4-(Phenylsulfonyl)piperidines: Novel, Selective, and Bioavailable 5-HT$_{2A}$ Receptor Antagonists

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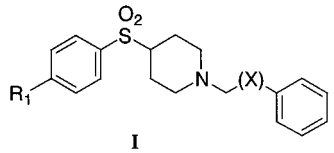
On the basis of a spirocyclic ether screening lead, a series of acyclic sulfones have been identifed as high-affinity, selective 5-HT$_{2A}$ receptor antagonists. Bioavailability lacking in the parent, 1-(2-(2,4-difluorophenyl)ethyl)-4-(phenylsulfonyl)piperidine (**12**), was introduced by using stability toward rat liver microsomes as a predictor of bioavailability. By this means, the 4-cyano- and 4-carboxamidophenylsulfonyl derivatives **26** and **31** were identified as orally bioavailable, brain-penetrant analogues suitable for evaluation in animal models. Bioavailability was also attainable by N substitution leading to the *N*-phenacyl derivative **35**. IKr activity detected through counterscreening was reduced to insignificant levels in vivo with the latter compound.

Introduction

It is generally accepted that activation of central 5-HT$_{2A}$ receptors (agonism) produces the psychomimetic effects of hallucinogenic drugs such as LSD and mescaline.[1,2] The resulting effects in man include major changes in mood, perception, and cognition. Blockade of 5-HT$_{2A}$ receptors (antagonism) has been implicated in the beneficial effects of newly released antidepressants such as mirtazepine, nefazodone, and atypical antipsychotic drugs such as risperidone and olanzapine.[3] However, these latter compounds bind at sites in addition to the 5-HT$_{2A}$ receptor.[4−7] Thus, while blockade of the 5-HT$_{2A}$ receptor has been demonstrated to give rise to quantifiable behavioral effects in animal models, such as the DOI-induced head-twitch,[8] it remains unclear whether specific blockade of central 5-HT$_{2A}$ receptors will be therapeutically beneficial.[9] Recently, compounds selective for the 5-HT$_2$ family of receptors such as fananserin (**1**),[10] MDL100907 (**2**),[11] and eplivanserin (**3**)[12] have been described (Figure 1). Both fananserin[13] and MDL100907[14] showed a lack of efficacy in trials of psychosis,[15] with PET labeling in the latter case being used to demonstrate high receptor occupancy.[16] Eplivanserin (SR 46349B) is currently undergoing clinical evaluation.[17] To fully evaluate the therapeutic potential of selective 5-HT$_{2A}$ antagonists, we wished to identify a novel series of orally active compounds suitable for evaluation in vivo both in animal models and clinically.

Comprehensive robotic screening of the Merck sample collection generated two leads **4** and **5** (Figure 2). Indole **4** was progressed to give **6** as recently described.[18] A limitation of the indole series was the 200-fold binding selectivity observed for the human vs the rodent form of the 5-HT$_{2A}$ receptor (Table 1), since this reduced the effectiveness of the compounds in animal behavioral models. Because comparable binding affinity at the rat and human 5-HT$_{2A}$ receptors was observed with the spirocyclic ether **5**, studies based on the alternative lead were undertaken. Comparison of the structure of MDL100907 and the spirocyclic ether initially suggested that spirocyclic alcohols would be high-affinity 5-HT$_{2A}$ ligands. Searching of the literature revealed that alcohol **7**, reported as a σ ligand, showed high affinity for the 5-HT$_{2A}$ receptor in counterscreening assays, and we were able to confirm this (Table 1).[19] The compound, however, like MDL100907 (**2**), showed very low exposure following oral dosing in rat at 1−2 mg/kg (Table 2), and this avenue was not pursued further.

In the following discussion, optimization of the screening lead **5** to give orally bioavailable, selective, high-affinity 5-HT$_{2A}$ antagonists of general structure **I**[20] will be described.



I

Results and Discussion

The receptor binding profile obtained for the screening lead **5** is shown in Table 1. High affinity at the rat and human 5-HT$_{2A}$ subtypes was observed (K_i of h5-HT$_{2A}$, 1.8 nM). Counterscreening, however, showed only modest selectivity over D$_2$ (320-fold) and high affinity at the outward delayed rectifier potassium channel IKr (K_i, 20 nM). We set out to eradicate this activity because it is now recognized that IKr blockade leads to prolongation of the QTc interval in vivo, which can lead to episodes of polymorphic ventricular dysrhythmias that occasionally culminate in sudden death.[21] A further issue was the poor oral bioavailability of **5**. Systemic exposure in rat following oral dosing at 1.5 mg/kg was found to be low (AUC 4 ng h/mL (Table 2)). To address these issues, the strategy adopted was to initially identify a frame-

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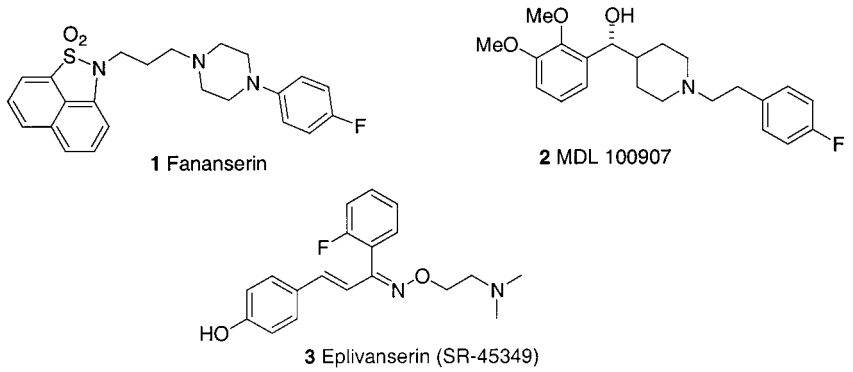


Figure 1. $5HT_2$ antagonists.

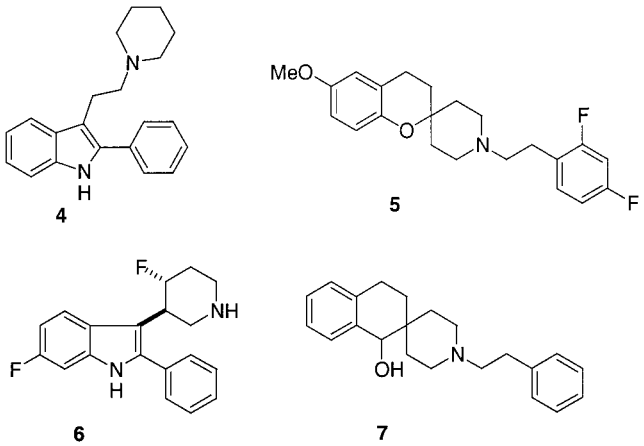


Figure 2. Lead and literature compounds.

work for optimization of activity in vitro, then to develop the structure−activity relationships relating to bioavailability.

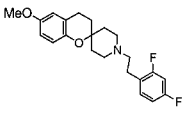
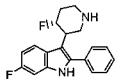
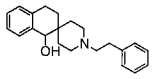
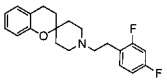
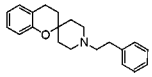
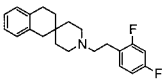
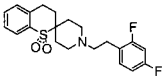
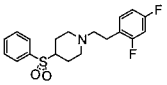
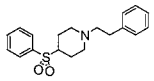
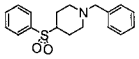
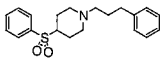
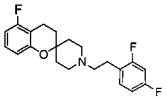
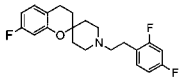
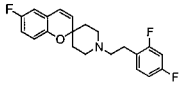
Deletion studies shown in Table 1 were carried out on the basis of **5** in order to determine the contribution to 5-HT_{2A} binding affinity provided by the substituents and the molecular architecture. Removal of the methoxy group to give **8** results in little loss of binding affinity. The two fluorine atoms, on the other hand, produce a 10-fold increase in binding as shown by the loss of affinity observed with **9** (Table 1). Most strikingly, desoxy derivative **10** showed that the spirocyclic ether oxygen contributes little to 5-HT_{2A} receptor binding affinity. It thus became apparent that there might be an opportunity to introduce a linking group in place of the ether that would retain high affinity at the 5-HT_{2A} receptor but reduce IKr activity and enhance bioavailability. From a wide range of groups evaluated, the sulfone was found to be most advantageous. Thus, spirocyclic sulfone **11** binds with high binding affinity at both the rat and human forms of the 5-HT_{2A} receptor with good selectivity over 5-HT_{2C}, D_2, and α1-Adr receptors. Furthermore, IKr binding is reduced when compared to the corresponding ether **8** and the methylene compound **10**. Enhancement in oral bioavailability was not, however, observed as shown in Table 2.

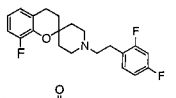
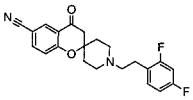
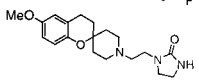
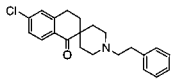
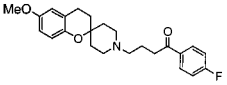
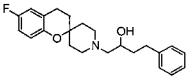
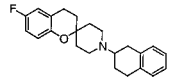
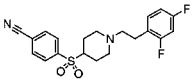
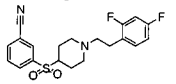
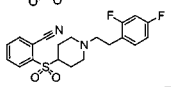
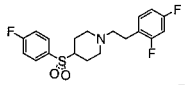
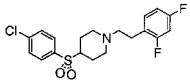
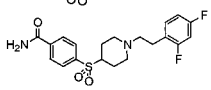
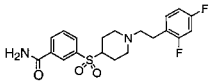
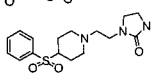
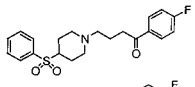
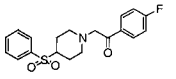
The influence of ring constraint on binding affinity was assessed through preparation of acyclic sulfone **12**. This compound was found to bind with high affinity at both human and rat 5-HT_{2A} receptors (K_i of h5-HT_{2A}, 0.33 nM). Selectivity over D_2 and α1 receptors comparable to the spirocyclic sulfone **11** was observed, and IKr activity was further reduced. Exploration of changes to the N substituent showed that 2,4-difluoro substitution of the phenethyl group gives a modest but significant increase in 5-HT_{2A} binding affinity, as shown by a comparison of **12** and **13** (Table 1). Furthermore, the *N*-benzyl and *N*-phenpropyl derivatives (**14** and **15**, respectively) have considerably reduced 5-HT_{2A} binding affinity compared to the phenethyl derivative (**13**). Consequently, **12** was selected for further optimization studies to address the remaining issue of low oral bioavailability.

Assessment of the pharmacokinetics of **12** after iv dosing in rat revealed plasma clearance to be relatively high (CL, 34 mL/min/kg), as shown in Table 2. On this basis, it was reasoned that reduction of metabolism would enhance bioavailability. Evaluation of routes of metabolism in vitro using rat liver microsomes showed oxidation to occur at several positions and via several CYP450 isozymes. Thus, little insight could be gained into how metabolism might be blocked through specific substitution. In an effort to identify global structural changes that might lead to enhancement of stability, analogues of the cyclic ether **5**, available from the company collection, were evaluated, with stability toward rat liver microsomes being used as a surrogate measure of bioavailability.

The stability toward rat liver microsomes of available compounds structurally related to **5** is shown graphically in Chart 1. Enhanced stability was attained through substitution of the spirocyclic ring system as with **20** and through appropriate substitution of the nitrogen atom as with **21** and **23**. Attention was first directed toward aromatic substitution. It was not a straightforward task to ascertain whether reduced turnover of **20** was derived from the presence of the keto or the cyano group because neither the des-cyano or des-keto derivatives were available for evaluation. Because the 5-HT_{2A} affinity for **20** was low, and undesired, high IKr activity was observed in the ether series; synthesis of the des-cyano or des-keto derivatives was not considered. Instead, aromatic substitution within the acyclic phenyl sulfone series was explored. The 4-cyanophenyl sulfone **26** was prepared. This compound binds with high affinity at both rat and human 5-HT_{2A} receptors (Table 1). Functional studies showed the compound to be an antagonist. Counterscreening showed a 250-fold selectivity over 5-HT_{2C} and a >2000-fold selectivity over D_2 and α1-Adr receptors. More significantly, assessment of pharmacokinetics in rat showed the compound to have 23% oral bioavailability with a mean residence time of 2.3 h (Table 2). The stability of a selection of

Table 1. Binding Data

No	Structure	Ki (nM)[a] h5HT$_{2A}$	r5HT$_{2A}$	h5HT$_{2C}$	hD$_2$	radrα1	hIKr
1	Fananserin	0.04	0.06	1	180	13	200
2	MDL 100907	0.31	0.10	13	1300	420	1100
5		1.8	0.69	150	570	660	20
6		0.06	12.0	10	>1500	4	4000
7		0.40	0.59	230	1700	1300	1200
8		2.4	0.72	450	750	240	110
9		16	2.6		530	250	
10		2.9		320	1000	250	69
11		0.41	0.61	41	1500	>1500	570
12		0.33	0.18	25	1400	>1500	1000
13		1.2		46	>1500	>1500	1800
14		630			>1500		
15		15			>1500	>1500	2500
16		5.0	4.0	440	710	430	
17		3.1	3.2	600	490	330	
18		16.0			650		

No	Structure	Ki (nM)[a] h5HT$_{2A}$	r5HT$_{2A}$	h5HT$_{2C}$	hD$_2$	radrα1	hIKr
19		3.3	3.2	190	840	210	
20		150					
21		970					
22		16	25.0	850	1100	160	
23		0.36	0.38	28	2	8	
24		31	29.0	1500	1100	460	
25		95			1800		
26		2.6	1.5	640	>1500	>1500	560
27		0.66	0.54	39	>1500	>1500	1900
28		0.53	4.8	47	680	>1500	4000
29		0.42		92	>1500	>1500	710
30		1.4	0.25	58	1100	550	150
31		0.52	1.1	100	1000	>1500	1300
32		0.50		18	650	>1500	7143
33		>2000			>1500		
34		15	3.3		1100	110	
35		2.4	0.51	130	>1500	>1500	6800

[a] Affinities at human cloned 5-HT2A, 5-HT2C, and D2 receptors, the IKr channel (hERG), and rat 5-HT2A and α1Adrenergic receptors.

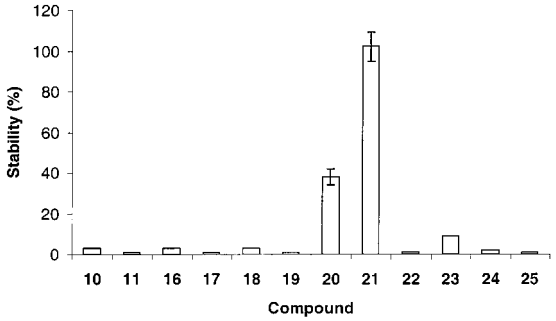
substituted phenyl sulfones in the presence of rat microsomal stability is shown in Chart 2. Comparison of the 4-cyano derivative **26** with the 2- and 3-cyano derivatives **27** and **28** showed that enhanced stability is only obtained with a cyano group at the 4-position. Substitution with F and Cl at the 4-position (**29** and **30**, respectively) does not confer stability, but a carboxamide group at the 4-position does (**31**). Furthermore, contrary to the findings with the nitriles, turnover is reduced when a carboxamide is introduced at the 3-position (**32**). Pharmacokinetic studies in rat confirmed the correlation of turnover with bioavailability. Thus, **31** and **32** were found to have bioavailability comparable with that of **26** (Table 2). It was anticipated that brain penetration of these amides would be compromised relative to nitrile because of the increased polarity and increased H-bonding capability of the carboxamide.[22] Blood and brain levels of **31** and **26** measured following po dosing to mice confirmed this. A brain/blood ratio of 10 was obtained for the nitrile **26** compared with 0.3 for the carboxamide **31**. Nevertheless, high brain levels were obtained with both compounds in mouse 30 min following po dosing at 1 mg/kg (**26**, brain 406 ng/mL, plasma 41ng/mL; **31**, brain 135 ng/mL, plasma 397 ng/mL), indicating suitability for use in animal behavioral studies.

Table 2. Rat Pharmacokinetics

compd	C_{max}[a] ng/mL	AUC[b] ng h mL^{-1}	F[c] %	Cl[d] mL min^{-1} kg^{-1}	Vd[e] L/kg	Mrt[f] h	dose mg/kg
2	2	8	3	77	4.6	1.0	1.2
5	2	4	1	53	4.9	1.5	1.5
7	2	3					2.0
11	1	1					2.0
12	23	100	2	34	2.0	1.0	10
26	30	177	23	20	2.8	2.3	1
27	0	0					2
28	0	0					2
31	70	199	22	19	1.0	0.9	1
32	38	115	24	36	2.3	1.1	1
35	140	171	30	29	1.2	0.7	1

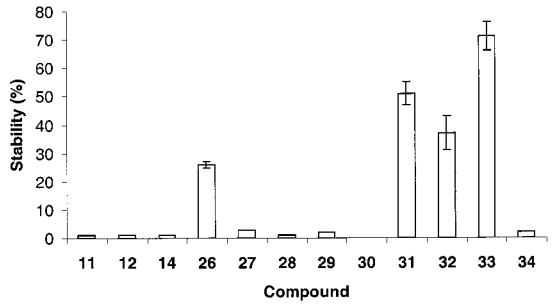
[a] Maximum blood concentration after oral dosing. [b] Area under the concentration−time curve for 0−4 h after oral dosing. [c] Bioavailability calculated from dosing iv and po. [d] Clearance from plasma calculated following iv dosing. [e] Volume of distribution calculated from dosing iv. [f] Mean residence time following iv dosing.

Chart 1. Stability of Spirocyclic Ether Derivatives in the Presence of Rat Liver Microsomes[a]



[a] See Experimental Section for details.

Chart 2. Stability of Sulfone Derivatives toward Rat Liver Microsomes[a]

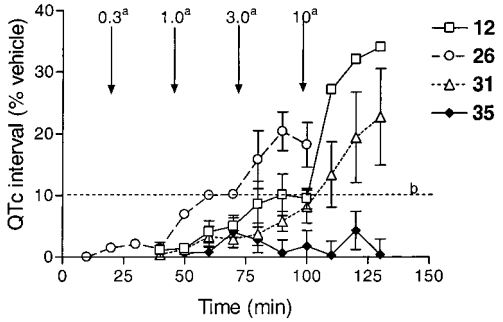


[a] See Experimental Section for details.

To identify bioavailable analogues with reduced IKr activity, the alternative approach to exploring N substitution was investigated. Preparation of the 4-(phenylsulfonyl)piperidine analogues of the stable spirocyclic ethers **21** and **23** gave **33** and **34**, respectively. Compound **33** lacked affinity for the 5-HT$_{2A}$ receptor, but moderate affinity was observed with **34** (K_i h5-HT$_{2A}$, 15 nM). Since the earlier comparison of binding data for **13**−**15** suggested a two-carbon linker to be optimal for high 5-HT$_{2A}$ binding affinity, **35** (the lower homologue of **34**) was prepared. This led to enhanced affinity for both human and rat 5-HT$_{2A}$ receptors (K_i of h5-HT$_{2A}$, 2.4 nM) and good selectivity over other receptors including enhanced selectivity over IKr (Table 1).

To confirm that the reduction in IKr binding affinity had pharmacological significance, studies were carried out to investigate the effect of the compounds in vivo on the QTc interval in the anesthetized ferret following iv infusion (Chart 3). The ferret model was developed as an alternative to the dog for simplicity and to reduce the amount of compound required for evaluation. The studies showed that **12**, **26**, and **31** caused a significant prolongation of the QTc interval (>10% increase). Since it is not currently clear what level of receptor occupancy of 5HT$_{2A}$ receptors would be required therapeutically, the QTc data obtained for **12**, **26**, and **31** cannot be used to establish a safety margin between the QTc interval and 5HT$_{2A}$ activity. A better option is to eliminate QTc prolongation in vivo. This was achieved with compound **35**, which had no significant effect on the QTc interval following infusion dosing up to 10 mg kg^{-1} h^{-1}. Pharmacokinetic evaluation of **35** showed the compound to be orally bioavailable in rat (F, 30% (Table 2)).

Chart 3. Effect of 5-HT$_{2A}$ Receptor Antagonists on QTc Interval in the Anaesthetised Ferret[c]



[a] Infusion dose (mg kg^{-1} h^{-1}). [b] Line showing 10% increase in QTc interval. [c] Error bars show standard error of the mean of three determinations.

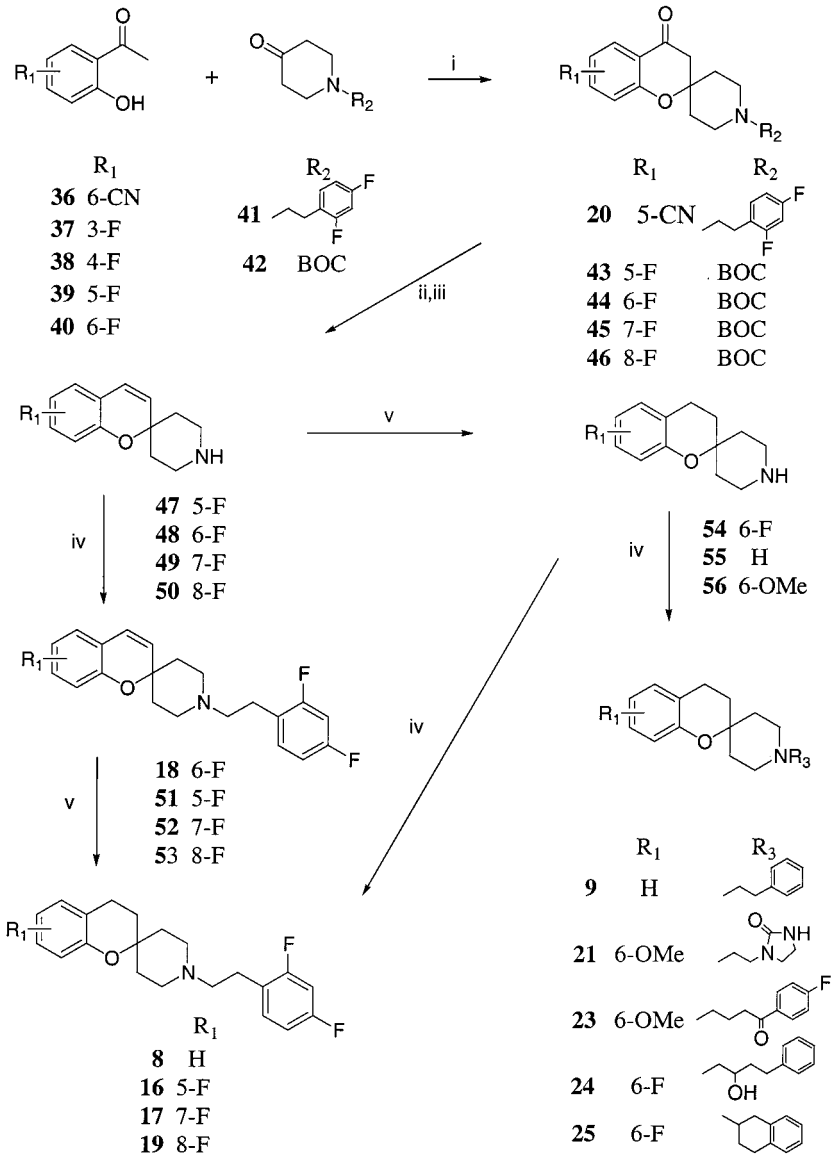
Chemistry

Spirocyclic derivatives **5**,[23] **7**,[21] **22**,[21] **55**,[24] **57**,[23] and **59**[23] have been reported previously. Compounds **8**, **9**, **16**−**21**, and **23**−**25** were prepared in a manner similar to that described for **5** as shown in Scheme 1. The desoxy derivative **10** was obtained by reduction of alcohol **58** using triethylsilane in TFA (Scheme 2). Spirocyclic sulfone **11** was prepared from the previously reported thioether **59**,[23] as outlined in Scheme 3. The 4-(phenylsulfonyl)piperidine derivatives (**12**−**15** and **26**−**35**) were prepared as shown in Scheme 4. The thioethers (**64a**−**f**) were initially obtained via condensation of *N*-BOC 4-piperidinol (**62**) with diphenyl disulfide in the presence of tributylphosphine.[25] Subsequently alkylation of the appropriate thiophenol with *N*-BOC 4-mesyloxypiperidine (**63**)[20] was employed. Oxidation to the sulfones (**65a**−**f**) was best achieved using oxone on alumina in CH_2Cl_2 in accordance with the method of Greenhalgh.[26] Deprotection with HCl afforded piperidines **66a**−**f** as precursors for alkylation.

Biology

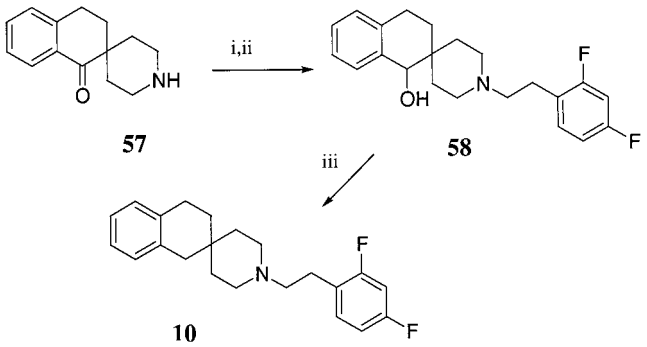
Compounds were evaluated for displacement of [^{3}H]-ketanserin binding to human 5HT$_{2A}$ receptors[27] stably expressed in Chinese hamster ovary (CHO) cells, [^{3}H]-mesurgeline binding to human 5-HT$_{2C}$ receptors stably expressed in CHO cells, [^{3}H]-spiperone binding to CHO cells stably expressing hD2 receptors,[28] [^{3}H]-prazosin binding to rat cortical membranes,[29] and [^{3}H]-dofetilide binding to HEK cells stably expressing hERG, which encodes the IKr potassium channel. For h5-HT$_{2A}$ recep-

Scheme 1[a]



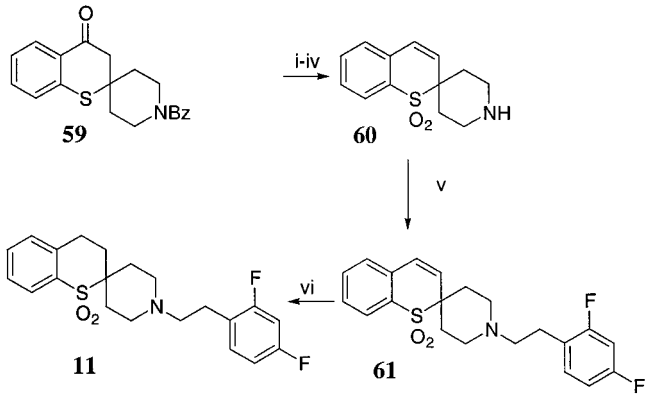
[a] Reagents: (i) pyrrolidine, EtOH, room temp, 18 h; (ii) borane/THF, reflux, 16 h; (iii) 5 N HCl, reflux, 2.5 h; (iv) RX, K_2CO_3, CH_3CN, reflux, 10 h; (v) Pd/C, H_2 (55psi), EtOH, 1 N HCl, 8 h.

Scheme 2[a]



[a] Reagents: (i) 2,4-difluorophenethyl bromide, K_2CO_3, CH_3CN, reflux, 15 h; (ii) $NaBH_4$, EtOH, room temp, 12 h; (iii) Et_3SiH, TFA, CH_2Cl_2, room temp.

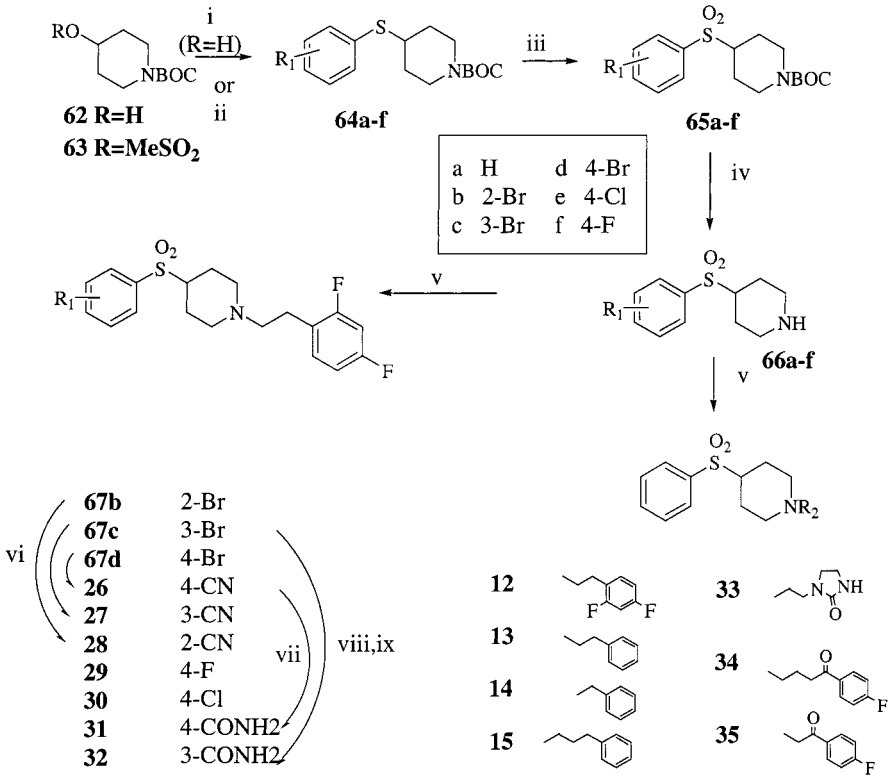
Scheme 3[a]



[a] Reagents: (i) 30% H_2O_2, HOAc, 90 °C, 2 h; (ii) $NaBH_4$, EtOH; (iii) *p*-toluenesulfonic acid, toluene, reflux, 72 h; (iv) 6 N HCl, 90 °C, 12 h; (v) 2,4-difluorophenethyl bromide, K_2CO_3, CH_3CN, reflux, 18 h; (vi) Pd/C, H_2 (55psi), EtOH, 18 h.

tors, the K_i values are quoted as the geometric mean of at least three separate determinations, and the errors of the mean are within 2-fold of the mean. In counter-screening binding assays, K_i values are the geometric mean of at least two independent determinations (Table 1). In a functional assay, compounds were evaluated for their effect alone (agonist activity) and their ability to

Scheme 4[a]



[a] Reagents: (i) nBu_3P, PhSSPh, THF, reflux, 48 h; (ii) ArSH, K_2CO_3, CH_3CN, reflux, 18 h; (iii) oxone, wet alumina, $CHCl_3$, reflux, 18 h, (iv) 5 N HCl, MeOH, reflux, 3 h; (v) RX, K_2CO_3, CH_3CN, reflux, 18 h; (vi) CuCN, *N*-methylpyrrolidinone, reflux, 16 h; (vii) 85% H_2SO_4, 100 °C, 30 min; (viii) CO, $Pd(OAc)_2$, MeOH; (ix) NH_4Cl, Me_3Al, toluene, reflux, 18 h.

block (antagonist activity) 5HT (1 μM) mediated accumulation of inositol phosphates in CHO cells stably expressing h5-HT_{2A} receptors.[27,30]

The methodology for determination of compound stability toward rat liver microsomes is described in the Experimental Section. The results shown in Charts 1 and 2 are expressed as the percent of material remaining after incubation for 30 min, with each determination carried out three times. Methods for determination of pharmacokinetics (Table 2) are also included in the Experimental Section.

The QTc interval was determined in the anesthetized ferret for assessment of IKr activity in vivo. Changes in QTc interval were measured following infusion dosing at increased dose levels (0.3, 1, 3, and 10 mg kg^{-1} h^{-1}) administered sequentially over three time periods (30 min) in triplicate (Chart 3).

Conclusions

On the basis of the spirocyclic ether screening lead **5**, a series of acyclic sulfones have been identified as high-affinity, selective 5-HT_{2A} receptor antagonists. Oral bioavailability, initially lacking in the unsubstituted derivative **12**, has been achieved through aromatic substitution with cyano- or carboxamide groups leading to compounds such as **26** and **31**. The compounds have high affinity at both rat and human cloned 5-HT_{2A} receptors and are brain-penetrant. Thus, they represent useful tools for the evaluation of 5-HT_{2A} antagonists in CNS related animal models. N substitution based on **12** also gives rise to bioavailable derivatives such as **35**. IKr activity, which may lead to cardiac dysrhythmias in man, is not significant with this derivative. These compounds thus provide the opportunity of determining the therapeutic potential of selective 5-HT_{2A} receptor antagonists.

Experimental Section

Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. Proton NMR spectra were recorded on Bruker DPX 400, AM 360, and AC 250 spectrometers, and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Mass spectra were recorded on a VG 70/250 spectrometer. Merck Kieselgel (230−400) mesh (silica) was used as bought from Aldrich. Reactions were carried out under nitrogen, and organic solutions were dried with anhydrous magnesium sulfate unless indicated otherwise. Elemental analyses were determined by Butterworth Laboratories, Ltd., Teddington, Middlesex, U.K. Compounds **36**−**42** and **56** were obtained commercially.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydrospiro[2*H*-1-benzopyran-2,4′-piperidine] (8). To a mixture of 3,4-dihydrospiro[2*H*-1-benzopyran-2,4′-piperidine] hydrochloride (**55**)[24] (0.37 g, 1.5 mmol) and 2,4-difluorophenylacetic acid (0.39 g, 2.2 mmol) in DMF (20 mL) stirring at room temperature were added HOBt (0.31 g, 2.2 mmol), EDCI (0.44 g, 2.2.mmol), and Et_3N (0.63 mL, 3.8 mmol). The mixture was stirred at room temperature for 24 h and partitioned between EtOAc (3 × 25 mL) and water (25 mL). The organic phase was dried and concentrated, and the residue was purified by column chromatography (silica; EtOAc/isohexane 1:3 → 1:1) to give the intermediate amide as a gummy solid (0.29 g, 54%). MS *m*/*z* (ES^+): 358 ($M + H^+$). This was dissolved in THF (10 mL), and LAH powder (60 mg, 1.6 mmol) was added in one portion at room temperature. After the mixture was stirred for 2 h, 20% KOH solution (3 mL) was added and the mixture partitioned between EtOAc and water. The residue obtained

on workup was purified by column chromatography (silica; EtOAc/isohexane 1:1 → 1:0), and the product was converted to the hydrochloride salt using 1 M HCl solution in ether to give **8** (110 mg, 36%). Mp 252−4 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.64−1.72 (2H, m), 1.78−1.88 (4H, m), 2.50−2.57 (2H, m), 2.60−2.64 (2H, m), 2.73−2.90 (6H, m), 6.73−6.84 (4H, m), 7.03−7.26 (3H, m). MS *m*/*z* (ES^+): 344 ($M + H^+$). Anal. ($C_{21}H_{24}ClF_2NO$) C, H, N.

3,4-Dihydro-1′-[2-phenylethyl]spiro[2*H*-1-benzopyran-2,4′-piperidine] (9). Compound **55**[24] (0.7 g, 2.9 mmol) was added in one portion to a mixture of phenethyl bromide (0.4 mL, 2.9 mmol), anhydrous K_2CO_3 (0.81 g, 5.8 mmol), and NaI (0.48 g, 3.2 mmol) in acetonitrile (10 mL), and the resulting slurry was heated at 85 °C for 18 h. The mixture was then partitioned between EtOAc (4 × 15 mL) and water (15 mL). The organic phase was dried and concentrated, the residue was purified by column chromatography (silica; EtOAc/isohexane 1:3 → 1:1), and the product was converted to the hydrochloride salt using 1 M HCl solution in ether to give **9** (194 mg, 19%). Mp 275−6 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.64−1.72 (2H, m), 1.75−1.88 (4H, m), 2.48−2.54 (2H, m), 2.63−2.67 (2H, m), 2.72−2.85 (6H, m), 6.77−6.84 (2H, m), 7.03−7.10 (2H, m), 7.16−7.29 (5H, m). MS *m*/*z* (ES^+): 308 ($M + H^+$). Anal. ($C_{21}H_{26}ClNO$) C, H, N.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydrospiro[naphthalene-2(1*H*),4′-piperidine] (10). To a solution of ketospiropiperidine **57**[23] (0.92 g, 43 mmol) in acetonitrile (50 mL) was added potassium carbonate (1.48 g, 11 mmol) followed by sodium iodide (0.77 g, 5.1 mmol) and 2,4-difluorophenethyl bromide (1.13 g, 5.1 mmol), and the mixture was heated under nitrogen for 15 h while stirring. After cooling to room temperature, the reaction mixture was partitioned between water (20 mL) and EtOAc (100 mL) and the phases were separated. The aqueous layer was extracted again with EtOAc (50 mL), and the organic phases were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and adsorbed onto silica gel (20 g). Flash chromatography yielded 0.52 g (35%) of the desired ketone intermediate (MS *m*/*z* (ES^+): 355 ($M + H^+$)) as a yellow semisolid, which was dissolved in ethanol (10 mL), and sodium borohydride (0.4 g, 10.6 mmol) was added under nitrogen over 1 min at room temperature. Stirring was continued for 12 h, and the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL). The mixture was concentrated under vacuum and the mixture partitioned between EtOAc and water (50 mL/20 mL). After separation of the organic phase, the aqueous phase was extracted twice and the organic phases were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and evaporated to give 0.5 g of a syrup that was purified via column chromatography to yield 0.2 g (37%) of alcohol **58** as a foam. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.19−1.73 (4H, m), 1.92−2.04 (2H, m), 2.48−2.95 (10H, m), 4.38 (1H, broad s), 6.74−6.84 (2H, m), 7.12−7.26 (4H, m), 7.33−7.36 (1H, m).

To a solution of **58** (0.2 g, 0.56 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.25 mL, 3.2 mmol) followed by triethylsilane (0.4 mL, 5.6 mmol), and the solution was heated under nitrogen for 12 h while stirring. After cooling to room temperature, the reaction mixture was concentrated and partitioned between 2 N NaOH (20 mL) and chloroform (100 mL) and the phases were separated. The aqueous layer was extracted again with chloroform (50 mL), and the organic phases were combined, washed with brine (20 mL), dried over sodium sulfate, filtered, and adsorbed onto silica gel (10 g). Flash chromatography yielded **10** (0.07 g, 37%) as a colorless semisolid. HCl salt, mp 270−2 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.19−1.73 (4H, m), 1.92−2.04 (2H, m), 2.48−2.95 (10H, m), 4.38 (1H, broad s), 6.74−6.84 (2H, m), 7.12−7.26 (4H, m), 7.33−7.36 (1H, m). MS *m*/*z* (ES^+): 342 ($M + H^+$). Anal. ($C_{22}H_{26}ClF_2N\cdot 0.5H_2O$) C, H, N.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydrospiro[2*H*-1-benzothiopyran-2,4′-piperidine]-1,1-dioxide (11). Compound **59**[23] (4.13 g, 12 mmol) was dissolved in glacial acetic acid (20 mL) at room temperature, and 30% aqueous hydrogen peroxide (5 mL) was added. The resulting solution was heated at 90 °C for 2 h, cooled to room temperature, and concentrated to $^1/_3$ the volume in vacuo. The mixture was partitioned between water (20 mL) and CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with saturated sodium thiosulfate solution (20 mL) and brine and dried over sodium sulfate, filtered, and concentrated to yield a yellow gum (4.2 g), which was dissolved in EtOH (25 mL) at room temperature under nitrogen. Sodium borohydride (0.65 g, 17 mmol) was added portionwise, and the mixture was stirred for 12 h at room temperature. Saturated ammonium chloride solution (50 mL) was then added followed by CH_2Cl_2 (200 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to yield a semisolid (MS *m*/*z* (ES^+): 371 ($M + H^+$)), which was dissolved in toluene (50 mL). *p*-Toluenesulfonic acid (200 mg) was added, and the resulting mixture was stirred and heated at reflux for 72 h. After cooling to room temperature, the solution was partitioned between saturated sodium carbonate (20 mL) and CH_2Cl_2 (100 mL) and the phases were separated. After extraction with CH_2Cl_2 (×2) the organic phases were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated to yield a yellow syrup (4.2 g), which was dissolved in EtOH (100 mL), and 6 N HCl (25 mL) was added. The mixture was heated at 90 °C for 12 h, cooled to room temperature, concentrated, and azeotroped with toluene (50 mL) to yield a semisolid that was recrystallized from methanol to give **60** as a colorless solid. ^{1}H NMR δ_H (free base, 360 MHz, $CDCl_3$): 1.79−1.89 (3H, m), 2.09−2.21 (2H, m), 2.80−2.93 (2H, m), 3.13−3.21 (2H, m), 6.38 (1H, d J = 11.8 Hz), 6.68 (1H, d J = 11.8 Hz), 7.28 (1H, d J = 8.1 Hz), 7.42−7.61 (2H, m), 8.01 (1H, d J = 8.1 Hz). A mixture of **60** (0.5 g, 1.7 mmol), 2,4-difluorophenethyl bromide (0.39 g, 1.8 mmol), and K_2CO_3 (0.48 g, 3.4 mmol) in CH_3CN (20 mL) was heated at reflux for 18 h. The reaction mixture was then concentrated and partitioned between EtOAc and water. The residue obtained from the organic phase was purified by column chromatography (silica; CH_2Cl_2/MeOH 99:1 → 95:5) to give **61** (0.33 g, 47%) as an oil. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.75−1.89 (2H, m), 2.29−2.40 (4H, m), 2.59−2.63 (2H, m), 2.77−2.82 (2H, m), 2.93−3.00 (2H, m), 6.31 (1H, d, J = 10 Hz), 6.64 (1H, d, J = 10 Hz), 6.72−6.80 (2H, m), 7.13−7.19 (1H, m), 7.27 (1H, d, J = 7 Hz), 7.48 (1H, t, J = 7 Hz), 7.58 (1H, t, J = 7 Hz), 8.00 (1H, d, J = 7 Hz). A solution of **61** (0.18 g, 0.46 mmol) in EtOH (20 mL) was shaken with 10% palladium-on-carbon (0.05 g) on a Parr hydrogenator at 55 psi of H_2 for 18 h. The catalyst was then removed by filtration and the filtrate concentrated. The residue was purifed by column chromatography (silica; CH_2Cl_2/MeOH 99:1 → 95:5) followed by recrystallization from EtOAc to give **11** (0.078 g, 43%). HCl salt, colorless solid; mp 218−20 °C. ^{1}H NMR δ_H (400 MHz, $CDCl_3$): 1.75−1.82 (2H, m), 2.29−2.47 (6H, m), 2.56−2.67 (2H, m), 2.75−2.82 (2H, m), 2.90−3.05 (4H, m), 6.72−6.80 (2H, m), 7.08−7.21 (2H, m), 7.35−7.50 (2H, m), 7.95 (1H, d, J = 8 Hz). MS *m*/*z* (ES^+): 392 ($M + H^+$). Anal. ($C_{21}H_{24}ClF_2NO_2S$) C, H, N.

1-(2-(2,4-Difluorophenyl)ethyl)-4-(phenylsulfonyl)piperidine (12). a. *N*-BOC 4-(Phenylthio)piperidine (64a). Tri(*n*-butyl)phosphine (7.4 mL, 0.045 mol) was added to a solution of *N*-BOC 4-hydroxypiperidine (**62**) (4.0 g, 0.02 mol) and diphenyl disulfide (6.5 g, 0.03 mol) in dry THF (20 mL) at room temperature, and the resulting mixture was heated at reflux for 48 h. The mixture was then partitioned between EtOAc (3 × 40 mL) and 2 N NaOH (40 mL). The organic phase was washed with brine, dried, and concentrated to give **64a** (3.3 g, 54%) as a solid after trituration with isohexane.

b. *N*-BOC 4-(Phenylsulfonyl)piperidine (65a). Water (10 mL) was added to alumina (50 g), which was slurried (5 min), and chloroform (100 mL) added followed by a solution of **64a** (15.8 g, 54 mmol) in chloroform (200 mL). Oxone (100 g, 0.16 mol) was added, and the resulting slurry was stirred and heated at reflux for 18 h. After cooling to room temperature,

the mixture was filtered and the mother liquor washed with water, dried, and evaporated to give **65a** (16.2 g) as a colorless solid.

c. 4-(Phenylsulfonyl)piperidine (66a). *N*-BOC 4-(phenylsulfonyl)piperidine (**65a**) (5.6 g, 0.0175 mol) was dissolved in methanol (50 mL) and 5 N HCl (10 mL) and heated at reflux for 3 h. After a warm filtration to remove insolubles, the solution was poured into saturated aqueous sodium carbonate solution and extracted with CH_2Cl_2 to afford 3.2 g of a colorless, gummy solid as the free base. Trituration with diethyl ether afforded **66a** (3.0 g) as a colorless solid. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.52−1.64 (2H, m), 1.98 (2H, broad d, J = 10 Hz), 2.34 (1H, s), 2.49−2.59 (2H, m), 2.98−3.07 (1H, m), 3.19 (2H, broad d, J = 10 Hz), 7.42−7.59 (2H, m), 7.59−7.66 (1H, m), 7.87 (2H, d, J = 4.7 Hz). A mixture of **66a** (0.63 g, 2.8 mmol), 2,4-difluorophenethyl bromide (0.74 g, 0.0033 mol), K_2CO_3 (0.77 g, 5.6 mmol), and NaI (0.5 g, 3.3 mmol) in CH_3CN (15 mL) was heated at reflux under nitrogen for 18 h. The reaction mixture was then concentrated and partitioned between water and EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography (silica; isohexane/EtOAc 3:1) gave **12** (0.4 g, 39%) as a colorless solid. Mp 86−87 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.66−1.77 (2H, m), 1.96−2.04 (4H, m), 2.49−2.53 (2H, m), 2.71−2.75 (2H, m), 2.86−2.95 (1H, m), 3.03−3.07 (2H, m), 6.72−6.80 (2H, m), 7.08−7.15 (1H, m), 7.54−7.59 (2H, m), 7.64−7.68 (1H, m), 7.87 (2H. d J = 4.2 Hz). MS m/z (ES$^+$): 366 (M + H$^+$). Anal. ($C_{19}H_{22}ClF_2NO_2S$) C, H, N.

1-(2-Phenylethyl)-4-(phenylsulfonyl)piperidine (13). A mixture of **66a** (0.2 g, 0.88 mmol), phenethyl iodide (0.13 mL, 0.88 mmol), and K_2CO_3 in CH_3CN (20 mL) was stirred and heated at reflux for 18 h. The solvent was then evaporated and the residue partitioned between EtOAc and water. The residue obtained from workup was purified by column chromatography (silica; CH_2Cl_2 → CH_2Cl_2/MeOH 97:3) followed by recrystallization from EtOAc to give **13** (0.17 g, 59%) as a colorless solid. Mp 116−8 °C. ^{1}H NMR δ_H (400 MHz, $CDCl_3$): 1.66−1.77 (2H, m), 1.96−2.04 (4H, m), 2.52−2.62 (2H, m), 2.71−2.75 (2H, m), 2.86−2.95 (1H, m), 3.03−3.07 (2H, m), 7.14−7.20 (3H, m), 7.20−7.30 (2H, m), 7.54−7.59 (2H, m), 7.64−7.68 (1H, m), 7.88 (2H, d, J = 7 Hz). MS m/z (ES$^+$): 330 (M + H$^+$). Anal. ($C_{19}H_{23}NO_2S$) C, H, N.

Similarly prepared using the appropriate bromide were the following.

1-Phenylmethyl-4-(phenylsulfonyl)piperidine (14). ^{1}H NMR δ_H (360 MHz, DMSO-d_6): 1.40−1.55 (2H, m), 1.70−1.80 (2H, m), 1.80−1.95 (2H, m), 2.83−2.90 (2H, m), 3.05−3.10 (1H, m), 3.43 (2H, s), 7.16−7.32 (5H, m), 7.62−7.70 (2H, m), 7.70−7.80 (1H, m), 7.84 (2H, d, J = 7 Hz). MS m/z (ES$^+$): 316 (M + H$^+$). Anal. ($C_{18}H_{21}NO_2S$) C, H, N.

1-(3-Phenylpropyl)-4-(phenylsulfonyl)piperidine (15). ^{1}H NMR, free base δ_H (360 MHz, $CDCl_3$): 1.40−1.55 (2H, m), 1.64−1.80 (2H, m), 1.88 (2H, t, J = 12 Hz), 2.01 (2H, dd, J = 13 and 7 Hz), 2.31 (2H, t, J = 7.5 Hz), 2.59 (2H, t, J = 7.5 Hz), 2.84−2.93 (1H, m), 2.99 (2H, d, J = 12 Hz), 7.13−7.18 (3H, m), 7.20−7.28 (2H, m), 7.54−7.58 (2H, m), 7.63−7.71 (1H, m), 7.86 (2H, d, J = 7 Hz). MS m/z (ES$^+$): 344 (M + H$^+$). Anal. ($C_{20}H_{25}NO_2S$) C, H, N.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydro-5-fluorospiro[2*H*-1-benzopyran-2,4′-piperidine] (16). A solution of 6-fluoro-2-hydroxyacetophenone (**40**) (4.4 g, 0.029 mol) and pyrrolidine (2.4 mL, 0.029 mol) in MeOH (20 mL) was stirred at room temperature for 15 min. *N*-BOC 4-piperidone (**42**) (5.7 g, 0.029 mol) was added portionwise, and the resulting solution was stirred at room temperature for 24 h. The mixture was concentrated and partitioned between EtOAc (3 × 40 mL) and 2 N HCl (40 mL). The organic phase was washed with 1 N NaOH and brine, dried, and concentrated to give **43** (3.0 g, 31%), a yellow oil that was used without further purification. ^{1}H NMR δ_H (250 MHz, $CDCl_3$): 1.46 (9H, s), 1.56−1.69 (2H, m), 2.0 (2H, s), 2.72 (2H, s), 3.16−3.26 (2H, m), 3.80−3.96 (2H, m), 6.70 (1H, dd, J = 8, 9 Hz), 6.80 (1H, d, J = 8 Hz), 7.37−7.47 (1H, m). A solution of **43** in THF (100 mL) was treated with a solution of borane/THF complex in THF (1 M, 54 mL, 0.054 mol) and heated at reflux for 16 h. The solution was then cooled, treated with 5 N HCl (200 mL), and refluxed for a further 3.5 h. The resulting solution was concentrated, basified with 2 N NaOH solution, and extracted into CH_2Cl_2 (3 × 50 mL). The residue obtained from the organic extracts was purified by column chromatography (silica; CH_2Cl_2/MeOH 9:1 → CH_2Cl_2/MeOH/NH_3 90:10:1) to give **47** (1.31 g, 67%) as an orange oil. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.66−1.78 (2H, m), 1.98−2.01 (2H, m), 2.87−2.94 (2H, m), 3.07−3.25 (3H, m), 5.63−5.66 (1H, d, J = 10 Hz), 6.57−6.66 (3H, m), 6.99−7.01 (1H, d, J = 8 Hz). A mixture of **47** (0.5 g, 2.28 mmol), 2,4-difluorophenethyl bromide (0.656 g, 2.97 mmol), and K_2CO_3 in CH_3CN (7 mL) was heated at reflux for 10 h. The mixture was then concentrated and partitioned between water (15 mL) and CH_2Cl_2 (2 × 15 mL). The residue obtained from the organic phase was purified by column chromatography (silica; CH_2Cl_2/MeOH 97:3) to give **51** (0.54 g, 65%), a tan solid. Mp 55−7 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.74−1.80 (2H, m), 2.03−2.07 (2H, m), 2.53−2.69 (6H, m), 2.84−2.97 (2H, m), 5.61−5.63 (1H, d, J = 10 Hz), 6.56−6.63 (3H, m), 6.74−6.82 (2H, m), 7.01−7.06 (1H, dd, J = 7 and 7 Hz), 7.14−7.18 (1H, m). MS m/z (ES$^+$): 360 (M + H$^+$). Anal. ($C_{21}H_{20}F_3NO\cdot0.075H_2O$) C, H, N. A solution of **51** (0.394 g, 1 mmol) in 1 N HCl (2 mL) and EtOH (7 mL) was shaken on a Parr hydrogenator at 55 psi of hydrogen in the presence of 10% palladium-on-carbon (0.1 g) for 8 h. The catalyst was removed by filtration, the filtrate concentrated, and the residue purified by recrystallization from EtOH to give **16** (0.39 g, 99%) as the HCl salt. Mp 216−8 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.91−1.95 (2H, t, J = 6.5 Hz), 2.01−2.05 (2H, m), 2.54 (2H, m), 2.75−2.79 (2H, t, J = 6.5 Hz), 3.18 (4H, broad s), 3.34 (2H, broad s), 3.46 (2H, m), 6.27−6.61 (2H, dd, J = 8 and 8 Hz), 6.80−6.87 (2H, m), 7.05−7.11 (1H, m), 7.35−7.36 (1H, m). MS m/z (ES$^+$): 362 (M + H$^+$). Anal. ($C_{21}H_{22}F_3NO\cdot HCl$) C, H, N.

Similarly prepared from the appropriate acetophenone were the following.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydro-7-fluorospiro[2*H*-1-benzopyran-2,4′-piperidine] Hydrochloride (17). Mp 240−3 °C. ^{1}H NMR δ_H (360 MHz, DMSO-d_6): 1.82 (2H, m), 1.97 (4H, m), 2.74 (2H, m), 3.24 (4H, m), 3.32 (2H, m), 3.48 (2H, m), 6.70 (2H, m), 7.12−7.14 (2H, m), 7.23−7.29 (1H, m), 7.44−7.46 (1H, m). MS m/z (ES$^+$): 362 (M + H$^+$). Anal. ($C_{21}H_{22}F_3NO\cdot HCl$) C, H, N.

1′-[2-(2,4-Difluorophenyl}ethyl]-6-fluorospiro[2*H*-1-benzopyran-2,4′-piperidine] (18). Mp 102−3 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.75−1.78 (2H, m), 2.02−2.04 (2H, m), 2.54−2.63 (4H, m), 2.70 (2H, m), 2.80−2.84 (2H, m), 5.63−5.66 (1H, d, J = 10 Hz), 6.31−6.33 (1H, d, J = 10 Hz), 6.68−6.81 (5H, m), 7.14−7.23 (1H, m). MS m/z (ES$^+$): 360 (M + H$^+$). Anal. ($C_{21}H_{20}F_3NO$) C, H, N.

1′-[2-(2,4-Difluorophenyl)ethyl]-3,4-dihydro-8-fluorospiro[2*H*-1-benzopyran-2,4′-piperidine] Hydrochloride (19). ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.97 (2H, m), 2.04−2.08 (2H, m), 2.57 (2H, m), 2.82 (2H, m), 3.2 (4H, broad s), 3.35 (2H, m), 3.46 (2H, m), 6.8−6.95 (5H, m), 7.34 (1H, m). MS m/z (ES$^+$): 362 (M + H$^+$). Anal. ($C_{21}H_{22}F_3NO\cdot HCl$) C, H, N.

1′-(2-(2,4-Difluorophenyl)ethyl)-3,4-dihydro-4-oxospiro-[2*H*-1-benzopyran-2,4′-piperidine]-6-carbonitrile (20). Pyrrolidine (0.082 mL) was added to a solution of **36** (0.16 g, 1 mmol) in EtOH (5 mL) at room temperature. After 15 min **41** (0.24 g, 1 mmol) was added and the mixture was stirred at room temperature for 18 h. A 2 N HCl (5 mL) solution was added, and the mixture was concentrated. The residue was partitioned between CH_2Cl_2 and NaOH. The residue obtained after workup was purified by column chromatography (silica; EtOAc) to give **20** (0.73 g, 20%) as a colorless solid. Mp 125−7 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.74−1.83 (2H, m), 2.04−2.07 (2H, m), 2.46−2.54 (2H, m), 2.59−2.63 (2H, m), 2.70−2.84 (6H, m), 6.74−6.85 (2H, m), 7.08−7.19 (2H, m), 7.69−7.73 (1H, dd, J = 3 and 8 Hz), 8.18 (1H, d, J = 3 Hz). MS m/z (ES$^+$): 383 (M + H$^+$). Anal. ($C_{22}H_{20}F_2N_2O_2$) C, H, N.

3,4-Dihydro-6-methoxy-1′-[2-(2-oxo-1-imidazolidinyl)-ethyl]spiro[2*H*-1-benzopyran-2,4′-piperidine] (21). A mixture of **56**[24] (0.23 g, 1 mmol), *N*-(2-chloroethyl)imidazolidino-

ne[31] (0.16 g, 1.1 mmol), K_2CO_3 (0.15 g, 1.1 mmol), and KI (0.18 g, 1.1 mmol) in DMF (10 mL) was heated at 80 °C for 18 h. The mixture was then cooled and partitioned between water (50 mL) and EtOAc (3 × 50 mL). The organic extracts were washed with brine, dried, and concentrated to give a solid that was purified by recrystallization from EtOAc to give **21** (0.072 g, 21%), a colorless solid. Mp 118−9 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.57−1.65 (2H, m), 1.65−1.85 (4H, m), 2.45−2.57 (4H, m), 2.64−2.76 (4H, m), 3.32−3.42 (4H, m), 3.50−3.55 (2H, m), 3.75 (3H, s), 4.36 (1H, s), 6.59 (1H, d, J = 3 Hz), 6.67 (1H, dd, J = 3 and 8 Hz), 6.74 (1H, d, J = 8 Hz). MS m/z (ES^+): 346 ($M + H^+$). Anal. ($C_{19}H_{27}N_3O_3$) C, H, N.

3,4-Dihydro-6-methoxy-1′-[4-oxo-4-(4-fluorophenyl)-butyl]spiro[2*H*-1-benzopyran-2,4′-piperidine] (23). A mixture of **56**[24] (0.5 g, 2.1 mmol), 2-(4-fluorophenyl)-2-(1-chloro-3-propyl)-1,3-dioxolane (0.61 g, 2.5 mmol), K_2CO_3 (0.3 g, 2.2 mmol), and KI (0.32 g, 2.2 mmol) in CH_3CN (20 mL) was heated at reflux under nitrogen for 18 h. The reaction mixture was concentrated, and the syrup obtained (MS m/z (ES^+) 442 ($M + H^+$)) was dissolved in a mixture of EtOH (10 mL) and 3 N HCl (10 mL). After being heated at reflux for 2 h, the mixture was cooled to room temperature and the resulting precipitate collected to give **23** as a colorless solid. Mp 210−2 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.91 (2H, t, J = 7 Hz), 1.98−2.02 (2H, m), 2.35−2.55 (4H, m), 2.78 (2H, t, J = 7 Hz), 3.10−3.25 (4H, m), 3.27 (2H, t, J = 7 Hz), 3.42−3.46 (2H, m), 3.75 (3H, s), 6.62 (1H, d, J = 3 Hz), 6.69−6.77 (2H, m), 7.13−7.18 (2H, m), 7.99−8.04 (2H, m). MS m/z (ES^+): 398 ($M + H^+$). Anal. ($C_{24}H_{28}FNO_3$·HCl) C, H, N.

3,4-Dihydro-6-fluoro-1′-[2-hydroxy-4-phenyl)butyl]spiro-[2*H*-1-benzopyran-2,4′-piperidine] (24). A mixture of **54** (0.22 g, 1.0 mmol) and 2-(phenylethyl)oxirane (0.16 g, 1.1 mmol) in methanol (5 mL) was heated at reflux for 2 h. The solvent was then evaporated and the residue purified by column chromatography (silica; CH_2Cl_2/MeOH 98:2 → 95:5) to give an oil that was converted to the hydrochloride salt using 1 N HCl in ether, giving **24** (0.28 g, 69%) as a colorless solid. Mp 250−2 °C. ^{1}H NMR δ_H (360 MHz, DMSO-d_6): 1.35−1.45 (2H, m), 1.45−1.50 (2H, m), 1.50−1.80 (4H, m), 2.25−2.55 (4H, m), 2.70−3.15 (6H, m), 3.60−3.75 (1H, m), 6.45−6.70 (3H, m), 6.80−7.00 (5H, m). MS m/z (ES^+): 370 ($M + H^+$). Anal. ($C_{23}H_{28}FNO_2$·HCl) C, H, N.

3,4-Dihydro-6-fluoro-1′-(1,2,3,4-tetrahydro-2-naphthalenyl)spiro[2*H*-1-benzopyran-2,4′-piperidine] (25). A mixture of **54** (0.25 g, 1.1 mmol), β-tetralone (0.26 mL, 1.6 mmol), and 4-toluenesulfonic acid (0.03 g) in toluene (50 mL) was heated at reflux for 18 h. The reaction mixture was then concentrated and redissolved in THF (20 mL). A 1 M solution of HCl in ether (10 mL) was added followed by a solution of sodium cyanoborohydride (0.1 g) in MeOH (10 mL). After 4 h, further sodium cyanoborohydride was added (0.1 g) and the mixture stirred at room temperature for 18 h. The reaction mixture was then concentrated and partitioned between EtOAc and water. The residue obtained on workup was purifed by column chromatography (silica; CH_2Cl_2 → CH_2Cl_2/MeOH 95:5) to give **25** as an oil that was characterized as the HCl salt. Mp 248−50 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.22−1.27 (4H, m), 1.48−1.52 (2H, m), 1.92−2.04 (2H, m), 2.61−2.68 (1H, m), 2.78−2.81 (1H, m), 2.90−3.60 (5H, m), 3.69−3.74 (4H, m), 6.76−6.86 (3H, m), 7.10−7.18 (4H, m). MS m/z (ES^+): 352 ($M + H^+$). Anal. ($C_{23}H_{26}FNO$·HCl) C, H, N.

4-[[1-(2-(2,4-Difluorophenyl)ethyl)-4-piperidinyl]sulfonyl]benzonitrile (26). *N*-BOC 4-mesyloxypiperidine (**63**)[20] (40 g, 0.14 mol), 4-bromothiophenol (32 g, 0.17 mol), and K_2CO_3 (30 g, 0.22 mol) were mixed at room temperature in CH_3CN (300 mL) and heated at reflux for 18 h. Workup by partitioning between water and EtOAc afforded 50 g (96%) of *N*-BOC 4-(4-bromophenylthio)piperidine (**64d**) as a yellow oil. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.44 (9H, s), 1.45−1.55 (2H, m), 1.85−1.95 (2H, m), 2.85−2.95 (2H, m), 3.1−3.2 (1H, m), 3.95−4.05 (2H, m), 7.25−7.3 (2H, m), 7.4−7.45 (2H, m).

Water (26 mL) was added to alumina (130 g), the mixture slurried (5 min), and chloroform (500 mL) added, followed by a solution of **64d** (50 g, 0.13 mol) in chloroform (300 mL). Oxone (250 g, 0.39 mol) was added and the resulting slurry stirred and heated at reflux for 18 h. After cooling to room temperature, the mixture was filtered and the mother liquor washed with water, dried, and evaporated to give *N*-BOC 4-(4-bromophenylsulfonyl)piperidine (**65d**), 36 g (69%), as a colorless solid. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.43 (9H, s), 1.5−1.7 (2H, m), 1.9−2.0 (2H, m), 2.55−2.7 (2H, m), 2.9−3.1 (1H, m), 4.15−4.25 (2H, m), 7.73 (4H. s). This material (36 g, 0.09 mol) was dissolved in a mixture of methanol (300 mL) and 5 N HCl (63 mL) and heated at reflux for 3 h. After a warm filtration to remove insolubles, the solution was cooled to afford the crystalline 4-(4-bromophenylsulfonyl)piperidine HCl salt (**66d**) (15.4 g), which was collected by filtration. Neutralization of the mother liquor with sodium carbonate and extraction with CH_2Cl_2 afforded 16 g of additional material, a colorless solid, as the free base. ^{1}H NMR, hydrochloride, δ_H (400 MHz, DMSO-d_6): 1.65−1.8 (2H, m), 1.95−2.05 (2H, m), 1.8−2.9 (2H, m), 3.25−3.35 (2H, m), 3.6−3.7 (1H, m), 7.8 (2H, d, J = 8 Hz), 7.9 (2H, d, J = 8 Hz). Free base (360 MHz, $CDCl_3$): 1.45−1.6 (2H, m), 1.95−2.0 (2H, m), 2.5−2.6 (2H, m), 2.95−3.05 (1H, m), 3.15−3.25 (2H, m), 7.7 (4H, s). A mixture of **66d** (7.6 g, 0.025mol), 2,4-difluorophenethyl bromide (8.3 g, 0.38 mol), K_2CO_3 (7.5 g, 0.054 mol), and NaI (5.6 g, 0.037 mol) in CH_3CN (70 mL) was heated at reflux under nitrogen for 18 h. The reaction mixture was then concentrated and partitioned between water and EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Trituration with hexane gave 6.5 g of *N*-(2,4-difluorophenethyl) 4-(4-bromophenylsulfonyl)piperidine (**67d**) as a colorless solid. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.55−1.75 (2H, m), 1.95−2.05 (4H, m), 2.45−2.55 (2H, m), 2.7−2.75 (2H, m), 2.85−2.95 (1H, m), 3.05−3.1 (2H, m), 6.7−6.85 (2H, m), 7.1−7.15 (1H, m), 7.72 (4H, s). A mixture of **67d** (2.2 g, 4.9 mmol) and copper(I) cyanide (2.3 g, 25 mmol) in *N*-methylpyrrolidinone (3 mL) was heated under nitrogen at 160 °C for 16 h with stirring. The hot solution was poured into water/CH_2Cl_2 (100 mL/200 mL), and the organic phase was washed with water, dried (Na_2SO_4), and evaporated to yield a syrup. Column chromatography (silica; isohexane/EtAc 1:1) followed by recrystallization from EtOAc yielded **26** (1.05 g, 55%). Mp 175−6 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.56−1.76 (2H, m), 1.97−2.04 (4H, m), 2.50−2.54 (2H, m), 2.71−2.75 (2H, m), 2.90−2.97 (1H, m), 3.05−3.10 (2H, m), 6.72−6.80 (2H, m), 7.08−7.12 (1H, m), 7.87−7.89 (2H, m), 7.99−8.02 (2H, m). MS m/z (ES^+): 391 ($M + H^+$). Anal. ($C_{20}H_{20}F_2N_2O_2S$) C, H, N.

Similarly prepared were the following.

3-[[1-(2-(2,4-Difluorophenyl)ethyl)-4-piperidinyl]sulfonyl]benzonitrile (27). Mp 138−9 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.66−1.76 (2H, m), 1.95−2.10 (4H, m), 2.51−2.54 (2H, m), 2.71−2.75 (2H, m), 2.90−2.97 (1H, m), 3.05−3.10 (2H, m), 6.72−6.80 (2H, m), 7.08−7.15 (1H, m), 7.72 (1H, t, J = 8 Hz), 7.95 (1H, d, J = 8 Hz), 8.12 (1H, d, J = 8 Hz), 8.17 (1H, s). MS m/z (ES^+): 391 ($M + H^+$). Anal. ($C_{20}H_{20}F_2N_2O_2S$) C, H, N.

2-[[1-(2-(2,4-Difluorophenyl)ethyl)-4-piperidinyl]sulfonyl]benzonitrile (28). Mp 135−7 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.78−1.90 (2H, m), 1.95−2.10 (4H, m), 2.51−2.56 (2H, m), 2.72−2.76 (2H, m), 3.05−3.10 (2H, m), 3.20−3.29 (1H, m), 6.72−6.80 (2H, m), 7.09−7.16 (1H, m), 7.78−7.82 (2H, m), 7.94 (1H, d, J = 8 Hz), 8.13 (1H, d, J = 8 Hz). MS m/z (ES^+): 391 ($M + H^+$). Anal. ($C_{20}H_{20}F_2N_2O_2S$) C, H, N.

The following were prepared in a manner similar to that described for **12**, replacing diphenyl disulfide with the appropriately substituted derivative.

1-(2-(2,4-Difluorophenyl)ethyl)-4-(4-fluorophenylsulfonyl)piperidine (29). Mp 136−7 °C. ^{1}H NMR δ_H (400 MHz, $CDCl_3$): 1.59−1.75 (2H, m), 1.96−2.02 (4H, m), 2.49−2.54 (2H, m), 2.70−2.75 (2H, m), 2.85−2.92 (1H, m), 3.07−3.17 (2H, m), 6.72−6.85 (2H, m), 7.08−7.18 (1H, m), 7.22−7.28 (2H, m), 7.85−7.92 (2H, m). MS m/z (ES^+): 384 ($M + H^+$). Anal. ($C_{19}H_{20}F_3NO_2S$·0.5H_2O) C, H, N.

4-(4-Chlorophenylsulfonyl)-1-(2-(2,4-difluorophenyl)-ethyl)piperidine (30). Mp 135−6 °C. ^{1}H NMR δ_H (360 MHz, $CDCl_3$): 1.59−1.75 (2H, m), 1.96−2.02 (4H, m), 2.49−2.54 (2H,

m), 2.70−2.75 (2H, m), 2.86−2.95 (1H, m), 3.07−3.19 (2H, m), 6.72−6.80 (2H, m), 7.10−7.15 (1H, m), 7.54−7.56 (2H, d, J = 8.5 Hz), 7.79−7,81 (2H, d, J = 8.5 Hz). MS m/z (ES^+): 400, 402 ($M + H^+$). Anal. ($C_{19}H_{20}ClF_2NO_2S$) C, H, N.

4-[[1-(2-(2,4-Difluorophenyl)ethyl)-4-piperidinyl]sulfonyl]benzamide (31). A solution of **26** (0.5 g, 1.28 mmol) in 85% H_2SO_4 (10 mL) was heated at 100 °C for 30 min. The cooled solution was diluted with water (40 mL) and neutralized with solid KOH. At pH 7 a precipitate was collected and dissolved in CH_2Cl_2. The organic phase was dried and concentrated to yield **31**. Mp 195−197 °C (softens, 186−189 °C). ^1H NMR δ_H (360 MHz, $CDCl_3$): 1.7−1.77 (2H, m), 1.97−2.03 (4H, m), 2.5−2.54 (2H, m), 2.71−2.75 (2H, m), 2.89−2.92 (1H, m), 3.04−3.07 (2H, m), 5.74 (1H, s), 6.15 (1H, s), 6.73−6.8 (2H, m), 7.08−7.12 (1H, m), 7.94−8.00 (4H, s). MS m/z (ES^+): 409 ($M + H^+$). Anal. ($C_{20}H_{22}F_2N_2O_3S$) C, H, N.

3-[[1-(2-(2,4-Difluorophenyl)ethyl)-4-piperidinyl]sulfonyl]benzamide (32). Carbon monoxide was bubbled through a solution of **67c** (3.95 g, 9 mmol), Et_3N (2.5 mL, 18 mmol), palladium(II) acetate (0.06 g, 0.3 mmol), and 1,1-bis(diphenylphosphino)ferrocene (0.3 g, 0.5 mmol) in a mixture of methanol (30 mL) and DMF (30 mL) at room temperature. The mixture was heated at 60 °C for 18 h and then partitioned between EtOAc and water. Product from the organic phase was purified by column chromatography (silica; EtOAc/isohexane 1:1) to give 2.75 g (73% yield) of methyl ester as a colorless solid. Mp 116−7 °C. ^1H NMR δ_H (360 MHz, $CDCl_3$): 1.72−1.77 (2H, m), 1.97−2.03 (4H, m), 2.49−2.54 (2H, m), 2.70−2.75 (2H, m), 2.90−2.94 (1H, m), 3.04−3.07 (2H, m), 3.97 (3H, s), 6.72−6.80 (2H, m), 7.08−7.12 (1H, m), 7.67 (1H, t, 7.8 Hz), 8.07−8.5 (1H, m), 8.34−8.32 (1H, m), 8.55 (1H, s). A solution of *N*-(2,4-difluorophenethyl)-4-(3-(carbomethoxy)phenylsulfonyl)piperidine (0.2 g, 0.47 mmol) in toluene (10 mL) was added to a mixture of trimethylaluminum (0.71 mL, 1.4 mmol) and ammonium chloride (0.077 g, 1.4 mmol) in toluene (8 mL) at 0 °C. The mixture was heated at reflux for 18 h, cooled to room temperature, quenched with 2 M HCl, basified with 2 M NaOH, and extracted with CH_2Cl_2. The crude product obtained from the organic phase was purified by column chromatography (silica; CH_2Cl_2/MeOH 97:3) to give **32** (41 mg, 21%). Mp 142−3 °C. ^1H NMR δ_H (400 MHz, $CDCl_3$): 1.68−1.78 (2H, m), 1.97−2.02 (4H, m), 2.50−2.54 (2H, m), 2.71−2.75 (2H, m), 2.90−3.00 (1H, m), 3.04−3.07 (2H, m), 5.75−5.85 (1H, s), 6.2−6.3 (1H,s), 6.70−6.80 (2H, m), 7.1−7.15 (1H, m), 7.7 (1H, t, 7.8 Hz), 8.05 (1H, d, 7.8 Hz), 8.15 (1H, d, 7.8 Hz), 8.28 (1H, s). MS m/z (ES^+): 409 ($M + H^+$). Anal. ($C_{20}H_{22}F_2N_2O_3S$) C, H, N.

1-[2-(4-(4-Phenylsulfonyl)-1-piperidinyl)ethyl]-2-imidazolidinone (33). A mixture of **66a** (0.2 g, 0.88 mmol), *N*-(2-chloroethyl)imidazolidinone[31] (0.13 g, 0.88 mmol), NaI (0.13 g, 0.88 mol), and K_2CO_3 (0.12 g, 0.9 mmol) in acetonitrile (20 mL) was heated at reflux for 18 h. The solvent was then evaporated and the residue partitioned between EtOAc and water. The residue obtained from workup was purified by column chromatography (silica; $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 97:3) followed by recrystallization from EtOAc to give **33** (0.17 g, 64%). Mp 169−71 °C. ^1H NMR δ_H (400 MHz, $CDCl_3$): 1.59−1.78 (2H, m), 1.88−1.98 (4H, m), 2.47 (2H, t, J = 6.5 Hz), 2.84−2.92 (1H, m), 3.02−3.10 (2H, m), 3.27 (2H, t, J = 6.5 Hz), 3.35−3.50 (4H, m), 4.32 (1H, broad s), 7.55−7.63 (2H, m), 7.63−7.70 (1H, m), 7.87 (2H, d, J = 8 Hz). MS m/z (ES^+): 338 ($M + H^+$). Anal. ($C_{16}H_{23}N_3O_3S$) C, H, N.

1-(4-Fluorophenyl)-4-[4-(phenylsulfonyl)-1-piperidinyl]-butan-1-one (34). A mixture of **66a** (0.2 g, 1 mmol), 2-(4-fluorophenyl)-2-(1-chloro-3-propyl)-1,3-dioxolane (0.3 g, 1.2 mmol), K_2CO_3 (0.28 g, 2 mmol), and NaI (0.18 g, 1.2 mmol) in CH_3CN (10 mL) was heated at reflux under nitrogen for 18 h. The reaction mixture was then concentrated and partitioned between water and EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated, and the syrup obtained was redissolved in a mixture of methanol (15 mL) and 6 N HCl (5 mL). After being heated at reflux for 30 min, the mixture was cooled to room temperature, concentrated under vacuum, and partitioned between 1 M NaOH (20 mL) and DCM (100 mL). After separation of the phases, the aqueous phase was extracted twice with DCM (20 mL) and the combined organic phases were washed with brine, dried over potassium carbonate, filtered, and concentrated. Column chromatography (silica; isohexane/EtOAc 1:1) gave **34** (0.23 g, 59%) as a colorless solid. Mp 107−8 °C. ^1H NMR δ_H (360 MHz, $CDCl_3$): 1.57−1.67 (2H, m), 1.87−1.97 (6H, m), 2.33−2.38 (2H, m), 2.83−2.98 (5H, m), 7.08−7.13 (2H, m), 7.54−7.58 (2H, m), 7.64−7.68 (1H, m), 7.85 (2H, d J = 5.8 Hz), 7.94−7.97 (2H, m). MS m/z (ES^+): 390 ($M + H^+$). Anal. ($C_{21}H_{24}FNO_3S$) C, H, N.

1-(4-Fluorophenyl)-2-[4-(phenylsulfonyl)-1-piperidinyl]-ethanone (35). A mixture of **66a** (0.22 g, 1 mmol), 2-bromo-4′-fluoroacetophenone (0.22 g, 1 mmol), and triethylamine (0.14 g, 1.4 mmol) in CH_3CN (20 mL) was stirred at room temperature for 18 h. The solvent then evaporated, and the residue was partitioned between EtOAc and water. The residue obtained from workup was purified by recrystallization from CH_3CN to give **35** (0.18 g, 50%). Mp 161−3 °C. ^1H NMR δ_H (400 MHz, $CDCl_3$): 1.75−1.85 (2H, m), 2.00−2.05 (2H, m), 2.19−2.22 (2H, m), 2.89−2.98 (1H, m), 3.05−3.08 (2H, m), 3.74 (2H, s), 7.12 (2H, t, 8 Hz), 7.56 (2H, t, 8 Hz), 7.65−7.69 (1H, m), 7.87 (2H, d, 8 Hz), 7.98−8.02 (2H, m). MS m/z (ES^+): 362 ($M + H^+$). Anal. ($C_{19}H_{20}FNO_3S$) C, H, N.

5-HT_{2A} Receptor Binding. Chinese hamster ovary (CHO) cells stably expressing the human or rat 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 [^3H]-ketanserin (66.4 Ci/mmol, NEN) 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 compound.

5-HT_{2C} Receptor Binding. Chinese hamster ovary cells stably expressing the human 5-HT_{2C} receptors 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 [^3H]-mesulergine (77 Ci/mmol, Amersham, U.K.) and initiated by addition of 400 μL of membranes in a final assay volume of 500 μL. Nonspecific binding was determined with 1 μM mianserin, and radioactivity was determined as described above for [^3H]-ketanserin binding studies.

Rat α1 Receptor Binding. Rat cortical membranes 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 suspended 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 [^3H]-prazosin (77.2 Ci/mmol, NEN) and initiated by the addition of microliters 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 the [^3H]-ketanserin binding studies.

IKr Binding. Binding to the voltage-dependent potassium channel (delayed rectifier current, IKr) was evaluated by displacement of 4 nM [3H]-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 of 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 for the [^{3}H]-ketanserin binding studies.

Determination of the Stability of Compounds 16−25 toward Rat Liver Microsomes. Rat liver microsomes were prepared from male Sprague-Dawley rats (final protein concentration of 0.4 mg/mL) in Dulbecco's phosphate-buffered saline.[32] Each compound was preincubated for 5 min at 37 °C. The reaction was initiated by addition of NADPH (final concentration of 2 mM) and was allowed to proceed for a further 30 min at 37 °C before termination with an equal volume of acetonitrile and centrifugation (6000 rpm for 10 min). The supernatant was analyzed by LC−MS. Each reaction was carried out in triplicate, turnover being calculated by comparison of peak areas obtained with those from control incubations lacking NADPH. For analysis by LC−MS, 5 μL injections were made onto a KR100-5C18 HPLC column (5 cm × 4.6 mm i.d.) with an isocratic 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.

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 iv 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 was collected. Samples were analyzed as described below.

Plasma, Blood, and Brain Analysis. Typically, to aliquots of plasma, blood, or brain homogenate (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 the 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, blood or brain homogenate, 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 isocratic 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 independent pharmacokinetic parameters were determined using standard formulas in a Microsoft Excel spreadsheet.

Determination of QTc Interval Changes. Three male ferrets, approximately 1.3 kg, were anaesthetised (pentobarbitone sodium 45 mg/kg ip), and both femoral veins and one femoral artery were cannulated for infusion of maintenance anaesthetic (pentobarbitone sodium, 18 mg kg^{-1} h^{-1}), test compound, and measurement of blood pressure. Heart rate was derived from the blood pressure signal. The trachea was cannulated, and animals were artificially respired to maintain blood gases within normal limits. Body temperature was maintained between 36 and 37 °C. ECG was measured by a lead II configuration. All variables were measured using a po-ne-mah data acquisition system. Recordings were taken, 10 min predose, 10 min postvehicle dose, and at 10 min intervals, over a 30 min time period with the postinfusion dose at levels of 0.3, 1, 3, and 10 mg kg^{-1} h^{-1}.

Supporting Information Available: Data for compounds **1**, **2**, **5**, **7**, **12**, **26**, and **31** in the DOI-induced head-twitch model, demonstrating 5HT$_{2A}$ receptor antagonism in vivo. This material is available free of charge via the Internet at http://pubs.acs.org.

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