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CCR5 antagonists as anti-HIV-1 agents. Part 3: Synthesis and biological evaluation of piperidine-4-carboxamide derivatives

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Abstract—Replacement of the 5-oxopyrrolidin-3-yl fragment in the previously reported lead structure with a 1-acetylpiperidin-4-yl group led to the discovery of a novel series of potent CCR5 antagonists. Introduction of small hydrophobic substituents on the central phenyl ring increased the binding affinity, providing low to sub-nanomolar CCR5 antagonists. The selected compound **11f** showed excellent antiviral activity against CCR5-using HIV-1 replication in human peripheral blood mononuclear cells (EC_{50} = 0.59 nM) and an acceptable pharmacokinetic profile in dogs.

1. Introduction

Despite efforts to prevent the spread of human immunodeficiency virus type 1 (HIV-1), the worldwide population of HIV-1-infected patients is still increasing.[1] Although highly active antiretroviral therapy (HAART) has been successful in reducing HIV-1-associated mortality and morbidity, there remain difficulties with the currently available HAART including the development of viral resistance as well as the toxicity and complexity of the drug regimens.[2] Thus it is strongly desired to develop new anti-HIV-1 agents with superior efficacy and safety profiles.

The discovery of chemokine receptors as major HIV-1 co-receptors has provided a greater understanding of how HIV-1 enters human cells and has led to a novel approach for controlling HIV-1 infection.[3] HIV-1 strains that cause the initial infection predominantly utilize CC chemokine receptor 5 (CCR5),[4] and the CCR5-using (R5) HIV-1 is isolated exclusively during the asymptomatic stage of the infection, which usually persists 5–10 years.[5] CCR5 belongs to the seven-transmembrane G protein-coupled receptor superfamily, and its natural ligands include the CC chemokines [regulated on activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, and MIP-1β], which have been reported to inhibit R5 HIV-1 infection in vitro.[6] A 32-base pair deletion in the CCR5 gene (CCR5Δ32) generates a nonfunctional receptor, and the CCR5Δ32-homozygous individuals are highly resistant to HIV-1 infection, while this defect does not represent a significant health problem.[7–9] In addition, infected individuals heterozygous for the defective CCR5 gene appear to have delayed disease progression.[10] These observations suggest that CCR5 antagonists functioning as HIV-1 entry inhibitors could be promising anti-HIV-1 therapeutic agents.[11]

We recently described the details of structure–activity relationships (SAR) developed for newly discovered 5-oxopyrrolidine-3-carboxamide CCR5 antagonists (**1**, Fig. 1).[12] In an effort to further improve potency, we introduced various acyl groups as a replacement for the 5-oxopyrrolidine-3-carbonyl group in the original lead structure. These efforts identified several promising series of CCR5 antagonists including

Keywords: CCR5 antagonist; Chemokine; HIV-1; Piperidine-4-carboxamide.
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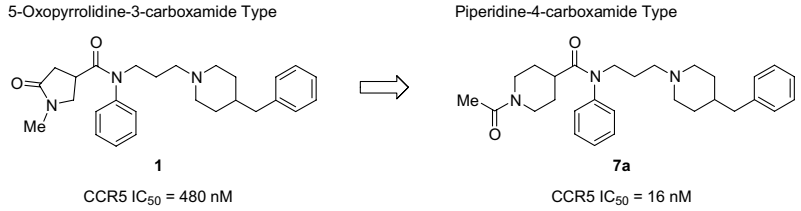


Figure 1.

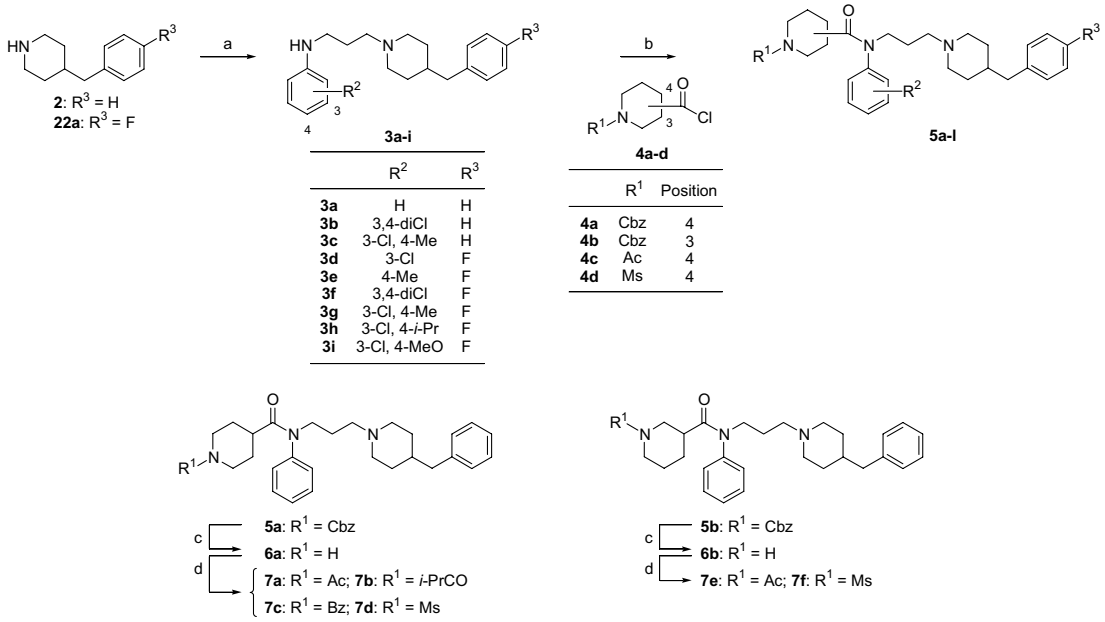
N,*N*′-diphenylureas[13] and piperidine-4-carboxamides (**7a**). In this paper, we describe the synthesis and SAR of the piperidine-4-carboxamide derivatives, which have led to a new class of potent CCR5 antagonists.

2. Chemistry

Target compounds were synthesized by two different routes as outlined in Schemes 1 and 2. The first route (Scheme 1) was used for the investigation of the acyl and central phenyl moiety. Treatment of 4-benzylpiperidines **2** and **22a** with acrolein in tetrahydrofuran (THF) in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided β-aminoaldehydes in situ,[14] which were transformed into the anilines **3a**–**i** by reductive amination with the corresponding anilines using sodium triacetoxyborohydride. Acylation of the anilines **3a**–**i** with the acid chlorides **4a**–**d** furnished the target compounds **5a**–**l**. The benzyloxycarbonyl (Cbz) group of **5a**,**b** was removed by hydrogenolysis to give the amines **6a**,**b**, which were converted to the amides **7a**–**c**,**e** or sulfonamides **7d**,**f** by reaction with the corresponding acyl chlorides or methanesulfonyl chloride, respectively.

To explore substitution on the phenyl ring of the 4-benzylpiperidine moiety, as well as to access the compound with a four-carbon chain, we employed an alternative route which utilized the chlorides **10a**,**b** as key intermediates (Scheme 2). Treatment of 3,4-dichloroaniline (**8**) with acetic formic anhydride gave *N*-(3,4-dichlorophenyl)formamide.[15] Subsequent *N*-alkylation with bromochloroalkane in the presence of cesium carbonate followed by removal of the formyl group under acidic conditions afforded the *N*-(ω-chloroalkyl)anilines **9a**,**b**. Acylation of **9a**,**b** with the acid chlorides **4d**,**c** gave the chlorides **10a**,**b**, which were reacted with R^3-substituted 4-benzylpiperidines in the presence of potassium iodide and potassium carbonate in acetonitrile to afford the target compounds **11a**–**l** and **12**. The nitro group in compound **11b** was reduced with tin(II) chloride dihydrate affording the amine **13**, which was treated with acetyl chloride or methanesulfonyl chloride to give **14a** or **14b**, respectively.

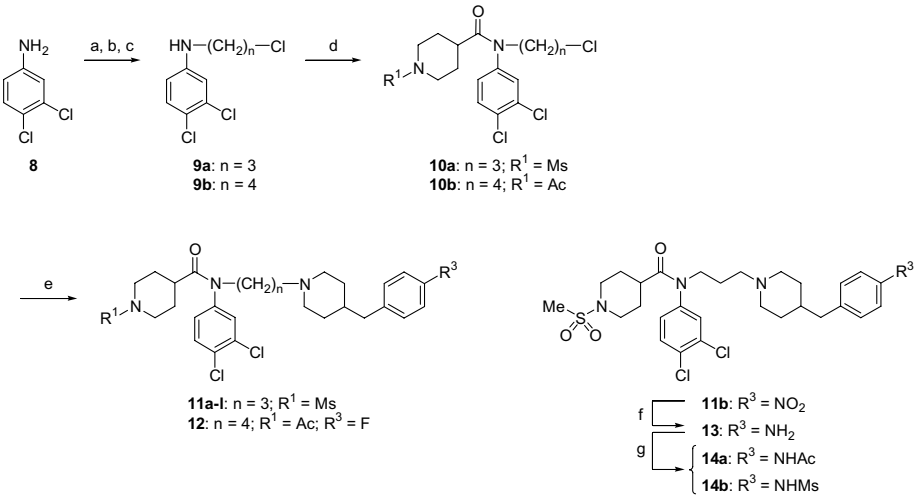
In order to synthesize the compound with a two-carbon chain, 3,4-dichloroaniline (**8**) was reacted with chloroacetic anhydride to give the chloride **15** (Scheme 3). *N*-Alkylation of 4-(4-fluorobenzyl)piperidine (**22a**) with **15** yielded compound **16**. The amide group of **16** was



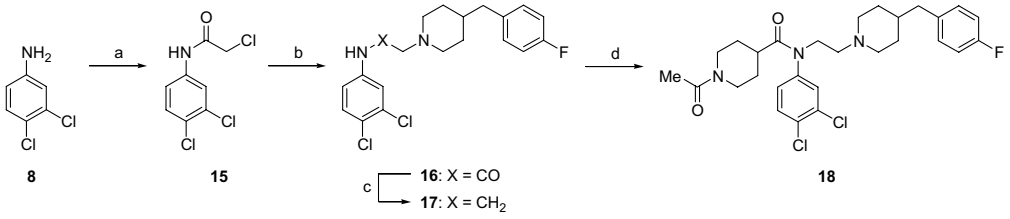
	R^2	R^3
3a	H	H
3b	3,4-diCl	H
3c	3-Cl, 4-Me	H
3d	3-Cl	F
3e	4-Me	F
3f	3,4-diCl	F
3g	3-Cl, 4-Me	F
3h	3-Cl, 4-*i*-Pr	F
3i	3-Cl, 4-MeO	F

	R^1	Position
4a	Cbz	4
4b	Cbz	3
4c	Ac	4
4d	Ms	4

Scheme 1. Reagents: (a) acrolein, cat. DBU, THF, then R^2-$PhNH_2$, $NaBH(OAc)_3$; (b) **4a**–**d**, Et_3N, DCM; (c) H_2, Pd/C, MeOH; (d) R^1-Cl, Et_3N, THF.



Scheme 2. Reagents: (a) HCO_2Ac; (b) $Br(CH_2)_nCl$, Cs_2CO_3, acetone; (c) concd HCl, *i*-PrOH; (d) **4d** or **4c**, Et_3N, DCM; (e) 4-(R^3-benzyl)piperidine, KI, K_2CO_3, MeCN; (f) $SnCl_2{\cdot}2H_2O$, EtOH; (g) AcCl or MsCl, Et_3N, THF.



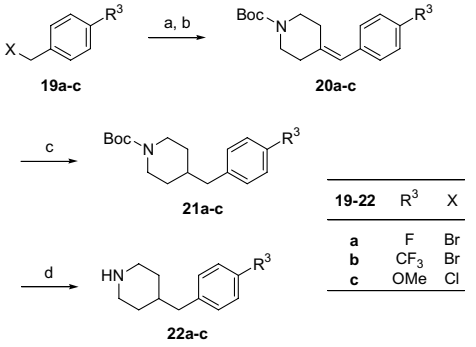
Scheme 3. Reagents: (a) $(ClCH_2CO)_2O$, THF; (b) **22a**, K_2CO_3, DMF; (c) $BH_3{\cdot}Me_2S$, THF; (d) **4c**, Et_3N, DCM.

reduced with borane–methyl sulfide to give the aniline **17**, and subsequent coupling reaction with **4c** furnished the target compound **18**.

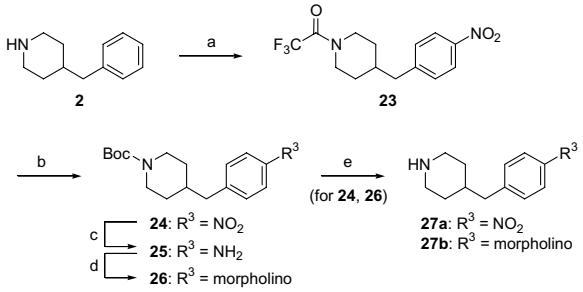
The required 4-benzylpiperidines were synthesized as shown in Schemes 4–7. The preparation of the 4-benzylpiperidines **22a**–**c** was based on the Wittig reaction (Scheme 4). Arbuzov reaction of commercially available benzyl halides **19a**–**c** with triethyl phosphite gave the corresponding phosphonates. Treatment of the phosphonates with sodium hydride followed by addition of *tert*-butyl 4-oxopiperidine-1-carboxylate formed the olefins **20a**–**c**. Hydrogenation of compounds **20a**–**c** followed by removal of the *tert*-butoxycarbonyl (Boc) group gave the 4-benzyl piperidine **22a**–**c**.

The nitro (**27a**) and morpholino (**27b**) analogues were prepared from compound **23**, which was described in the patent literature (Scheme 5).[16] Replacement of the trifluoroacetyl group of **23** with a Boc group followed by reduction of the nitro group gave compound **25**. Heating of **25** with bis(2-chloroethyl) ether resulted in the formation of a morpholine ring (**26**). Deprotection of the compounds **24** and **26** afforded the 4-benzylpiperidines **27a** and **27b**, respectively.

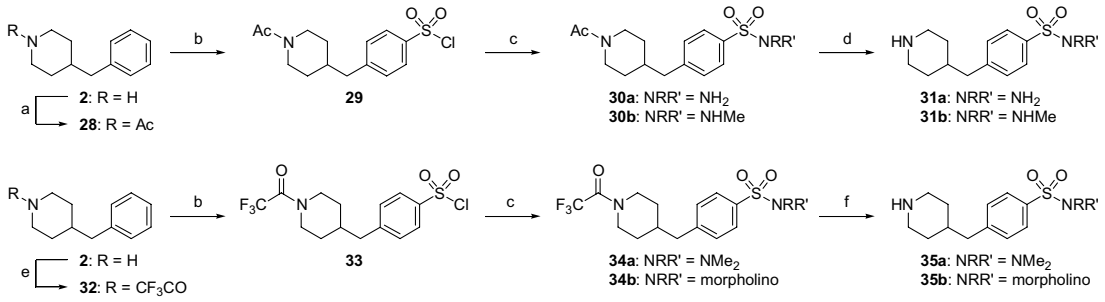
The synthesis of sulfonamide derivatives **31a**,**b** and **35a**,**b** is presented in Scheme 6. The amino group of **2** was



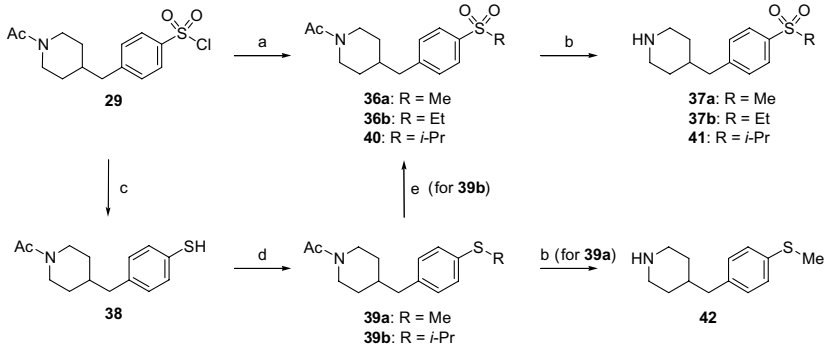
Scheme 4. Reagents: (a) $(EtO)_3P$; (b) 1-Boc-4-piperidone, NaH, THF; (c) H_2, Pd/C, MeOH; (d) HCl, EtOAc.



Scheme 5. Reagents: (a) TFAA, then KNO_3, TFA; (b) aq NaOH, EtOH, then Boc_2O; (c) $NH_2NH_2{\cdot}H_2O$, $FeCl_3$, activated C, THF; (d) $(ClCH_2CH_2)_2O$, KI, K_2CO_3, DMF; (e) HCl, EtOAc.



Scheme 6. Reagents: (a) Ac_2O; (b) $ClSO_3H$, DCM; (c) HNRR′, (Et_3N), THF; (d) concd HCl; (e) TFAA; (f) K_2CO_3, H_2O, MeOH.



Scheme 7. Reagents: (a) Na_2SO_3, $NaHCO_3$, H_2O, then $ClCH_2CO_2H$ or $CH_3CH(Br)CO_2H$, aq NaOH; (b) concd HCl, then aq NaOH; (c) Zn, H_2SO_4; (d) RI, K_2CO_3, DMF; (e) *m*CPBA, DCM.

protected by acetylation affording **28**, which was treated with chlorosulfonic acid to give the sulfonyl chloride **29**. Treatment of **29** with ammonia or methylamine provided the sulfonamides **30a**,**b**, which on deprotection by heating in concentrated hydrochloric acid yielded the piperidines **31a**,**b**. In the case of *N*,*N*-disubstituted sulfonamides **35a**,**b**, this procedure suffered from the concomitant cleavage of the sulfonamide bond, thus a trifluoroacetyl group was alternatively used for amino protection.

Reaction of **2** with trifluoroacetic anhydride followed by chlorosulfonylation gave the sulfonyl chloride **33**. Treatment of **33** with dimethylamine or morpholine afforded the sulfonamide **34a**,**b**, which on deprotection using potassium carbonate yielded the piperidines **35a**,**b**.

The sulfones **37a**,**b**, **41**, and sulfide **42** were synthesized as shown in Scheme 7. Conversion of the sulfonyl chloride **29** into the sulfones **36a**,**b** was accomplished by the literature method.[17] Deprotection of the acetyl group in **36a**,**b** using concentrated hydrochloric acid followed by neutralization provided the desired piperidines **37a**,**b**. The isopropyl sulfone analogue **41** was prepared in a different manner as follows. Reduction of **29** with zinc in aqueous sulfuric acid gave the thiol **38**, which was *S*-alkylated with 2-iodopropane yielding the sulfide **39b**. Oxidation of **39b** with 3-chloroperoxybenzoic acid (*m*CPBA) followed by deprotection afforded the requisite piperidine **41**. The methyl sulfide **42** was prepared by *S*-methylation of **38** followed by deprotection.

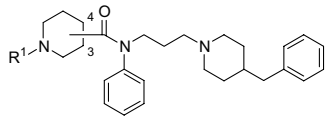
3. Results and discussion

The synthesized compounds were evaluated for their potency to inhibit the binding of ^{125}I-labeled RANTES to Chinese hamster ovary (CHO) cells expressing human CCR5, and the results are reported as IC_{50} values.

We have recently identified the 5-oxopyrrolidine-3-carboxamide derivatives as novel CCR5 antagonists (**1**, Fig. 1).[12] Our previous study demonstrated that the 5-oxopyrrolidine-3-carbonyl group was critical for CCR5 binding affinity, implying that the amide moiety of the γ-lactam plays an important role in interaction with CCR5. We hypothesized that the preferred orientation of the amide group would provide more potent CCR5 antagonists. We therefore designed and introduced a 1-acetylpiperidine group as a replacement for the 5-oxopyrrolidine in the lead structure.

Replacement of the 5-oxopyrrolidin-3-yl group in compound **1** (IC_{50} = 480 nM) with a 1-acetylpiperidin-4-yl group afforded compound **7a** (IC_{50} = 16 nM) with significant improvement in CCR5 binding affinity (Table 1). The marked enhancement in the binding affinity of compound **7a** encouraged us to further explore the SAR of this class. Removal of the acetyl group in **7a** to provide compound **6a** resulted in a substantial reduction of binding affinity, indicating that the amide carbonyl group is critical for binding affinity. Replacement of the acetyl group in **7a** with an isobutyryl (**7b**, IC_{50} = 39 nM) or benzoyl (**7c**, IC_{50} = 33 nM) group resulted in a slight loss of potency relative to **7a**, while

Table 1. Modification of the acyl moiety



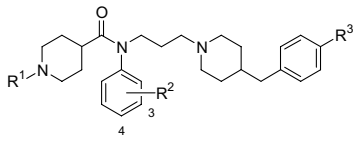
Compound	R^1	Position	CCR5[a] IC_{50} (nM)
1			480
5a	Cbz	4	48
6a	H	4	4300
7a	Ac	4	16
7b	*i*-PrCO	4	39
7c	Bz	4	33
7d	Ms	4	40
5b	Cbz	3	1200
6b	H	3	780
7e	Ac	3	680
7f	Ms	3	180

[a] Inhibition of ^{125}I-labeled RANTES binding to CCR5-expressing CHO cells.

maintaining improved affinity over the 5-oxopyrrolidine-3-carboxamide derivative **1**. It seems that the 1-position of the piperidine ring is sterically less restricted. Interestingly, methylsulfonyl analogue **7d** (IC_{50} = 40nM) also had improved potency, suggesting that the 1-position of the piperidine ring prefers a wide range of polar substituents. Indeed, carbamate **5a** (IC_{50} = 48 nM) had comparable potency to the amide analogue **7c**. Compounds having a 1-acylpiperidin-3-yl group, on the other hand, had no advantage in CCR5 binding affinity (**5b**, **7e**,**f**). This indicates that the appropriate orientation of the polar moiety is required for high binding potency.

Having identified the 1-acylpiperidin-4-yl group as critical for potent CCR5 binding affinity, we then searched for the optimal substituent of the central phenyl ring (Table 2, R^2). Introduction of a chlorine atom at the 3-position of the phenyl ring of **7a** resulted in a 5-fold improvement in the binding potency (**5c**, IC_{50} = 3.0 nM). The additional incorporation of a chlorine atom at the 4-position of the phenyl ring of **5c** afforded **5f** (IC_{50} = 1.2 nM), which was 10-fold more potent than **7a**. The 4-methyl substituted derivative **5d** (IC_{50} = 2.8 nM) also showed enhanced activity comparable to the 3-chlorinated compound **5c**. These observations were similar to those seen for the central phenyl ring of the 5-oxopyrrolidine-3-carboxamide derivatives.[12] Combination of 3-chloro and 4-methyl substituents provided **5g** and **5h**, which exhibited a dramatic improvement in CCR5 binding potency relative to **7a**. In particular, compound **5h** showed binding affinity with an IC_{50} of 0.29 nM and was one of the most potent CCR5 binding ligands in this study. Replacement of the methyl group of **5h** with a bulky isopropyl (**5i**) or polar methoxy (**5j**) group resulted in a moderate loss of binding affinity, indicating that the central phenyl group may interact with a sterically restricted and hydrophobic pocket of the receptor. A similar trend was also observed for a series of methylsulfonyl analogues (Table 2, R^1 = Ms). The 3,4-dichloro derivative **5k** had an IC_{50} of 3.3 nM for the binding affinity, while compound **5l**, with the 3-chloro-4-methyl group, showed a higher affinity with an IC_{50} of 0.50 nM. The presence of a fluorine substituent in the 4-benzylpiperidine moiety (R^3 = F) had a slightly better effect on binding affinity (**5e** vs **5f**, **5g** vs **5h**).

Table 2. Substitution on the central phenyl ring



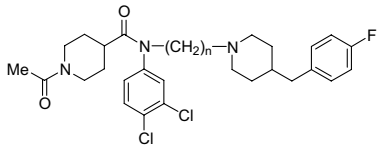
Compound	R^1	R^2	R^3	CCR5[a] IC_{50} (nM)	Fusion[b] IC_{50} (nM)
7a	Ac	H	H	16	72
5c	Ac	3-Cl	F	3.0	6.1
5d	Ac	4-Me	F	2.8	6.8
5e	Ac	3,4-diCl	H	1.9	4.2
5f	Ac	3,4-diCl	F	1.2	3.0
5g	Ac	3-Cl, 4-Me	H	0.62	0.73
5h	Ac	3-Cl, 4-Me	F	0.29	0.23
5i	Ac	3-Cl, 4-*i*-Pr	F	18	22
5j	Ac	3-Cl, 4-MeO	F	30	31
5k	Ms	3,4-diCl	F	3.3	2.3
5l	Ms	3-Cl, 4-Me	F	0.50	0.47

[a] Inhibition of ^{125}I-labeled RANTES binding to CCR5-expressing CHO cells.
[b] Inhibition of HIV-1 envelope-mediated membrane fusion.

With the potent compounds in hand, we examined the alkyl linker length to confirm that it was still optimal in the newly identified piperidine-4-carboxamide series (Table 3). It has been demonstrated that a three-carbon linker was optimal for CCR5 binding in the 5-oxopyrrolidine-3-carboxamide series.[12] As shown in Table 3, a compound with a three-carbon chain (**5f**) again showed the best activity in the piperidine-4-carboxamide series. Increasing (**12**) or decreasing (**18**) the alkyl chain length led to decreased potency.

We next turned our attention to the substitution on the phenyl ring of the 4-benzylpiperidine moiety. As shown in Table 4, a variety of functional groups were allowed at the 4-position of the phenyl ring. Introduction of a trifluoromethyl group (**11a**) resulted in a 2-fold decrease in CCR5 binding potency compared to the

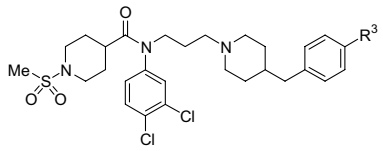
Table 3. Modification of the alkyl linker length



Compound	*n*	CCR5[a] IC_{50} (nM)
5f	3	1.2
12	4	52
18	2	480

[a] Inhibition of ^{125}I-labeled RANTES binding to CCR5-expressing CHO cells.

Table 4. Substitution on the phenyl ring of the 4-benzylpiperidine moiety



Compound	R^3	CCR5[a] IC_{50} (nM)	Fusion[b] IC_{50} (nM)
5k	F	3.3	2.1
11a	CF_3	8.7	NT
11b	NO_2	2.4	NT
13	NH_2	9.2	NT
14a	NHAc	5.9	NT
14b	NHMs	2.2	0.15
11c	Morpholino	2.8	1.8
11d	OMe	7.9	4.3
11e	SMe	3.1	2.3
11f	SO_2Me	2.2	0.80
11g	SO_2Et	1.9	NT
11h	SO_2i-Pr	1.5	0.60
11i	SO_2NH_2	3.4	1.4
11j	SO_2NHMe	1.5	0.33
11k	SO_2NMe_2	1.2	0.25
11l	SO_2 (morpholino)	1.3	0.045

[a] Inhibition of ^{125}I-labeled RANTES binding to CCR5-expressing CHO cells.
[b] Inhibition of HIV-1 envelope-mediated membrane fusion.

fluoro analogue **5k** (IC_{50} = 3.3 nM), while the nitro compound **11b** retained activity (IC_{50} = 2.4 nM), suggesting that polar substituents were preferable at this position. Reduction of the nitro group in **11b** provided the amino derivative **13**, which showed lower potency than **11b**, but the methylsulfonylamino (**14b**, IC_{50} = 2.2 nM) and morpholino (**11c**, IC_{50} = 2.8 nM) compounds restored binding potency comparable to that of **11b**. Substitution with an electron-donating methoxy group (**11d**) slightly decreased the activity, whereas a methylsulfanyl group (**11e**) was found to be well tolerated (IC_{50} = 3.1 nM). The alkylsulfonyl (**11f–h**) and aminosulfonyl (**11i–l**) derivatives also exhibited good activity, in which the larger groups had a better effect on the activity (**11h**,**k**,**l**).

Selected compounds were further tested in an HIV-1 envelope-mediated membrane fusion assay to assess the activities for inhibition of HIV-1 cell entry. The membrane fusion assay was performed using R5 HIV-1 (JR-FL strain) envelope-expressing COS-7 cells and CCR5-expressing MOLT-4 cells, and the results are reported as IC_{50} values. The results for the effect of the central phenyl substitution are presented in Table 2, showing that the inhibitory activity of the membrane fusion roughly correlated with the CCR5 binding affinity. The most potent compound **5g**, **5h**, and **5l**, containing the 3-chloro-4-methyl substitution pattern on the central phenyl ring, inhibited the membrane fusion with IC_{50} values of 0.73, 0.23, and 0.47 nM, respectively. 3,4-Dichloro analogues **5e**, **5f**, and **5k** also exhibited good inhibitory activity (IC_{50} = 4.2, 3.0, and 2.3 nM). Interesting results were obtained in the exploration of the 4-benzylpiperidine moiety, where the inhibitory activity of the membrane fusion was more potent than expected from the CCR5 binding potency (Table 4). The methylsulfonyl derivative **11f** inhibited the membrane fusion with an IC_{50} of 0.80 nM, which was lower than that of the methylsulfanyl compound **11e** (IC_{50} = 2.3 nM). The methylsulfonylamino (**14b**), isopropylsulfonyl (**11h**), and aminosulfonyl (**11j–l**) derivatives also inhibited the membrane fusion at sub-nanomolar concentrations. In particular, the morpholinosulfonyl derivative **11l** showed the inhibitory activity with an IC_{50} of 0.045 nM. These results suggest that polar substituents on the phenyl ring of the 4-benzylpiperidine moiety can interfere effectively with the HIV-1 cell entry.

Finally, we selected compound **11f** for further profiling. Compound **11f** was tested against a panel of other chemokine receptors and found to be selective for CCR5. It did not inhibit ligand binding to CHO cells expressing CCR1, CCR2, CCR3, CCR4, or CCR7 even at a concentration of 10 μM. Compound **11f** inhibited the replication of R5 HIV-1 (Ba-L strain) in human peripheral blood mononuclear cells (PBMC) with an EC_{50} value of 0.59 nM. No cytotoxicity of **11f** against human PBMC was observed even at a concentration of 20 μM, indicating that the selectivity index of **11f** is >34,000. Preliminary pharmacokinetic parameters for **11f** were measured in beagle dogs. After oral administration (10 mg/kg), the peak plasma concentration (C_{max}) was 0.57 μg/mL at 4.0 h. The area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0-24\,h}$) was 8.06 μg·h/mL.

4. Conclusion

A novel series of potent CCR5 antagonists, piperidine-4-carboxamides, was designed and synthesized. Replacement of the 5-oxopyrrolidin-3-yl fragment in the original lead structure (**1**) with a 1-acetylpiperidin-4-yl group afforded the compound **7a**, which had 30-fold enhanced activity in CCR5 binding. The acetyl group needed to be in the appropriate position for potent binding and could be replaced with other polar groups such as methylsulfonyl. Substitutions (3,4-diCl, 3-Cl, 4-Me) on the central phenyl ring led to the potent CCR5 antagonists (**5e–h**,**k**,**l**) with low to sub-nanomolar activity. Compound **11f** was found to be a potent and orally bioavailable CCR5 antagonist, and inhibited the replication of R5 HIV-1 in PBMC with an EC_{50} of 0.59 nM. Further development of this series will be reported in the near future.

5. Experimental

Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out on silica gel (Daiso, IR-60-40/63-W) or basic alumina (ICN Biomedicals, activity III). Yields were not optimized. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 or Mercury 300

spectrometer. Chemical shifts (δ) are given in ppm with tetramethylsilane (organic solvents) or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (D_2O) as an internal standard, and coupling constants (J) are given in hertz (Hz). Elemental analyses were carried out at Takeda Analytical Research Laboratories, Ltd. Mass spectra were obtained using a Platform II mass spectrometer (APCI).

5.1. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]aniline dihydrochloride (3a)

To a stirred solution of 4-benzylpiperidine (**2**) (52.6 g, 0.30 mol) and DBU (0.45 mL, 3.0 mmol) in THF (600 mL) was added dropwise a solution of acrolein (90%, 18.7 g, 0.30 mol) in THF (60 mL) at −20 °C, and the mixture was stirred for 1 h maintaining a temperature of −20 to −10 °C. To the mixture was added aniline (27.9 g, 0.30 mol) followed by $NaBH(OAc)_3$ (127.2 g, 0.60 mol) at −10 °C, and the mixture was stirred for 19 h allowing to warm to room temperature. The mixture was diluted with 2 N NaOH (900 mL) under ice cooling, stirred for 30 min, and extracted with Et_2O (400 mL, 2 × 200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue dissolved in *i*-PrOH (400 mL) was treated with 4 N HCl (EtOAc solution, 200 mL) under stirring. The resulting precipitate was collected by filtration, washed with *i*-PrOH (3 × 100 mL), and dried in vacuo to afford **3a** (75.7 g, 66%) as a white solid, mp 215–217 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.40–1.90 (5H, m), 2.00–2.25 (2H, m), 2.45–2.60 (2H, m), 2.83 (2H, br t, J = 11.4 Hz), 3.12 (2H, br t, J = 7.2 Hz), 3.29 (2H, br t, J = 6.9 Hz), 3.41 (2H, br d, J = 12.6 Hz), 7.05–7.50 (10H, m). Anal. Calcd for $C_{21}H_{28}N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 64.61; H, 8.00; N, 7.18. Found: C, 64.71; H, 7.92; N, 7.32. ^{1}H NMR (free base, $CDCl_3$): δ 1.05–1.85 (9H, m), 2.34 (2H, t, J = 6.8 Hz), 2.46 (2H, d, J = 6.6 Hz), 2.83 (2H, br d, J = 11.8 Hz), 3.06 (2H, t, J = 6.4 Hz), 6.45–6.65 (3H, m), 7.00–7.25 (7H, m).

The following compounds **3b–i** were prepared using a procedure similar to that described for **3a** from **2**, **22a** and the appropriate aniline.

5.2. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3,4-dichloroaniline dihydrochloride (3b)

Yield 53%, mp 200–203 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.49–1.76 (5H, m), 1.91–1.96 (2H, m), 2.50–2.55 (2H, m), 2.79–3.17 (6H, m), 3.38–3.44 (2H, m), 6.68 (1H, dd, J = 2.8, 8.8 Hz), 6.75 (1H, d, J = 2.6 Hz), 7.17–7.30 (6H, m). Anal. Calcd for $C_{21}H_{26}Cl_2N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 54.92; H, 6.36; N, 6.10. Found: C, 55.11; H, 6.64; N, 6.37.

5.3. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-chloro-4-methylaniline dihydrochloride (3c)

Yield 70%, mp 195–200 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.40–2.15 (7H, m), 2.21 (3H, s), 2.45–2.60 (2H, m), 2.60–2.95 (2H, m), 2.95–3.30 (2H, m), 3.15 (2H, t, J = 7.0 Hz), 3.41 (2H, br d, J = 11.0 Hz), 6.77 (1H, d, J = 7.6 Hz), 6.93 (1H, s), 7.10–7.40 (6H, m). Anal. Calcd for $C_{22}H_{29}ClN_2 \cdot 2HCl \cdot 0.8H_2O$: C, 59.48; H, 7.40; N, 6.31. Found: C, 59.41; H, 7.41; N, 6.31.

5.4. 3-Chloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}aniline dihydrochloride (3d)

Yield 59%, mp 202–208 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.35–2.05 (7H, m), 2.45–2.60 (2H, m), 2.60–2.95 (2H, m), 2.95–3.30 (2H, m), 3.09 (2H, t, J = 6.6 Hz), 3.41 (2H, br d, J = 12.0 Hz), 6.50–6.70 (3H, m), 7.00–7.30 (5H, m). Anal. Calcd for $C_{21}H_{26}ClFN_2 \cdot 2HCl \cdot 0.9H_2O$: C, 56.05; H, 6.67; N, 6.22. Found: C, 56.09; H, 6.62; N, 6.27.

5.5. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-4-methylaniline dihydrochloride (3e)

Yield 61%, mp 206–208 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.40–1.90 (5H, m), 2.00–2.25 (2H, m), 2.30 (3H, s), 2.45–2.60 (2H, m), 2.83 (2H, m), 3.12 (2H, m), 3.29 (2H, m), 3.41 (2H, m), 7.05–7.40 (8H, m). Anal. Calcd for $C_{22}H_{29}FN_2 \cdot 2HCl$: C, 63.92; H, 7.56; N, 6.78. Found: C, 63.82; H, 7.52; N, 6.65.

5.6. 3,4-Dichloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]-propyl}aniline dihydrochloride (3f)

Yield 48%, mp 203–209 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.35–2.05 (7H, m), 2.45–2.60 (2H, m), 2.60–3.30 (6H, m), 3.41 (2H, br d, J = 10.6 Hz), 6.57 (1H, dd, J = 2.7, 8.8 Hz), 6.75 (1H, d, J = 2.7 Hz), 7.05–7.30 (5H, m). Anal. Calcd for $C_{21}H_{25}Cl_2FN_2 \cdot 2HCl \cdot 0.5H_2O$: C, 52.85; H, 5.91; N, 5.87. Found: C, 52.90; H, 6.12; N, 5.94.

5.7. 3-Chloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-4-methylaniline dihydrochloride (3g)

Yield 63%, mp 218–221 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.40–2.15 (7H, m), 2.22 (3H, s), 2.45–2.60 (2H, m), 2.82 (2H, m), 3.08 (2H, m), 3.16 (2H, t, J = 7.0 Hz), 3.41 (2H, br d, J = 12.2 Hz), 6.75–7.35 (7H, m). Anal. Calcd for $C_{22}H_{28}ClFN_2 \cdot 2HCl \cdot 0.1H_2O$: C, 58.77; H, 6.77; N, 6.23. Found: C, 58.78; H, 6.91; N, 6.08.

5.8. 3-Chloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-4-isopropylaniline dihydrochloride (3h)

Yield 66%, mp 174–176 °C (dec). ^{1}H NMR (CD_3OD): δ 1.25 (6H, d, J = 7.0 Hz), 1.50–1.65 (2H, m), 1.86–2.02 (3H, m), 2.12–2.28 (2H, m), 2.60 (2H, d, J = 6.6 Hz), 2.88–3.00 (2H, m), 3.16–3.24 (2H, m), 3.38–3.50 (3H, m), 3.54–3.61 (2H, m), 6.97–7.05 (2H, m), 7.16–7.23 (2H, m), 7.34–7.39 (1H, m), 7.48–7.54 (2H, m). Anal. Calcd for $C_{24}H_{32}ClFN_2 \cdot 2HCl$: C, 60.57; H, 7.20; N, 5.89. Found: C, 60.31; H, 7.23; N, 5.86.

5.9. 3-Chloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-4-methoxyaniline dihydrochloride (3i)

Yield 65%, mp 178–184 °C (dec). ^{1}H NMR (CD_3OD): δ 1.40–2.00 (5H, m), 2.22 (2H, m), 2.60 (2H, d,

J = 6.6 Hz), 2.95 (2H, dt, J = 2.2, 12.7 Hz), 3.21 (2H, m), 3.47 (2H, m), 3.58 (2H, br d, J = 12.2 Hz), 3.93 (3H, s), 7.01 (2H, m), 7.20 (2H, m), 7.25 (1H, d, J = 8.9 Hz), 7.49 (1H, dd, J = 2.7, 8.9 Hz), 7.63 (1H, d, J = 2.7 Hz). Anal. Calcd for $C_{22}H_{28}ClFN_2O{\cdot}2HCl$: C, 56.97; H, 6.52; N, 6.04. Found: C, 56.70; H, 6.47; N, 6.11.

5.10. Benzyl 4-{[[3-(4-benzylpiperidin-1-yl)propyl](phenyl)amino]carbonyl}piperidine-1-carboxylate fumarate (5a)

5.10.1. Step 1: 1-[(Benzyloxy)carbonyl]piperidine-4-carboxylic acid. To an ice-cooled stirred solution of isonipecotic acid (64.6 g, 0.50 mol) and NaOH (44.0 g, 1.1 mol) in water (250 mL) was added dropwise benzyl chloroformate (93.8 g, 0.55 mol). After stirring at room temperature for 4 h, the mixture was washed with Et_2O (3 × 150 mL), acidified with 6 N HCl (140 mL), and extracted with EtOAc (3 × 200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was recrystallized from toluene/hexane to give the product (121.5 g, 92%) as a white solid, mp 71–73 °C. ^{1}H NMR ($CDCl_3$): δ 1.55–1.80 (2H, m), 1.80–2.05 (2H, m), 2.53 (1H, tt, J = 4.0, 10.7 Hz), 2.85–3.05 (2H, m), 4.10 (2H, br d, J = 13.0 Hz), 5.13 (2H, s), 7.30–7.40 (5H, m). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.85; H, 6.45; N, 5.26.

5.10.2. Step 2: Benzyl 4-{[[3-(4-benzylpiperidin-1-yl)propyl](phenyl)amino]carbonyl}piperidine-1-carboxylate fumarate (5a). To a stirred solution of the product from step 1 (2.37 g, 9.0 mmol) and *N*,*N*-dimethylformamide (DMF) (7 μL) in dichloromethane (DCM) (15 mL) was added oxalyl chloride (1.00 mL, 12 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo followed by addition of toluene (10 mL) and evaporation to remove traces of oxalyl chloride, affording 1-[(benzyloxy)carbonyl]piperidine-4-carbonyl chloride (**4a**). The residue was dissolved in DCM (5 mL), and the solution was added dropwise to a stirred solution of **3a** (1.91 g, 5.0 mmol) and Et_3N (3.97 mL, 28 mmol) in DCM (45 mL) at −20 °C. The mixture was stirred for 1 h allowing to warm to room temperature. The mixture was treated with saturated aqueous $NaHCO_3$ (45 mL), and the organic solvent was removed in vacuo. The aqueous layer was extracted with EtOAc (40 mL, 2 × 20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–9/1) to afford the free base of **5a** (2.54 g) as a colorless oil. The free base (206 mg) was treated with fumaric acid (1 equiv) and recrystallized from EtOAc/EtOH to give the fumarate **5a** (224 mg, 83%) as a white solid, mp 165–168 °C. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.15–2.35 (1H, m), 2.27 (2H, t, J = 7.3 Hz), 2.40–2.65 (2H, m), 2.50 (2H, d, J = 6.6 Hz), 2.82 (2H, br d, J = 11.8 Hz), 3.67 (2H, t, J = 7.7 Hz), 4.00–4.20 (2H, m), 5.09 (2H, s), 7.05–7.50 (15H, m). Anal. Calcd for $C_{35}H_{43}N_3O_3{\cdot}C_4H_4O_4$: C, 69.93; H, 7.07; N, 6.27. Found: C, 69.70; H, 7.05; N, 6.25.

5.11. Benzyl 3-{[[3-(4-benzylpiperidin-1-yl)propyl](phenyl)amino]carbonyl}piperidine-1-carboxylate hydrochloride (5b)

5.11.1. Step 1: 1-[(Benzyloxy)carbonyl]piperidine-3-carboxylic acid. The product was prepared using a procedure similar to that described for 1-[(benzyloxy)carbonyl]piperidine-4-carboxylic acid from nipecotic acid. Yield 89%, mp 96–98 °C. ^{1}H NMR ($CDCl_3$): δ 1.35–1.85 (3H, m), 2.00–2.20 (1H, m), 2.40–2.65 (1H, m), 2.85–3.25 (2H, m), 3.90–4.05 (1H, m), 4.05–4.35 (1H, m), 5.12 and 5.15 (2H, ABq, J = 12.4 Hz), 7.20–7.40 (5H, m). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.44; N, 5.33.

5.11.2. Step 2: Benzyl 3-{[[3-(4-benzylpiperidin-1-yl)propyl](phenyl)amino]carbonyl}piperidine-1-carboxylate hydrochloride (5b). Compound **5b** was prepared using a procedure similar to that described for **5a** from 1-[(benzyloxy)carbonyl]piperidine-3-carboxylic acid. Yield 71%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.00–1.90 (13H, m), 2.15–2.35 (1H, m), 2.26 (2H, t, J = 7.7 Hz), 2.50 (2H, d, J = 6.6 Hz), 2.55–3.05 (2H, m), 2.81 (2H, br d, J = 11.8 Hz), 3.55–3.80 (2H, m), 3.95–4.20 (2H, m), 5.03 (2H, br s), 7.00–7.50 (15H, m). Anal. Calcd for $C_{35}H_{43}N_3O_3{\cdot}HCl{\cdot}0.9H_2O$: C, 69.32; H, 7.61; N, 6.93. Found: C, 69.26; H, 7.69; N, 7.05.

5.12. 1-Acetyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)piperidine-4-carboxamide hydrochloride (5e)

To an ice-cooled stirred solution of **3b** (450 mg, 1.0 mmol) and Et_3N (836 μL, 6.0 mmol) in DCM (10 mL) was added 1-acetylpiperidine-4-carbonyl chloride (**4c**)[18] (569 mg, 3.0 mmol), and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL), and the organic solvent was removed in vacuo. The residue was extracted with EtOAc (3 × 15 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–9/1) to afford the free base of **5e** (522 mg) as a colorless oil. The free base (522 mg) was converted to the hydrochloride salt using 4 N HCl (EtOAc solution) to afford **5e** (477 mg, 84%) as an amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.04 (3H, s), 2.20–2.55 (2H, m), 2.27 (2H, t, J = 7.4 Hz), 2.51 (2H, d, J = 6.2 Hz), 2.75–2.95 (1H, m), 2.82 (2H, br d, J = 11.2 Hz), 3.65 (2H, t, J = 7.5 Hz), 3.77 (1H, br d, J = 13.4 Hz), 4.52 (1H, br d, J = 13.4 Hz), 7.00–7.35 (5H, m), 7.04 (1H, dd, J = 2.4, 8.4 Hz), 7.32 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{37}Cl_2N_3O_2{\cdot}HCl{\cdot}0.9H_2O$: C, 59.72; H, 6.88; N, 7.21. Found: C, 59.76; H, 6.81; N, 7.19.

The following compounds **5c**,**d**,**f**–**j** were prepared using a procedure similar to that described for **5e** from the anilines **3c**–**i**.

5.13. 1-Acetyl-*N*-(3-chlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide hydrochloride (5c)

Yield 77%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.05 (3H, s), 2.20–2.55 (2H, m), 2.27 (2H, t, J = 7.5 Hz), 2.48 (2H, d, J = 6.6 Hz), 2.70–2.95 (1H, m), 2.82 (2H, br d, J = 11.6 Hz), 3.67 (2H, t, J = 7.7 Hz), 3.77 (1H, br d, J = 13.1 Hz), 4.52 (1H, br d, J = 13.1 Hz), 6.94 (2H, t, J = 8.8 Hz), 7.00–7.15 (3H, m), 7.20 (1H, s), 7.38 (2H, d, J = 5.0 Hz). Anal. Calcd for $C_{29}H_{37}ClFN_3O_2\cdot HCl\cdot 0.5H_2O$: C, 62.25; H, 7.03; N, 7.51. Found: C, 62.34; H, 7.06; N, 7.64.

5.14. 1-Acetyl-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-*N*-(4-methylphenyl)piperidine-4-carboxamide hydrochloride (5d)

Yield 87%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.03 (3H, s), 2.20–2.55 (2H, m), 2.29 (2H, t, J = 7.7 Hz), 2.40 (3H, s), 2.48 (2H, d, J = 6.6 Hz), 2.70–2.95 (1H, m), 2.84 (2H, br d, J = 11.2 Hz), 3.65 (2H, t, J = 7.6 Hz), 3.74 (1H, br d, J = 13.2 Hz), 4.50 (1H, br d, J = 13.2 Hz), 6.85–7.15 (6H, m), 7.22 (2H, d, J = 7.6 Hz). Anal. Calcd for $C_{30}H_{40}FN_3O_2\cdot HCl\cdot 0.5H_2O$: C, 66.83; H, 7.85; N, 7.79. Found: C, 66.87; H, 8.08; N, 7.75.

5.15. 1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide hydrochloride (5f)

Yield 91%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.05 (3H, s), 2.20–2.55 (2H, m), 2.27 (2H, t, J = 7.5 Hz), 2.48 (2H, d, J = 6.6 Hz), 2.70–3.00 (1H, m), 2.81 (2H, br d, J = 11.8 Hz), 3.65 (2H, t, J = 7.5 Hz), 3.78 (1H, br d, J = 13.0 Hz), 4.52 (1H, br d, J = 13.0 Hz), 6.94 (2H, t, J = 8.6 Hz), 6.95–7.15 (3H, m), 7.32 (1H, d, J = 2.2 Hz), 7.52 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{36}Cl_2FN_3O_2\cdot HCl\cdot 0.5H_2O$: C, 58.64; H, 6.45; N, 7.07. Found: C, 58.61; H, 6.56; N, 7.03.

5.16. 1-Acetyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-(3-chloro-4-methylphenyl)piperidine-4-carboxamide (5g)

Yield 54%, mp 96–99 °C. ^{1}H NMR ($CDCl_3$): δ 1.10–1.90 (13H, m), 2.04 (3H, s), 2.20–2.45 (2H, m), 2.27 (2H, t, J = 7.5 Hz), 2.42 (3H, s), 2.51 (2H, d, J = 6.6 Hz), 2.70–2.95 (1H, m), 2.82 (2H, br d, J = 11.4 Hz), 3.64 (2H, t, J = 7.7 Hz), 3.76 (1H, br d, J = 13.9 Hz), 4.51 (1H, br d, J = 13.9 Hz), 6.96 (1H, dd, J = 2.2, 8.0 Hz), 7.05–7.35 (7H, m). Anal. Calcd for $C_{30}H_{40}ClN_3O_2$: C, 70.64; H, 7.90; N, 8.24. Found: C, 70.40; H, 8.01; N, 8.18.

5.17. 1-Acetyl-*N*-(3-chloro-4-methylphenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide hydrochloride (5h)

Yield 84%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.04 (3H, s), 2.20–2.55 (2H, m), 2.28 (2H, t, J = 7.5 Hz), 2.42 (3H, s), 2.48 (2H, d, J = 6.6 Hz), 2.70–2.95 (1H, m), 2.83 (2H, br d, J = 11.0 Hz), 3.65 (2H, t, J = 7.7 Hz), 3.76 (1H, br d, J = 12.8 Hz), 4.51 (1H, br d, J = 12.8 Hz), 6.85–7.15 (5H, m), 7.19 (1H, d, J = 2.2 Hz), 7.29 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{30}H_{39}ClFN_3O_2\cdot HCl\cdot 0.5H_2O$: C, 62.82; H, 7.20; N, 7.33. Found: C, 62.77; H, 7.20; N, 7.21.

5.18. 1-Acetyl-*N*-(3-chloro-4-isopropylphenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide hydrochloride (5i)

Yield 81%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.40 (2H, m), 1.28 (6H, d, J = 7.0 Hz), 1.50–1.97 (11H, m), 2.05 (3H, s), 2.23–2.42 (4H, m), 2.48 (2H, d, J = 6.6 Hz), 2.80–2.93 (3H, m), 3.42 (1H, septet, J = 7.0 Hz), 3.60–3.80 (3H, m), 4.47–4.54 (1H, m), 6.70–7.10 (5H, m), 7.16 (1H, d, J = 2.2 Hz), 7.33 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{32}H_{43}ClFN_3O_2\cdot HCl\cdot 4H_2O$: C, 57.82; H, 7.89; N, 6.32. Found: C, 57.95; H, 7.89; N, 6.34.

5.19. 1-Acetyl-*N*-(3-chloro-4-methoxyphenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide hydrochloride (5j)

Yield 80%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.95 (13H, m), 2.04 (3H, s), 2.20–2.55 (2H, m), 2.29 (2H, t, J = 7.5 Hz), 2.48 (2H, d, J = 6.6 Hz), 2.75–2.95 (3H, m), 3.63 (2H, t, J = 7.5 Hz), 3.76 (1H, br d, J = 13.4 Hz), 3.95 (3H, s), 4.52 (1H, br d, J = 13.4 Hz), 6.85–7.15 (6H, m), 7.21 (1H, d, J = 2.6 Hz). Anal. Calcd for $C_{30}H_{39}ClFN_3O_3\cdot HCl\cdot 0.6H_2O$: C, 60.93; H, 7.02; N, 7.11. Found: C, 60.94; H, 7.06; N, 7.25.

5.20. *N*-(3,4-Dichlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)-piperidin-1-yl]propyl}-1-(methylsulfonyl)piperidine-4-carboxamide (5k)

5.20.1. Step 1: Ethyl-1-(methylsulfonyl)piperidine-4-carboxylate. To an ice-cooled stirred solution of ethyl isonipecotate (157 g, 1.0 mol) and Et_3N (153 mL, 1.1 mol) in EtOAc (800 mL) was added dropwise methanesulfonyl chloride (85 mL, 1.1 mol). After stirring at room temperature for 2.5 h, the mixture was diluted with water (800 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 200 mL), and the combined organic layer was washed with 1 N HCl (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with i-Pr_2O (300 mL), collected by filtration, washed with i-Pr_2O (3 × 200 mL), and dried in vacuo to afford the product (210 g, 89%) as a white solid, mp 91–92 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.2 Hz), 1.75–2.10 (4H, m), 2.35–2.55 (1H, m), 2.78 (3H, s), 2.80–2.95 (2H, m), 3.60–3.75 (2H, m), 4.16 (2H, q, J = 7.2 Hz). Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.94; H, 7.28; N, 5.95. Found: C, 45.87; H, 7.19; N, 5.80.

5.20.2. Step 2: 1-(Methylsulfonyl)piperidine-4-carboxylic acid. To a stirred solution of NaOH (42.9 g, 1.1 mol) in water (525 mL) was added portionwise the product from step 1 (210 g, 0.89 mol), and the mixture was stirred for

3 h. The mixture was neutralized with concentrated HCl (98 mL, 1.2 mol) at 0 °C and stirred for 1 h. The resulting precipitate was collected by filtration, washed with water, and dried (P_2O_5) in vacuo to afford the product (170 g, 92%) as a white solid, mp 161–163 °C. ^{1}H NMR (D_2O): δ 1.60–1.85 (2H, m), 1.95–2.15 (2H, m), 2.45–2.65 (1H, m), 2.80–3.00 (2H, m), 2.98 (3H, s), 3.55–3.75 (2H, m). Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.57; H, 6.32; N, 6.76. Found: C, 40.73; H, 6.24; N, 6.79.

5.20.3. Step 3: 1-(Methylsulfonyl)piperidine-4-carbonyl chloride (4d). To a stirred mixture of the product from step 2 (51.8 g, 0.25 mol) and DMF (194 μL, 2.5 mmol) in DCM (250 mL) was added dropwise oxalyl chloride (32 mL, 0.37 mmol), and the mixture was stirred at room temperature for 3 h followed by concentration in vacuo. The residue was triturated with petroleum ether, collected by filtration, and dried in vacuo to afford **4d** (54.5 g, 97%) as a white solid.

5.20.4. Step 4: *N*-(3,4-Dichlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-1-(methylsulfonyl)piperidine-4-carboxamide (5k). To an ice-cooled stirred solution of **3f** (468 mg, 1.0 mmol) and Et_3N (836 μL, 6.0 mmol) in DCM (10 mL) was added **4d** (564 mg, 2.5 mmol), and the mixture was stirred at 0 °C for 3 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and extracted with DCM. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–9/1) followed by trituration with Et_2O to afford **5k** (485 mg, 83%) as a white solid, mp 148–150 °C. ^{1}H NMR ($CDCl_3$): δ 1.05–2.05 (13H, m), 2.10–2.35 (1H, m), 2.27 (2H, t, J = 7.5 Hz), 2.40–2.70 (2H, m), 2.48 (2H, d, J = 6.6 Hz), 2.74 (3H, s), 2.81 (2H, br d, J = 11.8 Hz), 3.55–3.80 (4H, m), 6.85–7.15 (5H, m), 7.31 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{28}H_{36}Cl_2FN_3O_3S{\cdot}0.5H_2O$: C, 56.66; H, 6.28; N, 7.08. Found: C, 56.88; H, 6.10; N, 7.01.

5.21. *N*-(3-Chloro-4-methylphenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-1-(methylsulfonyl)piperidine-4-carboxamide hydrochloride (5l)

Compound **5l** was prepared using a procedure similar to that described for **5k** from **3g**. Yield 67%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.00 (13H, m), 2.15–2.40 (1H, m), 2.28 (2H, t, J = 7.6 Hz), 2.41 (3H, s), 2.48 (2H, d, J = 6.4 Hz), 2.55 (2H, dt, J = 2.8, 11.4 Hz), 2.72 (3H, s), 2.84 (2H, br d, J = 11.6 Hz), 3.64 (2H, t, J = 7.5 Hz), 3.71 (2H, m), 6.85–7.15 (5H, m), 7.18 (1H, d, J = 2.2 Hz), 7.28 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{29}H_{39}ClFN_3O_3S{\cdot}0.6H_2O$: C, 56.97; H, 6.79; N, 6.87. Found: C, 56.99; H, 7.07; N, 6.80.

5.22. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-phenylpiperidine-4-carboxamide (6a)

A mixture of the free base of **5a** (2.32 g, 4.2 mmol) and 10% palladium on carbon (water ~50%, 0.93 g) in MeOH (30 mL) was stirred under a hydrogen atmosphere at room temperature for 16 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give **6a** (1.70 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.10–1.95 (13H, m), 2.05–2.45 (5H, m), 2.51 (2H, d, J = 6.6 Hz), 2.84 (2H, br d, J = 11.8 Hz), 3.01 (2H, br d, J = 12.8 Hz), 3.67 (2H, t, J = 7.7 Hz), 7.05–7.50 (10H, m).

5.23. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-phenylpiperidine-3-carboxamide (6b)

Compound **6b** was prepared using a procedure similar to that described for **6a** from **5b**. Yield 95%, oil. ^{1}H NMR ($CDCl_3$): δ 1.00–2.05 (13H, m), 2.15–2.40 (1H, m), 2.26 (2H, t, J = 7.5 Hz), 2.45–2.70 (1H, m), 2.51 (2H, d, J = 6.6 Hz), 2.70–3.00 (5H, m), 3.66 (2H, t, J = 7.5 Hz), 7.05–7.50 (10H, m).

5.24. 1-Acetyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-phenylpiperidine-4-carboxamide hydrochloride (7a)

To an ice-cooled stirred solution of **6a** (252 mg, 0.60 mmol) and Et_3N (201 μL, 1.4 mmol) in THF (5 mL) was added acetyl chloride (85 μL, 1.2 mmol), and the mixture was stirred at 0 °C for 30 min. The mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–4/1) to give the free base of **7a** (237 mg) as a colorless oil. The free base (237 mg) in MeOH was treated with an excess of HCl in Et_2O followed by evaporation of the solvent. The resulting foam was triturated with Et_2O, collected by filtration, and dried in vacuo to give the hydrochloride **7a** (216 mg, 72%) as an amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.90 (13H, m), 2.03 (3H, s), 2.20–2.45 (2H, m), 2.28 (2H, t, J = 7.5 Hz), 2.50 (2H, d, J = 6.6 Hz), 2.70–2.90 (1H, m), 2.83 (2H, br d, J = 11.6 Hz), 3.68 (2H, t, J = 7.7 Hz), 3.74 (1H, br d, J = 12.8 Hz), 4.50 (1H, br d, J = 12.8 Hz), 7.05–7.50 (10H, m). Anal. Calcd for $C_{29}H_{39}N_3O_2{\cdot}HCl{\cdot}0.9H_2O$: C, 67.72; H, 8.19; Cl, 6.89; N, 8.17. Found: C, 67.80; H, 8.02; Cl, 7.18; N, 8.03.

The following compounds **7b**–**f** were prepared using a procedure similar to that described for **7a** from the appropriate acyl chloride and **6a**,**b**.

5.25. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-isobutyryl-*N*-phenylpiperidine-4-carboxamide hydrochloride (7b)

Yield 62%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 0.95–2.00 (19H, m), 2.15–2.60 (2H, m), 2.32 (2H, t, J = 7.7 Hz), 2.51 (2H, d, J = 6.6 Hz), 2.60–2.95 (2H, m), 2.87 (2H, br d, J = 11.8 Hz), 3.68 (2H, t, J = 7.5 Hz), 3.87 (1H, br d, J = 14.1 Hz), 4.54 (1H, br d, J = 14.1 Hz), 7.05–7.50 (10H, m). Anal. Calcd for $C_{31}H_{43}N_3O_2{\cdot}HCl{\cdot}0.6H_2O$: C, 69.34; H, 8.48; N, 7.83. Found: C, 69.42; H, 8.36; N, 7.68.

5.26. 1-Benzoyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-phenylpiperidine-4-carboxamide hydrochloride (7c)

Yield 88%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–1.95 (13H, m), 2.20–2.90 (3H, m), 2.29 (2H, t, J = 7.7 Hz), 2.50 (2H, d, J = 6.2 Hz), 2.83 (2H, br d, J = 11.8 Hz), 3.45–3.90 (1H, m), 3.69 (2H, t, J = 7.7 Hz), 4.40–4.85 (1H, m), 7.05–7.50 (15H, m). Anal. Calcd for $C_{34}H_{41}N_3O_2$·HCl·0.8H_2O: C, 71.07; H, 7.65; N, 7.31. Found: C, 71.00; H, 7.61; N, 7.23.

5.27. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(methylsulfonyl)-*N*-phenylpiperidine-4-carboxamide (7d)

Yield 37%, mp 116–118 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$): δ 1.10–2.00 (13H, m), 2.15–2.40 (3H, m), 2.40–2.60 (2H, m), 2.51 (2H, d, J = 6.2 Hz), 2.72 (3H, s), 2.75–2.95 (2H, m), 3.60–3.80 (4H, m), 7.05–7.50 (10H, m). Anal. Calcd for $C_{28}H_{39}N_3O_3S$·0.2H_2O: C, 67.09; H, 7.92; N, 8.38. Found: C, 67.10; H, 8.06; N, 8.34.

5.28. 1-Acetyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-phenylpiperidine-3-carboxamide hydrochloride (7e)

Yield 85%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.00–2.00 (16H, m), 2.10–2.55 (1H, m), 2.29 (2H, t, J = 7.5 Hz), 2.51 (2H, d, J = 6.6 Hz), 2.65–3.40 (2H, m), 2.83 (2H, br d, J = 11.0 Hz), 3.50–3.85 (3H, m), 4.40–4.65 (1H, m), 7.05–7.50 (10H, m). Anal. Calcd for $C_{29}H_{39}N_3O_2$·HCl·0.8H_2O: C, 67.96; H, 8.18; N, 8.20. Found: C, 67.86; H, 8.17; N, 8.18.

5.29. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(methylsulfonyl)-*N*-phenylpiperidine-3-carboxamide hydrochloride (7f)

Yield 41%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.00 (13H, m), 2.20–2.65 (2H, m), 2.28 (2H, t, J = 7.5 Hz), 2.51 (2H, d, J = 6.6 Hz), 2.68 (3H, s), 2.75–2.95 (3H, m), 3.50–3.85 (4H, m), 7.05–7.50 (10H, m). Anal. Calcd for $C_{28}H_{39}N_3O_3S$·HCl·0.6H_2O: C, 61.71; H, 7.62; N, 7.71. Found: C, 61.79; H, 7.46; N, 7.76.

5.30. 3,4-Dichloro-*N*-(3-chloropropyl)aniline hydrochloride (9a)

5.30.1. Step 1: *N*-(3,4-Dichlorophenyl)formamide. A mixture of acetic anhydride (189 mL, 2.0 mol) and formic acid (91 mL, 2.4 mol) was stirred at 60 °C for 2 h, then cooled to 0 °C. To the mixture was added 3,4-dichloroaniline (**8**) (162 g, 1.0 mol) portionwise, and the mixture was stirred at room temperature for 20 h. After dilution with Et_2O (500 mL), the mixture was washed with water (2 × 500 mL), 1 N NaOH (3 × 200 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O, collected by filtration, and dried in vacuo to give the product (145 g, 76%) as a white solid, mp 107–108 °C. Anal. Calcd for $C_7H_5Cl_2NO$: C, 44.24; H, 2.65; N, 7.37. Found: C, 44.23; H, 2.82; N, 7.40.

5.30.2. Step 2: *N*-(3-Chloropropyl)-*N*-(3,4-dichlorophenyl)formamide. To a stirred mixture of the product from step 1 (133 g, 0.70 mol) and 1-bromo-3-chloropropane (132 g, 0.84 mol) in acetone (700 mL) was added Cs_2CO_3 (274 g, 0.84 mol). After stirring at reflux for 5 h, the mixture was concentrated in vacuo, diluted with EtOAc (500 mL), and filtered. The filtrate was washed with water (300 mL) and brine (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1/0–7/3) to give the product (144 g, 77%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.9–2.2 (2H, m), 3.5–3.6 (2H, m), 3.85–4.0 (2H, m), 7.06 (7/8 × 1H, dd, J = 2.7, 8.7 Hz), 7.22 (1/8 × 1H, dd, J = 2.4, 8.7 Hz), 7.31 (7/8 × 1H, d, J = 2.7 Hz), 7.50 (1/8 × 1H, d, J = 2.4 Hz), 7.50 (1/8 × 1H, d, J = 8.7 Hz), 7.51 (7/8 × 1H, d, J = 8.7 Hz), 8.37 (1/8 × 1H, s), 8.40 (7/8 × 1H, s).

5.30.3. Step 3: 3,4-Dichloro-*N*-(3-chloropropyl)aniline hydrochloride (9a). To a stirred solution of the product from step 2 (142 g, 0.53 mol) in *i*-PrOH (500 mL) was added concentrated HCl (100 mL). After stirring at 60 °C for 3 h, the mixture was cooled to room temperature, and the resulting precipitate was collected by filtration. The precipitate was washed with *i*-PrOH (3 × 100 mL) and dried in vacuo to give **9a** (133 g, 91%) as a white solid, mp 173–174 °C. ^{1}H NMR (CD_3OD): δ 2.20 (2H, m), 3.51 (2H, m), 3.71 (2H, t, J = 6.2 Hz), 7.33 (1H, dd, J = 2.9, 8.7 Hz), 7.59 (1H, d, J = 2.9 Hz), 7.66 (1H, d, J = 8.7 Hz). Anal. Calcd for $C_9H_{10}Cl_3N$·HCl: C, 39.31; H, 4.03; N, 5.09. Found: C, 39.47; H, 4.18; N, 5.07.

5.31. 3,4-Dichloro-*N*-(4-chlorobutyl)aniline hydrochloride (9b)

Compound **9b** was prepared using a procedure similar to that described for **9a** from 1-bromo-4-chlorobutane. Mp 134–136 °C. ^{1}H NMR (CD_3OD): δ 1.75–2.05 (4H, m), 3.43 (2H, m), 3.64 (2H, m), 7.44 (1H, dd, J = 2.8, 8.8 Hz), 7.72 (1H, d, J = 2.8 Hz), 7.72 (1H, d, J = 8.8 Hz). Anal. Calcd for $C_{10}H_{12}Cl_3N$·HCl: C, 41.56; H, 4.53; N, 4.85. Found: C, 41.52; H, 4.43; N, 4.95.

5.32. *N*-(3-Chloropropyl)-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (10a)

To an ice-cooled stirred suspension of **9a** (35.0 g, 0.13 mmol) in DCM (500 mL) was added Et_3N (71 mL, 0.51 mol) followed by **4d** (86.2 g, 0.38 mol), and the mixture was stirred at room temperature for 12 h. The mixture was diluted with water (300 mL), and the organic solvent was removed in vacuo. The residue was diluted with EtOAc (300 mL)/THF (300 mL), and the insoluble material was removed by filtration. The organic layer was separated, washed with 1 N NaOH (3 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM/EtOAc 1/2) followed by recrystallization from DCM/EtOAc/*i*-Pr_2O to afford **10a** (42.2 g, 78%) as a white solid, mp 167–168 °C. ^{1}H NMR ($CDCl_3$): δ 1.60–2.01 (6H, m), 2.05–2.37 (1H, m), 2.39–2.68 (2H, m), 2.74 (3H, s), 3.55 (2H, t, J = 6.4 Hz), 3.65–3.83 (4H, m), 7.05 (1H, dd, J = 2.2, 8.4 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.55 (1H, d,

J = 8.4 Hz). Anal. Calcd for $C_{16}H_{21}Cl_3N_2O_3S$: C, 44.92; H, 4.95; N, 6.55. Found: C, 44.75; H, 5.00; N, 6.34.

5.33. 1-Acetyl-*N*-(4-chlorobutyl)-*N*-(3,4-dichlorophenyl)-piperidine-4-carboxamide (10b)

Compound **10b** was prepared using a procedure similar to that described for **10a** from **9b** and **4c**. Yield 79%, mp 99–101 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$): δ 1.45–1.90 (8H, m), 2.06 (3H, s), 2.20–2.50 (2H, m), 2.87 (1H, m), 3.55 (2H, t, J = 6.0 Hz), 3.68 (2H, t, J = 7.0 Hz), 3.78 (1H, br d, J = 12.8 Hz), 4.54 (1H, br d, J = 12.8 Hz), 7.05 (1H, dd, J = 2.6, 8.4 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.55 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{18}H_{23}Cl_3N_2O_2$: C, 53.28; H, 5.71; N, 6.90. Found: C, 53.25; H, 5.69; N, 6.94.

5.34. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-(3-{4-[4-(trifluoromethyl)benzyl]piperidin-1-yl}propyl)piperidine-4-carboxamide (11a)

A mixture of **10a** (428 mg, 1.0 mmol), **22b** (336 mg, 1.2 mmol), KI (199 mg, 1.2 mmol), K_2CO_3 (498 mg, 3.6 mmol) in MeCN (24 mL) was stirred at 80 °C for 13 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (40 mL) and water (10 mL). The organic layer was separated, washed with 1 N NaOH (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) followed by recrystallization from EtOAc/*i*-Pr_2O to afford **11a** (393 mg, 62%) as a white solid, mp 120–124 °C. ^{1}H NMR ($CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.45–2.90 (4H, m), 2.57 (2H, d, J = 6.2 Hz), 2.74 (3H, s), 3.55–3.85 (4H, m), 7.02 (1H, dd, J = 2.4, 8.4 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{36}Cl_2F_3N_3O_3S$: C, 54.89; H, 5.72; N, 6.62. Found: C, 54.64; H, 5.54; N, 6.52.

The following compounds **11b**–**l** were prepared using a procedure similar to that described for **11a** from the corresponding piperidines.

5.35. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-{3-[4-(4-nitrobenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide (11b)

Yield 47%, oil. ^{1}H NMR ($CDCl_3$): δ 1.10–2.10 (13H, m), 2.10–2.40 (3H, m), 2.45–2.70 (2H, m), 2.63 (2H, d, J = 5.8 Hz), 2.70–2.95 (2H, m), 2.74 (3H, s), 3.60–3.85 (4H, m), 7.03 (1H, dd, J = 2.5, 8.5 Hz), 7.29 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 2.5 Hz), 7.52 (1H, d, J = 8.5 Hz), 8.14 (2H, d, J = 8.8 Hz). MS *m*/*z*: 611 (MH^+).

5.36. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-{3-[4-(4-morpholin-4-ylbenzyl)piperidin-1-yl]propyl}piperidine-4-carboxamide (11c)

Yield 37%, amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.20–2.10 (13H, m), 2.10–2.65 (5H, m), 2.46 (2H, d, J = 6.9 Hz), 2.73 (3H, s), 2.90–3.05 (2H, m), 3.12 (4H, t, J = 4.7 Hz), 3.60–3.80 (4H, m), 3.85 (4H, t, J = 4.7 Hz), 6.83 (2H, d, J = 8.3 Hz), 7.00–7.15 (1H, m), 7.03 (2H, d, J = 8.3 Hz), 7.33 (1H, d, J = 2.4 Hz), 7.53 (1H, d, J = 8.4 Hz). MS *m*/*z*: 651 (MH^+).

5.37. *N*-(3,4-Dichlorophenyl)-*N*-{3-[4-(4-methoxybenzyl)-piperidin-1-yl]propyl}-1-(methylsulfonyl)piperidine-4-carboxamide (11d)

Yield 73%, amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.45 (2H, d, J = 6.6 Hz), 2.45–2.65 (2H, m), 2.70–2.90 (2H, m), 2.74 (3H, s), 3.55–3.80 (4H, m), 3.79 (3H, s), 6.81 (2H, d, J = 8.4 Hz), 6.95–7.10 (1H, m), 7.04 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.6 Hz). Anal. Calcd for $C_{29}H_{39}Cl_2N_3O_4S{\cdot}0.6H_2O$: C, 57.34; H, 6.67; N, 6.92. Found: C, 57.33; H, 6.75; N, 6.79.

5.38. *N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[4-(methylsulfanyl)-benzyl]piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide hydrochloride (11e)

Yield 92%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.40–2.70 (4H, m), 2.47 (3H, s), 2.70–2.90 (2H, m), 2.74 (3H, s), 3.55–3.80 (4H, m), 6.95–7.10 (1H, m), 7.05 (2H, d, J = 8.4 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.6 Hz). Anal. Calcd for $C_{29}H_{39}Cl_2N_3O_3S_2{\cdot}HCl{\cdot}0.8H_2O$: C, 52.49; H, 6.32; N, 6.33. Found: C, 52.51; H, 6.40; N, 6.46.

5.39. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-(3-{4-[4-(methylsulfonyl)benzyl]piperidin-1-yl}propyl)piperidine-4-carboxamide hydrochloride (11f)

Yield 66%, mp 172–176 °C (DCM/EtOH). ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.45–2.70 (2H, m), 2.61 (2H, d, J = 6.6 Hz), 2.70–2.90 (2H, m), 2.74 (3H, s), 3.05 (3H, s), 3.55–3.80 (4H, m), 7.02 (1H, dd, J = 2.2, 8.5 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.32 (2H, d, J = 8.6 Hz), 7.52 (1H, d, J = 8.5 Hz), 7.85 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{29}H_{39}Cl_2N_3O_5S_2{\cdot}HCl{\cdot}H_2O$: C, 49.82; H, 6.05; Cl, 15.21; N, 6.01; S, 9.17. Found: C, 49.87; H, 5.98; Cl, 15.22; N, 6.05; S, 9.19.

5.40. *N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[4-(ethylsulfonyl)-benzyl]piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide hydrochloride (11g)

Yield 84%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 1.28 (3H, t, J = 7.4 Hz), 2.10–2.35 (3H, m), 2.45–2.70 (2H, m), 2.61 (2H, d, J = 6.4 Hz), 2.74 (3H, s), 2.75–2.90 (2H, m), 3.11 (2H, q, J = 7.4 Hz), 3.55–3.80 (4H, m), 7.03 (1H, dd, J = 2.6, 8.4 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.80 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{30}H_{41}Cl_2N_3O_5S_2{\cdot}HCl{\cdot}0.5H_2O$: C, 51.17; H, 6.15; N, 5.97. Found: C, 51.14; H, 6.31; N, 5.74.

5.41. *N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[4-(isopropylsulfonyl)benzyl]piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide hydrochloride (11h)

Yield 77%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 1.29 (6H, d, J = 6.9 Hz), 2.10–2.35 (3H, m), 2.45–2.70 (2H, m), 2.61 (2H, d, J = 6.2 Hz), 2.74 (3H, s), 2.75–2.90 (2H, m), 3.18 (1H, septet, J = 6.9 Hz), 3.55–3.80 (4H, m), 7.03 (1H, dd, J = 2.4, 8.5 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.52 (1H, d, J = 8.5 Hz), 7.78 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{31}H_{43}Cl_2N_3O_5S_2 \cdot HCl \cdot 0.8H_2O$: C, 51.46; H, 6.35; N, 5.81. Found: C, 51.43; H, 6.64; N, 5.84.

5.42. *N*-(3-{4-[4-(Aminosulfonyl)benzyl]piperidin-1-yl}-propyl)-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (11i)

Yield 66%, mp 179–181 °C (DCM/EtOAc). ^{1}H NMR ($CDCl_3$): δ 1.10–2.00 (13H, m), 2.10–2.35 (3H, m), 2.45–2.65 (2H, m), 2.59 (2H, d, J = 6.2 Hz), 2.70–2.90 (2H, m), 2.74 (3H, s), 3.55–3.80 (4H, m), 4.93 (2H, br s), 7.03 (1H, dd, J = 2.4, 8.6 Hz), 7.27 (2H, d, J = 8.3 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.6 Hz), 7.83 (2H, d, J = 8.3 Hz). Anal. Calcd for $C_{28}H_{38}Cl_2N_4O_5S_2 \cdot 0.3H_2O$: C, 51.65; H, 5.98; N, 8.61. Found: C, 51.67; H, 6.10; N, 8.39.

5.43. *N*-(3,4-Dichlorophenyl)-*N*-[3-(4-{4-[(methylamino)-sulfonyl]benzyl}piperidin-1-yl)propyl]-1-(methylsulfonyl)-piperidine-4-carboxamide (11j)

Yield 60%, amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.45–2.95 (4H, m), 2.59 (2H, d, J = 6.2 Hz), 2.67 (3H, d, J = 5.4 Hz), 2.74 (3H, s), 3.55–3.80 (4H, m), 4.20–4.40 (1H, m), 7.03 (1H, dd, J = 2.2, 8.4 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.76 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{40}Cl_2N_4O_5S_2 \cdot 0.5H_2O$: C, 52.09; H, 6.18; N, 8.38. Found: C, 52.14; H, 5.95; N, 8.37.

5.44. *N*-(3,4-Dichlorophenyl)-*N*-[3-(4-{4-[(dimethylamino)-sulfonyl]benzyl}piperidin-1-yl)propyl]-1-(methylsulfonyl)-piperidine-4-carboxamide hydrochloride (11k)

Yield 64%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.40 (3H, m), 2.45–2.65 (2H, m), 2.60 (2H, d, J = 6.2 Hz), 2.70 (6H, s), 2.73 (3H, s), 2.80–2.95 (2H, m), 3.60–3.80 (4H, m), 7.06 (1H, dd, J = 2.4, 8.7 Hz), 7.29 (2H, d, J = 8.2 Hz), 7.32 (1H, d, J = 2.4 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.68 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{30}H_{42}Cl_2N_4O_5S_2 \cdot HCl \cdot 1.3H_2O$: C, 49.12; H, 6.27; N, 7.64. Found: C, 49.17; H, 6.32; N, 7.71.

5.45. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-(3-{4-[4-(morpholin-4-ylsulfonyl)benzyl]piperidin-1-yl}propyl)-piperidine-4-carboxamide hydrochloride (11l)

Yield 83%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$): δ 1.10–2.05 (13H, m), 2.10–2.35 (3H, m), 2.45–2.65 (2H, m), 2.60 (2H, d, J = 6.6 Hz), 2.74 (3H, s), 2.75–2.90 (2H, m), 2.90–3.10 (4H, m), 3.55–3.85 (8H, m), 7.02 (1H, dd, J = 2.2, 8.4 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{32}H_{44}Cl_2N_4O_6S_2 \cdot HCl \cdot 1.7H_2O$: C, 49.10; H, 6.23; N, 7.16. Found: C, 49.06; H, 6.34; N, 7.09.

5.46. 1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-{4-[4-(4-fluorobenzyl)piperidin-1-yl]butyl}piperidine-4-carboxamide (12)

Compound **12** was prepared using a procedure similar to that described for **11a** from **10b** and **22a**. Yield 58%, oil. ^{1}H NMR ($CDCl_3$): δ 1.10–1.90 (15H, m), 2.06 (3H, s), 2.20–2.55 (4H, m), 2.49 (2H, d, J = 6.6 Hz), 2.75–3.00 (1H, m), 2.85 (2H, br d, J = 11.6 Hz), 3.64 (2H, m), 3.78 (1H, br d, J = 13.7 Hz), 4.53 (1H, br d, J = 13.7 Hz), 6.95 (2H, m), 7.03 (1H, dd, J = 2.6, 8.5 Hz), 7.08 (2H, m), 7.30 (1H, d, J = 2.6 Hz), 7.53 (1H, d, J = 8.5 Hz). Anal. Calcd for $C_{30}H_{38}Cl_2FN_3O_2 \cdot 1.3H_2O$: C, 61.49; H, 6.98; N, 7.17. Found: C, 61.50; H, 6.62; N, 7.06.

5.47. *N*-{3-[4-(4-Aminobenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (13)

A mixture of **11b** (85 mg, 0.14 mmol) and $SnCl_2 \cdot 2H_2O$ (156 mg, 0.70 mmol) in EtOH (0.4 mL) was stirred at reflux for 30 min. The mixture was diluted with 1 N NaOH (10 mL) and EtOAc (10 mL), and the insoluble material was removed by filtration (Celite). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on basic alumina (hexane/EtOAc 1/2) to give **13** (72 mg, 89%) as a foam. ^{1}H NMR ($CDCl_3$): δ 1.10–2.00 (13H, m), 2.15–2.35 (1H, m), 2.27 (2H, t, J = 7.3 Hz), 2.40 (2H, d, J = 6.9 Hz), 2.57 (2H, br t, J = 11.3 Hz), 2.74 (3H, s), 2.81 (2H, br d, J = 11.7 Hz), 3.35–3.85 (2H, br), 3.65 (2H, t, J = 7.5 Hz), 3.72 (2H, br d, J = 12.6 Hz), 6.61 (2H, d, J = 8.4 Hz), 6.91 (2H, d, J = 8.4 Hz), 7.03 (1H, dd, J = 2.3, 8.6 Hz), 7.31 (1H, d, J = 2.3 Hz), 7.51 (1H, d, J = 8.6 Hz). MS m/z: 581 (MH^+).

5.48. *N*-(3-{4-[4-(Acetylamino)benzyl]piperidin-1-yl}propyl)-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (14a)

To an ice-cooled stirred solution of **13** (24 mg, 0.041 mmol) and Et_3N (6.3 mg, 0.062 mmol) in THF (0.3 mL) was added AcCl (3.8 μL, 0.053 mmol). After stirring at room temperature for 10 min, the mixture was diluted with 1 N NaOH and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on basic alumina to give **14a** (25 mg, 97%) as a foam. ^{1}H NMR ($CDCl_3$): δ 1.10–2.00 (13H, m), 2.10–2.35 (3H, m), 2.16 (3H, s), 2.45–2.65 (2H, m), 2.47 (2H, d, J = 6.9 Hz), 2.74 (3H, s), 2.83 (2H, br d, J = 12.0 Hz), 3.65 (2H, t, J = 7.5 Hz), 3.72 (2H, br d, J = 12.6 Hz), 7.00–7.10 (1H, m), 7.07 (2H, d,

$J = 8.4$ Hz), 7.31 (1H, d, $J = 2.4$ Hz), 7.39 (2H, d, $J = 8.4$ Hz), 7.52 (1H, d, $J = 8.4$ Hz). MS *m/z*: 623 (MH^+).

5.49. *N*-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-*N*-[3-(4-{4-[(methylsulfonyl)amino]benzyl}piperidin-1-yl)propyl]-piperidine-4-carboxamide (14b)

To an ice-cooled stirred solution of **13** (30 mg, 0.052 mmol) and Et_3N (21 mg, 0.21 mmol) in THF (0.3 mL) was added MsCl (12 μL, 0.16 mmol). After stirring at room temperature for 1 h, the mixture was diluted with 1 N NaOH (7 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was subjected to column chromatography on basic alumina (EtOAc) to give two fractions. The first fraction contained *N*-[3-(4-{4-[bis(methylsulfonyl)amino]benzyl}piperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (12 mg, 32%). ^{1}H NMR ($CDCl_3$): δ 1.10–1.40 (2H, m), 1.40–2.00 (11H, m), 2.10–2.40 (3H, m), 2.50–2.70 (2H, m), 2.55 (2H, d, $J = 5.8$ Hz), 2.74 (3H, s), 2.83 (2H, br d, $J = 10.4$ Hz), 3.40 (6H, s), 3.60–3.80 (4H, m), 7.02 (1H, dd, $J = 2.6$, 8.4 Hz), 7.17–7.40 (5H, m), 7.52 (1H, d, $J = 8.4$ Hz). The second fraction gave **14b** (13 mg, 38%) as a foam. ^{1}H NMR ($CDCl_3$): δ 1.10–2.00 (13H, m), 2.10–2.35 (3H, m), 2.40–2.70 (2H, m), 2.50 (2H, d, $J = 6.2$ Hz), 2.74 (3H, s), 2.83 (2H, br d, $J = 10.8$ Hz), 2.99 (3H, s), 3.60–3.80 (4H, m), 7.03 (1H, dd, $J = 2.6$, 8.4 Hz), 7.12 (4H, s), 7.31 (1H, d, $J = 2.6$ Hz), 7.52 (1H, d, $J = 8.4$ Hz).

5.50. 2-Chloro-*N*-(3,4-dichlorophenyl)acetamide (15)

To a stirred solution of 3,4-dichloroaniline (**8**) (8.10 g, 50 mmol) in THF (50 mL) was added chloroacetic anhydride (9.40 g, 55 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and the residue was diluted with EtOAc (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL, 2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O (30 mL) and collected by filtration to yield **15** (8.08 g) as a white solid, mp 105–106 °C. The mother liquor was concentrated in vacuo, triturated with *i*-Pr_2O/hexane (1/1) to give a second crop (3.01 g). The combined yield was 11.09 g (93%). ^{1}H NMR ($CDCl_3$): δ 4.20 (2H, s), 7.38 (1H, dd, $J = 1.9$, 8.8 Hz), 7.43 (1H, dd, $J = 0.8$, 8.8 Hz), 7.80 (1H, dd, $J = 0.8$, 1.9 Hz), 8.22 (1H, br s). Anal. Calcd for $C_8H_6Cl_3NO$: C, 40.29; H, 2.54; N, 5.87. Found: C, 40.28; H, 2.51; N, 5.92.

5.51. *N*-(3,4-Dichlorophenyl)-2-[4-(4-fluorobenzyl)piperidin-1-yl]acetamide (16)

To a stirred solution of the free base of **22a** (4.25 g, 22 mmol) in DMF (50 mL) were added **15** (4.77 g, 20 mmol) and K_2CO_3 (3.04 g, 22 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was concentrated in vacuo, and the residue was diluted with EtOAc (70 mL). The organic layer was washed with water (20 mL, 2 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O/Et_2O (2/1) and collected by filtration to give **16** (5.90 g) as a white solid, mp 98–99 °C. A second crop (1.20 g) was obtained from the mother liquor. The combined yield was 7.10 g (90%). ^{1}H NMR ($CDCl_3$): δ 1.20–1.80 (5H, m), 2.21 (2H, dt, $J = 2.1$, 11.6 Hz), 2.55 (2H, d, $J = 7.0$ Hz), 2.86 (2H, br d, $J = 11.8$ Hz), 3.08 (2H, s), 6.97 (2H, m), 7.10 (2H, m), 7.37 (1H, d, $J = 8.5$ Hz), 7.45 (1H, dd, $J = 2.5$, 8.5 Hz), 7.77 (1H, d, $J = 2.5$ Hz), 9.26 (1H, br s). Anal. Calcd for $C_{20}H_{21}Cl_2FN_2O$: C, 60.77; H, 5.35; N, 7.09. Found: C, 60.76; H, 5.35; N, 7.20.

5.52. 3,4-Dichloro-*N*-{2-[4-(4-fluorobenzyl)piperidin-1-yl]-ethyl}aniline dihydrochloride (17)

To a stirred solution of **16** (3.95 g, 10 mmol) in THF (30 mL) was added dropwise borane–methyl sulfide complex (3.0 mL) at room temperature, and the mixture was stirred at reflux for 3 h. MeOH (10 mL) was added dropwise to the mixture at room temperature. After being stirred for 18 h, the mixture was treated with a 1 N HCl (Et_2O solution, 30 mL) and concentrated in vacuo. The residue was diluted with MeOH (30 mL) and concentrated in vacuo. The residue was triturated with EtOAc and collected by filtration to give **17** (4.07 g, 90%) as a white solid, mp 143–146 °C. ^{1}H NMR (CD_3OD): δ 1.40–2.00 (5H, m), 2.60 (2H, d, $J = 6.2$ Hz), 2.98 (2H, m), 3.28 (2H, t, $J = 6.4$ Hz), 3.53 (2H, t, $J = 6.4$ Hz), 3.61 (2H, br d, $J = 12.4$ Hz), 6.64 (1H, dd, $J = 2.6$, 8.8 Hz), 6.85 (1H, d, $J = 2.8$ Hz), 7.01 (2H, m), 7.20 (2H, m), 7.24 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{20}H_{23}Cl_2FN_2 \cdot 2HCl$: C, 52.88; H, 5.55; N, 6.17. Found: C, 52.73; H, 5.56; N, 6.26.

5.53. 1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-{2-[4-(4-fluorobenzyl)piperidin-1-yl]ethyl}piperidine-4-carboxamide (18)

Compound **18** was prepared using a procedure similar to that described for **5e** from **17**. Yield 99%, oil. ^{1}H NMR ($CDCl_3$): δ 1.05–2.00 (11H, m), 2.06 (3H, s), 2.25–2.55 (2H, m), 2.40 (2H, t, $J = 6.4$ Hz), 2.49 (2H, d, $J = 7.0$ Hz), 2.70–3.00 (3H, m), 3.60–3.90 (3H, m), 4.53 (1H, br d, $J = 13.2$ Hz), 6.95 (2H, m), 7.08 (2H, m), 7.10 (1H, dd, $J = 2.9$, 8.5 Hz), 7.50 (1H, d, $J = 8.5$ Hz), 7.51 (1H, d, $J = 2.9$ Hz). Anal. Calcd for $C_{28}H_{34}Cl_2FN_3O_2 \cdot 0.7H_2O$: C, 61.47; H, 6.52; N, 7.68. Found: C, 61.53; H, 6.43; N, 7.62.

5.54. *tert*-Butyl-4-(4-fluorobenzylidene)piperidine-1-carboxylate (20a)

5.54.1. Step 1: Diethyl (4-fluorobenzyl)phosphonate. A mixture of 4-fluorobenzyl bromide (**19a**) (100 g, 0.53 mol) and triethyl phosphite (120 mL, 0.70 mol) was stirred at 150 °C for 22 h. The mixture was purified by vacuum distillation to give the product (125 g, 96%) as a colorless oil, bp 115–120 °C/0.15 Torr. ^{1}H NMR ($CDCl_3$): δ 1.25 (6H, t, $J = 7.3$ Hz), 3.12 (2H, d, $J = 21.4$ Hz), 4.02 (4H, dq, $J = 7.3$, 7.3 Hz), 6.90–7.10 (2H, m), 7.20–7.35 (2H, m).

5.54.2. Step 2: *tert*-Butyl-4-(4-fluorobenzylidene)piperidine-1-carboxylate (20a). To an ice-cooled stirred solution of the product from step 1 (60.8 g, 0.25 mol) and 15-crown-5 (4.0 mL, 0.02 mol) in THF (400 mL) was added NaH (60% in oil, 9.75 g, 0.24 mol), and the mixture was stirred at 0 °C for 30 min. A solution of *tert*-butyl-4-oxopiperidine-1-carboxylate (42.0 g, 0.21 mol) in THF (150 mL) was added dropwise to the mixture at 0 °C. After stirring at room temperature for 22 h, the mixture was diluted with water at 0 °C and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 30/1–10/1) to give **20a** (47.0 g, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.48 (9H, s), 2.32 (2H, t, J = 5.8 Hz), 2.42 (2H, t, J = 5.8 Hz), 3.40 (2H, t, J = 5.8 Hz), 3.50 (2H, t, J = 5.8 Hz), 6.31 (1H, s), 6.95–7.20 (4H, m).

5.55. *tert*-Butyl-4-[4-(trifluoromethyl)benzylidene]piperidine-1-carboxylate (20b)

Compound **20b** was prepared using a procedure similar to that described for **20a** from 4-(trifluoromethyl)benzyl bromide. ^{1}H NMR ($CDCl_3$): δ 1.47 (9H, s), 2.35 (2H, t, J = 6.2 Hz), 2.43 (2H, t, J = 6.2 Hz), 3.41 (2H, t, J = 6.2 Hz), 3.52 (2H, t, J = 6.2 Hz), 6.37 (1H, s), 7.28 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 8.0 Hz).

5.56. *tert*-Butyl-4-(4-methoxybenzylidene)piperidine-1-carboxylate (20c)

Compound **20c** was prepared using a procedure similar to that described for **20a** from 4-methoxybenzyl chloride. ^{1}H NMR ($CDCl_3$): δ 1.48 (9H, s), 2.31 (2H, t, J = 5.9 Hz), 2.45 (2H, t, J = 5.9 Hz), 3.40 (2H, t, J = 5.9 Hz), 3.49 (2H, t, J = 5.9 Hz), 3.81 (3H, s), 6.30 (1H, s), 6.86 (2H, d, J = 8.8 Hz), 7.13 (2H, d, J = 8.8 Hz).

5.57. *tert*-Butyl-4-(4-fluorobenzyl)piperidine-1-carboxylate (21a)

Compound **20a** (47.0 g, 0.16 mol) was dissolved in MeOH (450 mL) and hydrogenated over 10% Pd/C (water ~50%, 4.70 g) at room temperature for 5 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 10/1) to give **21a** (39.9 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.00–1.80 (5H, m), 1.45 (9H, s), 2.50 (2H, d, J = 6.8 Hz), 2.50–2.75 (2H, m), 3.95–4.20 (2H, m), 6.90–7.15 (4H, m).

The following compounds **21b**,**c** were prepared using a procedure similar to that described for **21a** form **20b**,**c**.

5.58. *tert*-Butyl-4-[4-(trifluoromethyl)benzyl]piperidine-1-carboxylate (21b)

Yield 90%. ^{1}H NMR ($CDCl_3$): δ 1.00–1.80 (5H, m), 1.45 (9H, s), 2.50–2.75 (2H, m), 2.59 (2H, d, J = 7.0 Hz), 3.95–4.20 (2H, m), 7.24 (2H, d, J = 8.0 Hz), 7.54 (2H, d, J = 8.0 Hz).

5.59. *tert*-Butyl-4-(4-methoxybenzyl)piperidine-1-carboxylate (21c)

Yield 97%. ^{1}H NMR ($CDCl_3$): δ 1.00–1.25 (2H, m), 1.45 (9H, s), 1.50–1.70 (3H, m), 2.47 (2H, d, J = 7.0 Hz), 2.50–2.75 (2H, m), 3.79 (3H, s), 3.95–4.20 (2H, m), 6.82 (2H, d, J = 8.7 Hz), 7.05 (2H, d, J = 8.7 Hz).

5.60. 4-(4-Fluorobenzyl)piperidine hydrochloride (22a)

To a stirred solution of **21a** (39.9 g, 0.14 mol) in EtOAc (30 mL) was added 4 N HCl (EtOAc solution, 100 mL). After stirring at room temperature for 1 h, the mixture was concentrated in vacuo. The residue was triturated with Et_2O, collected by filtration, washed with Et_2O, and dried in vacuo to give **22a** (30.1 g, 96%) as a white solid, mp 164–166 °C. ^{1}H NMR (CD_3OD): δ 1.30–1.50 (2H, m), 1.75–2.00 (3H, m), 2.60 (2H, d, J = 6.3 Hz), 2.93 (2H, dt, J = 2.9, 12.8 Hz), 3.30–3.40 (2H, m), 6.95–7.10 (2H, m), 7.15–7.25 (2H, m).

The following compounds **22b**,**c** were prepared using a procedure similar to that described for **22a** from **21b**,**c**.

5.61. 4-[4-(Trifluoromethyl)benzyl]piperidine hydrochloride (22b)

Yield 97%, mp 222–224 °C. ^{1}H NMR (CD_3OD): δ 1.35–1.55 (2H, m), 1.80–2.05 (3H, m), 2.71 (2H, d, J = 7.2 Hz), 2.93 (2H, dt, J = 3.0, 13.1 Hz), 3.30–3.40 (2H, m), 7.40 (2H, d, J = 7.8 Hz), 7.60 (2H, d, J = 7.8 Hz).

5.62. 4-(4-Methoxybenzyl)piperidine hydrochloride (22c)

Yield 76%, mp 175–177 °C. ^{1}H NMR (CD_3OD): δ 1.28–1.55 (2H, m), 1.73–1.95 (3H, m), 2.55 (2H, d, J = 6.8 Hz), 2.92 (2H, dt, J = 3.0, 13.0 Hz), 3.29–3.43 (2H, m), 3.75 (3H, s), 6.84 (2H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz).

5.63. *tert*-Butyl-4-(4-nitrobenzyl)piperidine-1-carboxylate (24)

To a stirred solution of **23**[16] (19.0 g, 60 mmol) in EtOH (200 mL) was added a solution of NaOH (9.6 g, 0.24 mol) in water (80 mL). After stirring at room temperature for 1 h, the mixture was treated with di-*tert*-butyl-dicarbonate (26.2 g, 0.12 mol), stirred for an additional 1 h, and concentrated in vacuo. The residue was partitioned between EtOAc and water, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 4/1) to give **24** (19.9 g, quant.) as a pale yellow oil, which solidified on standing, mp 97–100 °C. ^{1}H NMR ($CDCl_3$): δ 1.05–1.30 (2H, m), 1.45 (9H, s), 1.53–1.80 (3H, m), 2.55–2.72 (2H, m), 2.65 (2H, d, J = 7.2 Hz), 4.01–4.15 (2H, m), 7.30 (2H, d, J = 8.8 Hz), 8.16 (2H, d, J = 8.8 Hz).

5.64. *tert*-Butyl-4-(4-aminobenzyl)piperidine-1-carboxylate (25)

A mixture of **24** (10.00 g, 31 mmol), $FeCl_3 \cdot 6H_2O$ (0.81 g, 3 mmol), activated carbon (2.00 g), and $NH_2NH_2 \cdot H_2O$ (6.08 mL, 125 mmol) in THF (100 mL) was stirred at reflux for 18 h. The mixture was cooled to room temperature and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 3/1–1/1) to give **25** (8.51 g, 94%) as a colorless oil, which solidified on standing, mp 68–71 °C. ^{1}H NMR ($CDCl_3$): δ 0.95–1.25 (2H, m), 1.45 (9H, s), 1.50–1.70 (3H, m), 2.42 (2H, d, J = 6.6 Hz), 2.50–2.75 (2H, m), 3.57 (2H, br s), 3.95–4.15 (2H, m), 6.62 (2H, d, J = 8.5 Hz), 6.92 (2H, d, J = 8.5 Hz).

5.65. *tert*-Butyl-4-(4-morpholin-4-ylbenzyl)piperidine-1-carboxylate (26)

A mixture of **25** (970 mg, 3.3 mmol), bis(2-chloroethyl) ether (715 mg, 5.0 mmol), KI (1.66 g, 10 mmol), and K_2CO_3 (1.38 g, 10 mmol) in DMF (15 mL) was stirred at 80 °C for 18 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 3/1) followed by recrystallization from hexane/EtOAc to give **26** (880 mg, 73%) as a pale yellow solid, mp 126–127 °C. ^{1}H NMR ($CDCl_3$): δ 1.00–1.25 (2H, m), 1.45 (9H, s), 1.50–1.70 (3H, m), 2.46 (2H, d, J = 6.6 Hz), 2.50–2.75 (2H, m), 3.13 (4H, m), 3.86 (4H, m), 3.95–4.20 (2H, m), 6.84 (2H, d, J = 8.6 Hz), 7.05 (2H, d, J = 8.6 Hz).

5.66. 4-(4-Nitrobenzyl)piperidine hydrochloride (27a)

Compound **27a** was prepared using a procedure similar to that described for **22a** from **24**. Yield 91%, mp 205–207 °C. ^{1}H NMR (CD_3OD): δ 1.33–1.58 (2H, m), 1.79–2.10 (3H, m), 2.76 (2H, d, J = 7.0 Hz), 2.95 (2H, dt, J = 2.9, 13.0 Hz), 3.30–3.44 (2H, m), 7.46 (2H, d, J = 8.8 Hz), 8.18 (2H, d, J = 8.8 Hz).

5.67. 4-[4-(Piperidin-4-ylmethyl)phenyl]morpholine dihydrochloride (27b)

Compound **27b** was prepared using a procedure similar to that described for **22a** from **26**. Yield 79%. ^{1}H NMR (DMSO-d_6): δ 1.36–1.88 (5H, m), 2.52–2.80 (4H, m), 3.17–3.22 (2H, m), 3.42 (4H, m), 4.00 (4H, m), 7.25–7.30 (2H, m), 7.53–7.60 (2H, m), 8.89 (1H, m), 9.12 (1H, m).

5.68. 1-Acetyl-4-benzylpiperidine (28)

Acetic anhydride (110 mL, 1.17 mol) was added dropwise to 4-benzylpiperidine (**2**) (100 g, 0.57 mol) at 0 °C under stirring, and the mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was partitioned between EtOAc (500 mL) and saturated aqueous $NaHCO_3$ (1 L). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layer was washed with water (500 mL) and brine (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give **28** (129 g, quant.) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.00–1.30 (2H, m), 1.60–1.90 (3H, m), 2.07 (3H, s), 2.35–2.60 (3H, m), 2.85–3.05 (1H, m), 3.65–3.85 (1H, m), 4.50–4.70 (1H, m), 7.05–7.35 (5H, m).

5.69. 4-[(1-Acetylpiperidin-4-yl)methyl]benzenesulfonyl chloride (29)

A solution of **28** (60.0 g, 0.28 mol) in DCM (100 mL) was added dropwise to chlorosulfonic acid (92 mL, 1.4 mol) at 0 °C under stirring, and the mixture was stirred at 0 °C for 30 min and at room temperature for 1.5 h. The mixture was poured into ice water (1 L) and extracted with DCM (500 mL, 250 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (2 × 500 mL) and brine (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) to give **29** (54.2 g, 62%) as a white solid, mp 72–75 °C. ^{1}H NMR ($CDCl_3$): δ 1.05–1.35 (2H, m), 1.60–1.95 (3H, m), 2.09 (3H, s), 2.35–2.65 (1H, m), 2.68 (2H, d, J = 6.6 Hz), 2.85–3.15 (1H, m), 3.70–3.90 (1H, m), 4.50–4.75 (1H, m), 7.39 (2H, d, J = 8.4 Hz), 7.97 (2H, d, J = 8.4 Hz).

5.70. 4-[(1-Acetylpiperidin-4-yl)methyl]benzenesulfonamide (30a)

A solution of **29** (6.32 g, 20 mmol) in THF (50 mL) was added dropwise to 25% aqueous ammonia (30 mL) under stirring, and the mixture was stirred at room temperature for 2 h. The organic solvent was removed in vacuo, and the residue was treated with 1 N HCl (10 mL) and extracted with EtOAc (80 mL, 2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–9/1) to give **30a** (5.58 g, 94%) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ 1.03–1.32 (2H, m), 1.58–1.90 (3H, m), 2.08 (3H, s), 2.48 (1H, dt, J = 2.8, 13.2 Hz), 2.63 (2H, d, J = 6.8 Hz), 2.98 (1H, dt, J = 2.2, 12.4 Hz), 3.70–3.87(1H, m), 4.53–4.67 (1H, m), 4.90–5.05 (2H, m), 7.29 (2H, d, J = 8.4 Hz), 7.86 (2H, d, J = 8.4 Hz).

5.71. 4-[(1-Acetylpiperidin-4-yl)methyl]-*N*-methylbenzenesulfonamide (30b)

Compound **30b** was prepared using a procedure similar to that described for **30a** from 40% aqueous methylamine. Yield 46%, oil. ^{1}H NMR ($CDCl_3$): δ 1.05–1.30 (2H, m), 1.60–1.91 (3H, m), 2.08 (3H, s), 2.49 (1H, dt, J = 2.6, 12.8 Hz), 2.63 (2H, d, J = 8.4 Hz), 2.67 (3H, d, J = 6.2 Hz), 2.99 (1H, dt, J = 2.6, 12.8 Hz), 3.73–3.86 (1H, m), 4.53–4.80 (2H, m), 7.29 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz).

5.72. 4-(Piperidin-4-ylmethyl)benzenesulfonamide hydrochloride (31a)

A solution of **30a** (5.53 g, 19 mmol) in concentrated HCl (50 mL) was stirred at reflux for 6 h. The mixture was

concentrated in vacuo, and the residue was recrystallized from MeOH/*i*-PrOH to give **31a** (4.53 g, 83%) as a white solid, mp 218–220 °C. ^{1}H NMR (CD_3OD): δ 1.32–1.58 (2H, m), 1.78–2.05 (3H, m), 2.71 (2H, d, J = 6.8 Hz), 2.83–3.02 (2H, m), 3.28–3.43 (2H, m), 7.38 (2H, d, J = 8.4 Hz), 7.83 (2H, d, J = 8.4 Hz).

5.73. *N*-Methyl-4-(piperidin-4-ylmethyl)benzenesulfonamide hydrochloride (31b)

Compound **31b** was prepared using a procedure similar to that described for **31a** from **30b**. Yield 90%. ^{1}H NMR (CD_3OD): δ 1.30–1.60 (2H, m), 1.78–2.05 (3H, m), 2.50 (3H, s), 2.71 (2H, d, J = 7.0 Hz), 2.83–3.04 (2H, m), 3.30–3.45 (2H, m), 7.42 (2H, d, J = 8.4 Hz), 7.77 (2H, d, J = 8.4 Hz).

5.74. 4-Benzyl-1-(trifluoroacetyl)piperidine (32)

To a stirred solution of 4-benzylpiperidine (**2**) (98.8 g, 0.56 mol) in EtOAc (500 mL) was added trifluoroacetic anhydride (TFAA) (159 mL, 1.13 mol) at 0 °C. The mixture was stirred at room temperature for 3 h and concentrated in vacuo. The residue was partitioned between EtOAc (500 mL) and saturated aqueous $NaHCO_3$ (1 L). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), 1 N HCl (2 × 200 mL), and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1/0–9/1) to give **32** (149 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.10–1.40 (2H, m), 1.65–1.95 (3H, m), 2.57 (2H, d, J = 7.0 Hz), 2.60–2.80 (1H, m), 2.95–3.15 (1H, m), 3.90–4.10 (1H, m), 4.45–4.60 (1H, m), 7.05–7.40 (5H, m).

5.75. 4-{[1-(Trifluoroacetyl)piperidin-4-yl]methyl}benzenesulfonyl chloride (33)

A solution of **32** (54.3 g, 0.20 mol) in DCM (100 mL) was added dropwise to chlorosulfonic acid (117 g, 1.0 mol) at 0 °C under stirring, and the mixture was stirred at room temperature for 5 h. The mixture was poured into ice water (500 g) and extracted with DCM (400 mL, 2 × 200 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1/0–1/1) to give **33** (47.8 g, 65%) as a colorless oil, which solidified on standing in a refrigerator, mp 65–68 °C. ^{1}H NMR ($CDCl_3$): δ 1.26–1.39 (2H, m), 1.75–2.05 (3H, m), 2.66–2.78 (1H, m), 2.71 (2H, d, J = 7.0 Hz), 3.01–3.15 (1H, m), 3.98–4.10 (1H, m), 4.50–4.61 (1H, m), 7.40 (2H, d, J = 8.4 Hz), 7.98 (2H, d, J = 8.4 Hz).

5.76. *N*,*N*-Dimethyl-4-{[1-(trifluoroacetyl)piperidin-4-yl]-methyl}benzenesulfonamide (34a)

To an ice-cooled stirred solution of **33** (6.24 g, 17 mmol) in THF (40 mL) was added 50% aqueous dimethylamine (4.4 mL, 42 mmol). After stirring at room temperature for 0.5 h, the mixture was diluted with 1 N HCl (80 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was washed with water (100 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 3/1–3/2) to give **34a** (5.25 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.15–1.40 (2H, m), 1.68–2.00 (3H, m), 2.65–2.80 (1H, m), 2.66 (2H, d, J = 7.0 Hz), 2.72 (6H, s), 2.98–3.17 (1H, m), 3.93–4.07 (1H, m), 4.47–4.62 (1H, m), 7.32 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz).

5.77. 4-[(4-{[1-(Trifluoroacetyl)piperidin-4-yl]methyl}phenyl)sulfonyl]morpholine (34b)

To a stirred solution of morpholine (1.05 g, 12 mmol) and Et_3N (2.09 mL, 15 mmol) in THF (10 mL) was added a solution of **33** (3.70 g, 10 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (50 mL), washed with water (10 mL), 1N HCl (10 mL), and brine (3 × 10 mL), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 4/1–1/1) to give **34b** (3.99 g, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.17–1.38 (2H, m), 1.73–1.94 (3H, m), 2.66 (2H, d, J = 7.0 Hz), 2.68–2.78 (1H, m), 3.00 (4H, t, J = 4.8 Hz), 3.01–3.15 (1H, m), 3.76 (4H, t, J = 4.8 Hz), 3.98–4.10 (1H, m), 4.53–4.60 (1H, m), 7.33 (2H, d, J = 8.4 Hz), 7.69 (2H, d, J = 8.4 Hz).

5.78. 4-{[4-(Piperidin-4-ylmethyl)phenyl]sulfonyl}morpholine (35b)

To a stirred solution of **34b** (3.93 g, 9.3 mmol) in MeOH (40 mL) was added a solution of K_2CO_3 (3.88 g, 28 mmol) in water (20 mL), and the mixture was stirred at room temperature for 12 h. The organic solvent was removed in vacuo, and the residue was extracted with DCM (40 mL, 2 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give **34b** (3.08 g, quant.) as a white solid, mp 98–101 °C. ^{1}H NMR ($CDCl_3$): δ 1.21–1.82 (5H, m), 2.60–2.71 (4H, m), 3.00 (4H, t, J = 4.8 Hz), 3.19–3.26 (2H, m), 3.75 (4H, t, J = 4.8 Hz), 5.08 (1H, br s), 7.32 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.4 Hz).

5.79. *N*,*N*-Dimethyl-4-(piperidin-4-ylmethyl)benzenesulfonamide (35a)

Compound **35a** was prepared using a procedure similar to that described for **35b** from **34a**. Yield 89%, mp 66–70 °C. ^{1}H NMR ($CDCl_3$): δ 1.05–1.30 (2H, m), 1.50–1.80 (3H, m), 2.45–2.65 (2H, m), 2.61 (2H, d, J = 7.0 Hz), 2.71 (6H, s), 3.00–3.15 (2H, m), 7.31 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz).

5.80. 1-Acetyl-4-[4-(methylsulfonyl)benzyl]piperidine (36a)

To a solution of Na_2SO_3 (4.57 g, 36 mmol) and $NaHCO_3$ (6.10 g, 73 mmol) in water (40 mL) was added portionwise **29** (11.46 g, 36 mmol) at 75 °C. After being stirred at 75 °C for 1 h, the mixture was treated with chloroacetic

acid (5.14 g, 54 mmol) followed by a solution of NaOH (2.18 g, 55 mmol) in water (4.4 mL) and stirred at reflux for 20 h. The mixture was treated with 1 N HCl (20 mL) at 0 °C and extracted with EtOAc (60 mL, 30 mL). The organic layer was washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0–9/1) to give **36a** (8.76 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.05–1.35 (2H, m), 1.55–1.95 (3H, m), 2.08 (3H, s), 2.40–2.60 (1H, m), 2.66 (2H, d, J = 7.4 Hz), 2.90–3.10 (1H, m), 3.06 (3H, s), 3.70–3.90 (1H, m), 4.55–4.70 (1H, m), 7.34 (2H, d, J = 8.4 Hz), 7.87 (2H, d, J = 8.4 Hz).

5.81. 1-Acetyl-4-[4-(ethylsulfonyl)benzyl]piperidine (36b)

Compound **36b** was prepared using a procedure similar to that described for **36a** from 2-bromopropionic acid. Yield 61%, oil. ^{1}H NMR ($CDCl_3$): δ 1.05–1.30 (2H, m), 1.29 (3H, t, J = 7.2 Hz), 1.60–1.92 (3H, m), 2.09 (3H, s), 2.40–2.60 (1H, m), 2.65 (2H, dd, J = 2.0, 7.4 Hz), 2.90–3.05 (1H, m), 3.12 (2H, q, J = 7.2 Hz), 3.72–3.88 (1H, m), 4.55–4.70 (1H, m), 7.34 (2H, d, J = 8.4 Hz), 7.83 (2H, d, J = 8.4 Hz).

5.82. 4-[4-(Methylsulfonyl)benzyl]piperidine (37a)

A mixture of **36a** (8.76 g, 30 mmol) and concentrated HCl (100 mL) was stirred at reflux for 4 h and concentrated in vacuo. The residue was suspended in *i*-PrOH (100 mL) and concentrated in vacuo. The residue was suspended in *i*-PrOH (50 mL), stirred at reflux for 30 min, and cooled to room temperature. The precipitate was collected by filtration, washed with *i*-PrOH, and dried in vacuo to give the hydrochloride salt of **37a** (7.51 g) as a white solid. ^{1}H NMR (CD_3OD): δ 1.30–1.60 (2H, m), 1.75–2.10 (3H, m), 2.75 (2H, d, J = 7.0 Hz), 2.80–3.05 (2H, m), 3.10 (3H, s), 3.25–3.45 (2H, m), 7.49 (2H, d, J = 8.1 Hz), 7.89 (2H, d, J = 8.1 Hz). A solution of the hydrochloride salt (7.51 g) in water was basified with 1N NaOH (40 mL) and extracted with DCM (3 × 30 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O to give the free base **37a** (6.16 g, 82%) as a white solid, mp 97–99 °C. ^{1}H NMR ($CDCl_3$): δ 1.07–1.27 (2H, m), 1.50–1.73 (3H, m), 2.48–2.61 (2H, m), 2.62 (2H, d, J = 6.6 Hz), 3.03–3.08 (2H, m), 3.05 (3H, s), 7.34 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.4 Hz).

5.83. 4-[4-(Ethylsulfonyl)benzyl]piperidine (37b)

Compound **37b** was prepared using a procedure similar to that described for **37a** from **36b**. Yield 69%, oil. ^{1}H NMR ($CDCl_3$): δ 1.05–1.30 (2H, m), 1.28 (3H, t, J = 7.5 Hz), 1.55–1.78 (3H, m), 2.45–2.65 (4H, m), 3.00–3.15 (2H, m), 3.11 (2H, q, J = 7.5 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.81 (2H, d, J = 8.4 Hz).

5.84. 4-[(1-Acetylpiperidin-4-yl)methyl]benzenethiol (38)

To an ice-cooled stirred solution of concentrated H_2SO_4 (6.6 mL) in water (36 mL) was added **29** (3.00 g, 9.5 mmol) followed by Zn powder (6.33 g, 97 mmol), and the mixture was stirred at 60 °C for 6 h. After cooling to room temperature, the mixture was diluted with water (40 mL) and filtered (Celite). The filtrate was extracted with DCM (80, 50 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give **38** (2.22 g, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.00–1.25 (2H, m), 1.60–2.00 (3H, m), 2.07 (3H, s), 2.38–2.57 (3H, m), 2.88–3.03 (1H, m), 3.41 (1H, s), 3.72–3.83 (1H, m), 4.55–4.65 (1H, m), 7.01 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz).

5.85. 1-Acetyl-4-[4-(methylsulfanyl)benzyl]piperidine (39a)

To a stirred solution of **38** (2.22 g, 8.9 mmol) in DMF (50 mL) was added iodomethane (0.72 mL, 12 mmol) followed by K_2CO_3 (2.40 g, 17 mmol). After stirring at room temperature for 15 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) to give **39a** (2.03 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.00–1.25 (2H, m), 1.60–1.75 (3H, m), 2.07 (3H, s), 2.40–2.57 (3H, m), 2.47 (3H, s), 2.88–3.03 (1H, m), 3.71–3.84 (1H, m), 4.54–4.65 (1H, m), 7.06 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz).

5.86. 1-Acetyl-4-[4-(isopropylsulfanyl)benzyl]piperidine (39b)

Compound **39b** was prepared using a procedure similar to that described for **39a** from 2-iodopropane. Yield 80%, oil. ^{1}H NMR ($CDCl_3$): δ 1.02–1.30 (2H, m), 1.29 (6H, d, J = 6.6 Hz), 1.60–1.82 (3H, m), 2.07 (3H, s), 2.40–2.58 (3H, m), 2.90–3.05 (1H, m), 3.25–3.42 (1H, m), 3.70–3.85 (1H, m), 4.55–4.65 (1H, m), 7.06 (2H, d, J = 8.0 Hz), 7.33 (2H, d, J = 8.0 Hz).

5.87. 1-Acetyl-4-[4-(isopropylsulfonyl)benzyl]piperidine (40)

To an ice-cooled stirred solution of **39b** (1.06 g, 3.6 mmol) in DCM (30 mL) was added *m*CPBA (70%, 1.89 g, 7.7 mmol). After stirring at room temperature for 3 h, the mixture was diluted with DCM (30 mL), washed with 5% aqueous $Na_2S_2O_3$ (20 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 10/1) to give **40** (1.12 g, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.03–1.40 (2H, m), 1.29 (6H, d, J = 6.8 Hz), 1.53–2.00 (3H, m), 2.07 (3H, s), 2.40–2.70 (3H, m), 2.82–3.05 (1H, m), 3.10–3.25 (1H, m), 3.70–3.85 (1H, m), 4.55–4.70 (1H, m), 7.32 (2H, d, J = 8.2 Hz), 7.80 (2H, d, J = 8.2 Hz).

5.88. 4-[4-(Isopropylsulfonyl)benzyl]piperidine (41)

Compound **41** was prepared using a procedure similar to that described for **37a** from **40**. Yield 86%. ^{1}H NMR ($CDCl_3$): δ 1.07–1.25 (2H, m), 1.30 (6H, d, J = 7.0 Hz), 1.55–1.78 (3H, m), 2.55 (2H, dt, J = 2.6,

12.0 Hz), 2.62 (2H, d, $J = 6.8$ Hz), 3.00–3.30 (3H, m), 7.33 (2H, d, $J = 8.4$ Hz), 7.78 (2H, d, $J = 8.4$ Hz).

5.89. 4-[4-(Methylsulfanyl)benzyl]piperidine (42)

Compound **42** was prepared using a procedure similar to that described for **37a** from **39a**. Yield 73%. ^{1}H NMR ($CDCl_3$): δ 1.08–1.34 (2H, m), 1.52–1.72 (3H, m), 2.47 (3H, s), 2.47–2.67 (4H, m), 3.02–3.15 (2H, m), 7.06 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz).

5.90. Receptor binding assays

CHO-K1 and CCR5-expressing CHO cells[19] were incubated with various concentrations of test compounds in binding buffer (Ham's F-12 medium containing 20 mM HEPES and 0.5% bovine serum albumin, pH 7.2) containing 200 pM ^{125}I-labeled RANTES. Binding reactions were performed at room temperature for 40 min. The binding reactions were terminated by washing out the free ligand with cold phosphate-buffered saline, and the cell-associated radioactivity was counted by a TopCount scintillation counter (Packard). Binding assays for other chemokine receptors were carried out in a similar manner using the following ligands: RANTES for CCR1, monocyte chemoattractant protein 1 for CCR2, eotaxin for CCR3, thymus- and activation-regulated chemokine for CCR4, and MIP-3β for CCR7.

5.91. HIV-1 Envelope-mediated membrane fusion assay

COS-7 cells were maintained in Dulbecco's modified Eagle medium (D-MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin G, and 100 μg/mL streptomycin. MOLT-4/CCR5/Luc$^+$ cells, a lymphoblastoid cell line that expresses human CCR5 and that has an integrated copy of the HIV-1 long terminal repeat-driven luciferase reporter gene, were maintained in RPMI 1640 medium supplemented with 10% FBS, 100 U/mL penicillin G, 100 μg/mL streptomycin, and 500 μg/mL geneticin. Tat, Rev, and envelope cDNA were amplified from total RNA of R5 HIV-1 (JR-FL)-infected cells and cloned into an expression vector for mammalian cells. Those expression vectors were mixed at a ratio of 5:1:3 and co-transfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After a 2 day incubation, transfected COS-7 cells and MOLT-4/CCR5/Luc$^+$ cells were seeded in a 96-well plate at 10^4 cells in each well, and various concentrations of test compounds were added to the wells. The cell suspension was incubated at 37 °C. The mixture of D-MEM and RPMI 1640 medium supplemented with 10% FBS, 100 U/mL penicillin G, and 100 μg/mL streptomycin was used as a medium for the membrane fusion. After an overnight incubation, Luc-Screen (Tropix) was added to each well, and the mixtures were incubated at room temperature for 10 min. The luciferase activity was measured with a luminometer (Wallac 1420 ARVOsx).

5.92. Antiviral assay

Peripheral blood mononuclear cells (PBMC) obtained from healthy volunteers were isolated with Ficoll–Hypaque gradient density centrifugation and cultured in RPMI 1640 medium supplemented with 20% FBS, 5 μg/mL phytohemagglutinin-P (PHA), 100 U/mL recombinant human interleukin 2, 100 U/mL penicillin G, and 100 μg/mL streptomycin for 3 days. The above medium without PHA was used in the following assay. The PHA-stimulated PBMC were inoculated with 10 ng of p24 of R5 HIV-1 (Ba-L strain) per 4×10^6 cells and incubated for 2 h. The cells were washed with media to remove unadsorbed viral particles and then seeded into 96-well plates (2×10^5 cells/well) with media containing various concentrations of test compounds. On day 4 after infection, two-thirds of the culture supernatant was removed and replaced with media containing the same concentration of the test compounds. On day 7 after infection, the culture supernatants were collected, and their p24 antigen levels were determined using an HIV-1 p24 antigen ELISA kit (ZeptoMetrix).

5.93. Pharmacokinetic analysis in dogs

Test compounds (10 mg/2 mL/kg) suspended in 0.5% methylcellulose were administered to male beagle dogs ($n = 3$) by oral gavage. Blood samples were collected at different time points (pre, 15, 30 min, 1, 2, 4, 8, 24 h) from the jugular vein. Each blood sample was taken into a heparinized tube, and plasma was separated by centrifugation (3000 rpm, 15 min, 4 °C). The plasma sample (100 μL) was deproteinized with acetonitrile (100 μL), and the resulting protein precipitate was removed by centrifugation (15,000 rpm, 10 min). The compound concentrations in the supernatant were measured by LC/MS/MS. The LC/MS/MS analyses were performed on an API 3000 triple quadruple mass spectrometer (Perkin–Elmer Sciex) interfaced with an LC-10Avp HPLC system (Shimadzu). The mass spectrometer was equipped with a turbo ionspray source and operated in positive ion mode. The HPLC conditions were as follows: column, L-column ODS (2.1 × 150 mm); mobile phase, 0.01 M HCO_2NH_4 (adjusted to pH 3.0 with HCO_2H)/MeCN = 1/1; flow rate, 0.2 mL/min; column temperature, 40 °C.

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