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Bioorganic & Medicinal Chemistry 12 (2004) 319–326
Bioorganic & Medicinal Chemistry

Muscarinic M2 antagonists: anthranilamide derivatives with exceptional selectivity and in vivo activity

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Received 12 September 2003; revised 30 October 2003; accepted 10 November 2003

Abstract—Anthranilamide analogues such as **23** are potent and highly selective muscarinic M2 antagonists that also show good oral bioavailability and in vivo activity.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a profound cognitive impairment which progresses eventually to an inability to function independently and ultimately to death. One of the consistent findings in brains of AD patients is loss of cholinergic markers, including levels of acetylcholine (ACh). The cholinergic approach to treatment of AD involves counteracting this loss in cholinergic activity by pharmacologic intervention to increase cholinergic transmission.[1] While use of acetylcholinesterase inhibitors remains the most common approach to cholinergic therapy, an alternative approach involves inhibition of central presynaptic M_2 receptors, thus causing an increase in acetylcholine release. Successful implementation of this approach requires high selectivity for the M_2 receptor over the other four muscarinic receptor subtypes, especially the M_1 receptor that mediates the cognitive effects of acetylcholine.[2] Additionally, compounds need to have appropriate bioavailability and CNS penetration.

Previous reports from these laboratories have described a series of piperidine and piperazine derivatives which are potent muscarinic M_2 antagonists with promising selectivity versus other muscarinic receptor subtypes.[3–17] Some of these reports[3,4] have demonstrated that piperazines such as **1** and **2** show improved selectivity versus earlier compounds. In particular, compounds similar to **1** show $>100\times$ selectivity for the M_2 receptor. Key pharmacophore elements required to achieve this level of selectivity are the (*R*)-methylpiperazine moiety and the 2-substitituted benzamide. Unfortunately, the overall pharmacokinetic profile of this class of compounds is poor, resulting in low plasma levels after oral administration and low efficacy in several animal models predictive of cognitive activity. In this Letter, we describe our efforts in a piperidine series related to **1** (Fig. 1), which has yielded a compound suitable for clinical evaluation.[18,19]

2. Results and discussion

Several measures were used to evaluate progress in this program. In addition to determining activity at each of the five cloned human muscarinic receptors, in vivo activity was evaluated by measuring release of acetylcholine in conscious rats using microdialysis as previously described.[20] Activity was measured as the maximum percent increase in acetylcholine release over baseline up to three h after oral administration of drug. Although failure at several points (e.g., absorption, first-pass metabolism, brain penetration, and receptor occupancy) could result in lack of activity, we found this to be a particularly useful screen for identifying compounds with the best potential for showing activity in more detailed and time-intensive animal models of

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doi:10.1016/j.bmc.2003.11.005

cognition. In particular, compounds with good M_2 selectivity which also induced a sustained acetylcholine release of at least 150% over baseline generally showed good oral activity in the juvenile rat passive-avoidance response (PAR) model.[21] Activity in rat microdialysis generally paralleled plasma levels in an abbreviated rat pharmacokinetic screen which has previously been described.[22]

Among the variety of core structures available for this study, we focused on core **9** (Scheme 1) because it was achiral and gave us maximal flexibility for evaluating changes on either terminus of the core structure, that is, the left-hand aromatic substituent $\mathbf{R^1}$ and the piperidine substituent $\mathbf{R^2}$. From a survey of a variety of substituents on the piperidine nitrogen, including aryl and alkyl amides, sulfonamides, carbamates, and ureas, we focused primarily on a series aryl amides because they consistently provided the highest potency and selectivity for the M_2 receptor. The synthesis of the core structure and subsequent derivatization was carried out as shown in Schemes 1 and 2. Piperidine **3** was protected as its trifluoroacetamide and brominated with dibromodimethylhydantoin (DBDMH) to give primarily the 4-bromo derivative **4** after base-induced deprotection. Reductive alkylation of **4** with *N*-Boc piperidinone **5** gave **6**. This was treated with *n*-butyllithium followed by treatment with arylsulfonyl fluoride **7** to give diarylsulfone **8**. The Boc group was removed and the resulting piperidine was coupled with a carboxylic acid under standard conditions.

In an alternative synthesis (Scheme 2), methylidene piperidine **10** was treated with 9-BBN and the resulting borane was coupled with bromoarylsulfone **11** under palladium catalysis to give **12**.[23] The Boc group was removed, and the core was elaborated to target compounds using the same procedures as outlined in Scheme 1.

Initial results in the piperidine series indicated that 2-substituted benzamides provided potent muscarinic M_2 antagonists with very good selectivity versus the other muscarinic receptor subtypes (Table 1). A variety of substituents R^1 on the arylsulfone moiety were examined, but in general the structure–activity relationship trends are reflected by results where R^1 is either 4-methoxy or 3-chloro. Thus, toluamides **13** and **15** showed very good selectivity for the M_2 receptor which was further improved by addition of a chloro group at the 3-position (e.g., **14**, **16**). That this effect was primarily steric was suggested by the fact that the 2-chloro-

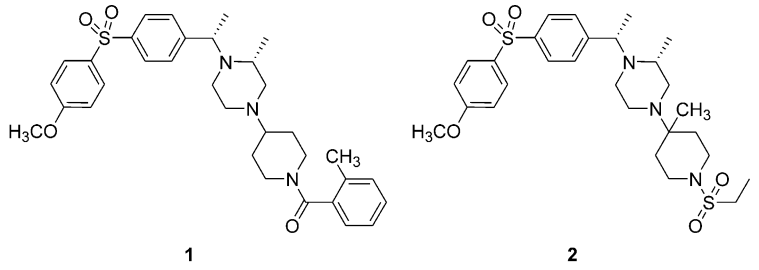
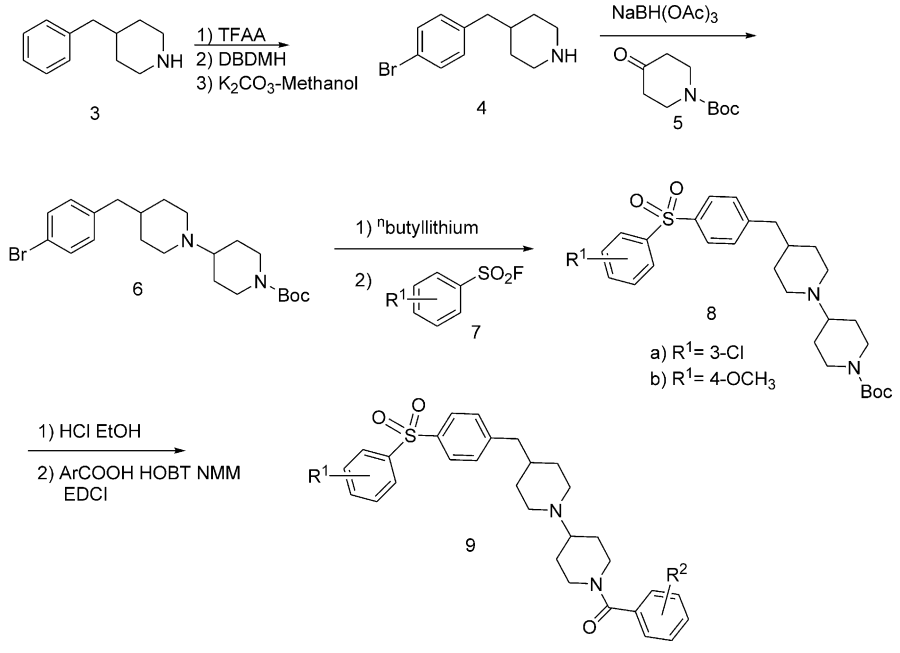
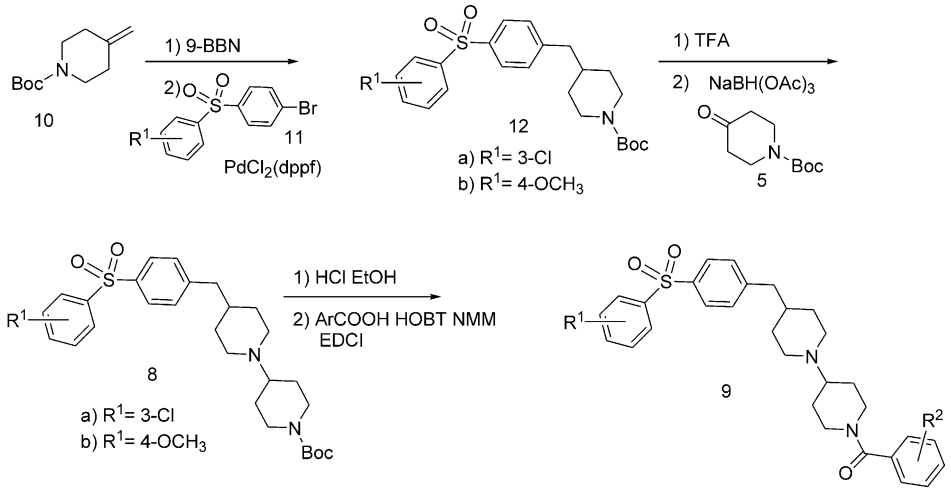


Figure 1. Piperazine M2 antagonists.

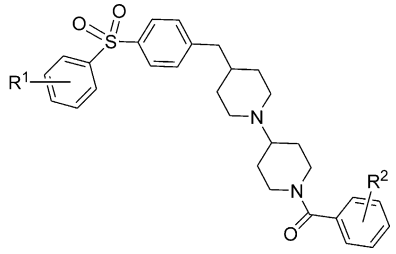


Scheme 1.



Scheme 2.

Table 1. 2-Substituted benzamides



No.	R^1	R^2	K_i (nM) M2[a]	M1/ M2	M3/ M2	M4/ M2	M5/ M2	AcCh release (%)[b]
13	4-CH_3O	2-CH_3	2.53	144	99	55	24	115
14	4-CH_3O	2-CH_3, 3-Cl	1.29	651	774	223	100	164
15	3-Cl	2-CH_3	2.7	230	172	14	48	ND
16	3-Cl	2-CH_3, 3-Cl	1.52	536	542	155	37	125
17	3-Cl	2-Cl, 3-CH_3	1.2	461	795	107	39	153
18	4-CH_3O	2-OH	17.1	70	ND	ND	ND	ND
19	4-CH_3O	2-CH_3O	4.9	141	62	7	20	ND
20	4-CH_3O	2-NH_2	2.2	414	495	42	89	137
21	3-Cl	2-NH_2	0.2	2926	2722	148	186	150

ND, not detected.

[a] Activity at the m2 receptor expressed as a K_i (nM). Selectivity versus the other receptors expressed as the ratio of the K_i (nM) at each receptor versus the K_i (nM) at the m2 receptor. All K_i values are the mean of at least two determinations.

[b] Acetylcholine release expressed as the maximum percent increase over predosing baseline.

3-methyl derivative **17** gave nearly identical potency and selectivity compared to **16**. Unfortunately, as was the case with analogous piperazines, none of these compounds showed exceptional in vivo activity as measured by the percent increase in acetylcholine release. Believing that these compounds might in fact be too lipophilic, we also examined several more polar benzamides. While initial results with 2-hydroxy and 2-methoxy derivatives **18** and **19** were not promising, we were pleasantly surprised to find that anthranilamides **20** and **21** gave very promising potency and selectivity.

Based on these promising results, we evaluated the anthranilamide class in more detail (Table 2). Unlike earlier benzamides, anthranilamides did not show significant improvement in either potency or selectivity with additional substitution at the 3-position of the anthranilamide, although potency and selectivity remained high except for 3-fluoro derivative **26**. However, the anthranilamides consistently caused a greater release of acetylcholine than other benzamides, with several compounds showing a sustained release of at least 150% of baseline. Based largely on its superior activity in microdialysis and correspondingly higher rat plasma levels, compound **23** was selected for more detailed evaluation.

Figure 2 shows the complete time course of acetylcholine release for compound **23** over a range of doses, demonstrating that **23** causes a robust and long-lasting increase in acetylcholine release. Consistent with these results, **23** improved cognition in the juvenile rat PAR model, with a maximally effective dose of 0.1 mg/kg po. Further details of these studies will be reported elsewhere.

3. Conclusions

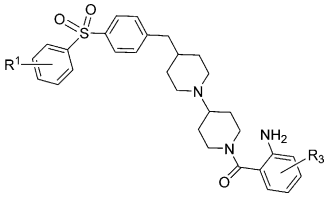
We have evaluated a series of benzamide derivatives for their potency and selectivity for the M_2 receptor versus other muscarinic receptors. Compounds have also been evaluated for their ability to increase acetylcholine release after oral administration. Simple toluamide derivatives show excellent potency and selectivity but cause only a modest increase in acetylcholine release in most cases. By contrast, anthranilamides gave both excellent in vitro activity and caused a robust increase in acetylcholine release. Compound **23** is also active in animal models of cognition. Based on these results, compound **23** was selected for clinical evaluation as a potential new treatment for Alzheimer's disease.

4. Experimental

4.1. Biology: in vitro assay using cloned human muscarinic receptors

Inhibition of muscarinic receptors was measured by displacement of tritiated QNB (l-quinuclidinyl benzilate) at

Table 2. Anthranilamides



No.	R^1	R^3	K_i (nM) M2[a]	M1/ M2	M3/ M2	M4/ M2	M5/ M2	AcCh release (%)	Rat $AUC_{0-6\ h}$ (h ng/ml)[a]
20	4-CH_3O	H	2.2	414	495	42	89	137	3484
21	3-Cl	H	0.22	2926	2722	148	186	150	4587
22	4-CH_3O	3-CH_3	2.37	456	481	67	140	130	2918
23	3-Cl	3-CH_3	0.89	734	787	69	95	180	7800
24	4-CH_3O	3-Cl	1.43	426	262	88	165	138	3349
25	3-Cl	3-Cl	0.67	1297	1650	80	65	145	4903
26	4-CH_3O	3-F	5.7	165	174	62	112	ND	ND
27	3-Cl	3-F	1.71	528	365	68	82	162	5324
28	4-CH_3O	4-F	3.5	259	285	86	89	ND	ND
29	3-Cl	4-F	2.63	350	194	54	27	128	2692
30	3-Cl	5-F	2.88	229	265	20	24	150	3750

ND, not detected.
[a] $AUC_{0-6\ h}$ after 10 mg/kg oral dose in an abbreviated rat PK protocol. See ref 22.

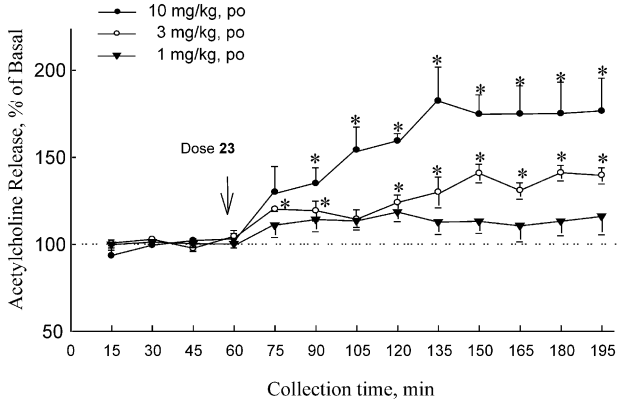


Figure 2. Effect of 23 on ACh release from striatum of conscious rat following po administration. * Significant stimulation over baseline ($p = 0.05$, Duncan's multiple range statistic).

the five cloned human receptors. For radioligand binding analysis, each muscarinic receptor subtype was stably expressed in CHO-K1 cells. Clonal cell lines were selected which expressed receptors at levels between 1 and 9 pmol/mg protein. The K_d of QNB at each receptor subtype was determined by saturation binding using 5–2500 pM [3H] QNB in 10 mM potassium phosphate buffer, pH 7.4. Protein concentrations were adjusted for each assay to achieve between 700 and 1500 cpm specific binding. Competition binding experiments were performed using 180 pM [3H] QNB. All binding experiments were performed in the presence of 1% DMSO and 0.4% methylcellulose. Nonspecific binding was determined by 0.5 mM atropine. After equilibrium was reached (120-min incubation at room temperature), bound and free radioactivity were separated by filtration using Whatman GF-C filters. K_i was expressed as mean of duplicate value (SEM < 15%). All determinations were performed at least twice. Acetylcholine release in conscious rats was measured via microdialysis as previously described. Activity is expressed as the maximum percent increase in acetylcholine versus the pre-dosing baseline.

4.2. Pharmacokinetics

Rat AUC values were determined using an abbreviated protocol as described in ref 22. All compounds were dosed orally at 30 mg/kg in 20% HPβCD. AUCs are expressed at h×ng per mL.

4.3. Chemistry

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were determined with a Gemini 300 MHz instrument using Me_4Si as an internal standard. Coupling constants are given in hertz.

4.3.1. Synthesis of intermediate 4-(4-bromo-benzyl)-[1,4′]bipiperidinyl-1′-carboxylic acid *tert*-butyl ester (6). A solution of 4-benzylpiperidine **3** (202 g, 1.15 mol) in dichloromethane (1.5 L) was treated with 216 mL (1.53 mol) of trifluoroacetic anhydride added drop-wise over 30 min. The mixture was allowed to stir an additional 90 min at room temperature, then cooled to 0 °C in an ice bath. Methanesulfonic acid (306 mL) was added in portions followed by dibromodimethylhydantoin (171 g, 0.6 mol) also added in portions, and the resulting mixture was stirred overnight while coming to room temperature. After again cooling in an ice bath, the mixture was quenched by addition of saturated Na_2SO_3 (1.6 L) added over 30 min. The aqueous layer was separated and washed with dichloromethane (2×2 L). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes (16 L), 5% ethyl acetate–hexane (16 L), and 10% ethyl acetate–hexane to yield 105 g of brominated compound, which was used directly in the next step. A solution of

the brominated compound in 1.7 L methanol was treated with 90 g potassium carbonate in 300 mL water. The mixture was stirred for 3 h, then concentrated under vacuum. The residue was treated with 2 N NaOH (2 L) and extracted with dichloromethane (2×2 L). The combined organic layers were dried over magnesium sulfate and evaporated to give 76 g of compound **4** as an oil which partially crystallized.

A suspension of compound **4** in 1 L dichloromethane was treated with 1-*tert*-butoxycarbonyl-4-piperidone **5** (64 g, 0.32 mol), glacial acetic acid (38 mL), and sodium triacetoxyborohydride (192.12 g, 0.9 mol). The mixture was allowed to stir overnight at room temperature, then poured into 2 N NaOH (2 L). After stirring an additional 30 min, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2×2 L). The combined organic layers were dried over magnesium sulfate and evaporated, and the residue was purified by flash chromatography, eluting with ethyl acetate (40 L) to give 30.2 g of compound **6**, as well as an additional 54.4 g of ~50% pure compound **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.8 (m, 7H), 1.40 (s, 9H), 2.05–2.40 (m, 2H), 2.40–2.70 (m, 7H), 2.80 (m, 2H), 4.15 (m, 2H), 7.18 (d, 2H, J = 9 Hz), 7.41 (d, 2H, J = 9 Hz).

4.3.2. Synthesis of 3-chlorophenylsulfonyl fluoride (7a). To a mixture of 3-chlorosulfonyl chloride (12 g, 0.12 mol) in 185 mL acetone was added drop-wise a solution of 17.4 g (0.24 mol) KF in 150 mL water. The mixture was stirred at room temperature overnight, then concentrated to one-half volume under vacuum. The residue was diluted with 100 mL ethyl acetate and extracted 3×30 mL ethyl acetate. The combined extracts were dried over magnesium sulfate. Toluene (5 mL) was added and the solution evaporated to give 16.64 g (72%) of a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, 1H, J = 8 Hz), 7.75 (d, 1H, J = 8 Hz), 7.96 (d, 1H, J = 8 Hz), 7.99 (s, 1H).

4.3.3. 4-Methoxyphenysulfonyl fluoride (7b). This was prepared in a similar manner from 4-methoxyphenylsulfonyl chloride.

4.3.4. Synthesis of intermediate 4-[4-(3-chloro-benzenesulfonyl) - benzyl] - [1,4′]bipiperidinyl - 1′ - carboxylic acid *tert*-butyl ester (8a). A solution of compound **6** (8.8 g, 0.02 mol) in 35 mL dry THF at −78 °C was treated with 8.05 mL (0.02 mol) of 2.5 M *n*-butyllithium in hexanes followed by a solution of 3-chlorobenzenesulfonyl fluoride (3.92 grams, 0.02 mol) in 20 mL dry THF. The mixture was stirred at −78 °C for 2 h then allowed to come to room temperature overnight. The reaction was quenched with water, concentrated under vacuum, and partitioned between ethyl acetate and 10% sodium carbonate. The organic layer was washed with water, dried over magnesium sulfate, and evaporated. The residue was purified over silica gel, eluting with 5% methanol–ethyl acetate, and the purified residue was crystallized from ethyl acetate to give 3.03 g of **8a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.53 (m, 2H), 1.35–1.55 (m, 3H), 1.55–1.68 (m, 2H), 1.70–1.90 (m, 2H), 2.00–2.20 (m, 4H), 2.30–2.45 (m, 1H), 2.50–2.65 (m, 4H), 2.80–2.95 (m, 2H), 3.08–3.20 (m, 2H), 7.21–7.30 (m, 3H), 7.40–7.55 (m, 2H), 7.81 (d, 2H, J = 8 Hz), 7.90 (s, 1).

4.3.5. 4-[4-(4-Methoxy-benzenesulfonyl)-benzyl]-[1,4′]bipiperidinyl-1′-carboxylic acid *tert*-butyl ester (8b). This was prepared in a similar manner from **6** and 4-methoxybenzenesulfonyl fluoride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.40 (m, 3H), 1.40–1.50 (m, 2H), 1.50–1.68 (m, 2H), 1.70–2.00 (m, 2H), 2.00–2.20 (m, 4H), 2.30–2.45 (m, 1H), 2.50–2.65 (m, 4H), 2.80–2.95 (m, 2H), 3.08–3.20 (m, 2H), 3.78 (s, 3H), 6.92 (d, 2H, J = 8 Hz), 7.20 (d, 2H, J = 8 Hz).

4.3.6. Alternate synthesis of intermediate 8a. To a cooled (0 °C) mixture of **12a**[17] (4.74 g; 10.5 mmol), CH_2Cl_2 (35 mL) and H_2O (0.19 mL) was added, dropwise, trifluoroacetic acid (7 mL). The cooling bath was removed and the mixture was stirred for 30 min. Trifluoroacetic acid (1.0 mL) and H_2O (0.18 mL) were added. The stirring was continued for 2 h, the volatile materials were removed in vacuo, CH_2Cl_2 (20 mL) and 10% NaOH (2 mL) was added, and the resulting mixture was stirred for 3 min. The CH_2Cl_2 layer was removed, the aqueous layer was extracted with CH_2Cl_2 (3×5 mL), the organic extracts were dried over Na_2SO_4, filtered and evaporated to give the free amine as a white foam (3.10 g) in 88% yield.

To a solution of the above amine (1.69 g), *N*-tert-butoxy piperidone **5** (4.80 g), CH_2Cl_2 (12 mL) and acetic acid (0.28 mL) was added $NaB(OAc)_3H$ (1.42 g) in four portions over 15 min. The resulting solution was stirred for 4 h when acetic acid (0.14 mL) and $NaB(OAc)_3H$ (1.42 g) were added. After stirring at room temperature for 16 h, the reaction was diluted with CH_2Cl_2 (50 mL) and made basic with 2 N NaOH (15 mL). The CH_2Cl_2 layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The organic extracts were combined, washed with water, brine and dried over $MgSO_4$, then filtered and evaporated to give a crude solid which was purified by silica gel chromatography (320 g silica; 1:1 hexanes–EtOAc then 76:19:5 EtOAc–hexanes: Et_3N as eluant) to give the product, **4**, as a waxy solid (2.27 g) in 88% yield.

4.4. General synthesis of amides 9

Compound **8** (2.6 mmol) was dissolved in 10 mL of dichloromethane was treated with 2 mL trifluoroacetic acid and 0.046 mL water for 30 min. The mixture was concentrated then partitioned between dichloromethane (20 mL) and 10% sodium hydroxide (2 mL). The aqueous layer was extracted with dichloromethane (3×5 mL), and the combined organic layers were dried over magnesium sulfate and evaporated to give the free amine.

EDCI (0.032 g, 0.21 mmol) was added to a mixture of the free amine (0.14 mmol), dimethylformamide (2 mL), hydroxobenzotriazole (0.028 g, 0.21 mmol), diisopropylethylamine (0.1 mL), and the appropriate benzoic acid (0.21 mmol). The resulting solution was stirred at room temperature overnight then partitioned between 10 mL

ethyl acetate and 1 mL 2 N sodium hydroxide. The aqueous layer was extracted with ethyl acetate (3×4 mL), and the combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by preparative silica gel thin-layer chromatography to give the desired compound as its free base.

The free base was dissolved in 2 mL ethyl acetate and treated with 50 μL of 4 M HCl in dioxane at 0 °C. The salt was precipitated by addition of ether, centrifuged, washed with ether, and dried under vacuum to give the HCl salt.

Using the above methods, the following compounds were prepared.

4.4.1. 4-[4-[(4-Methoxyphenyl)sulfonyl]phenyl]methyl]-1′-(2-methylbenzoyl)-1,4′-bipiperidine (13). HRMS calcd for $C_{32}H_{38}N_2O_4S$ 547.2631, found 547.2630.

4.4.2. 1′-(3-Chloro-2-methylbenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (14). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.2 (m, 11H), 2.25, 2.75 (two s, 3H), 2.4–2.6 (m, 3H), 2.6–2.8 (m, 1H), 2.8–2.95 (m, 3H), 3.35–3.48 (m,1H), 4.7–4.85 (m, 1H), 3.8 (s, 3H), 6.91 (d, 2H, $J=8$ Hz), 6.9–7.15 (m, 2H), 7.19 (d, 2H, $J=8$ Hz), 7.3 (d, 1H, $J=8$ Hz), 7.6 (d, 2H, $J=8$ Hz), 7.72 (d, 2H, $J=8$ Hz); HRMS calcd for $C_{32}H_{37}ClN_2O_4S$ 581.2241, found 581.2224.

4.4.3. 1′-(2-Methylbenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (15). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2–1.8 (m, 6H), 1.8–2.2 (m, 4H), 2.25 (m, 3H), 2.50 (m, 4H), 2.70 (m, 2H), 2.90 (m, 4H), 7.0–7.3 (m, 6H), 7.3–7.55 (m, 2H), 7.80 (m, 3H), 7.90 (s, 1H), HRMS calcd for $C_{31}H_{35}ClN_2O_3S$ 551.2135, found 551.2140.

4.4.4. 1′-(3-Chloro-2-methylbenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (16). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.2 (m,11H), 2.22,2.30 (two s, 3H), 2.4–2.6 (m, 3H), 2.65–2.8 (m, 1H), 2.8–3.0 (m, 3H), 3.40–3.50 (m, 1H), 4.8 (m, 1H), 6.95–7.2 (m, 2H), 7.25 (d, 2H, $J=8$ Hz), 7.3–7.5 (m, 3H), 7.77–7.82 (m, 3H), 7.9 (s, 1H);. HRMS calcd for $C_{31}H_{34}Cl_2N_2O_3S$ 585.1745, found 585.1744.

4.4.5. 1′-(2-Chloro-3-methylbenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (17). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–2.1 (m, 11H), 2.31 (s, 4H), 2.4–2.6 (m, 4H), 2.6–3.1 (m, 3H), 3.38–3.42 (m, 1H), 6.95–7.3 (m, 5H), 7.35–7.5 (m, 2H), 7.71–7.8 (m, 3H), 7.9 (s, 1H); HRMS calcd for $C_{31}H_{34}Cl_2N_2O_3S$ 585.1745, found 585.1747.

4.4.6. 1′-(2-Hydroxybenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (18). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.3 (m, 3H), 1.4–1.7 (m, 5H), 1.8–1.9 (m, 2H), 2.0–2.15 (m, 2H), 2.45–2.55 (m, 2H), 2.8–3.0 (m, 4H), 3.81 (s, 3H), 4.3–4.45 (m, 2H), 6.9–7.0 (m, 3H), 7.15–7.35 (m, 5H), 7.77 (d, 2H, $J=8$ Hz), 7.85 (d, 2H, $J=8$ Hz); HRMS calcd for $C_{31}H_{37}N_2O_5S$ 549.2423, found 549.2408.

4.4.7. 1′-(2-Methoxybenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (19). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.35 (m, 3H), 1.4–1.75 (m, 6H), 1.8–1.9 (m, 1H), 2.0–2.25 (m, 2H), 2.4–2.6 (m, 2H), 2.6–2.8 (m, 1H), 2.8–2.9 (m, 4H), 3.4–3.55 (m, 1H), 3.78 (s, 3H), 3.8 (s, 3H), 6.8–6.95 (m, 4H), 7.1–7.32 (m, 4H), 7.77 (d, 2H, $J=8$ Hz), 7.85 (d, 2H, $J=8$ Hz); HRMS calcd for $C_{32}H_{39}N_2O_5S$ 563.2579, found 563.2589.

4.4.8. 1′-(2-Aminobenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (20). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.35 (m, 2H), 1.35–1.7 (m, 4H), 1.7–1.9 (m, 3H), 2.0–2.2 (m, 3H), 2.4–2.6 (m, 4H), 2.7–3.0 (m, 4H), 3.8 (s, 3H), 4.25 (br s, 2H), 6.66 (m, 2H), 6.93 (d, 2H, $J=7$ Hz), 7.02 (d, 1H, $J=7$ Hz), 7.13 (dd, 1H, $J=7.7$ Hz), 7.22 (m, 2H), 7.79 (d, 2H, $J=7$ Hz), 7.85 (d, 2H, $J=7$ Hz); HRMS calcd for $C_{31}H_{38}N_3O_4S$ 548.2683, found 548.2700.

4.4.9. 1′-(2-Aminobenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (21). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 9H), 1.75–1.95 (m, 2H), 2.05–2.20 (m, 2H), 2.45–2.65 (m, 3H), 2.75–3.00 (m, 4H), 4.25 (br s, 2H), 6.65–6.72 (m, 2H), 7.05 (d, 1H, $J=8$ Hz), 7.15 (dd, 1H, $J=8.8$ Hz), 7.20–7.30 (m, 2H), 7.4 (dd, 1H, $J=8.8$ Hz), 7.5 (d, 1H, $J=8$ Hz), 7.78–7.81 (m, 3H), 7.9 (s, 1H); HRMS calcd for $C_{30}H_{35}ClN_3O_3S$ 552.2087, found 552.2088.

4.4.10. 1′-(2-Amino-3-methylbenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (22). Mp 150 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2–2.1 (m, 11H), 2.15 (m, 3H), 2.4–2.6 (m, 3H), 2.6–2.8 (m, 6H), 3.8 (s, 3H), 4.2 (br s, 2H), 6.6 (m, 1H), 6.9 (m, 3H), 7.05 (m, 1H), 7.2 (m, 2H), 7.78 (d, 2H, $J=7$ Hz), 7.82 (d, 2H, $J=7$ Hz); HRMS calcd for $C_{32}H_{39}N_3O_4S$ 562.2739, found 562.2734.

4.4.11. 1′-(2-Amino-3-methylbenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (23). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.90 (m, 11H), 2.05–215 (m, 2H), 2.18 (s, 3H), 2.47 (m, 1H), 2.58 (d, 2H, $J=7$ Hz), 2.80–2.95 (m, 4H), 4.28 (m, 2H), 6.66 (dd, 1H, $J=7.7$ Hz), 6.92 (d, 1H, $J=7$ Hz), 7.05 (d, 1H, $J=7$ Hz), 7.28 (m, 2H), 7.43 (dd, 1H, $J=7.7$ Hz), 7.52 (m, 1H), 7.82 (m, 3H), 7.92 (s, 1H). Anal: ($C_{31}H_{36}ClN_3O_3S{\cdot}2HCl{\cdot}H_2O$) C,H,N,S,Cl.

4.4.12. 1′-(2-Amino-3-chlorobenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (24). Mp 130 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 7H), 1.80–1.90 (m, 2H), 2.08 (m, 2H), 2.40–2.60 (m, 3H), 2.70–3.00 (m, 6H), 3.8 (s, 3H), 4.7 (s, 2H), 6.66 (dd, 1H, $J=7.7$ Hz), 6.92 (m, 3H), 7.18–7.25 (m, 3H), 7.78 (dd, 2H, $J=7$ Hz), 7.85 (dd, 2H, $J=7$ Hz); HRMS calcd for $C_{31}H_{36}ClN_3O_4S$ 582.2193, found 582.2204.

4.4.13. 1′-(2-Amino-3-chlorobenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (25). Mp 133 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 8H), 1.80–1.90 (m, 2H), 2.00–2.15 (m, 2H), 2.40–2.60 (m, 3H), 2.70–3.00 (m, 5H), 4.66 (s, 2H), 6.55–6.65 (m, 1H), 6.90–6.98 (m, 1H), 7.20–7.30 (m, 3H), 7.36–7.55 (m,

2H), 7.80–7.85 (m, 3H), 7.9 (s, 1H); HRMS calcd for $C_{30}H_{33}Cl_2N_3O_3S$ 586.1698, found 586.1698.

4.4.14. 1′-(2-Amino-3-fluorobenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (26). Mp 136 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 7H), 1.80–1.95 (m, 2H), 2.05–2.20 (m, 2H), 2.45–2.55 (m, 3H), 2.75–3.00 (m, 6H), 3.81 (s, 3H), 4.35 (s, 2H), 6.55–6.65 (m, 1H), 6.80–6.85 (m, 1H), 6.90–7.00 (m, 3H), 7.18–7.25 (m, 2H), 7.75 (d, 2H, $J=8$ Hz), 7.85 (d, 2H, $J=8$ Hz); HRMS calcd for $C_{31}H_{36}FN_3O_4S$ 566.2489, found 566.249.

4.4.15. 1′-(2-Amino-3-fluorobenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (27). Mp 138 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 11H), 1.80–2.20 (m, 3H), 2.40–2.60 (m, 3H), 2.70–3.10 (m, 3H), 4.35 (s, 2H), 6.60–6.68 (m, 1H), 6.85 (d, 1H, $J=8$ Hz), 6.95 (dd, 1H, $J=8.8$ Hz), 7.25 (d, 2H, $J=8$ Hz), 7.48 (d, 1H, $J=8$ Hz), 7.55 (d, 1H, $J=8$ Hz), 7.81–7.88 (m, 3H), 7.9 (s, 1H); HRMS calcd for $C_{30}H_{33}ClFN_3O_3S$ 570.1993, found 570.199.

4.4.16. 1′-(2-Amino-4-fluorobenzoyl)-4-[4-[(4-methoxyphenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (28). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.65 (m, 8H), 1.80–1.90 (m, 2H), 2.00–2.20 (m, 2H), 2.40–2.60 (m, 3H), 2.70–3.00 (m, 5H), 3.8 (s, 3H), 4.45 (s, 2H), 6.30–6.40 (m, 2H), 6.91 (d, 2H, $J=8$ Hz), 6.90–7.05 (m, 1H), 7.15–7.25 (m, 2H), 7.78 (d, 2H, $J=8$ Hz), 7.82 (d, 2H, $J=8$ Hz); HRMS calcd for $C_{31}H_{36}FN_3O_4S$ 566.2489, found 566.2499.

4.4.17. 1′-(2-Amino-4-fluorobenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (29). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 8H), 1.75–1.90 (m, 2H), 2.00–2.20 (m, 2H), 2.40–2.60 (m,3H), 2.70–3.00 (m, 5H), 4.5 (s, 2H), 6.30–6.40 (m, 2H), 6.95–7.05 (m, 1H), 7.25 (d, 2H, $J=8$ Hz), 7.40–7.55 (m, 2H), 7.75–7.82 (m, 3H), 7.9 (m, 1H); HRMS calcd for $C_{30}H_{33}ClFN_3O_3S$ 570.1993, found 570.1997.

4.4.18. 1′-(2-Amino-5-fluorobenzoyl)-4-[4-[(3-chlorophenyl)sulfonyl]phenyl]methyl]-1,4′-bipiperidine (30). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.70 (m, 8H), 1.70–1.95 (m, 2H), 2.00–2.20 (m, 2H), 2.40–2.60 (m, 3H), 2.70–3.00 (m, 5H), 4.5 (s, 2H), 6.60–6.70 (m, 1H), 6.70–6.80 (m, 1H), 6.80–6.90 (m, 1H), 7.25 (d, 2H, $J=8$ Hz), 7.40–7.60 (m, 2H), 7.77–7.88 (m, 3H), 7.9 (m, 1H); HRMS calcd for $C_{30}H_{33}ClFN_3O_3S$ 570.1993, found 570.1997.

Acknowledgements

We are grateful for the help and support of Drs. A. K. Ganguly and Catherine D. Strader throughout all phases of this project.

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