3-(4-Fluoropiperidin-3-yl)-2-phenylindoles as High Affinity, Selective, and Orally Bioavailable h5-HT$_{2A}$ Receptor Antagonists†

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The development of very high affinity, selective, and bioavailable h5-HT$_{2A}$ receptor antagonists is described. By investigation of the optimal position for the basic nitrogen in a series of 2-phenyl-3-piperidylindoles, it was found that with the basic nitrogen at the 3-position of the piperidine it was not necessary to further substitute the piperidine in order to obtain good binding at h5-HT$_{2A}$ receptors. This meant the compounds no longer had high affinity at the IKr potassium channel, an issue with previous series of 2-aryl-3-(4-piperidyl)indoles. Improvements could be made to oral bioavailability in this series by reduction of the pK_a of the basic nitrogen, by adding a fluorine atom to the piperidine ring, leading to 3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (**17**). Metabolic studies with this compound identified oxidation at the 6-position of the indole as a major route in vitro and in vivo in rats. Blocking this position with a fluorine atom led to 6-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (**22**), an antagonist with 0.06 nM affinity for h5-HT$_{2A}$ receptors, with bioavailability of 80% and half-life of 12 h in rats.

Introduction

Schizophrenia is a severe psychiatric illness which affects approximately 1% of the population. The disease is characterized by positive symptoms, including delusions, hallucinations, and irrational fears, negative symptoms, such as social withdrawal and the inability to experience pleasure, and cognitive disruption.[1] Classical neuroleptics, which are presumed to act by antagonism of dopamine D$_2$ receptors,[2,3] are useful for the treatment of the positive symptoms but cause mechanism based side effects such as movement disorders and increases in serum prolactin. The first of the 'atypical' neuroleptics, clozapine[4] (**1**, Figure 1), is used to treat both positive and negative symptoms of the illness, does not cause extrapyramidal side effects (EPS), and is also beneficial in a number of patients refractory to the effects of classical neuroleptics. However, in a small but significant number of patients, clozapine causes agranulocytosis, and its use must be closely monitored.[5] A decade ago it was suggested[6] that an important feature of atypical antipsychotic drugs was their relative affinities at serotonin 5-HT$_2$ and dopamine D$_2$ receptors, and that affinity higher at the former than the latter led to an atypical profile. Recent years have seen the introduction of a number of new drugs with combined 5-HT$_2$/D$_2$ (among others) affinities, such as risperidone (**2**),[7] olanzapine (**3**),[8] and sertindole (**4**).[9] These drugs have a decreased, though perhaps not completely absent, propensity to cause EPS compared to classical neuroleptics,[10] and the first two are being used increasingly. Sertindole has recently been withdrawn from use because of prolongation of corrected QT interval[11,12] in some patients, presumably due to this compound's effects at IKr channels, a voltage gated ion channel involved[13] in control of the heart rhythm. Side effects that still remain troublesome in the newer neuroleptics include weight gain, sexual dysfunction, and sedation

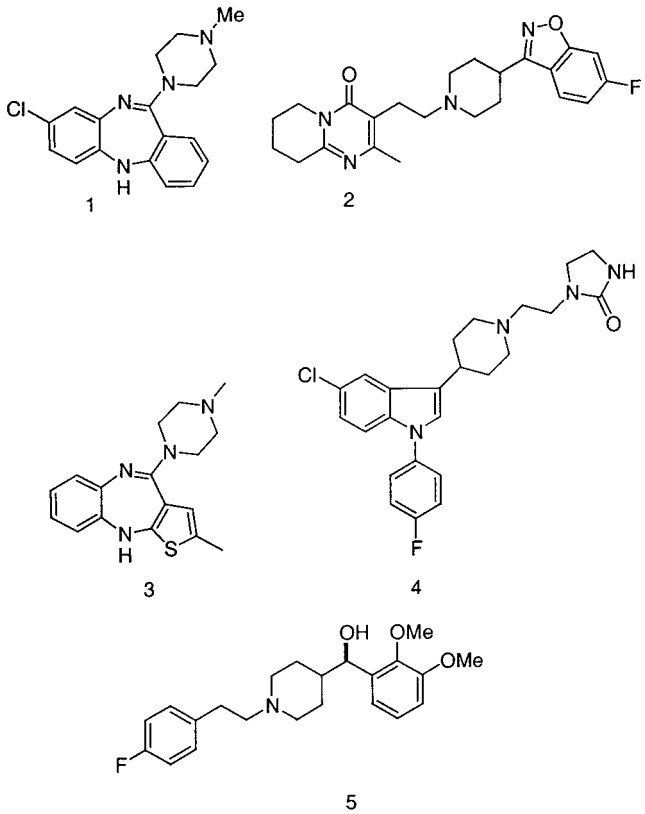

Figure 1. Recent and potential neuroleptics.

† Dedicated to Professor Ian Fleming on the occasion of his 65th birthday.

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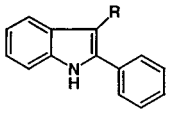
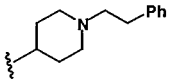
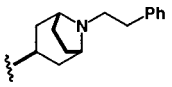
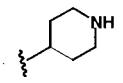
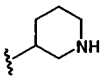
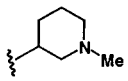
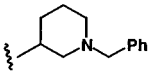
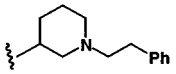
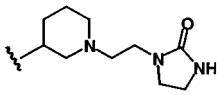
Table 1. Position of the Basic Nitrogen



Number	R	Ki / nM[a] h5HT$_{2A}$	hD$_2$	h5HT$_{2C}$	rat α_1	IKr
6		0.48	350	79	25	80
7		1.2	1000	400	250	18
8		12	>1600	400	2100	5700
9		0.99	>1300	89	21	4900
10		4.7	28	150	30	9600
11		14	>1700	2000	99	7000
12		20	1600	2000	47	290
13		59	500	2400		530
14		26	>1300	2500		

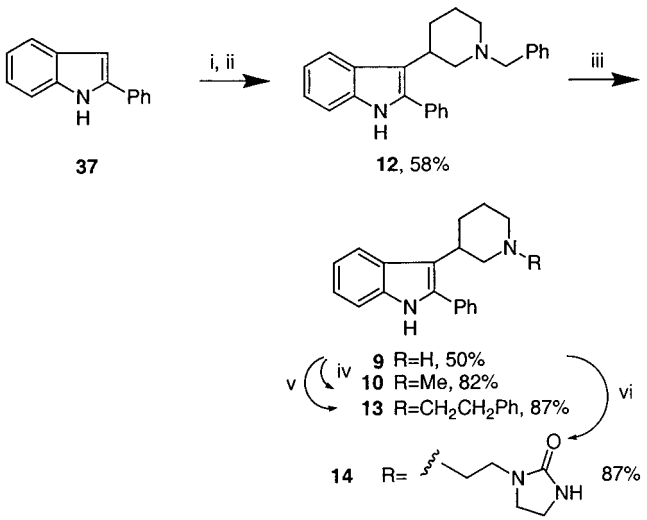
[a] Affinities at human cloned 5-HT$_{2A}$, 5-HT$_{2C}$, and D$_2$ receptors, rat α_1 adrenergic receptors, and the IKr potassium channel (hERG).

and orthostatic hypotension, the last two probably arising from antagonism of α1 adrenergic receptors.[10] There is clearly still a need for improved therapy in this area.

Although the importance of the 5-HT$_2$ receptor in schizophrenia was hypothesized more than 10 years ago, until recently no selective receptor antagonist had been tested in clinical trials. 5-HT$_2$ receptors have been cloned,[14] with the current classification being 5-HT$_{2A}$, 5-HT$_{2B}$, and what was 5-HT$_{1C}$ reclassified as 5-HT$_{2C}$. Compound **5** (MDL100907[15]) is a high affinity human 5-HT$_{2A}$ receptor antagonist with selectivity over h5-HT$_{2C}$ (40−50-fold in our binding assay) and α1 (>1000-fold) receptors and very low affinity at all the dopamine receptor subtypes. In a phase II clinical trial[16] for schizophrenia, **5** was claimed to improve both positive and negative symptoms, with no increase in body weight or serum prolactin, and EPS similar to placebo. This result seemed to indicate the first nondopamine D$_2$ mediated, well-understood mechanism for treating schizophrenia and offered a chance of a real breakthrough in the treatment of this disease.

We have described some of our own efforts in this area, with the objective of discovering a novel high affinity h5-HT$_{2A}$ antagonist with at least comparable

Scheme 1[a]



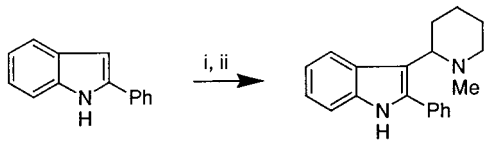
[a] Reagents: (i) 1-benzyl-3-piperidone, H_3PO_4, AcOH; (ii) H_2/Pd/C; (iii) NH_4CO_2H, Pd/C, MeOH, reflux; (iv) HCHO, $NaCNBH_3$, AcOH; (v) $PhCH_2CH_2Br$, $CsCO_3$, DMF; (vi) 1-(2-chloroethyl)-2-imidazolidinone, $CsCO_3$, DMF.

binding selectivity to **5** over 5-HT$_{2C}$ receptors and negligible affinity at dopamine receptors and IKr channels. We also considered good pharmacokinetics in two species vital both for safety assessment and to be predictive of appropriate pharmacokinetics in humans. Previous reports include the discovery of 2-aryltryptamines as high affinity selective h5-HT$_{2A}$ antagonists,[17] albeit with low oral bioavailability, and modifications to the amine side chain that led to compounds with modest rat oral bioavailability.[18] The phenethylpiperidine (**6**, Table 1) had subnanomolar 5-HT$_{2A}$ affinity and 12% oral bioavailability in rats, which was improved to 18% by the [3.2.1] bicyclic analogue (**7**). Along with the desire to further improve bioavailability, a major issue with this type of compound was the high affinity at the IKr potassium channel: compounds **6** and **7** had affinities of 80 and 18 nM, respectively. On the basis of our knowledge of the pharmacophore for binding to the IKr channel, we believed that this affinity was in large part due to the phenethyl group on the basic nitrogen, which in these series was necessary for high affinity binding to the 5-HT$_{2A}$ receptor. In this paper we describe the synthesis of 2-aryl-3-substituted indoles where the position of the basic nitrogen has been moved and show that with 3-substituted piperidines the phenethyl group is not necessary for high affinity. By modifications to the indole core, and adjustment of the pK_a of the basic nitrogen, compounds with good bioavailability have been discovered.

Synthesis

Compounds **6**, **7**, **8**,[18] **17**, and **18**[20] have been described. 3-Substituted piperidines (**9**, **10**, **12**−**14**) were made by the route shown in Scheme 1. 2-Phenylindole was condensed under acidic conditions[19] with *N*-benzyl-3-piperidone to give a mixture of regioisomeric tetrahydropyridines. This unstable mixture was hydrogenated without purification to give the *N*-benzylpiperidine (**12**). The benzyl group was then hydrogenolyzed from the basic nitrogen by transfer hydrogenation with ammonium formate as the reductant. Reductive alkylation

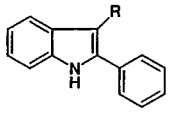
Scheme 2[a]

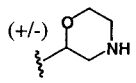
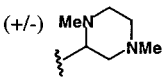
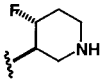
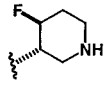
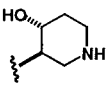


37 **11**, 73%

[a] Reagents: (i) 1-methyl-2-piperidone, $POCl_3$, 80 °C; (ii) $NaBH_4$, MeOH.

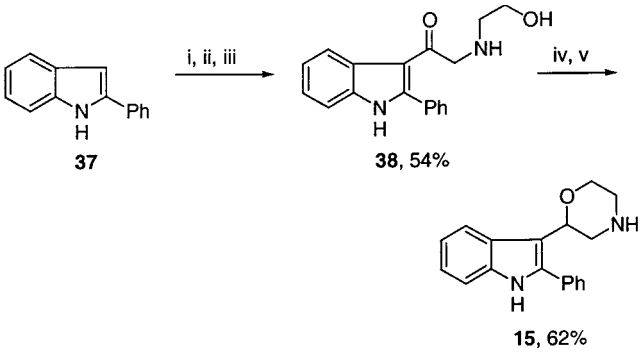
Table 2. Alternatives to Piperidine



Number	R	h5HT$_{2A}$	hD$_2$	Ki / nM[a] h5HT$_{2C}$	rat α_1	IKr
15	(+/-) 	18	1600			
16	(+/-) 	320	>1600			
17	(+) 	0.43	>1700	19	25	>1100
18	(-) 	220	>1700			
19	(+/-) 	3.3	>1600			

[a] See footnotes to Table 1.

Scheme 3[a]

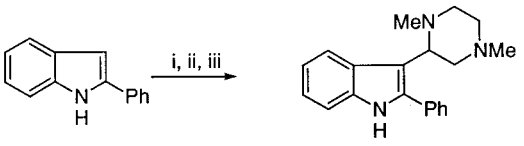


37 **38**, 54% **15**, 62%

[a] Reagents: (i) MeMgBr, benzene; (ii) chloroacetyl chloride; (iii) ethanolamine, Et_3N, MeOH; (iv) $NaBH_4$, MeOH; (v) HCl, MeOH.

of the basic nitrogen with formaldehyde and sodium cyanoborohydride gave the *N*-methyl analogue (**10**), and alkylation with the appropriate alkyl halide gave the phenethyl compound (**13**) and the imidazolidinone (**14**). The 2-substituted piperidine (**11**) was made (Scheme 2) by condensation of 2-phenylindole with 1-methyl-2-piperidone, followed by reduction of the resultant tetrahydropyridine without purification with sodium borohydride. Morpholine (**15**, Table 2) was made by acylation (Scheme 3) of the anion of 2-phenylindole with chloroacetyl chloride. The chloroketone was then displaced with ethanolamine to give the alcohol (**38**). Reduction of the ketone, followed by cyclization under acidic conditions, gave the desired product. Piperazine (**16**)

Scheme 4[a]

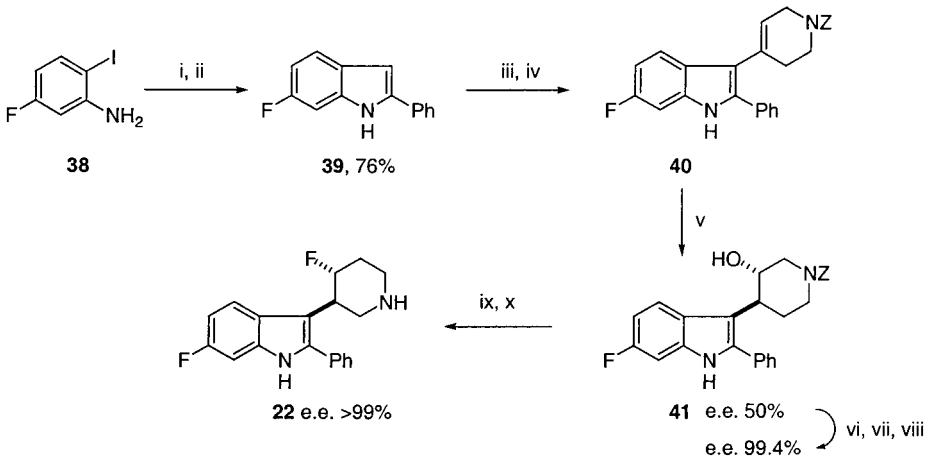


37 **16**, 55%

[a] Reagents: (i) sarcosine anhydride, $POCl_3$, 100 °C; (ii) $NaBH_4$, MeOH; (iii) $LiAlH_4$, THF, reflux.

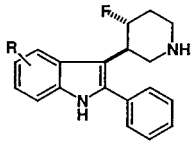
was made as shown in Scheme 4. Activation of *N*,*N*-dimethylpiperazinone with phosphorus oxychloride allowed its condensation with 2-phenylindole, which was then followed by in situ reduction with sodium borohydride. The resulting piperazinone was further reduced with lithium aluminum hydride to give the final compound. The synthesis of compounds **17** and **18** were the subject of a separate paper[20] in which we described a novel rearrangement to give trans 3-indolyl-4-fluoropiperidines as single enantiomers. The route is exemplified in Scheme 5 for the 6-fluoroindole analogue (**22**), along with one of the methods that was used to make the required substituted 2-arylindole starting material. Thus, 2-iodo-5-fluoroaniline (**38**) was condensed with phenylacetylene under palladium catalysis, then cyclized with copper catalysis to give 6-fluoro-2-phenylindole (**39**). Condensation with 4-piperidone under acidic conditions gave the tetrahydropyridine, which was protected as its benzyloxycarbonyl derivative (**40**). Hydroboration of the double bond with bis-isopinocampheylborane[21] (from (1*S*)-(−)-α-pinene) gave the trans secondary alcohol (**41**) in 50% enantiomeric excess. This ratio was increased by formation of the camphanate ester using the acid chloride derived from (1*R*)-(+)-camphanic acid, separation of diastereosiomers by chromatography, and hydrolysis of the ester back to the alcohol. Having obtained the alcohol with high e.e., this was treated with diethylaminosulfur trifluoride, giving as far as we could tell a completely regiospecific and enantioselective rearrangement to the 3-indolyl-4-fluoropiperidine, which on deprotection gave the target molecule (**22**). In this case both diastereoisomers of the camphanate were hydrolyzed and taken through to the final products. Having both enantiomers to handle allowed the determination of enantiomeric excess by chiral HPLC. In other cases in Table 3, the intermediate camphanate ester was chromatographed to purity by TLC and NMR, and the final product was then presumed to be essentially a single enantiomer. To use this route, it was necessary to make the required indole starting materials. Compounds **22**, **23**, **26**, and **33** were made through the route described above, making the indoles from the appropriate iodoaniline and substituted acetylene. The starting materials for compounds **20**, **21**, and **25** were made using a Madelung indole synthesis, illustrated for 5-fluoro-2-phenylindole (**43**) in Scheme 6. Thus, acylation of 2-amino-5-fluorotoluene (**42**) with benzoyl chloride gave the amide, in which the methyl group was deprotonated with an excess of *n*-butyllithium leading, after in situ cyclization and dehydration, to the required compound. 7-Fluoro-2-phenylindole (**46**) was not accessible via this route, and was made using the chemistry[22] shown in Scheme 7. 2-Fluoroaniline (**44**) was oxidized with *tert*-butylhypochlorite, and on treatment with methylthioacetophenone and

Scheme 5[a]



[a] Reagents: (i) phenylacetylene, $Pd(Ph_3P)_4$, CuI, Et_2NH, rt; (ii) CuI, $CaCO_3$, DMF, 120 °C; (iii) 4-piperidone, H_3PO_4, AcOH; (iv) BnOCOCl; (v) (−)-Ipc_2BH, H_2O_2, NaOH; (vi) camphanic acid chloride, pyridine; (vii) separate; (viii) K_2CO_3, MeOH; (ix) DAST, EtOAc, −50 °C to rt; (x) HCO_2H/Pd/C.

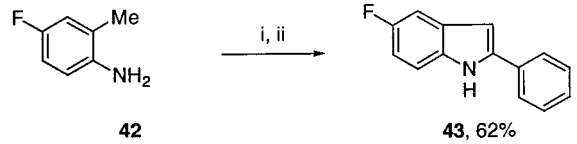
Table 3. Indole Substitution



Number	R	Ki / nM[a] h5HT$_{2A}$	hD$_2$	h5HT$_{2c}$	rat α_1	IKr
20	5-F	4.0	>1600	500	210	>7000
21	5-Cl	10.2	>1600		40	>7000
22	6-F	0.06	>1600	10	3.8	4000
23	6-Cl	2.3	>1600		16	1400
24	7-F	0.46	>1600	132	27	3000
25	7-Cl	0.69	>1600	154	6.7	2100

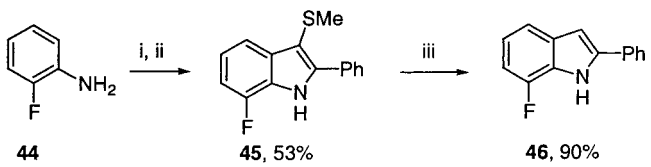
[a] See footnotes to Table 1.

Scheme 6[a]



[a] Reagents: (i) PhCOCl, Et_3N; (ii) *n*-BuLi, THF.

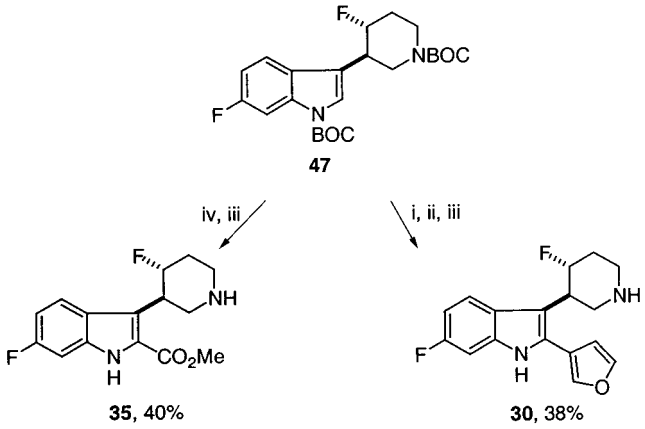
Scheme 7[a]



[a] Reagents: (i) *tert*-butyl hypochlorite, DCM, −78 °C; (ii) α-methylthioacetophenone, Et_3N; (iii) Raney nickel.

rearrangement with triethylamine gave the 3-methylthioindole (**45**). Desulfurization with Raney nickel led to the desired indole. Finally, to rapidly explore the effect of substitution at the 2-postion of the indole, chemistry was developed to introduce this substituent at the end of the synthesis. The bis BOC protected, 2-unsubstituted indole (**47**, Scheme 8) was made using the same DAST rearrangement chemistry that has been

Scheme 8[a]



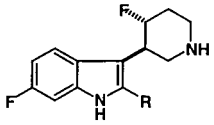
[a] Reagents: (i) LiTMP, $ZnCl_2$, 3-bromofuran, $Pd(Ph_3P)_4$; (ii) NaOMe; (iii) HCO_2H; (iv) LiTMP, MeOCOCN.

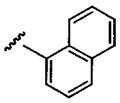
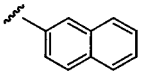
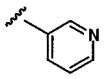
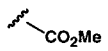
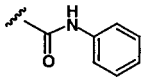
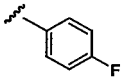
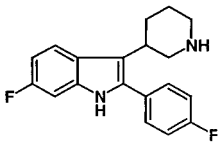
described, giving **47**[20] with 88% enantiomeric excess. Material was used with this e.e., since it was known that the minor enantiomer had low affinity for 5-HT$_{2A}$ receptors. Compounds in Table 4 were presumed to have this e.e. except **32** and **35**, made by the route shown in Scheme 5 and for which the e.e.'s were measured, and **36** which was racemic. Treatment of **47** with lithium tetramethylpiperidide gave the 2-lithioindole, which could then be transmetalated to the organozinc and cross coupled using Negishi type chemistry,[23] leading to compounds such as the furan (**30**), or directly quenched with electrophiles, leading for example to the amide (**35**). Compounds **27**−**32** were made using the Negishi chemistry, and **34** and **35** using the direct quench. Protected analogues of compounds **19** and **26** have been described,[20] and they were deprotected using standard methods. The final compound in Table 4, piperidine (**36**), was made from 2-(4-fluorophenyl)-6-fluoroindole, made via the iodoaniline/acetylene route, using the chemistry shown in Scheme 1.

Biology

Compounds were evaluated for their ability to displace [^{3}H]-ketanserin binding to human 5-HT$_{2A}$ receptors[24] stably expressed in CHO cells, [^{3}H]-mesurgeline

Table 4. Indole 2-Substituent



Number	R	h5HT$_{2A}$	hD$_2$	Ki / nM h5HT$_{2C}$	rat α_1	IKr
26	H	70				
27		0.34	1400		8.5	110
28		0.23	500		2.1	500
29		0.35	>1600	85	7.3	2500
30		0.54	>1600		3.6	
31		0.11	1600	50	2.8	1500
32		0.25	>1600	5.0	21	5400
33		10.4	>1600	>2000	7.3	8200
34		0.09	>1600	48	3.9	930
35		0.12	900	19	2.9	1600
36		0.09	28	16	1.1	1300

[a] See footnotes to Table 1.

binding to human 5-HT$_{2C}$ receptors stably expressed in CHO cells, [^{3}H]-spiperone binding to CHO cells stably expressing hD$_2$ receptors,[25] [^{3}H]-prazosin binding to rat cortical membranes,[26] and [^{3}H]-dofetilide binding to HEK cells stably expressing hERG, which encodes the IKr potassium channel. For h5-HT$_{2A}$ and hD2 receptors, the K_i values are quoted as the geometric means of at least three separate determinations, and the errors of the mean are within 2-fold of the mean. In other binding assays, K_i values are the geometric mean of at least two independent determinations. In a functional assay compounds were evaluated for their effect alone (agonist activity) and their ability to block (antagonist activity) 5-HT (1 μM) mediated accumulation of inositol phosphates in CHO cells stably expressing h5-HT$_{2A}$ receptors.[24,27]

Table 5. Pharmacokinetics

Number	Rat C_{max}[a] ng/mL	Rat AUC[b] ng.h/mL	Rat F[c] %	Rat $T_{1/2}$[d] h	Dog F %	Dog $T_{1/2}$ h
6			12	5.3	4	9.8
7	210	126	18	2.3		
9	26	47				
14	85	217				
17			18	1.4	37	7.4
22[e]			80	12	33	6.4
34	3	8				
35	149	350				

[a] Maximum blood concentration after oral dosing at 2 mg/kg po. [b] Area under the concentration−time curve for 0−4 h after 2 mg/kg po. [c] Bioavailability calculated from dosing at 0.5−2 mg/kg iv and po. [d] Terminal half-life following iv dosing. [e] Rat pharmacokinetics measured over 48 h.

Methods for determination of pharmacokinetics and metabolism are described in the Experimental Section.

Discussion

Table 1 shows the results of an investigation of the optimal position for the basic nitrogen in 2-phenyl-3-piperidinylindoles. It was known[18] that in 4-substituted piperidines a phenethyl group on the basic nitrogen gave a 30-fold increase in 5-HT$_{2A}$ receptor affinity (**6** compared to **8**). However, this also led to high IKr affinity, which was undesirable. Moving the nitrogen to the 3-position of the piperidine gave the racemic compound (**9**) which had a 15-fold improvement in binding affinity at 5-HT$_{2A}$ receptors over the 4-piperidine (**8**) and very little IKr affinity. Unlike the 4-substituted piperidines, in these 3-substituted analogues alkylation of the basic nitrogen was detrimental to 5-HT$_{2A}$ receptor affinity, with decreases along the series methyl, benzyl, phenethyl (**10**, **12**, **13**). Interestingly, the imidazolidinoneethyl group found in sertindole, while causing a moderate loss of affinity, gave a compound (**14**) with improved pharmacokinetics (Table 5), as it had in the 4-piperidinyl series. The reasons for this observation are not clear. Moving the nitrogen to the 2-position of the piperidine (**11**) gave a compound with lower affinity than the 3-piperidine (**9**), and this type of compound was not pursued.

To determine if these compounds were orally bioavailable, experiments were performed in which the compound was dosed orally at 2 mg/kg to three rats, and plasma samples were taken up to 6 h. From measurements of concentrations in these samples, maximal plasma concentration (C_{max}) and the area under the curve (AUC) from 0 to 6 h for oral dosing could be determined. If compounds looked promising in these experiments, then the intravenous leg of the pharmacokinetic experiment was also performed, allowing the calculation of bioavailability (F) and half-life ($T_{1/2}$). Results of these experiments are shown in Table 5. It can be seen that, while the 3-piperidine (**9**) had greater selectivity over IKr than its 4-substituted analogues (**6** and **7**), the AUC was lower for **9** than **7**, probably indicative of poorer oral bioavailability. We had already learned[28] from work on 5-HT$_{1D}$ agonists that

in another series of indole-3-alkylamines it was beneficial to pharmacokinetics to lower the pK_a of a basic nitrogen. With this in mind, we investigated a number of compounds in which the spatial relationship between the indole and the basic nitrogen was maintained, but electron withdrawing groups were introduced which would make the nitrogen less basic.

Introduction of an oxygen atom into the piperidine, giving the morpholine (**15**, Table 2), caused an 18-fold loss of affinity at 5-HT_{2A} receptors. This reduction was even more dramatic with the piperazine (**16**) where the loss was 2 orders of magnitude. However, attaching a heteroatom to the ring rather than including it in the ring proved more successful. The hydroxypiperidine (**19**) maintained affinity at 5-HT_{2A} receptors when compared to the parent compound (**9**), and its fluorinated analogue (**17**), if anything, improved affinity. The binding to 5-HT_{2A} receptors is stereospecific, with the enantiomer of **17**, compound **18**, showing at least 400-fold lower affinity than the active enantiomer (at this level it is hard to tell whether the inactive enantiomer has some affinity, or whether there is 0.25% of the active enantiomer present). The measured pK_a of **17** was 8.5, compared to 10.4 for the compound (**9**) without the fluorine atom. We were delighted to find that this change gave a compound with moderate bioavailability in rats (18%) and good pharmacokinetics in dogs (F 37%, $T_{1/2}$ 7.4 h). IKr affinity remains low in this compound, and it has good selectivity over hD_2 receptors and moderate selectivity over 5-HT_{2C} and α1 adrenergic receptors. In addition to these affinities, **17** was tested in a Panlabs screen at over 100 different receptors, enzymes, and uptake proteins and had greater than 1000-fold selectivity for the targeted receptor over off-target receptors, channels, and enzymes. In CHO cells, **17** was an antagonist at the 5-HT_{2A} receptor, as determined[24,27] by its lack of intrinsic efficacy, and its ability to block the 5-HT (1 μM) mediated accumulation of inositol phosphates.

With these results, studies were undertaken of the effect of substitution of the indole ring, and also of changes to the phenyl group at the 2-position of the indole. The results of the indole substitution work are shown in Table 3. Either a fluorine (**20**) or a chlorine (**21**) atom at the 5-position caused a reduction in affinity at 5-HT_{2A} receptors, and a small loss was observed with a chlorine at the 6-position (**23**). However, a fluorine atom at this position (**22**) gave an order of magnitude increase in binding affinity at 5-HT_{2A} receptor. This very high affinity led to a compound that is 50-fold selective over α1 receptors, is 100-fold selective over 5-HT_{2C} receptors, and had greater than 4 orders of magnitude selectivity over dopamine hD_2 and IKr receptors. In the functional assay **22** was an antagonist at 5-HT_{2A} receptors. Either a fluorine (**24**) or a chlorine (**25**) atom at the 7-position of the indole had little effect on binding at any of the receptors of interest, except 5-HT_{2C}, at which a 10-fold reduction in affinity was seen. It is not entirely clear what the effect in schizophrenia of binding to 5HT_{2C} receptors may be, so if it were to be an undesired effect, then this could be a useful finding.

The effects of altering the indole 2-substituent are shown in Table 4. A substituent in this position was necessary for high affinity, with the 2-unsubstituted indole (**26**) having only moderate binding. Large substituents were allowed, with both 1- (**27**) and 2- (**28**) substituted naphthalenes showing only a small loss in affinity at 5-HT_{2A} receptors compared to the phenyl compound (**22**). Aromatic heterocycles were also allowed, both six-membered (**29**) and five-membered, such as furan (**30**) and thiophene (**31**) which had a binding profile almost identical to **22**. The substituent did not need to be aromatic, with the cyclohexyl compound (**32**) having subnanomolar affinity. The ester (**33**) also maintained moderate binding, which could be increased back to very high binding with the anilide (**34**). However, the pharmacokinetics of **34** were poor, perhaps due to metabolism of the amide part of the molecule. The last two compounds in Table 4 again compare the effect of having the fluorine on the piperidine ring. Both are 2-(4-fluorophenyl)-6-fluoroindoles, compound **35** having the fluorine on the piperidine and therefore presumably a lower pK_a, while compound **36** does not. Both had the same very high affinity at 5-HT_{2A} receptors, but the compound with the lower pK_a had better selectivity, particularly over dopamine hD_2 receptors.

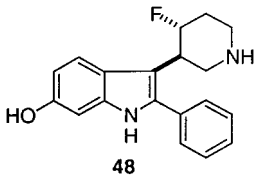


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Figure 2. Major metabolite of **17**.

Metabolic studies were performed on compound **17** both in vitro and in vivo. On incubation with rat liver microsomes at 1 μM the major metabolite had a molecular ion 16 mass units higher than the parent compound, indicative of oxidation. On oral dosing to rats and collection of urine and faeces, analysis indicated the presence of the same metabolite. This was isolated, purified, and analyzed by mass spectrometry and NMR spectroscopy and assigned as the 6-hydroxyindole metabolite (**48**, Figure 2). Following this result, the pharmacokinetic behavior of the 6-fluoroindole (**22**) was examined (Table 5). By blocking the major site of metabolism of **17**, the rat pharmacokinetics were dramatically improved with bioavailability increased to 80% and the half-life to 12 h. Dog pharmacokinetics remain essentially the same for **22** as **17**, with good bioavailability and half-life. Thus compound **22** is a very good example of a case in which knowledge of the route of metabolism of a series of compounds can lead to the design of structures with improved in vivo properties. In this case the fluorine atom introduced to give this increase in bioavailability also gave a 10-fold increase in binding affinity at the desired receptor, leading to an outstanding compound both in vitro and in vivo.

Conclusions

In a series of 2-phenyl-3-(3-piperidyl)indoles it was not necessary to alkylate on the basic nitrogen for optimal binding to 5-HT_{2A} receptors, and so earlier problems of binding to the IKr potassium channel were avoided. Oral bioavailability could be improved in this series by introduction of an electron withdrawing fluorine atom onto the piperidine, lowering the pK_a of the basic nitrogen, and in this way **17**, with moderate

bioavailability in rats, was found. To still further improve bioavailability, the metabolism of **17** was studied in rats both in vitro and in vivo, and it was found that the compound was metabolized primarily by hydroxylation at the 6-position of the indole. When this position was blocked with a fluorine atom to give compound **22**, thereby reducing the metabolism, the bioavailability in rats was increased to 80%, presumably by reduction in first-pass metabolism, and the half-life increased to 12 h due to reduced clearance**.** This fluorine atom at the 6-positon of the indole also gave an order of magnitude improvement in binding to the 5-HT_{2A} receptor, leading overall to an antagonist with high affinity at 5-HT_{2A} receptors, very good selectivity over hD_2 receptors and IKr channels, and good oral bioavailability in rats and dogs, with long plasma half-life in both species.

Experimental Section

Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. Proton NMR were measured on Bruker DPX 400, AM 360, or AC 250 spectrometers, chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard, and coupling constants are in hertz. Mass spectra were recorded on a VG 70/250 spectrometer. Merck Kieselgel (230−400) mesh was used for column chromatography. For reactions, dry solvents were used as bought from Aldrich. Organic solutions were dried with anhydrous magnesium sulfate. Elemental analyses were done by Butterworth Laboratories Ltd, Teddington, Middlesex, U.K.

Enantiomeric Excess. Compounds were analyzed on a Hewlett-Packard 1090M series 2 (HP, Germany) HPLC equipped with an autosampler and a diode array detector. Chiralcel OD-H (250 × 4.6 mm) and Chiralpak AD (250 × 4.6 mm) (J. T. Baker, U.K.) columns with mixtures of 2−20% of EtOH in isohexane with 0.1% diethylamine as eluent were used. Flow rates were between 1 and 2 mL/min, and the detection wavelength was 300 nm with a bandwidth of 10 nm. Typically, compounds were dissolved in ethanol, and 5 μL of a 1 mg/mL solution was injected on the column. All compounds were baseline resolved.

5-HT_{2A} Receptor Binding. Chinese hamster ovary (CHO) cells stably expressing the human 5-HT_{2A} receptor were lysed by homogenization in 50 mM Tris-HCl buffer (pH 7.5) and centrifuged at 50000*g* for 10 min at 4 °C. The resulting pellet was resuspended in assay buffer (50 mM Tris-HCl) at 2 mg wet weight/mL. Incubations were carried out in 96-well plates for 15 min at 37 °C in the presence of 1 nM [^{3}H]-ketanserin (66.4 Ci/mmol, NEN USA) for displacement studies and initiated by addition of 200 μL of membranes in a final assay volume of 500 μL. The reaction was terminated by rapid filtration over GF/B filters (presoaked in 0.1% BSA) and washed with ice-cold 50 mM Tris-HCl buffer. Nonspecific binding was determined with 1 μM Mianserin, and radioactivity was determined by counting on a Packard Topcount. Binding parameters were determined by nonlinear least squares regression analysis from which the inhibition constant K_i could be calculated for each test compound.

5-HT_{2C} Receptor Binding. Chinese hamster ovary (CHO) cells stably expressing the human 5-HT_{2C} receptor were lysed by homogenization in 50 mM Tris-HCl containing 0.1% ascorbate and 10 μM pargyline, pH 7.7, centrifuged at 50000*g* for 10 min at 4 °C, and the pellet was resuspended in assay buffer at 10 mg wet weight/mL. Incubations were performed for 30 min at 37 °C in the presence of 1 nM [^{3}H]-mesulergine (77 Ci/mmol, Amersham U.K.) and initiated by the addition of 400 μL membranes in a final assay volume of 500 μL. Nonspecific binding was determined with 1 μM Mianserin, and radioactivity determined as described above for [^{3}H]-ketanserin binding studies.

Rat α_1 Receptor Binding. Rat cortical membranes were lysed by homogenization in 50 mM Tris-HCl buffer, pH 7.5. The resulting pellet was resuspended in 50 mM Tris-HCl buffer, pH 7.5, at 2 mg original wet weight/mL. Incubations were carried out for 30 min at ambient temperature (22 °C) in the presence of 1 nM [^{3}H]-prazosin (77.2 Ci/mmol, NEN USA) and initiated by the addition of 400 μL of membranes in a final assay volume of 500 μL. Nonspecific binding was determined by 1 μM prazosin. The reaction was terminated by rapid filtration over GF/B filters (presoaked in 0.5% Triton) and washed with ice cold 50 mM Tris-HCl, pH 7.5. The radioactivity bound was determined as described for [^{3}H]-ketanserin binding studies.

IKr Binding. Binding to the voltage dependent potassium channel (delayed rectifier current, IKr) was evaluated by displacement of 4 nM [^{3}H]-dofetilide binding to HEK cells stably expressing hERG which encodes the IKr potassium channel. Incubations were carried out in assay buffer (10 mM HEPES containing 60 mM KCl, 71.5 mM NaCl, 1 mM $CaCl_2$, 2 mM $MgCl_2$, pH 7.4) for 75 min at ambient temperature (22 °C) and initiated with the addition of cell membranes (4 μg protein/well) in a total assay volume of 400 μL. Nonspecific binding was determined with 20 μM dofetilide. The reaction was terminated by rapid filtration over GF/B filters soaked in 0.1% BSA, and radioactivity bound was determined as described for [^{3}H]-ketanserin binding studies.

Oral Absorption and Pharmacokinetic Determinations. Male Sprague−Dawley rats weighing approximately 300 g were surgically prepared at least 36 h prior to dosing. Jugular veins were cannulated under anaesthesia (Isofluorane), and each rat was given a 100 unit dose of heparin (0.1 mL, 1000 units/mL) via the cannula. Rats were individually housed after surgery and had free access to food and water. Test compounds were administered i.v. to three rats via a bolus injection into a tail vein (1 mL/kg in a suitable vehicle) and orally via a gavage to the stomach (5 mL/kg in a suitable vehicle). Serial blood samples (approximately 400 μL) were collected from the jugular vein at time points up to 8 h postdose. In each case plasma was separated from the blood by centrifugation and stored at −20 °C until analysis. Systemic exposure after oral administration was alternatively determined by administering each test compound to five male Sprague−Dawley rats via a gavage to the stomach (5 mL/kg of a 0.5% methocel A4C suspension). At time points up to 4 h after dosing, one rat per time point was culled and blood collected.

Female Beagle dogs weighing approximately 10−12 kg were used for dog pharmacokinetic studies. Test compounds were administered i.v. to three dogs via a bolus injection into the cephalic vein (1 mL/kg of a PEG 300 /water solution) and orally to three dogs via a gavage to the stomach (5 mL/kg of a 0.5% methocel A4C suspension). Serial blood samples (approximately 1 mL) were taken from the jugular, saphenous, and cephalic (oral phase only) veins at time points up to 24 h post dose. Plasma was separated from the blood by centrifugation and stored at −20 °C until analysis.

Typically, to aliquots of plasma or blood (50−200 μL) was added internal standard (10 μL of a 10 ng/μL solution of a structural analogue), 100 μL of 0.1 M sodium hydroxide, 1 mL of water, and 4 mL of ethyl acetate. Samples were vortex mixed and centrifuged (3000 rpm, 10 min). The supernatant was removed and evaporated to dryness (70 °C, under nitrogen), and the residue was dissolved in mobile phase (100 μL) and transferred to an HPLC vial. Calibration standards covering appropriate ranges were prepared by spiking solutions of analyte at appropriate concentrations into the same volume of control plasma or blood, followed by the same sample preparation procedure. Typically 30 μL injections were made onto a KR100-5C18 HPLC column (5 cm × 4.6 mm i.d.) with an isochratic mobile phase consisting of appropriate ratios of acetonitrile and 25 mM ammonium formate, adjusted to pH 3 with formic acid at a flow rate of 1.0 mL/min split postcolumn 1:10 into a VG Platform II mass spectrometer operating in the electropositive mode. Detection was by single ion recording, monitoring for protonated parent ions. Model independant

pharmacokinetic parameters were determined using standard formulas in a Microsoft Excel spreadsheet.

Metabolism of Compound 17. For feces and urine collection in rat, **17** was administered orally at 3 mg/kg via a gavage to the stomach (5 mL/kg of a 0.6 mg/mL 0.5% methocel A4C suspension). Feces and urine were collected over a 18 h period into a metabowl. The feces was agitated with 30 mL of MeOH before centrifugation at 4000 rpm for 10 min. To 0.5 mL of the supernatant was added 0.5 mL of 25 mM ammonium formate, pH 3.0. The mixture was vortex mixed and centrifuged at 4000 rpm for 15 min before analysis of the supernatant by LC-MS and LC-fluorescence on the system described below. To 0.5 mL of urine collected over 0−18 h was added 0.5 mL acetonitrile. The mixture was vortex mixed and centrifuged (3000 rpm, 10 min), and the supernatant was analyzed by LC-MS and LC-fluorescence. The remaining c.a. 29 mL of fecal methanolic supernatant was concentrated under nitrogen, and the residue was reconstituted in 200 μL of DMSO and analyzed by ^{1}H LC NMR.

The metabolite was produced in vitro from liver microsomes. Compound **17** (final concentration 1 μM) was preincubated with rat liver microsomes prepared from male Sprague−Dawley rats (final protein concentration of 0.4 mg/mL) in Dulbecco's phosphate buffered saline. After incubation for 5 min at 37 °C, the reaction was initiated by the addition of NADPH (final concentration 2 mM) and was allowed to proceed for 45 min at 37 °C before termination with an equal volume of acetonitrile and centrifugation (3000 rpm, 10 min). The supernatant was analyzed by LC-MS and LC-fluorescence.

For analysis of the metabolite by LC-MS and LC-fluorescence, typically 50 μL injections were made onto a KR100-5C18 HPLC column (15 cm × 4.6 mm i.d.) with a mobile phase consisting of acetonitrile (A) and 25 mM ammonium formate, adjusted to pH 3 with formic acid (B) at a flow rate 1.0 mL/min split postcolumn 1:10 into the mass spectrometer with the following time program: 0 min, 20% A; 5 min, 20% A; 15 min, 60% A; 20 min, 60% A; 21 min, 20% A; 28 min, 20% A. Detection was both in scan mode and by single ion recording. Analysis by fluorescence was achieved in a similar way at a flow rate of 1 mL/min into the fluorescence detector, with excitation and emission at 235 and 370 nm, respectively.

For analysis of the metabolite by LC NMR a 50 μL injection of the fecal extract was made onto a KR100-5C18 HPLC column (15 cm × 4.6 mm i.d.) with a mobile phase consisting of acetonitrile (A) and 0.1% trifluoroacetic acid (B) at a flow rate of 1.0 mL/min into the NMR probe with the following time program (with UV detection at 300 nm): 0 min, 20% A; 5 min, 20% A; 15 min, 60% A; 20 min, 60% A; 21 min, 20% A; 28 min, 20% A. The major M + 16 metabolite peak was isolated in the flow cell of an LC NMR probe and gave a spectrum consistent with the 6-hydroxyindole structure: ^{1}H NMR (500 MHz, MeCN-d_3/D_2O) δ 6.84 (1H, dd, *J* 8.7, 2.3), 7.03 (1H, d, *J* 2.3), 7.57 (1H, t, *J* 8.1), 7.64 (2H, t, *J* 8.1), 7.66 (2H, t, *J* 8.1), 7.73 (1H, d, *J* 8.7); *m*/*z* (ES^+) 311 (M^+ + H). The aromatic region of the ^{1}H spectrum revealed the 2-phenyl moiety to be intact and the four-spin intact indole to have been replaced by resonances of a three-spin system. The coupling of the three-spin system was consistent with either 5- or 6-hydroxylation; however, chemical shift calculations clearly favored 6-hydroxylation.This result was in agreement with ^{19}F NMR work, where coincidence of the major metabolite and parent fluorine resonances (−180 ppm) were inconsistent with piperidine hydroxylation.

3-(1-Benzylpiperidin-3-yl)-2-phenyl-1*H*-indole (12). 2-Phenylindole (**37**) (2 g, 10.4 mmol) was stirred at 80 °C in AcOH (20 mL), and 1-benzyl-3-piperidone hydrochloride hydrate (5 g, 21.4 mmol) and 1 M phosphoric acid (10 mL) were added. After a further 4 h, the mixture was poured into ice/NH_3 and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O and brine, dried, evaporated in vacuo, and purified by flash chromatography, eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give a pale yellow oil (6 g). This was a mixture of the two isomeric tetrahydropyridine products which were unstable and starting benzylpiperidone. The oil was hydrogenated on Pd/C (10% w/w, 0.6 g) in EtOH (50 mL) and concentrated HCl (3 mL) at 50 psi overnight. The mixture was filtered, poured into saturated $NaHCO_3$, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O and brine, dried, evaporated in vacuo, and purified by flash chromatography, eluting with CH_2Cl_2:MeOH:880 ammonia (98.5:1.5:0.15 v/v) to give **12** (2.2 g, 58%) as a white solid, oxalate salt mp 267−270 °C (from EtOH): ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.7 (1H, m), 1.8−1.9 (2H, m), 2.0−2.1 (1H, m), 2.6−2.7 (1H, m), 3.0−3.1 (3H, m), 3.2−3.3 (1H, m), 3.95 (2 H, br s), 7.00 (1 H, t, *J* 7), 7.09 (1 H, t, *J* 7), 7.2−7.6 (11 H, m), 7.80 (1 H, d, *J* 7), 11.2 (1H, br s); *m*/*z* (ES^+) 367 (M^+ + H). Anal. ($C_{26}H_{26}N_2$·$0.7C_2H_2O_4$) C, H, N.

3-(Piperidin-3-yl)-2-phenyl-1*H*-indole (9). Compound **12** (2.1 g, 5.7 mmol), Pd/C (10% w/w, 0.21 g), and ammonium formate (2.3 g, 29 mmol) were refluxed in MeOH (30 mL) for 24 h. The mixture was cooled, filtered, and purified by flash chromatography, eluting with CH_2Cl_2:MeOH:880 ammonia (98.5:1.5:0.15 v/v) to give **9** (1.1 g, 50%) as a white solid: oxalate salt, white crystals mp 258−262 °C (from EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.6−1.8 (1 H, m), 1.8−1.9 (2 H, m), 2.2−2.4 (1 H, m), 3.00 (1 H, t, *J* 12), 3.2−3.5 (4 H, m), 6.98 (1 H, t, *J* 7), 7.09 (1 H, t, *J* 7), 7.2−7.5 (6 H, m), 7.84 (1 H, d, *J* 8), 11.3 (1H, br s); *m*/*z* (ES^+) 277 (M^+ + H). Anal. ($C_{19}H_{20}N_2$·$0.5C_2H_2O_4$) C, H, N.

3-(1-Methylpiperidin-3-yl)-2-phenyl-1*H*-indole (10). Compound **9** (200 mg, 0.7 mmol), $NaCNBH_3$ (51 mg, 0.8 mmol), formaldehyde (60 μL, 40% in H_2O, 0.8 mmol), and AcOH (97 μL, 1.7 mmol) were stirred in MeOH (5 mL) at 0 °C for 1 h, then room temperature for 2 h. The solution was poured into saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried, evaporated in vacuo, and purified by preparative thin-layer chromatography, eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give **10** (172 mg, 82%) as a colorless oil: oxalate salt, mp 287−290 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.7−1.8 (1 H, m), 1.8−1.9 (2 H, m), 2.0−2.1 (1 H, m), 2.5 (3 H, s), 2.6−2.7 (1 H, m), 3.0−3.2 (3 H, m), 3.2−3.3 (1 H, m), 6.99 (1 H, t, *J* 7), 7.09 (1 H, t, *J* 7), 7.2−7.5 (6 H, m), 7.82 (1 H, d, *J* 8), 11.2 (1H, br s); *m*/*z* (ES^+) 291 (M^+ + H). Anal. ($C_{20}H_{22}N_2$·$0.5C_2H_2O_4$·$0.7H_2O$) C, H, N.

3-(1-Methylpiperidin-2-yl)-2-phenyl-1*H*-indole (11). $POCl_3$ (2.7 mL, 29 mmol) was added dropwise to 1-methyl-2-piperidone (3.6 mL, 32 mmol), keeping the internal temperature below 15 °C. The resulting thick paste was stirred at 15 °C with occasional shaking for 30 min before adding a solution of **37** (5.0 g, 26 mmol) in 1-methyl-2-piperidone (5 mL). This mixture was stirred and shaken at room temperature for 30 min before heating at 80 °C for 3 h. The reaction was cooled, and the resulting brown solid triturated with 5% aqueous ammonia (300 mL) to give a yellow suspension. This was extracted into EtOAc (300 mL), and the organics were then washed with H_2O (300 mL) and brine (300 mL) and evaporated in vacuo to give a brown solid [*m*/*z* (ES^+) 289]. This solid was dissolved in MeOH (60 mL) and CH_2Cl_2 (60 mL) and cooled to 0 °C before adding $NaBH_4$ (5.0 g, 130 mmol) portionwise over 15 min. The reaction was stirred at room temperature for 90 min and then diluted with H_2O (50 mL). The mixture was evaporated and the residue partitioned between EtOAc (250 mL) and 5% aqueous ammonia (250 mL). The organics were then washed with H_2O and brine, dried, and evaporated in vacuo to give a pale green solid. This solid was suspended in warm ether (400 mL) and filtered while warm through glass microfiber paper (Whatman GF/A). The filtrate was concentrated to give the crude product as a yellow solid contaminated with 2-phenyl indole. Conversion to the oxalate salt gave **11** as colorless cubes (7.15 g, 73%): mp 186−187 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.48−1.66 (1 H, m), 1.77−1.98 (3 H, m), 2.00−2.12 (1 H, m), 2.27 (3 H, s), 2.34−2.50 (1 H, m), 2.82−2.98 (1 H, m), 3.32−3.40 (1 H, m), 3.98−4.10 (1 H, m), 7.08 (1 H, t, *J* 8), 7.18 (1 H, t, *J* 8), 7.42 (1 H, d, *J* 8), 7.44−7.60 (5 H, m), 8.00 (1 H, d, *J* 8), 11.63 (1 H, s); *m*/*z* (ES^+) 291 (M + H^+). Anal. ($C_{20}H_{22}N_2$·$C_2H_2O_4$·C_2H_6O) C, H, N.

3-(1-(2-Phenylethyl)piperidin-3-yl)-2-phenyl-1*H*-indole (13). Compound **9** (210 mg, 0.76 mmol), phenethyl bromide (140 μL, 1 mmol), and Cs_2CO_3 (0.35 g, 1 mmol) were stirred in DMF (3 mL) at 60 °C overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give **13** (251 mg, 87%) as a colorless oil: oxalate salt, white crystals, mp 142−145 °C (from Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.8−1.9 (2 H, m), 1.9−2.0 (1 H, m), 2.2−2.3 (1 H, m), 2.9−3.0 (2 H, m), 3.02 (1 H, t, *J* 12), 3.2−3.3 (2 H, m), 3.4−3.5 (4 H, m), 7.00 (1 H, t, *J* 7), 7.11 (1 H, t, *J* 7), 7.2−7.6 (11 H, m), 7.89 (1 H, d, *J* 8), 11.3 (1H, br s); *m*/*z* (ES$^+$) 381 (M^+ + H). Anal. ($C_{27}H_{28}N_2$·$C_2H_2O_4$·0.8H_2O) C, H, N.

1-{2-[3-(2-Phenyl-1*H*-indol-3-yl]-)piperidin-1-yl]ethyl}-imidazolidin-2-one (14). Compound **9** (172 mg, 0.62 mmol), 1-(2-chloro)ethyl-2-imidazolidinone (119 mg, 0.80 mmol), and Cs_2CO_3 (0.29 g, 0.8 mmol) were stirred in DMF (3 mL) at 70 °C for 6 h. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried, and evaporated in vacuo and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give **14** (201 mg, 83%) as a colorless oil: hemi oxalate salt containing 1 mol of ethanol, white crystals, mp 203−205 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.7−1.8 (1 H, m), 1.8−1.9 (2 H, m), 1.9−2.0 (1 H, m), 2.2−2.3 (1 H, m), 2.7−3.4 (13 H, m), 6.4 (1 H, s), 7.00 (1 H, t, *J* 7), 7.09 (1 H, t, *J* 7), 7.2−7.6 (11 H, m), 7.83 (1 H, d, *J* 8), 11.2 (1H, br s); *m*/*z* (ES$^+$) 389 (M^+ + H). Anal. ($C_{24}H_{28}N_4O$·0.5$C_2H_2O_4$·C_2H_6O) C, H, N.

3-Morpholin-2-yl-2-phenyl-1*H*-indole (15). A solution of **37** (15 g, 77.7 mmol) in anhydrous benzene (150 mL) was added via cannula over 10 min to a solution of EtMgBr (26 mL, 3.0 M in Et_2O, 77.7 mmol) at room temperature under N_2. After 15 min chloroacetyl chloride (6.2 mL, 77.7 mmol) was added, and the mixture was stirred for a further 20 min. The reaction was quenched with saturated NH_4Cl (200 mL), and the products were extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried, evaporated in vacuo, and purified by flash chromatography eluting with EtOAc:hexane (50:50 v/v) to give 2-chloro-1-(2-phenyl-1*H*-indole)-ethanone (6.8 g, 35%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 4.34 (2 H, s), 7.23−7.32 (2 H, m), 7.46−7.52 (1 H, m), 7.55−7.62 (3 H, m), 7.66−7.72 (2 H, m), 8.17−8.24 (1 H, m), 12.33 (1 H, br s). A solution of this material (6.8 g, 25 mmol), and ethanolamine (20 mL, 331 mmol) in anhydrous 1,2-dichloroethane (100 mL) under N_2 was heated at reflux for 5 h. The mixture was cooled and washed with saturated $NaHCO_3$ and brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (95:5:0.5 then 92:9:0.5 v/v) to give 2-(2-hydroxyethylamino)-1-(2-phenyl-1*H*-indol-3-yl)ethanone (**38**) (4 g, 54%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.62 (2 H, t, *J* 5.1), 3.44 (2 H, t, *J* 5.1), 3.51 (2 H, s), 7.26−7.31 (2 H, m), 7.36−7.38 (1 H, m), 7.46−7.52 (5 H, m), 8.29 (1 H, dd, *J* 7.7 and 2.1); *m*/*z* (ES+) 295 (M + H$^+$). A solution of **38** (4 g, 13.6 mmol) in MeOH (70 mL) was treated with $NaBH_4$ (770 mg, 20.4 mmol) at room temperature. Further quantities of $NaBH_4$ (514 mg, 13.6 mmol) were added after 1 and 2 h. After 3 h, the reaction was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was dried, evaporated in vacuo, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (95:5:0.5 v/v) to give 2-(2-hydroxyethylamino)-1-(2-phenyl-1*H*-indol-3-yl)ethanol (1.9 g, 47%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.71−2.98 (2 H, m), 2.95 (1 H, dd, *J* 12.3 and 4.0), 3.62−3.70 (2 H, m), 5.18 (1 H, dd, *J* 9.7 and 4.0), 7.08−7.23 (2 H, m), 7.38−7.51 (4 H, m), 7.54−7.58 (2 H, m), 7.90 (1 H, d, *J* 7.3). A solution of this material (1.9 g, 6.4 mmol) in MeOH (20 mL) was treated with 2 M HCl (10 mL, 20 mmol). After 5 min, the reaction was basified with 4 M NaOH, and the products were extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried, evaporated in vacuo, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (98:2:0.5 then 96:4:0.5 v/v) to give **15** (1.45 g, 62%): oxalate salt, mp 190−192 °C (from EtOH−Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.22−3.48 (3 H, m), 3.62 (1 H, t, *J* 12.2 and 11.9), 3.86 (1 H, t, *J* 11.6 and 10.3), 4.07 (1 H, d, *J* 12.1), 5.07 (1 H, dd, *J* 11.2 and 1.8), 7.04 (1 H, t, *J* 7.7 and 7.1), 7.14 (1 H, t, *J* 7.7 and 7.3), 7.40−7.46 (2 H, m), 7.51−7.61 (4 H, m), 7.86 (1 H, d, *J* 7.9), 9.87 (2 H, br s), 11.59 (1 H, br s); *m*/*z* (ES$^+$) 279 (M + H$^+$). Anal. ($C_{18}H_{18}N_2O$·$C_2H_2O_4$) C, H, N.

3-(1,4-Dimethylpiperazin-2-yl)-2-phenyl-1*H*-indole (16). $POCl_3$ (3.3 mL, 35 mmol) was added dropwise to a suspension of sarcosine anhydride (5.0 g, 35 mmol) in dichloromethane (10 mL), keeping the internal temperature below 15 °C. The resulting thick paste was stirred at 15 °C with occasional shaking for 30 min before adding a solution of **37** (6.18 g, 32 mmol) in dichloromethane (10 mL). This mixture was stirred at room temperature for 30 min before heating at 80 °C for 3 h. The reaction was cooled, and the resulting dark solid was suspended in MeOH (100 mL) and CH_2Cl_2 (100 mL) and cooled to 0 °C before adding $NaBH_4$ (5.0 g, 130 mmol) portionwise over 15 min. The resulting solution was stirred at room temperature for 16 h and then diluted with H_2O (50 mL). MeOH (100 mL) and CH_2Cl_2 (100 mL) were then added, and this mixture was adsorbed directly onto silica. Purification by flash chromatography, eluting with MeOH:CH_2Cl_2 (98:2 v/v), and trituration with ethanol gave 1,4-dimethyl-5-(2-phenyl-1*H*-indol-3-yl)piperazin-2-one as a white powder (8.15 g, 80%): mp 143−146 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.92 (3 H, s), 2.80 (1 H, d, *J* 16), 2.83 (3 H, s), 3.24−3.34 (1 H, m), 3.47 (1 H, d, *J* 16), 3.74−3.86 (2 H, m), 7.02 (1 H, t, *J* 8), 7.14 (1 H, t, *J* 8), 7.36−7.48 (2 H, m), 7.54 (2 H, t, *J* 7), 7.64 (2 H, d, *J* 7), 7.88 (1 H, d, *J* 8), 11.37 (1 H, s); *m*/*z* (ES$^+$) 320 (M + H$^+$). A suspension of this piperazinone (500 mg, 1.6 mmol) in THF (20 mL) was treated with $LiAlH_4$ (4 mL, 1 M in THF, 4 mmol). The resulting slurry was heated under reflux for 2 h. After cooling to 0 °C, powdered sodium sulfate decahydrate (2.5 g) was added portionwise and stirring continued for 30 min. The reaction was filtered, and the solids were washed with EtOAc (100 mL). The filtrate was washed with saturated aqueous NH_4Cl, H_2O, and brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (98:1.8:0.2 v/v) to give **16** (330 mg, 69%) as a foam: maleate salt, mp 191−194 °C (from EtOH); mp 143−146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95 (3 H, s), 2.30−2.45 (1 H, m), 2.82 (3 H, s), 3.07−3.17 (1 H, m), 3.20−3.55 (4 H, m), 3.67−3.78 (1 H, m), 6.02 (2 H, s), 7.03 (1 H, t, *J* 7), 7.13 (1 H, t, *J* 7), 7.38 (1 H, d, *J* 8), 7.45−7.48 (1 H, m), 7.50−7.64 (4 H, m), 8.00 (1 H, d, *J* 8), 9.63 (1 H, br), 11.43 (1 H, s); *m*/*z* (ES$^+$) 306 (M + H$^+$). Anal. ($C_{20}H_{23}N_3$·$C_4H_4O_4$·0.25H_2O) C, H, N.

(3*RS*,4*RS*)-3-(4-Hydroxypiperidin-3-yl)-2-phenyl-1*H*-indole (19). A solution of 4-hydroxy-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid benzyl ester[20] (1.0 g, 2.3 mmol) in EtOAc (20 mL) and MeOH (5 mL) was treated with 10% Pd/C (100 mg) and stirred under 1 atm of hydrogen at room temperature for 4 h. The reaction mixture was filtered and evaporated in vacuo, the residue was triturated with $CHCl_3$/Et_2O, and the solid was washed with MeOH to afford **19** as a white powder (583 mg, 85%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.49−1.59 (1 H, m), 1.96−2.03 (1 H, m), 3.00−3.45 (4 H, m), 4.19−4.28 (1 H, m), 4.76−4.86 (1 H, m), 7.01−7.10 (1 H, m), 7.37−7.52 (4 H, m), 7.70−7.88 (3 H, m), 11.22 (1H, s); *m*/*z* (ES$^+$) 293 (M$^+$ + H). Anal. ($C_{19}H_{20}N_2O$·0.2CH_3OH) C, H, N.

6-Fluoro-2-phenyl-1*H*-indole (39). A mixture of 5-fluoro-2-iodoaniline (7.55 g, 31 mmol) and phenylacetylene (5.8 mL, 62 mmol) in *N*-butylamine (100 mL) was degassed with N_2 for 15 min, and then $Pd(PPh_3)_2Cl_2$ (0.5 g) and CuI (0.1 g) were added. The mixture was heated to reflux for 16 h under N_2 and then evaporated. Flash chromatography eluting with EtOAc:hexane (5:95 v/v) as eluent gave 5-fluoro-2-phenylethynylphenylamine (5.23 g, 80%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.30 (2 H, br s), 6.39−6.47 (2 H, m), 7.29−7.53 (6 H, m). A stirred suspension of this acetylene (5.23 g, 25 mmol), CuI (2.36 g, 12 mmol), and $CaCO_3$ (2.48 g, 25 mmol) in DMF (35 mL)

was heated to 120 °C for 20 h. The mixture was cooled, filtered, evaporated, and partitioned between H_2O and EtOAc. The organic layer was washed with 10% NH_4OH, H_2O, and brine, dried, and evaporated to give 6-fluoro-2-phenyl-1*H*-indole (4.97 g, 95%) as a brown solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.8 (1 H, d, *J* 2), 6.9 (1 H, dt, *J* 10 and 2), 7.1 (1 H, dd, *J* 10 and 2), 7.25−7.35 (1 H, m), 7.4−7.5 (2 H, m), 7.5−7.6 (1 H, m), 7.6−7.7 (2 H, m), 8.3 (1 H, br s).

5-Fluoro-2-phenyl-1*H*-indole (43). Benzoyl chloride (4.6 mL, 40 mmol) was added dropwise over 10 min at 0 °C to a solution of 4-fluoro-2-methylaniline (**42**) (5.0 g, 40 mmol) in CH_2Cl_2. After complete addition, the reaction mixture was warmed to room temperature and stirred for a further 3 h. The mixture was evaporated, and the residue partitioned between 0.5 N NaOH and EtOAc. The organic layer was washed with 1 N HCl, H_2O, and brine, dried, and evaporated. Recrystallization from EtOAc gave *N*-(4-fluoro-2-methylphenyl)benzamide as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.29 (3 H, s), 6.87−6.95 (2 H, m), 7.44−7.68 (4 H, m), 7.85−7.90 (2 H, m). A solution of ^{n}BuLi (50 mL, 1.6 M in hexane, 80 mmol) was added slowly at −25 °C to a stirred solution of the benzamide in dry THF (75 mL) under N_2. After 1 h at −78 °C, the mixture was warmed to room temperature and stirred for a further 16 h. The reaction was quenched with 2 N HCl (60 mL), and the product was extracted with EtOAc (2 × 200 mL). The combined organic solutions were washed with H_2O (100 mL) and brine (100 mL), dried, and evaporated. Trituration with hexane gave **43** (5.26 g, 62%) as a pale brown solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.9 (1 H, dt, *J* 2 and 9), 7.2−7.7 (8 H, m), 8.4 (1 H, br s).

7-Fluoro-2-phenyl-1*H*-indole (46). Using a procedure similar to that of Gassman,[20] a cooled (−78 °C) solution of 2-fluoroaniline (**44**) (3.8 mL, 39 mmol) in CH_2Cl_2 (80 mL) was treated with a cooled (−78 °C) solution of *tert*-butyl hypochlorite (4.2 g, 39 mmol) in CH_2Cl_2 (20 mL). After the mixture was stirred at −78 °C for 1 h, a cooled (−78 °C) solution of 2-methylsulfanyl-1-phenylethanone (6.6 g, 40 mmol) in CH_2Cl_2 (20 mL) was added, and stirring continued at −78 °C for 1 h. A cooled (−78 °C) solution of Et_3N (6.0 mL, 43 mmol) in CH_2Cl_2 (20 mL) was then added, and after 20 min at −78 °C the mixture was allowed to stir to room temperature for 1 h. H_2O (200 mL) was added, and the CH_2Cl_2 evaporated in vacuo. The product was extracted into EtOAc (250 mL), and the organics were washed with brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with with isohexane on a gradient of diethyl ether (0−10%) to give 7-fluoro-3-methylsulfanyl-2-phenyl-1*H*-indole (**45**) as a red oil (5.4 g, 53%). This oil was dissolved in EtOH (100 mL), and the solution was stirred mechanically while Raney nickel (excess) was added in small portions until complete consumption of starting material had occurred. The reaction was filtered through a glass microfiber filter paper (Whatman GF/A) and the filtrate concentrated to furnish **46** as a yellow solid (4.0 g, 90%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.84−6.93 (2 H, m), 6.99−7.05 (1 H, m), 7.37 (2 H, t, *J* 7), 7.46 (2 H, t, *J* 7), 7.69 (2 H, d, *J* 7), 8.47 (1 H, br s).

The following compounds were made by the route shown in Scheme 5, using experimental procedures previously described in detail for compound **17**,[20] making the appropriately substituted indole using the routes described above. To obtain compounds with high e.e., the following is representative of the procedure used to increase optical purity:

Resolution of 41. Compound **41** (2.0 g, 4.5 mmol) and (1*R*)-(−)-camphanic chloride (1.95 g, 9.0 mmol) were dissolved in pyridine (15 mL) and heated at 45 °C for 18 h. The reaction mixture was diluted with EtOAc, washed with 1 N citric acid, H_2O, and brine, dried over Na_2SO_4, and evaporated. Flash chromatography eluting with EtOAc:^{i}Hex (1:4 v/v) gave 4-(6-fluoro-2-phenyl-1*H*-indol-3yl)-3-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxyloxy)piperidine-1-carboxylic acid benzyl ester (R_f EtOAc:^{i}Hex (3:7)) 0.35 (1.36 g, 48%) and its diastereoisomer (R_f EtOAc:^{i}Hex (3:7)) 0.25 (1.09 g, 38%). The major, less polar isomer (1.36 g, 2.18 mmol) was dissolved in methanol (10 mL), K_2CO_3 (1.58 g, 10.9 mmol) was added, and the mixture was stirred at room temperature overnight. Citric acid (3.05 g, 1.43 mmol) was added, and the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated to give **41** (0.94 g, 97%) which was shown by chiral HPLC to have an e.e. of 99.4%.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (22): maleate salt, e.e. = >99%, white needles, mp 224−225 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.80−2.00 (1 H, m), 2.32−2.42 (1 H, m), 3.20−3.65 (5 H, m), 5.20−5.50 (1 H, dm, *J* 48), 6.02 (2 H, s), 6.92 (1 H, dt, *J* 9 and 2), 7.15 (1 H, dd, *J* 9 and 2), 7.40−7.48 (1 H, m), 7.50−7.62 (4 H, m), 7.95−8.05 (1 H, m), 8.55 (1 H, br s), 11.56 (1 H, s); *m*/*z* (ES$^+$) 313 (M^+ + H). Anal. ($C_{19}H_{18}F_2N_2.C_4H_4O_4$) C, H, N.

(3*R*,4*R*)-5-Fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (20): maleate salt, white needles, mp 178−179 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.80−1.95 (1 H, m), 2.34−2.44 (1 H, m), 3.20−3.60 (5 H, m), 5.20−5.45 (1 H, dm, *J* 48), 6.02 (2 H, s), 7.00 (1 H, dt, *J* 9 and 2), 7.35−7.42 (1 H, m), 7.45−7.50 (1 H, m), 7.53−7.62 (4 H, m), 7.85 (1 H, dd, *J* 11 and 2), 8.80 (1 H, br s), 11.60 (1 H, s); *m*/*z* (ES$^+$) 313 (M^+ + H). Anal. ($C_{19}H_{18}F_2N_2\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

(3*R*,4*R*)-5-Chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (21): maleate salt, white needles, mp 224−225 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.75−1.95 (1 H, m), 2.34−2.54 (1 H, m), 3.20−3.70 (5 H, m), 5.20−5.45 (1 H, dm, *J* 49), 6.02 (2 H, s), 7.15 (1 H, dt, *J* 9 and 2), 7.42 (1 H, d, *J* 9), 7.47−7.53 (1 H, m), 7.55−7.64 (4 H, m), 8.05 (1 H, d, *J* 2), 8.60 (1 H, br s), 11.66 (1 H, s); *m*/*z* (ES$^+$) 329 (M^+ + H). Anal. ($C_{19}H_{18}ClFN_2\cdot C_4H_4O_4\cdot 0.1H_2O$) C, H, N.

(3*R*,4*R*)-6-Chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (23): maleate salt, white needles, mp 230−232 °C; $_1$H NMR (360 MHz, DMSO-d_6) δ 1.80−2.00 (1 H, m), 2.30−2.44 (1 H, m), 3.20−3.70 (5 H, m), 5.20−5.45 (1 H, dm, *J* 53), 6.07 (2 H, s), 7.07 (1 H, dt, *J* 9 and 2), 7.40−7.70 (6 H, m), 8.00 (1 H, d, *J* 9), 8.95 (1 H, br s), 11.65 (1 H, s); *m*/*z* (ES$^+$) 329 (M^+ + H). Anal. ($C_{19}H_{18}ClFN_2\cdot C_4H_4O_4\cdot 0.8H_2O$) C, H, N.

(3*R*,4*R*)-7-Fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (24): maleate salt, white needles, mp 212−213 °C; $_1$H NMR (360 MHz, DMSO-d_6) δ 1.80−2.00 (1 H, m), 2.32−2.40 (1 H, m), 3.20−3.60 (5 H, m), 5.20−5.45 (1 H, dm, *J* 49), 6.02 (2 H, s), 6.95−7.10 (2 H, m), 7.45−7.65 (5 H, m), 7.90 (1 H, d, *J* 8), 8.60 (1 H, br s), 11.86 (1 H, s); *m*/*z* (ES$^+$) 313 (M^+ + H). Anal. ($C_{19}H_{18}F_2N_2\cdot C_4H_4O_4\cdot 0.1H_2O$) C, H, N.

(3*R*,4*R*)-7-Chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (25): maleate salt, white needles, mp 218−219 °C; $_1$H NMR (360 MHz, DMSO-d_6) δ 1.75−1.95 (1 H, m), 2.32−2.40 (1 H, m), 3.20−3.60 (5 H, m), 5.20−5.45 (1 H, dm, *J* 49), 6.02 (2 H, s), 7.08 (1 H, t, *J* 8), 7.25 (1 H, d, *J* 8), 7.45−7.65 (5 H, m), 7.97 (1 H, d, *J* 8), 8.60 (1 H, br s), 11.69 (1 H, s); *m*/*z* (ES$^+$) 329 (M^+ + H). Anal. ($C_{19}H_{18}ClFN_2\cdot C_4H_4O_4$) C, H, N.

2-Cyclohexyl-3-(4-fluoro-piperidin-3-yl)-1*H*-indole (32): white crystals, e.e. = 76%, mp 223−225 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.2−1.4 (3 H, m), 1.5−1.9 (9 H, m), 2.2−2.3 (1 H, m), 2.7−2.8 (1 H, m), 3.1−3.4 (5 H, m), 5.0−5.3 (1 H, m), 6.7−6.8 (1H, m), 7.0 (dd, 1 H, *J* 10 and 2 Hz), 7.6−7.7 (1 H, m), 10.9 (1 H, s); *m*/*z* (ES$^+$) 319 (M^+ + H). Anal. ($C_{19}H_{24}F_2N_2\cdot C_2H_2O_4$) C, H, N.

(3*R*,4*R*)-5-Fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole (26): oxalate salt, Anal. ($C_{13}H_{14}F_2N_2\cdot 0.5C_2H_2O_4\cdot 0.3H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-furan-3-yl-1*H*-indole (30). A cooled (−10 °C) solution of 2,2,6,6-tetramethylpiperidine (506 μL, 3.0 mmol) in THF (20 mL) was treated with ^{n}BuLi (1.9 mL of a 1.6 M solution in hexane, 3.0 mmol). This mixture was stirred at −10 °C for 5 min and then cooled to −78 °C. To this solution a precooled (−78 °C) solution of **47**[18] (475 mg, 1.1 mmol, 88% e.e.) in THF (7 mL) was added via cannula, and stirring at −78 °C was continued for 2 h. $ZnCl_2$ (4.4 mL of a 0.5 M solution in diethyl ether, 2.2 mmol) was then added dropwise over 5 min to the reaction mixture, and stirring at −78 °C continued for 30 min before allowing the solution to warm to room temperature. 3-Bromofuran (200 μL, 2.2 mmol) was added, followed by tetrakis(triphenylphos-

phine)palladium(0) (65 mg), and the reaction was heated at 50 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (100 mL) and washed with a saturated solution of ammonium chloride, H_2O, and brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with hexane on a gradient of diethyl ether (10−35% v/v) to give *(3R,4R)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoro-2-furan-3-ylindole-1-carboxylic acid *tert*-butyl ester as a white foam (372 mg, 68%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.42 (18 H, s), 1.60−1.74 (1 H, m), 2.08−2.22 (1 H, m), 2.76−3.22 (3 H, m), 3.96−4.14 (1 H, m), 4.18−4.32 (1 H, m), 4.84−5.12 (1 H, m), 6.46 (1H, d, *J* 3), 7.00 (1 H, td, *J* 9 and 2), 7.30−7.44 (3H, m), 7.96−8.04 (1 H, m). A solution of this ester (370 mg, 0.74 mmol) in MeOH (10 mL) was treated with NaOMe (160 mg, 3 mmol), and the mixture was heated at 60 °C for 5 h. The reaction was cooled to room temperature, and the MeOH was removed on a rotary evaporator. The residue was suspended in EtOAc, washed with H_2O and brine, dried, and evaporated in vacuo to give an oil. This oil was dissolved in 95% formic acid (5 mL) and stirred at room temperature for 16 h. The reaction mixture was neutralized by the careful addition of a saturated solution of sodium hydrogen carbonate and then extracted with EtOAc. The organic extract was then washed with H_2O and brine, dried, evaporated in vacuo, and purified by flash chromatography eluting with dichloromethane:methanol:880 ammonia (95:4.5:0.5 v/v) to give the **30** as a cream-colored solid (125 mg, 56%): maleate salt, white powder, mp 211−213 °C (from EtOH/EtOAc); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.92−2.00 (1 H, m), 2.12−2.24 (1 H, m), 3.31−3.64 (5 H, m), 5.20−5.42 (1 H, m), 6.02 (2H, s), 6.86−6.96 (2H, m), 7.14 (1 H, dd, *J* 10 and 2), 7.84−7.92 (2H, m), 8.05 (1 H, s), 8.64 (1 H, br), 11.44 (1H, s). *m*/*z* (ES^+) 303 ($M^+ + H$). Anal. ($C_{21}H_{20}F_2N_2O_5$) C, H, N.

The following were made in the same way, with all having the same enantiomeric excess as the starting material (88% e.e.).

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-naphthalen-2-yl-1*H*-indole (27): hydrochloride salt, white needles, mp 279−280 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.80−2.05 (1 H, m), 2.30−2.40 (1 H, m), 3.40−3.60 (5 H, m), 5.25−5.50 (1 H, dm, *J* 49), 6.95 (1 H, dt, *J* 10 and 2), 7.42 (1 H, dd, *J* 10 and 2), 7.55−7.65 (2 H, m), 7.75 (1 H, d, *J* 8), 8.00−8.20 (5 H, m), 9.25 (1 H, br s), 11.73 (1 H, s); *m*/*z* (ES^+) 363 ($M^+ + H$). Anal. ($C_{23}H_{20}F_2N_2 \cdot HCl \cdot 0.7H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-naphthalen-1-yl-1*H*-indole (28): hydrochloride salt, white needles, mp 212−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.65−1.85 (1 H, m), 2.20−2.30 (1 H, m), 3.20−3.50 (5 H, m), 5.10−5.35 (1 H, dm, *J* 50), 6.95 (1 H, dt, *J* 9 and 2), 7.15 (1 H, dd, *J* 9 and 2), 7.40−7.70 (5 H, m), 7.90−8.10 (3 H, m), 9.00 (1 H, br s), 11.47 (1 H, s); *m*/*z* (ES^+) 363 ($M^+ + H$). Anal. ($C_{23}H_{20}F_2N_2 \cdot HCl \cdot 1.6H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoro-piperidin-3-yl)-2-pyridin-3-yl-1*H*-indole (29): hydrochloride salt, mp 212 °C (dec) (EtOAc); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.90−2.08 (1 H, m), 2.28−2.39 (1 H, m), 3.40−3.48 (2 H, m), 3.50−3.60 (2 H, m), 3.62−3.74 (1 H, m), 5.36 (1 H, dtd, *J* 48, 9 and 4), 6.98 (1 H, td, *J* 10 and 2), 7.25 (1 H, dd, *J* 10 and 2), 7.91 (1 H, dd, *J* 8 and 5), 8.08 (1 H, dd, *J* 9 and 5), 8.43 (1 H, d, *J* 8), 8.81 (1 H, d, *J* 4), 9.00 (1 H, s), 9.46 (2 H, br), 12.02 (1 H, s); *m*/*z* (ES^+) 314 ($M + H^+$). Anal. ($C_{18}H_{17}F_2N_3 \cdot 2HCl \cdot H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-thiophen-3-yl-1*H*-indole (31): maleate salt, white needles, mp 212−213 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.80−2.00 (1 H, m), 2.35−2.42 (1 H, m), 3.20−3.65 (5 H, m), 5.20−5.45 (1 H, dm, *J* 54), 6.02 (2 H, s), 6.93 (1 H, dt, *J* 9 and 2), 7.15 (1 H, dd, *J* 9 and 2), 7.40−7.45 (1 H, m), 7.70−7.80 (2 H, m), 7.95−8.00 (1 H, m), 8.65 (1 H, br s), 11.50 (1 H, s); *m*/*z* (ES^+) 319 ($M^+ + H$). Anal. ($C_{17}H_{16}F_2N_2S \cdot C_4H_4O_4 \cdot 1.15H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic Acid Methyl Ester (33). ^{n}BuLi (1.6 M, 3.4 mL, 5.4 mmol) was added dropwise over 10 min to a solution of 2,2,6,6-tetramethylpiperidine (0.93 mL, 5.50 mmol) in dry THF (20 mL) at 0 °C. After 15 min the solution was cooled to −78 °C, and **47** (1.20 g, 2.75 mmol) in dry THF (20 mL) was added over 10 min. The mixture was stirred at −78 °C for 3 h, and then methyl cyanoformate (0.33 mL, 4.13 mmol) was added. After 10 s, the reaction was quenched by the addition of glacial acetic acid (0.5 mL) in THF (4.5 mL) and allowed to warm to room temperature. The mixture was evaporated and partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried, and evaporated. Flash chromatography eluting with EtOAc:hexane (1:5 v/v) gave (3*R*,4*R*)-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (690 mg, 51%) as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (9 H, s), 1.57 (9 H, s), 1.60−1.80 (1 H, m), 2.15−2.25 (1 H, m), 2.80−2.95 (1 H, m), 3.10−3.35 (2 H, m), 3.95 (3 H, s), 4.20−4.40 (2 H, m), 5.20−5.45 (1 H, dm, *J* 54), 7.05 (1 H, dt, *J* 9 and 2), 7.60 (1 H, dd, *J* 9), 7.80 (1 H, dd, *J* 9 and 2). The ester (0.10 g, 0.20 mmol) was dissolved in 90% formic acid (10 mL) and heated at 50 °C for 2.5 h. The solvent was evaporated, and the residue basified with 10% NH_4OH and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried, and evaporated. Flash chromatography eluting with CH_2Cl_2:MeOH:NH_3 (98:2:0.2 v/v) gave **32** (47 mg, 79%) as a white solid: maleate salt, white needles, mp 182−183 °C: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.80−2.00 (1 H, m), 2.35−2.42 (1 H, m), 3.20−3.60 (4 H, m), 3.90−3.95 (3 H, s), 4.20−4.40 (1 H, m), 5.20−5.45 (1 H, dm, *J* 54), 6.02 (2 H, s), 7.00 (1 H, dt, *J* 9 and 2), 7.20 (1 H, dd, *J* 9 and 2), 8.00 (1 H, m), 8.75 (1 H, br s), 12.00 (1 H, s); *m*/*z* (ES^+) 295 ($M^+ + H$). Anal. ($C_{17}H_{16}F_2N_2O_2 \cdot 1.25C_4H_4O_4 \cdot 0.3H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid phenylamide (34): oxalate salt, mp 223−224 °C (from EtOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.85−2.00 (1 H, m), 2.33−2.41 (1 H, m), 3.23−3.32 (2 H, m), 3.50−3.60 (2 H, m), 4.12−4.25 (1 H, m), 5.37 (1 H, dtd, *J* 49, 10 and 5), 7.03 (1 H, t, *J* 9), 7.14 (1 H, t, *J* 7), 7.29 (1 H, dd, *J* 10 and 2), 7.38 (2 H, t, *J* 8), 7.76 (2 H, d, *J* 7), 7.93−7.99 (1 H, m), 10.30 (1 H, s); *m*/*z* (ES^+) 356 ($M + H^+$). Anal. ($C_{20}H_{19}F_2N_3O \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(3*R*,4*R*)-6-Fluoro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole (35): made in the same way as **23**, maleate salt, white crystals, mp 220−221 °C (from EtOAc), e.e. = 93.4%; $[\alpha]_D^{23}$ −0.7°(*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80−1.96 (1 H, m), 2.30−2.43 (1 H, m), 3.30−3.60 (6 H, m), 5.2−5.4 (1 H, dm, *J* 53), 6.03 (2 H, s), 6.89−6.96 (1 H, m), 7.16 (1 H, dd, *J* 9.8 and 2.3), 7.40 (2 H, t, *J* 8.8), 7.61 (2 H, dd, *J* 8.6 and 5.5), 7.97 (1 H, dd, *J* 8.8 and 5.3), 11.58 (1 H, br s); *m*/*z* (ES^+) 331 ($M + H^+$). Anal. ($C_{19}H_{17}N_2F_3 \cdot C_4H_4O_4$) C, H, N.

6-Fluoro-2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole (36): made in the same way as **9,** white crystals, mp 221−223 °C (from EtOAc); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.40−1.60 (1 H, m), 1.60−1.70 (1 H, m), 1.80−1.90 (1 H, m), 2.0−2.1 (1 H, m), 2.60−2.70 (1 H, m), 2.9−3.0 (3 H, m), 3.0−31. (1 H, m), 6.83 (1 H, dt *J* 9 2.3 and 9), 7.16 (1 H, dd, *J* 9.9 and 2.3), 7.35 (2 H, t, *J* 8.9), 7.52 (2 H, dd, *J* 8.7 and 5.5), 7.97 (1 H, dd, *J* 9 and 5.5), 11.24 (1 H, s); *m*/*z* (ES^+) 313 ($M + H^+$). Anal. ($C_{19}H_{18}F_2N_2 \cdot 0.3H_2O$) C, H, N.

Supporting Information Available: Microanalyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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