCl_3$, gradient) then gave **1-acetyl-5-(trifluoroacetyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (10a)** (6.28 g, 89%) as a light cream-colored solid which darkened slightly on standing: ^1H NMR ($CDCl_3$) δ 2.33 (3H, s), 3.37 (2H, t, J = 8 Hz), 4.17 (2H, t, J = 7 Hz), 6.76 (1H, d, J = 3 Hz), 7.45 (1H, m), 8.27 (1H, s), 8.44 (1H, s); MS *m/e* 296 (M^+).

This material (2.80 g, 9.4 mmol) was suspended with stirring in MeOH (100 mL), and anhydrous K_2CO_3 (1.96 g, 14.2 mmol) was added. The mixture was stirred for 30 min, evaporated to near-dryness, and partitioned between EtOAc and water. After separation, the aqueous portion was extracted with 5% MeOH/$CHCl_3$, and the combined organics were dried, filtered, and evaporated, giving **10b** (1.53 g, 80%) as a cream-colored solid: ^1H NMR (DMSO-d_6) δ 2.15 (3H, s), 3.18 (2H, t, J = 8 Hz), 4.08 (2H, t, J = 8 Hz), 6.33 (1H, b s), 7.2 (2H, m), 8.22 (1H, s), 10.9 (1H, b s); MS *m/e* 200 (M^+).

1-Acetyl-5-methyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (10c). NaH (80% dispersion in mineral oil, 0.25 g, 8.3 mmol) was stirred under nitrogen in dry DMF (5 mL), as **10b** (1.52 g, 7.6 mmol) was added in DMF (20 mL), with effervescence. The mixture was stirred for 30 min, and MeI (0.52 mL, 8.3 mmol) was then added in DMF (5 mL). After the mixture was stirred for a further 1 h, excess NaH was quenched by addition of water (1 mL), and the mixture was partitioned between EtOAc and water and separated. The organic portion was washed with water and brine, dried, and evaporated. Chromatography (0–50% EtOAc/$CHCl_3$, gradient) then gave **10c** (0.80g, 49%) as a pale yellow solid. NMR showed a *ca.* 5:1 mixture of rotamers: ^1H NMR ($CDCl_3$) δ 2.26 (major, 3H, s), 2.51 (minor, 3H, s), 3.16 (minor, 2H, t, J = 8 Hz), 3.3 (major, 2H, t, J = 8 Hz), 3.74 (major, 3H, s), 3.77 (minor, 3H, s), 4.1 (major, 2H, t, J = 8 Hz), 4.19 (minor, 2H, t, J = 8 Hz), 6.44 (both, 1H, d, J = 2 Hz), 6.98 (major, 1H, d, J = 2 Hz), 7.0 (minor, m), 7.09 (major, 1H, s), 7.18 (minor, 1H, s), 7.31 (minor, 1H, s), 8.48 (major, 1H, s); MS *m/e* 214 (M^+).

5-Methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (11). **10c** (0.70 g, 3.3 mmol) was stirred at reflux under N_2 in 2.5 M NaOH solution (50 mL) for 4 h. The mixture was cooled, diluted with water (200 mL), and extracted with EtOAc. The extract was dried and evaporated to give **5-methyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole** (0.58 g) as a light brown gum, still containing *ca.* 20% of the starting amide (NMR). This material was used without purification: ^1H NMR ($CDCl_3$) δ 3.12 (2H, t, J = 9 Hz), 3.33 (1H, b s), 3.56 (2H, t, J = 9 Hz), 3.7 (3H, s), 6.27 (1H, d, J = 3 Hz), 6.85 (1H, s), 6.9 (1H, d, J = 3 Hz), 7.08 (1H, s).

Nicotinoyl azide (0.56 g, 3.8 mmol) (**CAUTION!** See details concerning the potential hazard of this reagent, above) was stirred at reflux under N_2 in dry PhMe (20 mL) for 45 min and cooled to ambient temperature. The crude 5-methyl-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (0.58 g) was added in CH_2Cl_2 (20 mL) with stirring and with immediate precipitation. The suspension was stirred for 2.5 h, and the solid was then filtered off, washed with 1:1 CH_2Cl_2/PhMe, and thoroughly dried. This gave 11 (0.60 g, 63% from **10c**) as a light gray powder. Recrystallization (EtOH) of a portion of this material gave light gray crystals: mp 213–215.5 °C; ^1H NMR (DMSO-d_6) δ 3.28 (2H, t, J = 8 Hz), 3.73 (3H, s), 4.17 (2H, t, J = 8 Hz), 6.81 (1H, d, J = 3 Hz), 7.1–7.35 (3H, m), 8.0 (1H, m), 8.03 (1H, s), 8.21 (1H, m), 8.63 (1H, s), 8.76 (1H, d, J = 2 Hz); MS *m/e* 292 (M^+). Anal. ($C_{17}H_{16}N_4O$) C, H, N.

***N*-(1-Acetyl-1,2,3,4-tetrahydro-6-quinolyl)trifluoroacetamide (13).** 6-Aminoquinoline **12** (5.75 g, 40 mmol) and Et_3N (6.7 mL, 48 mmol) were stirred in $CHCl_3$ (100 mL), and $(CF_3CO)_2O$ (6.7 mL, 48 mmol) was added over 2 min. The mixture was stirred for 1 h, when water (100 mL) was added. After stirring for 5 min, the gummy precipitate was filtered off, washed with $CHCl_3$ and water, and dried *in vacuo* at 50 °C. This gave ***N*-(6-quinolyl)trifluoroacetamide** (7.68 g, 80%) as a straw-colored semisolid, containing residual triethylamine (NMR): ^1H NMR (DMSO-d_6) δ 7.57 (1H, dd, J = 9 Hz, 4 Hz), 7.97 (1H, dd, J = 9 Hz, 2 Hz), 8.08 (1H, d, J = 9 Hz), 8.4 (2H, m), 8.90 (1H, dd, J = 5 Hz, 2 Hz), 11.63 (1H, s); MS *m/e* 240 (M^+).

This material (6.84 g, 28.5 mmol) and $NiCl_2$·$6H_2O$ (1.36 g, 5.71 mmol) were stirred in MeOH (100 mL), and $NaBH_4$ (4.3 g, 113 mmol) was added portionwise over 30 min. After the mixture was stirred for a further 30 min, another portion of $NaBH_4$ (1.0g, 26 mmol) was added. After another 30 min, the mixture was evaporated to dryness, partitioned between 5 M HCl (25 mL) and EtOAc (100 mL), and stirred until clear. This mixture was neutralized with excess $NaHCO_3$ and separated. The aqueous portion was extracted with further EtOAc, and the combined organics were washed with brine, dried, and evaporated. Chromatography (0–30% EtOAc/$CHCl_3$, gradient) gave ***N*-(1,2,3,4-tetrahydro-6-quinolyl)trifluoroacetamide** (5.07 g, 73%) as a pale greenish solid: ^1H NMR ($CDCl_3$) δ 1.44 (2H, m), 2.75 (2H, t, J = 6 Hz), 3.31 (2H, t, J = 6 Hz), 3.92 (1H, b s), 6.45 (1H, d, J = 9 Hz), 7.09 (1H, dd, J = 9 Hz, 2 Hz), 7.16 (1H, d, J = 2 Hz), 7.65 (1H, b s); MS *m/e* 244 (M^+).

This material (5.64 g, 23.1 mmol) and AcCl (2.0 mL, 28 mmol) were stirred in CH_2Cl_2 (100 mL) as pyridine (2.25 mL, 28 mmol) was added. The mixture was stirred for 30 min, when water (100 mL) was added. After vigorous stirring for 15 min, it was acidified with 5 M HCl, and separated. The organic portion was washed with brine, dried, and evaporated, giving **13** (5.24 g, 79%) as a cream-colored solid: ^1H NMR ($CDCl_3$) δ 1.99 (2H, m), 2.25 (3H, s), 2.57 (2H, t, J = 6 Hz), 3.78 (2H, t, J = 6 Hz), 7.3 (b), 7.52 (1H, b s), 8.08 (1H, b s); MS *m/e* 286 (M^+).

5-Acetyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]quinoline (14a). **13** (1.85 g, 6.5 mmol) was stirred in EtOH (15 mL), and NaOH (0.52 g, 13.0 mmol) was added in water (3 mL). The mixture was stirred at ambient temperature for 30 min and then heated to reflux over 15 min. After 30 min at reflux, the mixture was cooled, acidified with 5 M HCl, basified with solid Na_2CO_3, diluted with water (100 mL), and extracted with $CHCl_3$. The extract was dried and evaporated to give **1-acetyl-6-amino-1,2,3,4-tetrahydroquinoline** (1.38 g) as a brown oil containing residual chloroform (NMR): ^1H NMR

($CDCl_3$) δ 1.92 (2H, m), 2.27 (3H, s), 2.60 (2H, m), 3.67 (2H, b s), 3.79 (2H, b m), 6.5 (2H, m), 6.87 (1H, b d, J = 6 Hz); MS *m/e* 190 (M^+).

This material (2.35 g, 12.4 mmol) and $^iPr_2NEt$ (2.7 mL, 15.5 mmol) were stirred in 1,2-dichloroethane (DCE) (50 mL) under Ar. 2,2-Diethoxyethyl trifluoromethanesulfonate (prepared from glycolaldehyde diethyl acetal and Tf_2O) (3.78 g, *ca.* 90% purity, *ca.* 13 mmol) was added dropwise in DCE (10 mL) over 5 min. The mixture was then stirred at reflux for 30 min, cooled, washed with water, dried, and evaporated to give a black oil. This was combined with material obtained by an identical procedure using 1.40 g of the aminoquinoline reagent and chromatographed (0–100% EtOAc/$CHCl_3$, gradient). This gave **1-acetyl-6-[(2,2-diethoxyethyl)amino]-1,2,3,4-tetrahydroquinoline** (3.72 g, 61%) as an amber oil, contaminated with a little dialkylated material (NMR, MS): ^1H NMR ($CDCl_3$) δ 1.25 (6H, t, J = 7 Hz), 1.92 (2H, m), 2.20 (3H, s), 2.63 (2H, b m), 3.25 (2H, t, J = 5 Hz), 3.5–3.9 (7H, m), 4.69 (1H, t, J = 6 Hz), 6.45 (2H, m), 6.89 (1H, b d, J = 6 Hz); MS *m/e* 306 (M^+).

This material (3.72 g, 12.2 mmol) was stirred at 0 °C under Ar in a mixture of CF_3CO_2H (20 mL) and $(CF_3CO)_2O$ (20 mL) for 30 min. Further CF_3CO_2H (30 mL) was added, and the solution was then stirred at reflux for 90 h, cooled, and evaporated to give a black gum. Chromatography (0–60% EtOAc/$CHCl_3$, gradient) gave **5-acetyl-1-(trifluoroacetyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]quinoline (14a)** (2.77 g, 73%) as an amber oil: ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.03 (2H, m), 2.25 (3H, s), 2.87 (2H, t, J = 6 Hz), 3.80 (2H, t, J = 7 Hz), 6.83 (1H, d, J = 4 Hz), 7.51 (2H, m), 8.25 (1H, s).

This material (2.76 g, 8.9 mmol) and anhydrous K_2CO_3 (3.7 g, 27 mmol) were stirred in MeOH (50 mL) for 1 h. The mixture was then concentrated *in vacuo*, diluted with water (100 mL), and extracted with $CHCl_3$. The extract was dried and evaporated, giving **14b** (1.40 g, 73%) as an orange-brown solid. NMR showed a mixture of rotamers in approximate ratio 9:1: ^1H NMR ($CDCl_3$) δ 1.97 (2H, major, m), 2.07 (2H, minor, m), 2.22 (3H, both, s), 2.73 (2H, major, t, J = 6 Hz), 3.01 (2H, minor, t, J = 6 Hz), 3.86 (2H, both, t, J = 7 Hz), 6.52 (1H, both, m), 7.20 (2H, both, m), 7.34 (1H, major, s), 8.33 (1H, both, b); MS *m/e* 214 (M^+).

5-Acetyl-1-methyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]quinoline (14c). **14b** (1.39 g, 6.5 mmol) in dry DMF (20 mL) was added, with stirring under Ar, to a suspension of NaH (80% dispersion in mineral oil, 0.25 g, 8.3 mmol) in DMF (5 mL). After the mixture was stirred for 20 min, MeI (0.61 mL, 9.8 mmol) was added. The resulting suspension was stirred for 1 h, diluted with water (100 mL), and extracted with EtOAc. The extract was washed with water and brine, dried, and evaporated to give a gum. Chromatography (0–100% EtOAc/$CHCl_3$, gradient) gave **14c** (0.97 g, 65%) as a pale, straw-colored oil which solidified on standing. NMR showed a mixture of rotamers in approximate ratio 6:1: ^1H NMR ($CDCl_3$) δ 1.97 (2H, both, m), 2.20 (3H, both, s), 2.75 (2H, major, t, J = 6 Hz), 2.98 (2H, minor, t, J = 6 Hz), 3.78 (3H, both, s), 3.84 (2H, both, t, J = 7 Hz), 6.45 (1H, both, d, J = 3 Hz), 7.04 (1H, both, d, J = 3 Hz), 7.12 (1H, both, s), 7.31 (1H, both, s); MS *m/e* 228 (M^+).

1-Methyl-*N*-(3-pyridyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo-[2,3-*g*]quinoline-5-carboxamide (15). **14c** (0.96 g, 4.2 mmol) was dissolved in EtOH (10 mL), and 2.5 M NaOH (90 mL) was added. This mixture was stirred at reflux under Ar for 23 h, cooled, diluted with water (200 mL), and extracted with EtOAc. The extract was dried and evaporated to give **1-methyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]quinoline** (0.64 g, 81%) as a light brown gum: ^1H NMR ($CDCl_3$) δ 2.00 (2H, m), 2.95 (2H, t, J = 6 Hz), 3.0 (1H, b), 3.30 (2H, t, J = 5.5 Hz), 3.68 (3H, s), 6.20 (1H, d, J = 3 Hz), 6.72 (1H, s), 6.87 (1H, d, J = 3 Hz), 6.92 (1H, s); MS *m/e* 186 (M^+).

Nicotinoyl azide (0.56 g, 3.8 mmol) (**CAUTION!** See details concerning the potential hazard of this reagent, above) was stirred at reflux under N_2 in dry PhMe (10 mL) for 45 min and cooled to ambient temperature. The crude 1-methyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]quinoline (0.64 g, 3.4 mmol) was added in CH_2Cl_2 (10 mL). The solution was stirred for 3 days (without precipitate formation) and then concentrated to remove CH_2Cl_2. The solid so formed was then filtered off, washed with dry PhMe, and thoroughly dried. This crude material (0.64 g) was recrystallized from EtOH/petroleum ether (bp 60–80 °C) to give **15** (0.56 g, 53%) as lustrous pale orange plates: mp 154.5–155.5 °C; ^1H NMR (DMSO-d_6) δ 1.93 (2H, m), 2.80 (2H, t, J = 7 Hz), 3.72 (2H, t, J = 7 Hz), 3.77 (3H, s), 6.34 (1H, d, J = 3 Hz), 7.25 (3H, m), 7.49 (1H, s), 7.89 (1H, dt, J = 8 Hz, 2 Hz), 8.15 (1H, dd, J = 4 Hz, 2 Hz), 8.65 (2H, m); MS *m/e* 306 (M^+). Anal. ($C_{18}H_{18}N_4O$) C, N; H.[23]

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