Design and Synthesis of *trans*-3-(2-(4-((3-(3-(5-Methyl-1,2,4-oxadiazolyl))-phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SB-414796): A Potent and Selective Dopamine D_3 Receptor Antagonist

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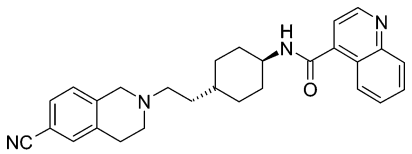
At their clinical doses, current antipsychotic agents share the property of both dopamine D_2 and D_3 receptor blockade. However, a major disadvantage of many current medications are the observed extrapyramidal side-effects (EPS), postulated to arise from D_2 receptor antagonism. Consequently, a selective dopamine D_3 receptor antagonist could offer an attractive antipsychotic therapy, devoid of the unwanted EPS. Using SAR information gained in two previously reported series of potent and selective D_3 receptor antagonists, as exemplified by the 2,3,4,5-tetrahydro-1*H*-3-benzazepine **10** and the 2,3-dihydro-1*H*-isoindoline **11**, a range of 7-sulfonyloxy- and 7-sulfonylbenzazepines has been prepared. Compounds of this type combined a high level of D_3 affinity and selectivity vs D_2 with an excellent pharmacokinetic profile in the rat. Subsequent optimization of this series to improve selectivity over a range of receptors and reduce cytochrome P450 inhibitory potential gave *trans*-3-(2-(4-((3-(3-(5-methyl-1,2,4-oxidiazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**58**, SB-414796). This compound is a potent and selective dopamine D_3 receptor antagonist with high oral bioavailability and is CNS penetrant in the rat. Subsequent evaluation in the rat has shown that **58** preferentially reduces firing of dopaminergic cells in the ventral tegmental area (A10) compared to the substantia nigra (A9), an observation consistent with a prediction for atypical antipsychotic efficacy. In a separate study, **58** has been shown to block expression of the conditioned place preference (CPP) response to cocaine in male rats, suggesting that it may also have a role in the treatment of cue-induced relapse in drug-free cocaine addicts.

Introduction

Dopaminergic neurotransmission is mediated via five receptor subtypes (D_1−D_5) which can be further divided into two families. D_1-like receptors encompass the D_1 and D_5 receptor, while D_2-like receptors account for D_2, D_3, and D_4 subtypes. A number of currently available antipsychotic drugs, when administered at their clinically effective dose, share the property of both dopamine D_2 and D_3 receptor antagonism.[1] As a consequence, their antipsychotic effects could be mediated via D_2 and/or D_3 receptors.[2] However, a major disadvantage of many current therapies are the observed extrapyramidal side-effects (EPS) which are postulated to arise from blockade of the D_2 receptors in the striatum.[3] By contrast, D_3 receptors are highly expressed in limbic regions such as the nucleus accumbens and antagonism of these receptors has been associated with beneficial antipsychotic effects.[4] Although a number of the recently marketed antipsychotic agents, such as olanzapine, show significant affinity for several serotonin receptors, a selective dopamine D_3 receptor antagonist could represent an attractive new antipsychotic therapy, devoid of the unwanted EPS associated with some currently marketed drugs.[5]

The emergence and in vivo evaluation of novel, selective tool compounds has provided new evidence in support of the attraction of the dopamine D_3 receptor as a target for antipsychotic therapy. We have recently reported on the novel 6-cyano-1,2,3,4-tetrahydroisoquinoline SB-277011 **1**, a selective dopamine D_3 receptor



SB-277011 **1**

antagonist with high oral bioavailability and CNS penetration in the rat.[6] In an in vivo microdialysis study, we have shown that SB-277011 dose-dependently inhibited the quinelorane-induced decrease in dopamine release from the rat nucleus accumbens at doses of 0.28 to 2.8 mg/kg po, whereas the compound had no effect

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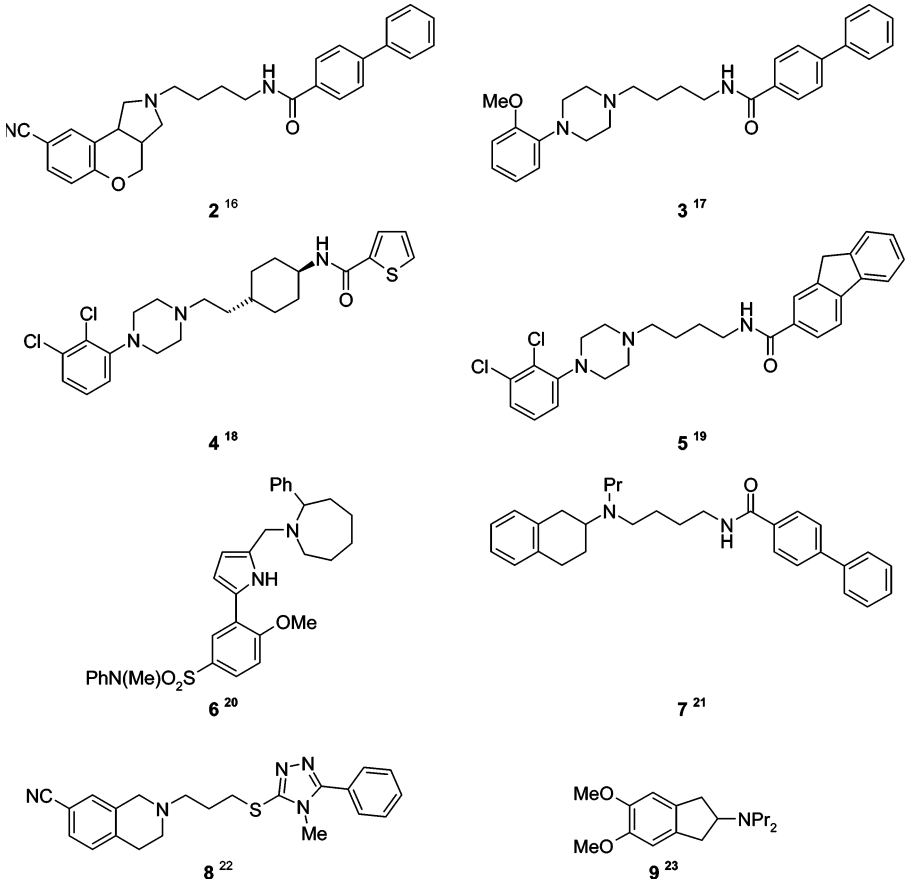


Figure 1. Dopamine D_3 receptor antagonists.

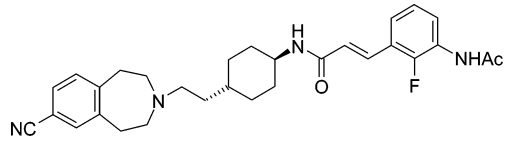
in the rat striatum when dosed at 93 mg/kg po.[7] In rats, prolonged treatment with the atypical antipsychotic clozapine has been reported to preferentially reduce firing of dopaminergic cells in the ventral tegmental area (A10) compared to the substantia nigra (A9)—a phenomenon which has been used to study atypical antipsychotic agents.[8] When SB-277011 was dosed chronically to adult male rats for 21 days, the compound was shown to inhibit dopaminergic cell firing in the A10 region but not in the A9 region, with a minimal effective dose of 1.0 mg/kg po.[9] These data further support the hypothesis that a selective dopamine D_3 receptor antagonist may have atypical antipsychotic properties.

There is also considerable evidence to suggest that dopamine is one of the key neurotransmitters present in a series of neurological networks known as the 'reward circuitry' and plays an important role in the behaviors related to the reward and reinforcement of natural and synthetic substances (i.e., drugs of addiction)[10,11]. Consequently, it has been postulated that blocking the action of dopamine in the CNS may represent one way in which to diminish the incentive value of drugs of addiction. It has previously been reported that dopamine D_2 receptor antagonists such as haloperidol can diminish the rewarding/reinforcing effects of various drugs of addiction; however, blockade of the D_2 receptor can produce significant EPS.[10] The presence of the dopamine D_3 receptor in projection regions of the mesocorticolimbic system has also suggested a role in incentive motivation and consequently a selective dopamine D_3 antagonist could find utility in reinforcement processes and in the treatment of drug abuse.[12] Indeed, studies[13,14] with SB-277011 have shown that it inhibits cocaine-seeking and cocaine-enhanced brain reward in rats.

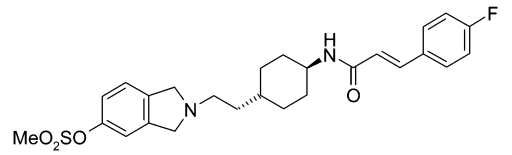
Unfortunately, during the early development of SB-277011, it was shown that while the compound was stable in the presence of NADPH and liver microsomes from rat, dog, cynomolgus monkey, and human, in total liver homogenates from cynomolgus monkey and human, the intrinsic clearance was 6- and 35-fold higher, respectively, than in the liver microsomes from these species. In the absence of NADPH, SB-277011 was also rapidly cleared in liver homogenates from cynomolgus monkey and human, demonstrating that a significant pathway of metabolism was via an NADPH independent, nonmicrosomal oxidative route. This pathway was sensitive to inhibition with isovanillin, suggesting that the enzyme responsible was aldehyde oxidase.[15] The involvement of aldehyde oxidase in the metabolism of SB-277011 indicates that the bioavailability in humans is likely to be low. Interestingly, the resulting metabolite from this pathway, containing the corresponding 4-substituted-2-quinolone group, had a much reduced affinity for the dopamine D_3 receptor (pK_i 6.5) and only 5-fold selectivity over the D_2 receptor. It has thus been the aim of our ongoing research program to design a series of new dopamine D_3 antagonists which are highly potent ($pK_i \geq 8$) and selective ($\geq$100-fold) over a wide range of other receptors and ion channels, are orally bioavailable and CNS penetrant, but which are devoid of the liability to be metabolized by aldehyde oxidase.

Several other antagonists of the D_3 receptor have also been disclosed in the journal and patent literature, although selectivity against D_2 and 5-HT receptors has varied widely (**2**−**9**) (Figure 1).[16−23]

In a previous communication, we described the design and SAR optimization of a novel series of 7-cyano-substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines, as exemplified by the cinnamide derivative **10**, which had high dopamine D_3 affinity (pK_i 8.4; K_i 4 nM) and 130-fold selectivity over the dopamine D_2 receptor.[24] This compound also displayed ≥100-fold selectivity against a range of other receptors, low potential to inhibit cytochrome P450, and good systemic exposure in the rat and was brain penetrant. However, in vitro metabolism studies with **10** showed a high clearance rate in human liver microsomes, precluding further development of this particular compound. To advance the development of the benzazepine series, suitable alternative templates were sought as a basis for further SAR investigations. We had previously shown in a related publication, which described the design of novel 2,3-dihydro-1*H*-isoindolines as selective D_3 antagonists,[25] that the 5-methylsulfonyloxy isoindoline **11** had high D_3 receptor affinity (pK_i 8.3), 100-fold selectivity over the D_2 receptor and had a highly desirable pharmacokinetic profile in the rat, with low blood clearance (14 mL/min/kg), high oral bioavailability (77%), and long terminal half-life (5.2 h). Therefore, we sought to explore the introduction of a sulfonyloxy group into the benzazepine series in an attempt to improve the overall in vivo properties of these particular compounds. Herein we now describe the SAR analysis of a range of 7-sulfonyloxy- and related 7-sulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines which has provided potent and selective dopamine D_3 receptor antagonists with high oral bioavailability and excellent in vivo profiles in the rat.



10



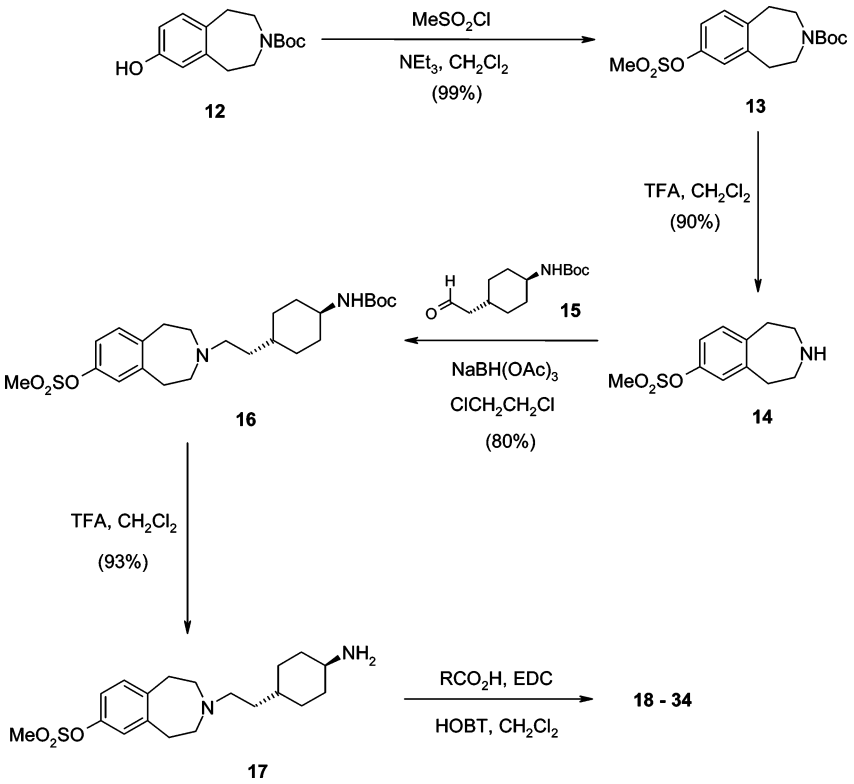
11

Chemistry

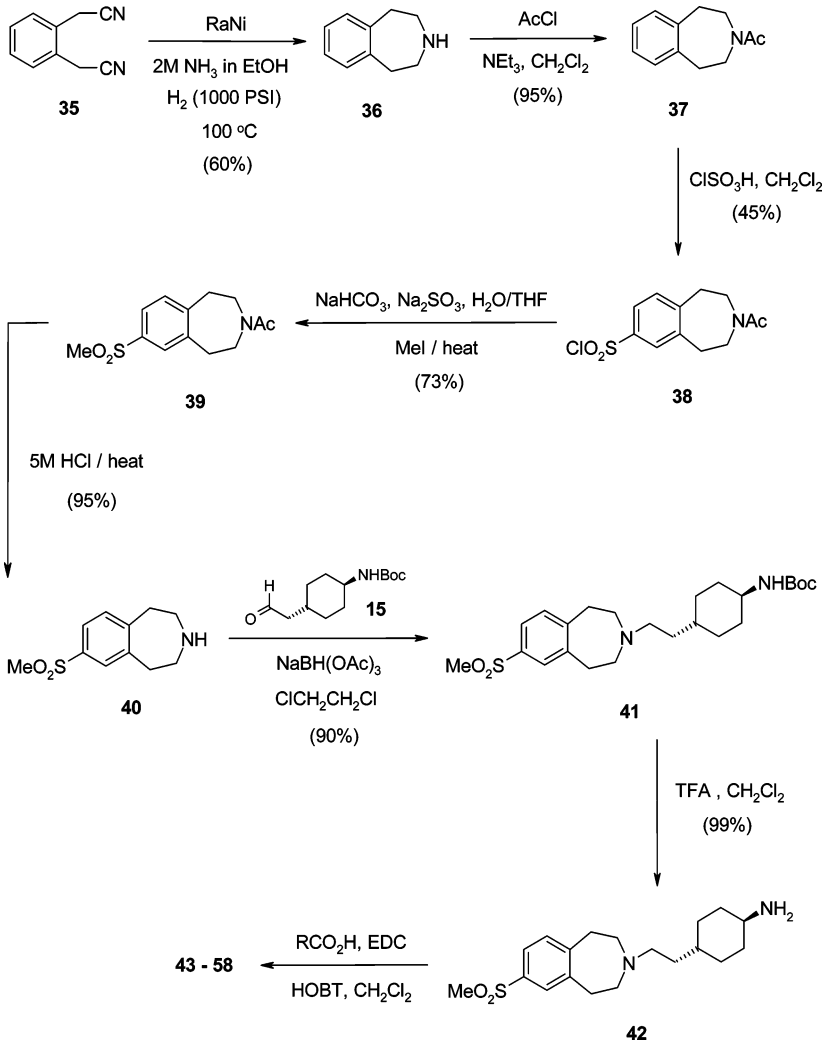
Compounds **18**−**34** (Table 1) were readily prepared via an extension of our previously reported route to 7-substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines (Scheme 1). Thus, reaction of 3-*tert*-butoxycarbonyl-7-hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **12**[24] with methanesulfonyl chloride afforded the sulfonate derivative **13** in 99% yield. Removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid followed by reductive amination with the previously disclosed[6] protected amino aldehyde **15** gave amine **16** in 80% yield. Subsequent deprotection with trifluoroacetic acid provided the corresponding amine **17**, which was coupled with the requisite acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazole in dichloromethane to give the targeted compounds **18**−**34**.

Compounds **43**−**58** (Table 2) were prepared by a similar process, although in this case, the required 7-substituted benzazepine intermediate **40** was derived from the unsubstituted benzazepine **36** (Scheme 2).[26] Thus, *o*-phenylene diacetonitrile **35** was cyclized in the presence of Raney nickel and hydrogen in ethanolic ammonia at high pressure and temperature to afford

Scheme 1



Scheme 2



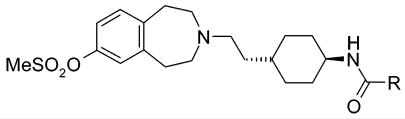
2,3,4,5-tetrahydro-1*H*-3-benzazepine **36** in 60% yield. This material was then protected and purified as the *N*-acetyl derivative **37**. Treatment of **37** with chlorosulfonic acid in dichloromethane followed by reductive methylation provided the *N*-acetyl-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **39** in 33% yield over two steps.

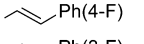
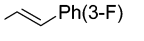
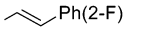
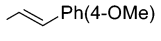
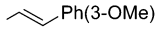
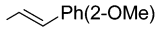
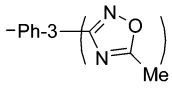
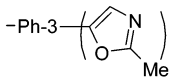
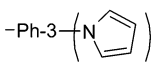
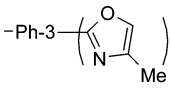
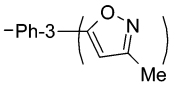
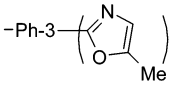
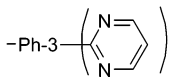
Removal of the *N*-acetyl group was carried out using aqueous hydrochloric acid at reflux to give the 7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **40** in excellent yield. Use of methodology similar to that outlined in Scheme 1 then afforded the targeted amides **43**−**58** in good overall yield.

Results and Discussion

To provide a direct comparison with the previously prepared isoindoline **11**, the corresponding 4-fluorocinnamide derivative **18** was first prepared in the 7-sulfonyloxy benzazepine series (Table 1). Compound **18** had an excellent dopamine D_3 receptor binding affinity (pK_i 9.1) and had 80-fold selectivity against the D_2 receptor. Unfortunately, **18** was shown to be an inhibitor of cytochrome P450 2D6 with an IC_{50} of 3 uM. The 3-fluoro and 2-fluoro analogues, **19** and **20** respectively, also showed high affinity for the D_3 receptor; however, selectivity vs D_2 receptors was not improved compared to **18**. In an attempt to achieve the desired selectivity over the D_2 receptor while maintaining the high D_3 affinity in this series, further analogues were prepared to explore the SAR around the amide moiety (**21**−**34**). Replacement of the fluoro substituent by an electron-donating group such as methoxy similarly provided compounds of high potency **21**−**23**, but this modification was generally detrimental to the selectivity profile with respect to D_2 receptors. Incorporation of the 1-naphthyl group, **24**, which had previously been examined as a tetrahydroisoquinoline derivative,[6] resulted in a reduction of D_3 affinity (pK_i 8.6), but interestingly >100-fold selectivity against the D_2 receptor was observed for the first time in this series. Further cross-screening, however, revealed that the selectivity of **24** vs 5-HT_{1D} receptors was only 15-fold. Replacement of the 1-naphthyl group of **24** with the 5-quinolinyl moiety, as exemplified by **25**, maintained both D_3 receptor affinity and 100-fold selectivity vs D_2 receptors. Introduction of a methyl substituent at C-2 of the quinolinyl group proved beneficial and resulted in a compound with both excellent affinity and improved selectivity (**26**; pK_i 8.9; 160-fold selective vs D_2). By contrast, the 2-Me-4-quinolinyl group **27** appeared detrimental to both D_3 affinity and selectivity in this series (**27** vs **26**). Compound **26** was therefore selected for further in vitro profiling against a range of 5-HT receptors and was shown to have ≥100-fold selectivity. Additionally, **26**

Table 1. Affinities (pK_i) of 7-Methylsulfonyloxy-2,3,4,5-Tetrahydro-1*H*-3-Benzazepiness



compd	R	mp °C (HCl salt)	formula	Anal.	D_3[a]	D_2[a]	D_3/D_2 Sel.[b]
18		270-272	$C_{28}H_{35}FN_2O_4S.HCl$	M^+	9.1	7.2	80
19		273-275	$C_{28}H_{35}FN_2O_4S.HCl.1.5H_2O$	C,H,N	8.9	7.1	65
20		264-265	$C_{28}H_{35}FN_2O_4S.HCl$	M^+	8.9	7.0	80
21		255-256	$C_{29}H_{38}N_2O_5S.HCl$	M^+	9.0	7.5	35
22		255-257	$C_{29}H_{38}N_2O_5S.HCl$	M^+	8.7	7.2	35
23		245-246	$C_{29}H_{38}N_2O_5S.HCl.2.5H_2O$	C,H,N	8.9	7.0	80
24	1-naphthyl	246-248	$C_{30}H_{36}N_2O_4S.HCl$	M^+	8.6	6.5	125
25	5-quinolinyl	233-235	$C_{29}H_{35}N_3O_4S.HCl$	M^+	8.7	6.7	100
26	2-Me-5-quinolinyl	237-238	$C_{30}H_{37}N_3O_4S.HCl$	M^+	8.9	6.7	160
27	2-Me-4-quinolinyl	236-237	$C_{30}H_{37}N_3O_4S.HCl$	M^+	7.7	6.2	35
28		248-250	$C_{29}H_{36}N_4O_5S.HCl.0.5H_2O$	C,H,N	8.6	6.7	80
29		235-237	$C_{30}H_{37}N_3O_5S.HCl.1.5H_2O$	C,H,N	8.9	6.7	160
30		249-251	$C_{30}H_{37}N_3O_4S.HCl.2.0H_2O$	C,H,N	8.5	6.6	80
31		239-240	$C_{30}H_{37}N_3O_5S.HCl$	M^+	8.5	6.7	65
32		233-235	$C_{30}H_{37}N_3O_5S.HCl.H_2O$	C,H,N	8.7	6.8	80
33		243-244	$C_{30}H_{37}N_3O_5S.HCl.0.5H_2O$	C,H,N	8.5	6.5	100
34		246-248	$C_{30}H_{36}N_4O_4S.HCl$	M^+	8.7	6.5	160

[a] pK_i values at the human cloned receptors represent the mean of at least three determinations. [b] D_3/D_2 selectivity is defined as the antilogarithm of the difference between D_3 and D_2 p*K*i values.

had low inhibitory potential against all the P450 enzymes (all IC_{50} values >40 uM), thus representing a marked improvement in the overall profile compared to **18**.

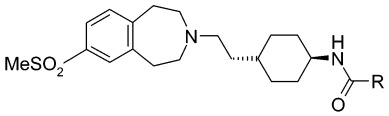
From subsequent in vivo evaluation, compound **26** was found to have an excellent pharmacokinetic profile in the rat, with blood clearance of 18 mL/min/kg, an oral bioavailability of 79%, and half-life of 5.2 h. A steady-state CNS penetration study showed that **26** had a brain:blood ratio of 1.3:1.

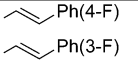
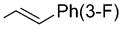
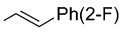
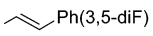
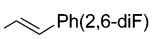
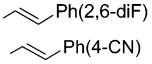
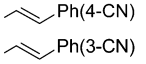
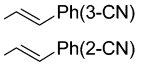
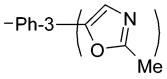
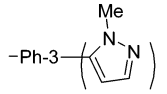
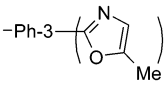
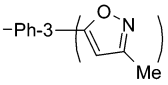
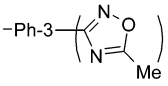
However, more extensive in vitro cross screening revealed that **26** had high affinity for muscarinic receptors (M_1, M_2, and M_3), with selectivity being particularly low against the M_2 subtype (10-fold). In an attempt to overcome this selectivity issue associated with compound **26**, a range of more diverse amide modifications was explored. From this investigation, a series of 3-substituted biaryl carboxamides (**28**−**34**) emerged as promising new leads (see Table 1). The 1,2,4-oxadiazolyl derivative **28** showed high D_3 receptor affinity (pK_i 8.6) and had 80-fold selectivity vs D_2 receptors. This compound had greater than 100-fold selectivity against 5-HT receptors, had low intrinsic clearance in microsomes, and showed no significant inhibition of cytochrome P450 enzymes. In contrast, although the 2-Me-1,3-oxazol-5-yl **29** showed exceptional D_3 affinity and 160-fold selectivity against D_2, the P450 profile was markedly worse than that of compound **28**.

A number of other variations of the five-membered heterocycle **30**−**32** were explored, but unfortunately, selectivity against either the D_2 receptor or 5-HT receptors remained an issue. A balance was obtained with the 5-Me-1,3-oxazol-2-yl derivative **33** which had high D_3 affinity (pK_i 8.5), was 100-fold selective against D_2, and had no significant P450 interactions. In addition, although affinity for the M_2 receptor had not been totally abolished, an improved selectivity of 25-fold was obtained. A subsequent in vivo study in the rat showed that **33** was CNS penetrant (brain:blood; 1.1:1) and had low blood clearance (21 mL/min/kg).

Further SAR investigations showed that a six-membered heterocyclic biaryl such as the 2-pyrimidinyl

Table 2. Affinities (pK_i) of 7-Methylsulfonyl-2,3,4,5-Tetrahydro-1*H*-3-Benzazepines



Compd	R	mp °C (HCl salt)	formula	Anal.	D_3[a]	D_2[a]	D_3/D_2 Sel.[b]
43		274-275	$C_{28}H_{35}FN_2O_3S.HCl$	M^+	9.0	7.1	80
44		278-280	$C_{28}H_{35}FN_2O_3S.HCl.2.0H_2O$	C,H,N	8.8	6.9	80
45		279-281	$C_{28}H_{35}FN_2O_3S.HCl.1.0H_2O$	C,H,N	8.9	6.9	100
46		269-271	$C_{28}H_{34}F_2N_2O_3S.HCl$	M^+	8.7	6.6	125
47		270-271	$C_{28}H_{34}F_2N_2O_3S.HCl$	M^+	8.6	6.4	160
48		277-279	$C_{29}H_{35}N_3O_3S.HCl$	M^+	8.7	6.9	65
49		275-277	$C_{29}H_{35}N_3O_3S.HCl$	M^+	8.7	6.8	80
50		260-262	$C_{29}H_{35}N_3O_3S.HCl$	M^+	8.8	6.8	100
51	1-naphthyl	249-251	$C_{30}H_{36}N_2O_3S.HCl.2.0H_2O$	C,H,N	8.2	6.2	100
52	2-Me-5-quinolinyl	235-237	$C_{30}H_{37}N_3O_3S.HCl$	M^+	8.4	6.5	80
53	(8-F,2-Me)-5-quinolinyl	254-255	$C_{30}H_{36}FN_3O_3S.HCl$	M^+	8.5	6.1	250
54		267-270	$C_{30}H_{37}N_3O_4S.HCl$	M^+	8.2	6.2	100
55		248-250	$C_{30}H_{38}N_4O_3S.HCl.2.5H_2O$	C,H,N	8.5	6.3	160
56		240-242	$C_{30}H_{37}N_3O_4S.HCl.2.0H_2O$	C,H,N	8.1	6.2	80
57		253-255	$C_{30}H_{37}N_3O_4S.HCl.H_2O$	C,H,N	8.4	6.3	125
58		250-252	$C_{29}H_{36}N_4O_4S.HCl.0.5H_2O$	C,H,N	8.4	6.4	100

[a] pK_i values at the human cloned receptors represent the mean of at least three determinations. [b] D_3/D_2 selectivity is defined as the antilogarithm of the difference between D_3 and D_2 p*K*i values.

group was also well tolerated with respect to D_3 affinity and selectivity. Compound **34**, in addition to being >100-fold selective against all the 5-HT receptors screened, also showed an improved selectivity of 50-fold against the M_2 receptor.

The encouraging overall in vitro and in vivo profile observed with the 7-methylsulfonyloxy benzazepine series prompted an extension of this program to examine the key SAR in the related 7-methylsulfonyl benzazepine series. Excellent D_3 receptor binding affinities were retained in this series (Table 2), as highlighted for example by the 4-fluorocinnamide derivative **43** with pK_i 9.0. Interestingly, in contrast to the corresponding sulfonyloxy derivatives, >100-fold selectivity vs D_2 receptors could be achieved with suitably substituted cinnamides, such as the mono- and difluoro derivatives **45** and **47** with 100 and 160-fold selectivity, respectively. The 2-fluorocinnamide **45** also showed a very encouraging cross screening profile and had no significant P450 liabilities. Unfortunately, compound **45** showed high intrinsic clearance in human liver microsomes. Other substituents such as cyano were also tolerated, with the C-2 position being marginally preferred for selectivity against D_2 receptors (**48**−**50**). However, 2-cyanocinnamide **50** was an inhibitor of cytochrome P450 2C9 with an IC_{50} of 7 uM, a recurrent theme with many of the substituted cinnamide derivatives.

As observed in the previous sulfonyloxy series (**25** and **26**), the quinolinyl carboxamide group was beneficial for maintaining high D_3 affinity and selectivity. The corresponding sulfone **52** also showed good affinity for the D_3 receptor (pK_i 8.4), but was only 80-fold selective against the 5-HT_{2B} receptor. Interestingly, introduction of an 8-fluoro substituent on the quinolinyl ring **53** significantly improved the selectivity over the 5-HT_{2B} receptor to 250-fold. Compound **52** had moderate in vivo clearance (46 mL/min/kg), excellent oral bioavailability (91%), and was CNS penetrant (brain:blood ratio of 1.2:1), comparable with the corresponding sulfonyloxy derivative **26**. Unfortunately, **52** had low selectivity against muscarinic receptors (M_1 10-fold; M_2 3-fold and M_3 8-fold), paralleling the data generated in the sulfonyloxy series.

As in the sulfonyloxy series, 3-biaryl carboxamides provided compounds with the most promising balance of in vitro properties. Although **54** and **55** showed the required levels of affinity and selectivity against the target receptors, both had extensive P450 liabilities. The 5-methyloxazol-2-yl replacement in **56** provided a solution for the P450 inhibitory potential, unfortunately

however at the expense of selectivity (<100-fold against D_2, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_4 receptors). The isoxazolyl **57** also had high D_3 receptor affinity and selectivity over the D_2 receptor; however, selectivity against the M_2 receptor was < 10-fold.

From this SAR investigation, the 5-methyl-1,2,4-oxadiazol-2-yl derivative **58** represented the most encouraging analogue to be prepared. Compound **58** (SB-414796) retained good affinity for the D_3 receptor (pK_i 8.4), was 100-fold selective against the D_2 receptor and a panel of 60 other receptors and ion channels, and 30-fold selective vs muscarinic M_2 receptors. An in vitro functional assay using microphysiometry in CHO cells expressing the human cloned D_3 and D_2 receptors[27] showed that **58** lacked any agonist activity and was a potent D_3 receptor antagonist (pK_b 8.5), with 100-fold selectivity over the D_2 receptor (pK_b 6.5). In addition, compound **58** showed no significant cytochrome P450 liabilities. The pharmacokinetic profile in the rat was also excellent (plasma clearance 29 mL/min/kg; oral bioavailability 85%; terminal half-life 3.5 h), and the compound was CNS penetrant with a brain:blood ratio of 0.3:1. In addition, as the HCl salt, compound **58** had an aqueous solubility of >3 mg/mL at pH 7.4.

Further in vivo evaluation was carried out in anesthetized male Sprague−Dawley rats to examine the effect of chronic administration of compound **58** on the number of spontaneously active dopamine neurons in the substantia nigra pars compacta (A9) and ventral tegmental area (A10). Repeated po administration for 21 days of either 0.3, 1, or 3 mg/kg of **58** produced a significant decrease in the number of spontaneously active neurons in the A10 region compared to vehicle-treated animals. In contrast, none of the doses of **58** significantly altered the number of spontaneously active neurons in the A9 region compared to vehicle-treated animals. These data are consistent with data previously obtained with the selective dopamine D_3 receptor antagonist SB-277011.

Data from established catalepsy and prolactin models suggest that a selective dopamine D_3 antagonist would have reduced liability to induce the EPS and hyperprolactinaemia associated with conventional antipsychotic agents. In agreement with this, compound **58** showed no cataleptic activity at doses up to 100 mg/kg po, and although levels of prolactin were increased at 30 and 100 mg/kg, these were not statistically significant. In these models, the typical antipsychotic compound haloperidol produced a complete cataleptic response and increased prolactin levels at doses of 3 mg/kg po.

A study was also conducted to determine the effects of **58** on the expression of cocaine-induced condition place preference (CPP) in male Sprague−Dawley rats. In the CPP paradigm, the primary motivational properties of a drug, defined as an unconditioned stimulus (UCS), is repeatedly paired with a previously neutral set of environmental stimuli. During a course of conditioning, these environmental stimuli can acquire secondary motivational properties and thus act as conditioned stimuli (CS) that can elicit approach when the animal is reexposed to the conditioned stimuli. The CPP paradigm also indicates that neutral stimuli associated with the pharmacological effects of psychoactive drugs eventually induce physiological states similar to those produced by the drug alone. Thus, all animals were administered either vehicle (methylcellulose, 1 mg/kg ip) or cocaine (15 mg/kg ip) in the appropriate chamber of the CPP apparatus every other day for 8 days (i.e., 4 vehicle/cocaine pairings). These chambers were designed to create a specific environment with distinct cues. On the ninth day, the cocaine treated rats showed a significant CPP response, similar to that previously reported.[28] Twenty-four hours after the last pairing, animals were randomly allocated to receive a single po injection of vehicle or 0.3, 1, 3, or 10 mg/kg of **58**, 3.5 h before being placed back in the CPP apparatus. The po administration of either 0.3, 1, 3, or 10 mg/kg of **58** produced a significant decrease in the time the animals spent in the chamber paired to cocaine on the test day. It can therefore be concluded that compound **58** blocks the expression of the CPP response to cocaine. Given that CPP is hypothesized to be a measure of the ability of neutral environmental cues to elicit approach behavior following pairing with substrates that are considered to produce incentive motivation, the results of this study suggest that compound **58** may have a potential use in the treatment of cue-induced relapse in drug-free cocaine addicts.

Conclusions

Starting from the previously reported 7-cyano-2,3,4,5-tetrahydro-1*H*-3-benzazepine **10**, two new series of 7-sulfonyl and 7-sulfonyloxy benzazepines have been designed. Both series have provided compounds with high affinity and selectivity for the dopamine D_3 receptor in addition to a highly desirable pharmacokinetic profile in the rat. This study has resulted in the identification of **58** (SB-414796) which is a potent and selective D_3 antagonist with low potential to inhibit cytochrome P450 enzymes, low blood clearance (29 mL/min/kg), and high oral bioavailability (85%) and is brain penetrant (0.3:1) in the rat. Preliminary biological evaluation in rats suggest that **58** produces a significant reduction in dopaminergic cell firing in the ventral tegmental (A10) but not in the substantia nigra (A9) brain region compared to vehicle-treated animals. This suggests that as a selective D_3 receptor antagonist, **58** may have the properties of an atypical antipsychotic agent. Initial data showing that **58** can block the expression of the conditioned place preference response to cocaine in male rats may also support the hypothesis that a selective D_3 antagonist could be a potential treatment for cue-induced relapse in drug addicts. In can therefore be concluded that compound **58** represents a novel and exciting pharmacological tool for the further understanding of the biological significance of dopamine D_3 receptors in the CNS.

Experimental Section

Chemistry. Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AMX 400, a JEOL GX 270, or a Bruker AC 250. High-resolution mass spectra were recorded using a Micromass Q-Tof 2 electrospray mass spectrometer. Low-resolution mass spectra were recorded using a Fisons VG Platform. LC-mass spectra (LCMS) were recorded using a Hewlett-Packard HP 1100 System attached to a Waters Micromass ZMD electrospray ionization mass spectrometer. A SORBAX SB C18 3.5 μm (30 × 2.1 mm) column was used with elution using the following conditions: eluent A, 0.1%

TFA/H_2O v/v, eluent B, 0.1% TFA/CH_3CN v/v; flow rate, 0.75 mL/min. The elution gradient was 5−95% B increased over 1.5 min and then held for 0.5 min A detection wavelength of 215 nm was used. Merck Kieselgel 60 was used for column chromatography. All solvent evaporation was performed under vacuum.

3-(*tert*-Butoxycarbonyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13). A solution of 3-(*tert*-butoxycarbonyl)-7-hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **12**[19] (3.00 g, 0.011 mol), methanesulfonyl chloride (1.44 g, 0.013 mol), triethylamine (1.27 g, 0.013 mol), and dichloromethane (50 mL) was stirred at room temperature for 18 h. The reaction mixture was then partitioned between dichloromethane (50 mL) and a saturated solution of sodium hydrogen carbonate (50 mL). The organic layer was separated, washed with water (50 mL), and then dried (Na_2SO_4). The solvent was then evaporated in vacuo to give **13** (3.85 g, 99%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.85−2.92 (4H, m), 3.13 (3H, s), 3.53−3.56 (4H, m), 7.00−7.03 (2H, m), 7.13−7.16 (1H, m). Mass spectrum (API$^+$): Found 242 (M − Boc)H$^+$. $C_{16}H_{23}NO_5S$ requires 341.

7-Methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14). A solution of 3-(*tert*-butoxycarbonyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **13** (3.8 g, 0.011 mol), trifluoroacetic acid (3.76 g, 0.033 mol), and dichloromethane (50 mL) was heated at 50 °C for 5 h. The solvents were then evaporated in vacuo, and the residue was partitioned between water (200 mL) and ethyl acetate (150 mL). The aqueous layer was washed with ethyl acetate (100 mL) and then basified (pH = 14) with a 40% solution of sodium hydroxide. The suspension was then extracted with ethyl acetate (3 × 150 mL), and the combined organic layers were then dried (Na_2SO_4). The solvent was then evaporated in vacuo to give **14** (2.42 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 2.88−3.00 (8H, m), 3.13 (3H, s), 7.00−7.05 (2H, m), 7.12 (1H, d). Mass spectrum (API$^+$): Found 242 (MH$^+$). $C_{11}H_{15}NO_3S$ requires 241.

***trans*-3-(2-(4-(*N*-*tert*-Butoxycarbonylamino)cyclohexyl)-ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (16).** A mixture of 7-(methylsulfonyloxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepine **14** (2.00 g, 8.30 mmol) and *trans*-2-(1-(4-*N*-*tert*-butoxycarbonyl)amino)cyclohexyl acetaldehyde **15**[6] (2.00 g, 8.30 mmol) in dichloroethane (30 mL) was stirred at room temperature for 5 min before sodium triacetoxyborohydride (1.85 g, 8.72 mmol) was added in a single portion. After the mixture was stirred at room temperature for 48 h, a saturated solution of sodium hydrogen carbonate (50 mL) was added and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 60 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was then evaporated in vacuo and the residue purified by column chromatography (silica gel, ethyl acetate) to give **16** (3.10 g, 80%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 0.9−1.25 (7H, m), 1.44 (9H, s), 1.70−1.80 (2H, m), 1.90−2.05 (2H, m), 2.40−2.50 (2H, m), 2.55−2.65 (4H, m), 2.88−2.95 (4H, m), 3.12 (3H, s), 3.36 (1H, br s), 4.34 (1H, br s), 6.98−7.02 (2H, m), 7.08−7.12 (1H, d). Mass spectrum (API$^+$): Found 467 (MH$^+$). $C_{24}H_{38}N_2O_5S$ requires 466.

***trans*-3-(2-(4-Aminocyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (17).** A solution of *trans*-3-(2-(4-(*N*-*tert*-butoxycarbonylamino)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **16** (2.45 g, 5.3 mmol), trifluoroacetic acid (8 mL), and dichloromethane (32 mL) were stirred at room temperature, under argon, for 2 h. The solvents were then evaporated in vacuo, and the residue was partitioned between water (150 mL) and ethyl acetate (60 mL). The aqueous layer was removed and washed with ethyl acetate (50 mL). The aqueous layer was then basified (pH = 14) with a 40% solution of sodium hydroxide. The resultant suspension was extracted with ethyl acetate (3 × 80 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated in vacuo to give **17** (1.79 g, 93%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 0.95−1.45 (7H, m), 1.70−1.80 (2H, m), 1.80−1.90 (2H, m), 2.49 (2H, t, J = 8 Hz), 2.55−2.65 (5 H, m), 2.88−2.95 (4H, m), 3.12 (3H, s), 7.00−7.02 (2H, m), 7.11 (1H, d, J = 8 Hz). Mass spectrum (API$^+$): Found 367 (MH$^+$). $C_{19}H_{30}N_2O_3S$ requires 366.

***trans*-3-(2-(4-((5-(2-Methylquinolinyl))carboxamido)-cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (26).** A mixture of *trans*-3-(2-(4-aminocyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **17** (150 mg, 0.41 mmol), 2-methylquinoline-5-carboxylic acid (92 mg, 0.49 mmol), 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (86 mg, 0.45 mmol), and 1-hydroxybenzotriazole (5 mg) in dichloromethane (10 mL) was shaken at room temperature for 18 h. A saturated solution of sodium bicarbonate (4 mL) was then added and the mixture shaken for a further 0.25 h. The organic phase was then applied directly to a silica gel column and eluted with a gradient of 30−100% ethyl acetate in hexane followed by 0−10% methanol in ethyl acetate to give **26** (161 mg, 74%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.45−1.50 (2H, m), 1.80−1.90 (2H, m), 2.15−2.20 (2H, m), 2.50−2.55 (2H, m), 2.60−2.70 (4H, m), 2.73 (3H, s), 2.90−3.00 (4H, m), 3.13 (3H, s), 4.00−4.15 (1H, m), 5.92 (1H, d, J = 8 Hz), 6.95−7.15 (3H, m), 7.30 (1H, br s), 7.50−7.55 (1H, m), 7.70−7.75 (1H, m), 8.00−8.15 (2H, d). Mass Spectrum (API$^+$): Found 536 (MH$^+$). $C_{30}H_{37}N_3O_4S$ requires 535. The purity was determined as >98% by LC-MS, retention time 0.68 min.

The following compounds were prepared in a manner similar to compound **26**.

***trans*-3-(2-(4-((3-(4-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (18).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.35 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.00−2.10 (2H, m), 2.50−2.60 (2H, m), 2.60−2.75 (4H, m), 2.90−3.00 (4H, m), 3.13 (3H, s), 3.80−3.90 (1H, m), 5.38 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 7.00−7.15 (5H, m), 7.45−7.50 (2H, m), 7.56 (1H, d, J = 16 Hz). Mass Spectrum (API$^+$): Found 515 (MH$^+$). $C_{28}H_{35}FN_2O_4S$ requires 514. The purity was determined as >98% by LC-MS, retention time 0.87 min.

***trans*-3-(2-(4-((3-(3-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (19).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.30 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.00−2.10 (2H, m), 2.45−2.55 (2H, m), 2.55−2.65 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 3.80−3.90 (1H, m), 5.42 (1H, d, J = 8 Hz), 6.33 (1H, d, J = 16 Hz), 6.95−7.35 (7H, m), 7.56 (1H, d, J = 16 Hz). Mass Spectrum (API$^+$): Found 515 (MH$^+$). $C_{28}H_{35}FN_2O_4S$ requires 514.

***trans*-3-(2-(4-((3-(2-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (20).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.30 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.00−2.10 (2H, m), 2.45−2.55 (2H, m), 2.55−2.65 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 3.80−3.90 (1H, m), 5.44 (1H, d, J = 8 Hz), 6.49 (1H, d, J = 16 Hz), 6.95−7.05 (2H, m), 7.05−7.15 (3H, m), 7.25−7.35 (1H, m), 7.40−7.50 (1H, m), 7.65 (1H, d, J = 16 Hz). Mass Spectrum (API$^+$): Found 515 (MH$^+$). $C_{28}H_{35}FN_2O_4S$ requires 514. The purity was determined as >98% by LC-MS, retention time 0.86 min.

***trans*-3-(2-(4-((3-(4-Methoxyphenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (21).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.10 (2H, m), 2.45−2.55 (2H, m), 2.55−2.65 (4H, m), 2.85−3.95 (4H, m), 3.13 (3H, s), 3.83 (3H, s), 3.85 (1H, br m), 5.35 (1H, d, J = 8 Hz), 6.20 (1H, d, J = 16 Hz), 6.88 (2H, d, J = 8 Hz), 6.97−7.05 (2H, m), 7.11 (1H, d, J = 8 Hz), 7.43 (2H, d, J = 8 Hz), 7.55 (1H, d, J = 16 Hz). Mass Spectrum (API$^+$): Found 527 (MH$^+$). $C_{29}H_{38}N_2O_5S$ requires 526. The purity was determined as >98% by LC-MS, retention time 0.84 min.

***trans*-3-(2-(4-((3-(3-Methoxyphenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (22).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.10 (2H, m), 2.45−2.55 (2H, m), 2.55−2.65 (4H, m), 2.85−3.95 (4H, m), 3.13 (3H, s), 3.82 (3H, s), 3.85 (1H, br m), 5.47

(1H, d, $J = 8$ Hz), 6.35 (1H, d, $J = 16$ Hz), 6.85−6.90 (1H, m), 6.95−7.15 (5H, m), 7.27 (1H, t, $J = 7$ Hz), 7.56 (1H, d, $J = 16$ Hz). Mass Spectrum (API^+): Found 527 (MH^+). $C_{29}H_{38}N_2O_5S$ requires 526. The purity was determined as >98% by LC-MS, retention time 0.86 min.

***trans*-3-(2-(4-((3-(2-Methoxyphenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (23).** ^1H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.10 (2H, m), 2.45−2.55 (2H, m), 2.55−2.65 (4H, m), 2.85−3.95 (4H, m), 3.13 (3H, s), 3.85 (1H, br m), 3.88 (3H, s), 5.40 (1H, d, $J = 8$ Hz), 6.47 (1H, d, $J = 16$ Hz), 6.85−7.05 (4H, m), 7.13 (1H, d, $J = 7$ Hz), 7.31 (1H, m), 7.45 (1H, dd, $J = 7.5$, 1.5 Hz), 7.80 (1H, d, $J = 16$ Hz). Mass Spectrum (API^+): Found 527 (MH^+). $C_{29}H_{38}N_2O_5S$ requires 526.

***trans*-3-(2-(4-((1-Naphthalenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (24).** ^1H NMR ($CDCl_3$) δ: 1.15−1.30 (5H, m), 1.45−1.50 (2H, m), 1.80−1.90 (2H, m), 2.15−2.25 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 4.00−4.05 (1H, m), 5.78 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.10 (1H, d), 7.40−7.60 (4H, m), 7.80−7.90 (2H, m), 8.28 (1H, m). Mass Spectrum (API^+): Found 521 (MH^+). $C_{30}H_{36}N_2O_4S$ requires 520. The purity was determined as >98% by LC-MS, retention time 0.87 min.

***trans*-3-(2-(4-((5-Quinolinyl)carboxamido)cyclohexyl)-ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (25).** ^1H NMR ($CDCl_3$) δ: 1.15−1.35 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.15−2.25 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.90−2.95 (4H, m), 3.13 (3H, s), 4.00−4.05 (1H, m), 5.85 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.10 (1H, d, $J = 8$ Hz), 7.45−7.50 (1H, m), 7.60−7.70 (2H, m), 8.17 (1H, d, $J = 8$ Hz), 8.72 (1H, d), 8.95(1H, m). Mass Spectrum (API^+): Found 522 (MH^+). $C_{29}H_{35}N_3O_4S$ requires 521. The purity was determined as >98% by LC-MS, retention time 0.71 min.

***trans*-3-(2-(4-((4-(2-Methylquinolinyl))carboxamido)-cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (27).** ^1H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.45−1.50 (2H, m), 1.80−1.90 (2H, m), 2.15−2.20 (2H, m), 2.50−2.55 (2H, m), 2.60−2.65 (4H, m), 2.73 (3H, s), 2.90−3.00 (4H, m), 3.13 (3H, s), 4.00−4.15 (1H, m), 5.92 (1H, d, $J = 8$ Hz), 7.00−7.15 (3H, m), 7.30 (1H, br s), 7.50−7.55 (1H, m), 7.70−7.75 (1H, m), 8.00−8.15 (2H, d). Mass Spectrum (API^+): Found 536 (MH^+). $C_{30}H_{37}N_3O_4S$ requires 535. The purity was determined as >98% by LC-MS, retention time 0.73 min.

***trans*-3-(2-(4-((3-(3-(5-Methyl-1,2,4-oxadiazolyl))phenyl)-carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (28).** ^1H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.40−1.50 (2H, m), 1.80−1.85 (2H, m), 2.05−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.68 (3H, s), 2.90−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 6.00 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.10 (1H, d, $J = 8$ Hz), 7.57 (1H, t, $J = 8$ Hz), 7.95−8.00 (1H, m), 8.20 (1H, d), 8.32 (1H, s). Mass Spectrum (API^+): Found 553 (MH^+). $C_{29}H_{36}N_4O_5S$ requires 552.

***trans*-3-(2-(4-((3-(5-(2-Methyloxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (29).** ^1H NMR ($CDCl_3$) δ: 1.10−1.35 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.10−2.20 (2H, m), 2.49 (2H, t, $J = 8$ Hz), 2.55 (3H, s), 2.60−2.70 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 5.92 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.10 (1H, d, $J = 8$ Hz), 7.25 (1H, m), 7.45 (1H, t, $J = 8$ Hz), 7.60−7.75 (2H, m), 8.30 (1H, s). Mass Spectrum (API^+): Found 552 (MH^+). $C_{30}H_{37}N_3O_5S$ requires 552.

***trans*-3-(2-(4-((3-(*N*-Pyrrolyl)phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (30).** ^1H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.40−1.50 (2H, m), 1.80−1.85 (2H, m), 2.10−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.65 (4H, m), 2.90−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 5.95 (1H, d, $J = 8$ Hz), 6.35−6.40 (2H, m), 7.00−7.05 (2H, m), 7.10−7.15 (3H, m), 7.45−7.55 (3H, m), 7.80 (1H, br s). Mass Spectrum (API^+): Found 536 (MH^+). $C_{30}H_{37}N_3O_4S$ requires 535.

***trans*-3-(2-(4-((3-(2-(4-Methyloxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (31).** ^1H NMR ($CDCl_3$) δ: 1.10−1.35 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.05−2.15 (2H, m), 2.27 (3H, s), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 6.05 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.10 (1H, d, $J = 9$ Hz), 7.45−7.60 (2H, m), 7.90−7.95 (1H, d), 8.05−8.15 (1H, d, $J = 8$ Hz), 8.3 (1H, s). Mass Spectrum (API^+): Found 552 (MH^+). $C_{30}H_{37}N_3O_5S$ requires 552. The purity was determined as >98% by LC-MS, retention time 0.84 min.

***trans*-3-(2-(4-(3-(5-(3-Methylisoxazolyl)phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (32).** ^1H NMR ($CDCl_3$) δ: 1.10−1.40 (5H, m), 1.40−1.55 (2H, m), 1.70−1.80 (2H, m), 2.05−2.20 (2H, m), 2.37 (3H, s), 2.45−2.60 (2H, m), 2.60−2.70 (4H, m), 2.85−3.00 (4H, m), 3.13 (3H, s), 3.85−4.05 (1H, m), 6.00 (1H, d, $J = 8$ Hz), 6.45 (1H, s), 6.95−7.05 (2H, m), 7.05−7.15 (1H, m), 7.52 (1H, t, $J = 9$ Hz), 7.75−7.90 (2H, m), 8.10 (1H, s). Mass Spectrum (API^+): Found 552 (MH^+). $C_{30}H_{37}N_3O_5S$ requires 551.

***trans*-3-(2-(4-((3-(2-(5-Methyloxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (33).** ^1H NMR ($CDCl_3$) δ: 1.10−1.35 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.05−2.15 (2H, m), 2.41 (3H, s), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.90−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 6.03 (1H, d, $J = 8$ Hz), 6.86 (1H, br s), 7.00−7.05 (2H, m), 7.10−7.15 (1H, m), 7.52 (1H, t, $J = 8$ Hz), 7.90−7.95 (1H, m), 8.05−8.10 (1H, m), 8.30 (1H, br s). Mass Spectrum (API^+): Found 552 (MH^+). $C_{30}H_{37}N_3O_5S$ requires 551.

***trans*-3-(2-(4-((3-(2-pyrimidinyl)phenyl)carboxamido)-cyclohexyl)ethyl)-7-methylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (34).** ^1H NMR ($CDCl_3$) δ: 1.10−1.35 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.05−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.85−2.95 (4H, m), 3.13 (3H, s), 3.90−4.00 (1H, m), 6.10 (1H, d, $J = 8$ Hz), 7.00−7.05 (2H, m), 7.11 (1H, d, $J = 8$ Hz), 7.20−7.30 (2H, m), 7.58 (1H, t, $J = 8$ Hz), 8.00 (1H, d, $J = 8$ Hz), 8.58 (1H, d, $J = 8$ Hz), 8.70 (1H, s) 8.84 (1H, d, $J = 5$ Hz). Mass Spectrum (API^+): Found 549 (MH^+). $C_{30}H_{36}N_4O_4S$ requires 548. The purity was determined as >98% by LC-MS, retention time 0.79 min.

2,3,4,5-Tetrahydro-1*H*-3-benzazepine (36). To a suspension of Raney Ni (2.00 g) (prewashed with ethanol (3 × 20 mL)) in ethanol (50 mL) was added a solution of 1,2-phenylenediacetonitrile **35** (7.50 g, 48 mmol) in 2 M NH_3 in ethanol (100 mL). The mixture was then hydrogenated at 50 °C and 1000 psi pressure, with shaking, for 24 h. The reaction mixture was then cooled to room temperature, filtered through a pad of Kieselguhr, and washed with ethanol (100 mL). The filtrate was then evaporated in vacuo to give a brown oil which was purified by column chromatography (silica gel, 2−10% methanol: CH_2Cl_2) to give **36** as a brown oil (4.25 g, 60%). Mass spectrum (API^+) Found: 148 (MH^+). $C_{10}H_{13}N$ requires 147.

3-Acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (37). A solution of acetic anhydride (6.37 g, 0.062 mol) in dichloromethane (50 mL) was added dropwise to a stirred solution of 2,3,4,5-tetrahydro-1*H*-3-benzazepine **36** (8.35 g, 0.057 mol) and triethylamine (8.7 mL) in dichloromethane (50 mL) at 0 °C under argon. After the mixture was stirred at room temperature for 18 h, water (80 mL) was added and the organic layer separated. The organic layer was washed with 0.5 M hydrochloric acid (50 mL), a saturated solution of sodium bicarbonate (50 mL), water (50 mL), and then dried (Na_2SO_4). Evaporation of the solvent in vacuo gave **37** (10.24 g, 95%) as a yellow oil which solidified on standing. ^1H NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.85−3.00 (4H, m), 3.55−3.60 (2H, m), 3.72−3.80 (2H, m), 7.10−7.20 (4H, m). Mass Spectrum (API^+): Found 190 (MH^+). $C_{12}H_{15}NO$ requires 189.

3-Acetyl-7-chlorosulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (38). A solution of 3-acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **37** (4.0 g, 0.021 mol) in dichloromethane (25 mL)

was added dropwise to a stirred solution of chlorosulfonic acid in dichloromethane (25 mL) at −70 °C under argon. After being warmed to room temperature, the reaction was stirred for 18 h and then poured onto ice/water (200 mL). The resultant mixture was then extracted with ethyl acetate (3 × 100 mL) and dried (Na_2SO_4) and the solvent evaporated in vacuo to give **38** (2.74 g, 45%) as a pale yellow solid. ^{1}H NMR δ ($CDCl_3$): 2.21 (3H, s), 3.0−3.10 (4H, m), 3.60−3.70 (2H, m), 3.74−3.80 (2H, m), 7.35−7.40 (1H, m), 7.80−7.85 (2H, m). Mass spectrum (API$^+$): Found 288 & 290 (MH^+). $C_{12}H_{14}ClNO_3S$ requires 287 & 289.

3-Acetyl-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (39). To a stirred solution of sodium sulfite (1.60 g, 12. 6 mmol) and sodium hydrogen carbonate (1.14 g, 13.56 mmol) in water (25 mL) was added 3-acetyl-7-chlorosulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **38** (2.60 g, 9.03 mmol) in tetrahydrofuran (10 mL). The reaction mixture was heated at 75 °C for 2 h and cooled to 30 °C and methyl iodide (2.8 mL, 45.2 mmol) added. After being stirred at 50 °C for 24 h, the reaction mixture was cooled to room temperature and partitioned between water (50 mL) and ethyl acetate (100 mL). The aqueous layer was then separated and further extracted with ethyl acetate (2 × 80 mL). The combined extracts were then dried (Na_2SO_4), and the solvent was evaporated in vacuo to give **39** (1.77 g, 73%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) 2.20 (3H, s), 2.99−3.05 (4H, m), 3.06 (3H, s), 3.61−3.64 (2H, m), 3.73−3.77 (2H, m), 7.32−7.37 (1H, m), 7.7−7.75 (2H, m). Mass Spectrum (API$^+$) Found 268 (MH^+). $C_{13}H_{17}NO_3S$ requires 267.

7-Methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (40). A solution of 3-acetyl-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **39** (1.75 g, 6.55 mmol) in 5 M hydrochloric acid (50 mL) was heated at reflux for 18 h. The reaction mixture was then cooled to room temperature and basified (pH = 12) with solid potassium carbonate, and the solvent was evaporated in vacuo. The solid residue was redissolved in water (20 mL) and extracted with ethyl acetate (5 × 60 mL), and then the combined extracts were dried (Na_2SO_4). The solvent was then evaporated in vacuo to give **40** (1.40 g, 95%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) 1.88 (1H, br s), 2.95−3.13 (8H, m), 3.04 (3H, s), 7.25−7.30 (1H, d), 7.65−7.72 (2H, m). Mass Spectrum (API$^+$): Found 226 (MH^+). $C_{11}H_{15}NO_2S$ requires 225.

***trans*-3-(2-(4-(*N*-*tert*-Butoxycarbonylamino)cyclohexyl)-ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (41).** A solution of 7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **40** (1.00 g, 4.44 mmol) and *trans*-(1-(4-*N*-*tert*-butoxycarbonyl)amino)cyclohexyl acetaldehyde **15** (1.07 g, 4.44 mmol) in 1,2-dichloroethane (20 mL) was stirred at room temperature for 5 min before sodium triacetoxyborohydride (0.99 g, 4.66 mmol) was added in a single portion. After being stirred at room temperature for 48 h, the reaction mixture was partitioned between water (50 mL) and dichloromethane (100 mL). The aqueous layer was separated and reextracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was then evaporated in vacuo to give a pale yellow solid which was purified by column chromatography (silica gel, ethyl acetate:methanol; 9:1) to give **41** (1.80 g, 90%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 0.99−1.14 (4H, m), 1.23−1.29 (1H, m), 1.41−1.46 (2H, m), 1.46 (9H, s), 1.73−1.79 (2H, m), 2.00−2.06 (2H, m), 2.50 (2H, t, J = 7.6 Hz), 2.62−2.65 (4H, m), 2.99−3.02 (4H, m), 3.05 (3H, s), 3.38 (1H, br s), 4.38 (1H, br s), 7.27−7.30 (1H, d), 7.67−7.74 (2H, m). Mass spectrum: (API$^+$) Found: 351 (M − Boc)H$^+$. $C_{24}H_{38}N_2O_4S$ requires 450.

***trans*-3-(2-(4-Aminocyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (42).** A solution of *trans*-3-(2-(1-(4-*N*-*tert*-butoxycarbonyl)amino)cyclohexyl)ethyl-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **41** (1.3 g, 2.89 mmol) in dichloromethane (24 mL) and trifluoroacetic acid (6 mL) was stirred at room temperature for 2 h. The reaction mixture was then concentrated in vacuo and the residue partitioned between water (60 mL) and ethyl acetate (20 mL). The aqueous layer was separated, extracted with ethyl acetate (30 mL), and then basified (pH = 14) with a 40% solution of sodium hydroxide. The oily suspension was then extracted with ethyl acetate (3 × 60 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated in vacuo to give **42** (1.00 g, 99%) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 0.90−1.12 (4H, m), 1.15−1.22 (1H, m), 1.35−1.40 (2H, m), 1.72−1.78 (2H, m), 1.82−1.90 (2H, m), 2.45−2.52 (2H, m), 2.55−2.62 (5H, m), 2.98−3.02 (4H, m), 3.04 (3H, s), 7.27 (1H, d, J = 7.8 Hz), 7.56 (1H, s), 7.68 (1H, d). Mass spectrum (API$^+$) 351 (MH^+). $C_{19}H_{30}N_2O_2S$ requires 350.

The following compounds were prepared in a manner similar to compound **26**.

***trans*-3-(2-(4-((3-(4-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (43).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.20 (5H, m), 1.40−1.45 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.50−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.05 (3H, s), 3.80−3.90 (1H, m), 5.43 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 7.00−7.05 (2H, m), 7.25 (1H, m), 7.45−7.55 (2H, m), 7.56 (1H, d, J = 16 Hz), 7.65−7.70 (2H, m). Mass Spectrum (API$^+$): Found 499 (MH^+). $C_{28}H_{35}FN_2O_3S$ requires 498. The purity was determined as >98% by LC-MS, retention time 0.80 min.

***trans*-3-(2-(4-((3-(3-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (44).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.30 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.00−2.10 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.05 (3H, s), 3.80−3.90 (1H, m), 5.44 (1H, d, J = 8 Hz), 6.33 (1H, d, J = 16 Hz), 6.95−7.05 (1H, m), 7.10−7.40 (4H, m), 7.56 (1H, d, J = 16 Hz), 7.60−7.70 (2H, m). Mass Spectrum (API$^+$): Found 499 (MH^+). $C_{28}H_{35}FN_2O_3S$ requires 498.

***trans*-3-(2-(4-((3-(2-Fluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (45).** ^{1}H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.50 (2H, t, J = 7 Hz), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.05 (3H, s), 3.80−3.95 (1H, m), 5.43 (1H, d, J = 8 Hz), 6.48 (1H, d, J = 16 Hz), 7.05−7.15 (2H, m), 7.20−7.40 (2H, m), 7.45−7.50 (1H, m), 7.65−7.75 (3H, m). Mass Spectrum (API$^+$): Found 499 (MH^+). $C_{28}H_{35}FN_2O_3S$ requires 498.

***trans*-3-(2-(4-((3-(3,5-Difluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (46).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (7H, m), 3.85 (1H, br m), 5.50 (1H, d, J = 8 Hz), 6.35 (1H, d, J = 16 Hz), 6.70−6.80 (1H, m), 6.95−7.05 (2H, m), 7.28 (1H, d, J = 7 Hz), 7.50 (1H, d, J = 16 Hz), 7.65−7.70 (2H, m). Mass Spectrum (API$^+$): Found 517 (MH^+). $C_{28}H_{34}F_2N_2O_3S$ requires 516. The purity was determined as >98% by LC-MS, retention time 0.83 min.

***trans*-3-(2-(4-((3-(2,6-Difluorophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (47).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.00−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (7H, m), 3.87 (1H, br m), 5.45 (1H, d, J = 8 Hz), 6.66 (1H, d, J = 16 Hz), 6.80−7.00 (2H, m), 7.20−7.35 (2H, m), 7.60−7.75 (3H, m). Mass Spectrum (API$^+$): Found 517 (MH^+). $C_{28}H_{34}F_2N_2O_3S$ requires 516. The purity was determined as >98% by LC-MS, retention time 0.82 min.

***trans*-3-(2-(4-((3-(4-Cyanophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (48).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.3(5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (7H, m), 3.85 (1H, br m), 5.55 (1H, d, J = 8 Hz), 6.43 (1H, d, J = 16 Hz), 7.28 (1H, d, J = 7 Hz), 7.50−7.70 (7H, m). Mass Spectrum (API$^+$): Found 506 (MH^+). $C_{29}H_{35}N_3O_3S$ requires 505. The purity was determined as >98% by LC-MS, retention time 0.75 min.

***trans*-3-(2-(4-((3-(3-Cyanophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahy-**

dro-1*H*-3-benzazepine (49). ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.35−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (7H, m), 3.85 (1H, br m), 5.50 (1H, d, J = 8 Hz), 6.39 (1H, d, J = 16 Hz), 7.28 (1H, d, J = 7 Hz), 7.45−7.80 (7H, m). Mass Spectrum (API^+): Found 506 (MH^+). $C_{29}H_{35}N_3O_3S$ requires 505. The purity was determined as >98% by LC-MS, retention time 0.76 min.

***trans*-3-(2-(4-((3-(2-Cyanophenyl)prop-2-enyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (50).** ^{1}H NMR ($CDCl_3$) δ: 1.00−1.30 (5H, m), 1.38−1.50 (2H, m), 1.70−1.85 (2H, m), 2.0−2.15 (2H, m), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (7H, m), 3.85 (1H, br m), 5.58 (1H, d, J = 8 Hz), 6.66 (1H, d, J = 16 Hz), 7.28 (1H, d, J = 7 Hz), 7.35−7.50 (1H, m), 7.50−7.71 (5H, m), 7.77 (1H, d, J = 16 Hz). Mass Spectrum (API^+): Found 506 (MH^+). $C_{29}H_{35}N_3O_3S$ requires 505. The purity was determined as >98% by LC-MS, retention time 0.77 min.

***trans*-3-(2-(1-(4-(1-Naphthalenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (51).** ^{1}H NMR ($CDCl_3$) δ: 1.10−1.35 (5H, m), 1.40−1.55 (2H, m), 1.75−1.85 (2H, m), 2.15−2.25 (2H, m), 2.50−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.05 (3H, s), 4.00−4.10 (1H, m), 5.80 (1H, d, J = 8 Hz), 7.25 (1H, m), 7.45−7.60 (4H, m), 7.65−7.75 (2H, m), 7.80−7.95 (2H, m), 8.25 (1H, m). Mass Spectrum (API^+): Found 505 (MH^+). $C_{30}H_{36}N_2O_3S$ requires 504.

***trans*-3-(2-(4-((5-(2-Methylquinolinyl))carboxamido)-cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (52).** ^{1}H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.45−1.50 (2H, m), 1.80−1.90 (2H, m), 2.15−2.20 (2H, m), 2.50−2.55 (2H, m), 2.60−2.70 (4H, m), 2.75 (3H, s), 2.95−3.05 (4H, m), 3.04 (3H, s), 3.95−4.05 (1H, m), 5.82 (1H, d, J = 8 Hz), 7.20−7.25 (1H, d, J = 7 Hz), 7.34 (1H, d, J = 9 Hz), 7.55−7.70 (4H, m), 8.05−8.10 (1H, d), 8.62 (1H, d). Mass Spectrum (API^+): Found 520 (MH^+). $C_{30}H_{37}N_3O_3S$ requires 519. The purity was determined as >98% by LC-MS, retention time 0.58 min.

***trans*-3-(2-(4-((5-(8-Fluoro-2-methylquinolinyl))carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (53).** ^{1}H NMR ($CDCl_3$) δ: 1.10−1.30 (5H, m), 1.40−1.50 (2H, m), 1.80−1.90 (2H, m), 2.10−2.20 (2H, m), 2.45−2.50 (2H, m), 2.55−2.65 (4H, m), 2.80 (3H, s), 2.95−3.05 (4H, m), 3.04 (3H, s), 3.90−4.00 (1H, m), 5.88 (1H, d, J = 8 Hz), 7.20−7.35 (2H, m), 7.40 (1H, d, J = 9 Hz), 7.45−7.55 (1H, m), 7.60−7.70 (2H, m), 8.60−8.70 (1H, m). Mass Spectrum (API^+): Found 538 (MH^+). $C_{30}H_{36}FN_3O_3S$ requires 537. The purity was determined as >98% by LC-MS, retention time 0.69 min.

***trans*-3-(2-(4-((3-(5-(2-Methyloxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (54).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.35 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.45−2.55 (2H, m), 2.54 (3H, s), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.04 (3H, s), 3.90−4.00 (1H, m), 5.94 (1H, d, J = 8 Hz), 7.15−7.25 (2H, m), 7.45 (1H, t, J = 8 Hz), 7.60−7.75 (4H, m), 7.98 (1H, br s). Mass Spectrum (API^+): Found 536 (MH^+). $C_{30}H_{37}N_3O_4S$ requires 535. The purity was determined as >98% by LC-MS, retention time 0.74 min.

***trans*-3-(2-(4-((3-(5-(1-Methylpyrazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (55).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.30 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.50−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.05 (3H, s), 3.90 (3H, s), 3.90−3.95 (1H, m), 5.79 (1H, d, J = 8 Hz), 6.35 (1H, d, J = 2 Hz), 7.25 (1H, d), 7.45−7.55 (3H, m), 7.65−7.80 (3H, m), 7.82 (1H, br s). Mass Spectrum (API^+): Found 535 (MH^+). $C_{30}H_{38}N_4O_3S$ requires 534.

***trans*-3-(2-(4-((3-(2-(5-Methyloxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (56).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.35 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.41 (3H, s), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.04 (3H, s), 3.90−4.00 (1H, m), 6.03 (1H, d, J = 8 Hz), 6.86 (1H, d, J = 1 Hz), 7.25 (1H, d, J = 11 Hz), 7.45−7.55 (1H, m), 7.60−7.70 (2H, m), 7.89 (1H, d, J = 8 Hz), 8.10 (1H, d, J = 8 Hz), 8.29 (1H, s). Mass Spectrum (API^+): Found 536 (MH^+). $C_{30}H_{37}N_3O_4S$ requires 535.

***trans*-3-(2-(4-((3-(5-(3-Methylisoxazolyl))phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (57).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.45 (5H, m), 1.50−1.60 (2H, m), 1.75−1.90 (2H, m), 2.05−2.20 (2H, m), 2.37 (3H, s), 2.50−2.60 (2H, m), 2.60−2.70 (4H, m), 2.95−3.10 (4H, m), 3.05 (3H, s), 3.85−4.05 (1H, m), 6.03 (1H, d, J = 8 Hz), 6.45 (1H, s), 7.25−7.30 (1H, m), 7.52 (1H, t, J = 9 Hz)), 7.60−7.75 (2H, m), 7.80−7.90 (2H, m), 8.12 (1H, s). Mass Spectrum (API^+): Found 536 (MH^+). $C_{30}H_{37}N_3O_4S$ requires 535.

***trans*-3-(2-(4-((3-(3-(5-Methyl-1,2,4-oxadiazolyl))phenyl)-carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (58).** ^{1}H NMR ($CDCl_3$) δ: 1.05−1.35 (5H, m), 1.40−1.50 (2H, m), 1.75−1.85 (2H, m), 2.05−2.15 (2H, m), 2.41 (3H, s), 2.45−2.55 (2H, m), 2.60−2.70 (4H, m), 2.95−3.05 (4H, m), 3.04 (3H, s), 3.90−4.00 (1H, m), 6.03 (1H, d, J = 8 Hz), 7.25 (1H, d, J = 11 Hz), 7.45−7.55 (1H, m), 7.60−7.70 (2H, m), 7.89 (1H, d, J = 8 Hz), 8.10 (1H, d, J = 8 Hz), 8.29 (1H, s). Mass Spectrum (API^+): Found 537 (MH^+). $C_{29}H_{36}N_4O_4S$ requires 536.

Biological Test Methods. In vivo studies were conducted in compliance with the Home Office Guidance on the operation of UK Animals (Scientific Procedures) Act 1986 and were approved by the SmithKline Beecham Procedures Review Panel.

Cloned Cell Lines Expressing D_2 and D_3 Receptors. Human cloned D_2 (long) receptors (hD_2) expressed in CHO cells were obtained from the Garvan Intitute of Medical Research, Sydney, Australia. Human cloned D_3 receptors (hD_3) expressed in CHO or NG108−15 cells were obtained from Unite de Neurobiologie et Pharmacologie (U.109) de l'INSERM, Paris, France.

Radioligand Binding Assays. Radioligand binding assays at hD_2 and hD_3 receptors were carried out using membranes from CHO cells. Membranes (5−15 mg of protein) were incubated with with 0.1 nM [^{125}I]iodosulpride in a buffer containing 50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ (pH 7.4) for 30 min at 37 °C in the presence or absence of competing ligands. Nonspecific binding was defined with 0.1 mM iodosulpride. Radioligand binding assays were also performed on 55 receptors, ion channels, and enzymes by CEREP, Le Bois l'Eveque, B. P. 1,86000 Celle L'Evescault, France.

Cell Culture. CHO cells expressing hD_2 receptors were grown in 50:50 Dulbecco's Modified Eagles Medium (DMEM; without sodium pyruvate, with glucose):Ham's F-12 containing 10% (v/v) foetal bovine serum (FBS). For hD_3 CHO clones, the growth medium was DMEM (without sodium pyruvate, with glucose) containing 10% FBS, 100 nM methotrexate, 2 nM glutamine, 500 nM (−)-sulpiride, and 1% (v/v) essential amino acids. Cells were removed from confluent plates by scraping and were harvested by centrifugation (200*g*, 5 min, room temperature). Following resuspension in 10 mL of fresh culture medium, an aliquot was counted and the cells passaged at 12 500 or 25 000 cells cm^2. Cultures between passages 5 and 30 were used for functional studies.

Determination of Extracellular Acidification rates in Microphysiometer. Cells were seeded into 12 mm transwell inserts (Costar) at 300 000 cells/cup in FBS-containing growth medium. The cells were incubated for 6h at 37 °C in 95% O_2/5% CO_2, before changing to FBS and sulpiride-free medium. After a further 16−18 h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices). The chambers were perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 μL/min and temperature of 37 °C. Each pump cycle lasted 90 s. The pump was on for the first 60 s and the acidification rate determined between 68 and 88 s, using the Cytosoft program. Cells were exposed (4.5 min for hD_2, 7.5 min for hD_3)

to increasing concentrations (at half log unit intervals) of quinpirole at half-hour intervals. For antagonist studies, a control concentration−response curve to quinpirole was conducted, and the cells were then exposed to antagonist for at least 42 min prior to construction of a further quinpirole concentration-effect curve in the presence of antagonist. Each chamber therefore acted as its own control. Drug additions were performed using the Cytosensor autosampler (Molecular Devices) from deep well blocks.

Data Analysis and Statistics. Radioligand binding studies were analyzed using an iterative four-parameter logistic model to generate IC_{50} values, and from these were determined pK_i values. Concentration−effect curves from microphysiometry experiments were constructed from the peak acidification response and analyzed using a four-parameter logistic equation. Antagonist data were analyzed as the concentration required to shift the quinpirole concentration−effect curve. Antagonist affinity was expressed as pK_b ($-\log K_b$).

P450 Inhibition. Cytochrome P450 inhibition profiles were determined using the protocols outlined in a number of patents.[29] Inhibition against cytochrome P450 1A2 was determined as described in the literature.[30]

Conditioned Place Preference. Albino, male Sprague−Dawley rats (150−175 g at the start of handling, Taconic Farms, Germantown, NY) were used in all studies. An automated, three-chambered Conditioned Place Preference apparatus (Iris Ophthalmic, Mt. Sinai, NY) was used, of which two chambers were identical in dimensions, the two chambers being separated by plexiglass guillotine doors. The pairing chambers were composed of distinct visual and tactile cues. One of the pairing chambers was entirely white, and the second chamber had white and black checkered boxes. The two pairing chambers were separated by a third, neutral connecting tunnel, with white/white with black checkered boxes on the walls and clear plexiglass floors. Each of the chambers had an infrared microbeam that was wired to a timer. The beams were arranged such that when the animals leave one chamber, a mechanism would shut off the timer. After 3 days habituation and conditioning to the apparatus, rats ($n = 10$ per group) received four daily pairings each of 15 mg/kg ip of cocaine or 1 mL/kg ip of distilled water. On the test day, the animals being tested in the expression phase received either vehicle (2% methylcellulose, 1 mL/kg po) or SB-414796 (0.3, 1, 3, or 10 mg/kg po) 4 h before they were placed in the apparatus and allowed free access to both the chambers for 15 min. The time spent in each chamber was recorded as described above.

Catalepsy. Catalepsy was assessed by positioning rats with their hindpaws on the bench and their forelimbs rested on a 1 cm diameter horizontal bar, 10 cm above the bench. The length of time in this position was recorded to a maximum of 120 s. Vehicle (1% methylcellulose, 2 mL/kg po) or SB-414796 was injected (2 mL/kg). Catalepsy was assessed 180 and 210 min (for habituation purposes) and 240 min after drug administration. Rats were judged cataleptic and assigned a score of 1 if they maintained an immobile attitude for 30 s or more at the 240 min time point; otherwise, they were given a score of 0. A logistic regression analysis (SAS−RA, version 6.11; SAS Institute Inc.) was used to analyze the data at the 240 min time point.

Plasma Prolactin Levels. Animals were pretreated with either haloperidol (3 mg/kg po), SB-414796 (10, 30, or 100 mg/kg po), or vehicle (1% methylcellulose, 2 mL/kg po). After 2 h, the animals were decapitated, and the blood was collected into glass vials. Samples were kept at 4 °C overnight, and then the serum was separated and stored at −70 °C until subsequent assay. Serum prolactin was assayed by radioimmunoassay (Amersham Life Sciences). Serum prolactin measures were transformed (log) prior to analysis by analysis of variance and Dunnett's *t*-test (Statistica Version 6.0)

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