Discovery of a Piperidine-4-carboxamide CCR5 Antagonist (TAK-220) with Highly Potent Anti-HIV-1 Activity

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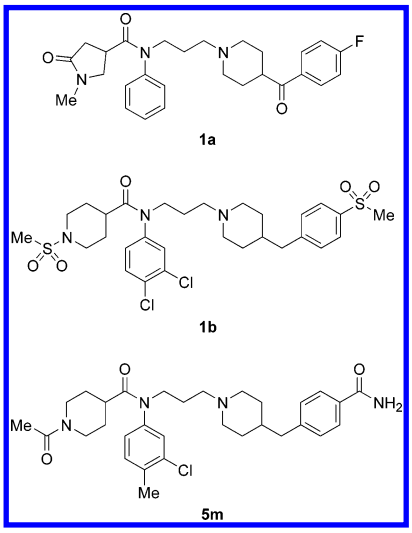
We incorporated various polar groups into previously described piperidine-4-carboxamide CCR5 antagonists to improve their metabolic stability in human hepatic microsomes. Introducing a carbamoyl group into the phenyl ring of the 4-benzylpiperidine moiety afforded the less lipophilic compound **5f**, which possessed both high metabolic stability and good inhibitory activity of HIV-1 envelope-mediated membrane fusion (IC_{50} = 5.8 nM). Further optimization to increase potency led to the discovery of 1-acetyl-*N*-{3-[4-(4-carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3-chloro-4-methylphenyl)piperidine-4-carboxamide (**5m**, TAK-220), which showed high CCR5 binding affinity (IC_{50} = 3.5 nM) and potent inhibition of membrane fusion (IC_{50} = 0.42 nM), as well as good metabolic stability. Compound **5m** strongly inhibited the replication of CCR5-using HIV-1 clinical isolates in human peripheral blood mononuclear cells (mean EC_{50} = 1.1 nM, EC_{90} = 13 nM) and exhibited a good pharmacokinetic profile in monkeys (BA = 29%). This compound has been chosen as a clinical candidate for further development.

Introduction

Despite worldwide efforts to prevent the spread of human immunodeficiency virus type 1 (HIV-1), the number of HIV-1-infected people still continues to rise.[1] Although highly active antiretroviral therapy (HAART) has been successful in suppressing viral replication and in reducing HIV-1-associated mortality, there remain problems in currently available HAART including the development of viral resistance and the toxicity of the antiretroviral drugs.[2] Thus it is strongly desired to develop a new class of anti-HIV-1 agents with superior efficacy and safety profiles.

Recent advances in our knowledge of chemokine receptors functioning as HIV-1 co-receptors have provided a novel strategy for controlling HIV-1 infection.[3] HIV-1 strains that cause the initial infection primarily utilize CC chemokine receptor 5 (CCR5),[4] and CCR5-using (R5) HIV-1 is isolated predominantly 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 CCR5Δ32-homozygous individuals are highly resistant to HIV-1 infection; however, 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, and indeed several compounds (UK-427857,[11] SCH-417690,[12] GW-873140[13]) are now being evaluated in clinical trials.

Chart 1



Our laboratories previously reported that TAK-779[14,15] is an injectable CCR5 antagonist. To develop an orally bioavailable CCR5 antagonist, further high throughput screening was carried out, which led to the discovery of a novel lead compound **1a**[16] (Chart 1, IC_{50} = 1900 nM), whose chemical structure differs from that of TAK-779. Subsequent optimization identified a series of piperidine-4-carboxamide derivatives, exemplified by **1b**, which had low nanomolar affinity for CCR5 and exhibited good anti-HIV-1 activity.[17] In vitro metabolic stability studies in human hepatic microsomes, however, showed these compounds to be rapidly metabolized. In this paper, we describe our efforts to identify potent and metabolically stable CCR5 antagonists from the piperidine-4-carboxamide derivatives, which eventually led to the discovery of the clinical candidate **5m**.

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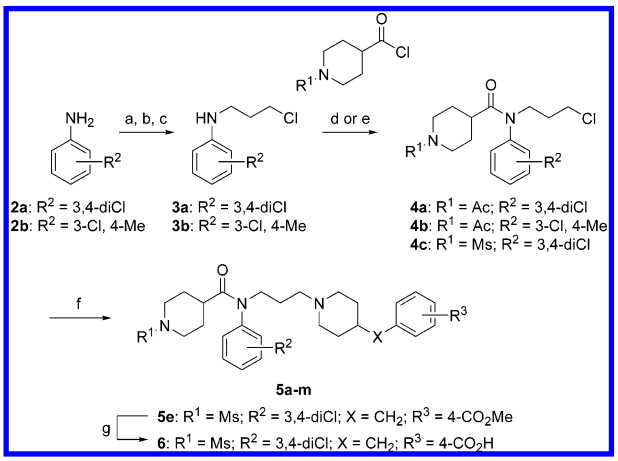
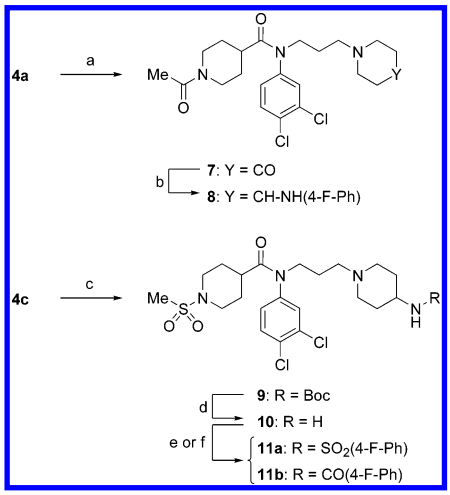
Scheme 1[a]



[a] Reagents: (a) HCO_2Ac; (b) $Br(CH_2)_3Cl$, Cs_2CO_3, acetone; (c) concd HCl, *i*-PrOH; (d) Et_3N, DCM; (e) NMP; (f) 4-substituted piperidine, KI, K_2CO_3, MeCN or MeCN/DMF; (g) aq KOH, MeOH.

Scheme 2[a]



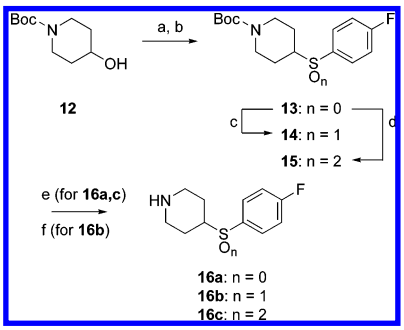
[a] Reagents: (a) 4-piperidone hydrochloride, KI, K_2CO_3, MeCN; (b) 4-F-$PhNH_2$, $NaBH(OAc)_3$, THF; (c) 4-(Boc-amino)piperidine, KI, K_2CO_3, MeCN; (d) HCl/EtOAc, MeOH; (e) 4-F-$PhSO_2Cl$, Et_3N, DCM; (f) 4-F-PhCOCl, Et_3N, DCM.

Chemistry

Target compounds were synthesized as outlined in Schemes 1 and 2. N-Formylation of the anilines **2a** and **2b** using acetic formic anhydride gave the corresponding formamides (Scheme 1). Subsequent N-alkylation with 1-bromo-3-chloropropane in the presence of cesium carbonate followed by removal of the formyl group under acidic conditions afforded the *N*-(3-chloropropyl)anilines **3a** and **3b**. Acylation of **3a** and **3b** with the piperidine-4-carbonyl chlorides gave the chlorides **4a**−**c**, which were reacted with 4-substituted piperidines in the presence of potassium iodide and potassium carbonate to afford the target compounds **5a**−**m**. The ester group of compound **5e** was hydrolyzed with aqueous sodium hydroxide affording the carboxylic acid **6**.

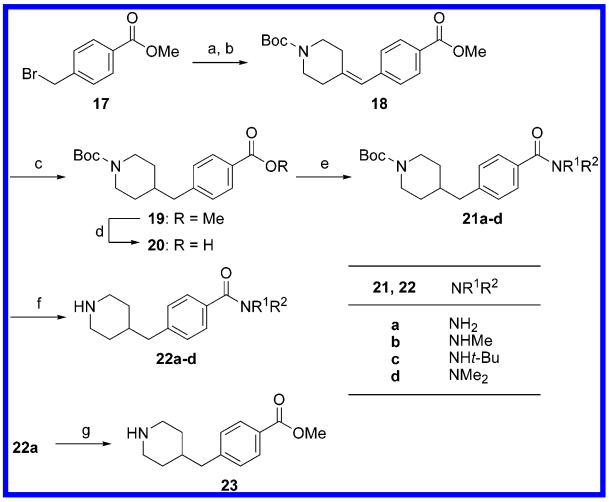
Compounds **8**, **11a**, and **11b** were accessed as shown in Scheme 2. Chloride **4a** was reacted with 4-piperidone followed by reductive amination with 4-fluoroaniline to afford **8**. N-Alkylation of 4-(*tert*-butoxycarbonylamino)piperidine with the chloride **4c** gave compound **9**, which on deprotection by acid yielded the diamine **10**. Compound **10** was converted to the sulfonamide **11a** and amide **11b** by reaction with the corresponding acid chlorides.

Scheme 3[a]



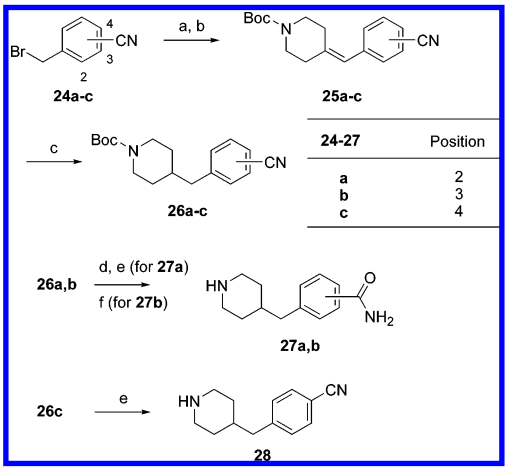
[a] Reagents: (a) MsCl, Et_3N, THF; (b) 4-F-PhSH, K_2CO_3, DMF; (c) 1 equiv *m*CPBA, DCM; (d) 2.2 equiv *m*CPBA, DCM; (e) HCl/EtOAc, MeOH; (f) TFA, DCM.

Scheme 4[a]



[a] Reagents: (a) $(EtO)_3P$; (b) 1-Boc-4-piperidone, NaH, THF; (c) H_2, Pd/C, MeOH; (d) aq NaOH, EtOH; (e) $R^1R^2NH{\cdot}HCl$, Et_3N, EDC, HOBt, DMF; (f) HCl/EtOAc, MeOH; (g) concd H_2SO_4, MeOH.

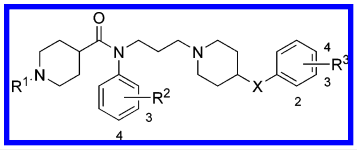
Scheme 5[a]



[a] Reagents: (a) $(EtO)_3P$; (b) 1-Boc-4-piperidone, NaH, THF; (c) H_2, Pd/C, MeOH; (d) H_2O_2, aq NaOH, EtOH; (e) HCl/EtOAc, MeOH or EtOAc; (f) concd HCl.

The required piperidines were prepared as shown in Schemes 3−5. Mesylation of the alcohol **12** followed by displacement with 4-fluorobenzenethiol using potassium carbonate as base, provided the sulfide **13** (Scheme 3). Mono-oxidation of **13** with 1 equiv of 3-chloroperoxybenzoic acid (*m*CPBA) at 0 °C afforded the sulfoxide **14**. Alternatively, use of 2.2 equiv of *m*CPBA at room temperature yielded the sulfone **15**. Removal of the *tert*-butoxycarbonyl (Boc) group of **13** and **15** using

Table 1. Biological Activity and Metabolic Stability of Piperidine-4-carboxamide Derivatives



compd	R^1	R^2	X	R^3	CCR5[a] IC_{50} (nM)	fusion[b] IC_{50} (nM)	stability[c] % remaining	ClogP[d]
1b	Ms	3,4-diCl	CH_2	4-Ms	2.2	0.80	62	3.9
1c	Ms	3,4-diCl	CH_2	4-F	3.3	2.1	67	5.6
1d	Ac	3,4-diCl	CH_2	4-F	1.2	3.0	47	5.0
1e	Ac	H	CH_2	H	16	72	80	3.6
5a	Ac	3,4-diCl	S	4-F	1.7	1.8	30	4.5
5b	Ac	3,4-diCl	SO	4-F	3.2	2.7	36	2.5
5c	Ac	3,4-diCl	SO_2	4-F	2.9	3.9	31	2.4
8	Ac	3,4-diCl	NH	4-F	20	26	70	3.7
11a	Ms	3,4-diCl	$NHSO_2$	4-F	4.6	4.1	55	3.6
11b	Ms	3,4-diCl	NHCO	4-F	730	NT[e]	87	3.4
5d	Ms	3,4-diCl	CH_2	4-CN	1.7	1.4	50	4.9
5e	Ms	3,4-diCl	CH_2	4-CO_2Me	4.6	7.0	66	5.3
6	Ms	3,4-diCl	CH_2	4-CO_2H	66	44	94	3.0
5f	Ms	3,4-diCl	CH_2	4-$CONH_2$	8.9	5.8	88	4.0
5g	Ms	3,4-diCl	CH_2	3-$CONH_2$	2.8	2.0	81	4.0
5h	Ms	3,4-diCl	CH_2	2-$CONH_2$	12	6.4	91	3.7
5i	Ms	3,4-diCl	CH_2	4-CONHMe	5.1	9.8	83	4.1
5j	Ms	3,4-diCl	CH_2	4-CONH*t*-Bu	11	12	57	5.3
5k	Ms	3,4-diCl	CH_2	4-$CONMe_2$	19	8.2	74	3.8
5l	Ac	3,4-diCl	CH_2	4-$CONH_2$	3.8	2.2	88	3.4
5m	Ac	3-Cl, 4-Me	CH_2	4-$CONH_2$	3.5	0.42	92	3.3

[a] Inhibition of ^{125}I-labeled RANTES binding to CCR5-expressing CHO cells. [b] Inhibition of HIV-1 envelope-mediated membrane fusion. [c] Metabolic stability in human hepatic microsomes. The remaining percentage of the parent compounds was measured after incubation for 20 min. [d] Daylight CLOGP 4.82. [e] Not tested.

hydrogen chloride gave piperidines **16a** and **16c**, respectively. Piperidine **16b** was obtained by deprotection of **14** using trifluoroacetic acid.

The preparation of the piperidines **22a**−**d** was based on the Horner−Wadsworth−Emmons reaction (Scheme 4). Arbuzov reaction of methyl 4-(bromomethyl)benzoate (**17**) with triethyl phosphite gave the corresponding phosphonate, which on treatment with sodium hydride followed by *tert*-butyl 4-oxopiperidine-1-carboxylate formed the olefin **18**. Hydrogenation of **18** followed by hydrolysis of the ester group gave the carboxylic acid **20**. Coupling of **20** with the corresponding amines using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) afforded the amides **21a**−**d**, which were deprotected to yield the piperidines **22a**−**d**. Compound **23** was prepared by heating of **22a** in methanolic sulfuric acid. Carbamoyl piperidines **27a** and **27b** were accessed from the corresponding nitrile derivatives **26a** and **26b**, which were prepared using the same route as above (Scheme 5). Treatment of **26a** with hydrogen peroxide in basic medium followed by deprotection gave **27a**. Alternatively, acid hydrolysis of the cyano group of **26b** and concomitant deprotection of the Boc group afforded **27b**. The cyano piperidine **28** was prepared by removal of the Boc group of **26c** under acidic conditions.

Results and Discussion

The synthesized compounds were evaluated for their potency in the inhibition of ^{125}I-labeled RANTES binding to Chinese hamster ovary (CHO) cells expressing human CCR5 on their surface; the results are reported as IC_{50} values (Table 1). To assess the activities for inhibition of HIV-1 cell entry, an HIV-1 envelope-mediated 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. Metabolic stability was evaluated in vitro by incubating compounds with human hepatic microsomes; the percentage of parent compound remaining after incubation was measured.

We have recently reported the identification of the piperidine-4-carboxamide derivative **1b**, which was found to be a potent CCR5 antagonist with good inhibitory effect on HIV-1 entry.[17] Although compound **1b** showed excellent anti-HIV-1 activity and a good pharmacokinetic profile in dogs, in vitro metabolic studies revealed that **1b** suffered from rapid oxidative metabolism in human hepatic microsomes (stability = 62%, stability = % remaining at 20 min), and the human metabolic liability precluded further development. We therefore investigated a series of compounds designed for improved metabolic stability in human hepatic microsomes. Further metabolic profiling of **1b** showed that the oxidation of the left-side piperidine ring was a major metabolic pathway. The 4-fluoro derivative **1c**[17] also had insufficient metabolic stability, and compound **1d**,[17] acetyl analogue of **1c**, was metabolized more rapidly than **1c**. These compounds **1c** and **1d** were used as a starting point for the development of metabolically stable compounds. It is known that decreasing the lipophilicity of a molecule reduces the affinity of metabolic enzymes, particularly the cytochrome P450 family, and hence improves metabolic stability.[18] As shown in Table 1, compound **1e**[17] (stability = 80%), having lower lipophilicity (ClogP[19] = 3.6), displayed improved metabolic stability compared to the more lipophilic compound **1d** (ClogP = 5.0, stability = 47%), suggesting that less lipophilic molecules in this series might have higher metabolic stability. On the basis of these data, we introduced various polar groups into a molecule with potent activity (**1c**,**d**). Our goal was to identify compounds that possessed both high metabolic stability and high potency, in particular fusion inhibitory activity.

From our previous SAR studies, modification of the 4-benzylpiperidine moiety was more plausible to reduce lipophilicity without sacrificing potency than modification of the left-side

piperidine and central phenyl ring. In fact, some polar groups turned out to be well tolerated on the right-side phenyl ring.[17,20] We first derivatized the benzylic site of the 4-benzylpiperidine moiety. Replacing the methylene group of **1d** (ClogP = 5.0, stability = 47%) with an amino group provided modest improvement in metabolic stability (**8**, ClogP = 3.7, stability = 70%), while potency decreased somewhat. Sulfoxide **5b** and sulfone **5c**, designed to reduce the lipophilicity (ClogP = 2.5, 2.4), showed good activity comparable to **1d**. Unfortunately, these compounds exhibited no advantage in metabolic stability, suggesting that lowering lipophilicity is not sufficient for increasing stability. Indeed, amide **11b** (stability = 87%) possessed a greater improvement in metabolic stability than sulfonamide **11a** (stability = 55%) though both had the same level of reduced lipophilicity (ClogP = 3.4, 3.6). Although compound **11b** resulted in a substantial loss of CCR5 binding affinity, it was noteworthy that the amide group could more effectively reduce the oxidative metabolism of the 3,4-dichlorinated derivative.

We next turned our attention to substitution of the phenyl ring of the 4-benzylpiperidine. Replacing the fluorine atom of **1c** with a cyano group yielded compound **5d**, which retained good activity, but with poor metabolic stability. Introduction of a methoxycarbonyl group (**5e**), as expected from the relatively high lipophilicity (ClogP = 5.3), did not improve the stability. Carboxylic acid derivative **6** was found to be metabolically stable with 94% of the parent compound remaining, whereas activity was unacceptably decreased.

More promising results were obtained with carboxamide derivatives, where a reasonable balance of potency and metabolic stability was achieved. Conversion of the carboxyl group in **6** to a carbamoyl to give **5f** resulted in a 7-fold improvement in CCR5 binding affinity, while retaining good metabolic stability (stability = 88%). Moreover, the carbamoyl compound **5f** displayed potent activity in the membrane fusion assay (IC_{50} = 5.8 nM). To explore the effect of the substitution position of the carbamoyl group, compounds **5g** and **5h** were synthesized, which showed good activity and stability comparable to the 4-carbamoyl derivative **5f**. Attempts to modulate the steric and hydrogen-bonding factors in this carboxamide series through N-alkylation diminished the metabolic stability to some extent (**5i**−**k**). In the carboxamide series, increasing lipophilicity was found to be correlated with decreasing stability.

With the metabolically stable and potent compound **5f** in hand, we investigated the substituents R^1 and R^2 to increase potency further. Replacing the R^1 methylsulfonyl group with an acetyl group provided compound **5l**, which was twice as potent as **5f** in both the binding (IC_{50} = 3.8 nM) and fusion (IC_{50} = 2.2 nM) assays. Subsequent replacement of the R^2 substituent with 3-chloro and 4-methyl substituents afforded **5m**, which exhibited a 5-fold potency increase in the membrane fusion assay (IC_{50} = 0.42 nM). Compound **5m** was also found to be metabolically stable in human hepatic microsomes (stability = 92%).

Some discrepancy was observed between activity in the CCR5 binding and activity in the HIV-1 membrane fusion assay. Compound **5m** inhibited membrane fusion with an IC_{50} of 0.42 nM, which was more potent than expected from the CCR5 binding potency. On the contrary, compound **1e** was 4-fold less potent in the fusion assay compared to the CCR5 binding assay. These results indicate compound **5m** can inhibit membrane fusion more effectively than compound **1e**. It has been reported that the CCR5 binding site of CC chemokines such as RANTES does not completely overlap with that of HIV-1 envelope gp120.[21] The difference in the ligands utilized in these assays (RANTES and HIV-1 envelope gp120-expressing cells) probably causes the discrepancy in activity. The binding site of **5m** to CCR5 might be closer to the gp120-CCR5 binding site than to the RANTES-CCR5 binding site.

On the basis of its excellent activity in the membrane fusion assay and good stability in human hepatic microsomes, compound **5m** was chosen for further evaluation.[22] Compound **5m** blocked RANTES-induced Ca^{2+} mobilization in CCR5-expressing HeLa cells in a dose dependent manner. Compound **5m** was also 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, CCR2b, CCR3, CCR4, or CCR7 even at a concentration of 10 μM. These results clearly indicate that compound **5m** is a potent and specific CCR5 antagonist. Compound **5m** inhibited the replication of the R5 HIV-1 strain JR-FL in human peripheral blood mononuclear cells (PBMC) with an EC_{50} value of <1 nM and also inhibited the replication of six R5 HIV-1 clinical strains isolated from treatment-naive and -experienced Japanese patients with mean EC_{50} and EC_{90} values of 1.1 and 13 nM, respectively. More importantly, anti-HIV-1 activity of **5m** was unaffected by addition of high concentrations of human serum. This result indicates low plasma protein binding of **5m** (human, 53−57%). No cytotoxicity of **5m** against human PBMC was observed even at a concentration of 10 μM, indicating that the selectivity index of **5m** is >8900. Pharmacokinetic parameters for **5m** were measured in fasted cynomolgus monkeys. After oral administration (5 mg/kg), the peak plasma concentration was 298 ng/mL at 0.7 h with a plasma half-life of 6.0 h. The area under the plasma concentration−time curve from 0 to 24 h was 538 ng·h/mL, and the oral bioavailability was 29%. These results suggest that **5m** appears to be a promising anti-HIV-1 agent and should be further evaluated in clinical trials.

Conclusion

We prepared a series of the piperidine-4-carboxamide CCR5 antagonists containing various polar groups to improve their metabolic stability in human hepatic microsomes. These efforts led to the discovery of the carbamoyl derivative **5m**, which showed good metabolic stability as well as potent inhibition of CCR5 binding and membrane fusion. Compound **5m** exhibited excellent antiviral efficacy against R5 HIV-1 clinical isolates in PBMC and a good pharmacokinetic profile in monkeys. Following further profiling, compound **5m** (TAK-220) was ultimately selected as a clinical candidate for treatment of HIV-1 infection.

Experimental Section

All commercial reagents and solvents were used as obtained without further purification. Column chromatography was carried out on Daiso silica gel (IR-60-40/63-W). 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 as an internal standard, and coupling constants (J) are given in hertz (Hz). Elemental analyses were carried out at Takeda Analytical Research Laboratories, Ltd.

3-Chloro-*N*-(3-chloropropyl)-4-methylaniline Hydrochloride (3b). Step 1: *N*-(3-Chloro-4-methylphenyl)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-chloro-4-methylaniline (**2b**) (142 g, 1.0mol) dropwise, and the mixture was stirred at room temperature for 18 h. After dilution with Et_2O (500 mL) and EtOAc (200 mL), the

mixture was washed with water (2 × 500 mL) followed by 1 N aqueous NaOH (4 × 250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with EtOAc/*i*-Pr_2O, collected by filtration, and dried in vacuo to afford the product (121 g, 72%) as a cream-colored solid, mp 96−97 °C.

Step 2: *N*-(3-Chloro-4-methylphenyl)-*N*-(3-chloropropyl)-formamide. To a mixture of the product from step 1 (127 g, 0.75 mol) and 1-bromo-3-chloropropane (142 g, 0.90 mol) in acetone (750 mL) was added Cs_2CO_3 (293 g, 0.90 mol), and the mixture was stirred at reflux for 8 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was diluted with EtOAc (500 mL), washed with water (300 mL) and brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1:0 to 7:3) to afford the product (140 g, 76%) as a pale yellow oil.

Step 3: 3-Chloro-*N*-(3-chloropropyl)-4-methylaniline Hydrochloride (3b). To a solution of the product from step 2 (139 g, 0.56 mol) in *i*-PrOH (500 mL) was added concentrated HCl (100 mL), and the mixture was stirred at 60 °C for 3 h, then cooled to room temperature. The resulting precipitate was collected by filtration, washed with *i*-PrOH (2 × 100 mL), and dried in vacuo to give **3b** (110 g, 77%) as a white solid, mp 152−154 °C. ^{1}H NMR (CD_3OD) δ 2.22 (2H, m), 2.42 (3H, s), 3.55 (2H, m), 3.71 (2H, t, J = 6.2 Hz), 7.39 (1H, dd, J = 2.3, 8.3 Hz), 7.52 (1H, d, J = 8.3 Hz), 7.60 (1H, d, J = 2.3 Hz). Anal. ($C_{10}H_{13}Cl_2N$·HCl) C, H, N.

1-Acetyl-*N*-(3-chloropropyl)-*N*-(3,4-dichlorophenyl)-4-piperidinecarboxamide (4a). To an ice-cooled stirred suspension of **3a**[17] (33.8 g, 0.12 mmol) in dichloromethane (DCM) (500 mL) was added Et_3N (96 mL, 0.69 mol) followed by 1-acetylpiperidine-4-carbonyl chloride[23] (70.1 g, 0.37 mol), and the mixture was stirred at 0 °C for 4 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (300 mL), and the organic layer was separated. The aqueous layer was extracted with DCM (200 mL), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL), 1 N aqueous HCl (2 × 300 mL), and brine (2 × 300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) followed by trituration with *i*-Pr_2O to afford **4a** (40.4 g, 84%) as a white solid, mp 118−120 °C. ^{1}H NMR ($CDCl_3$) δ 1.62−1.87 (4H, m), 1.94−2.06 (2H, m), 2.06 (3H, s), 2.34−2.44 (2H, m), 2.81−2.94 (1H, m), 3.54 (2H, t, J = 6.6 Hz), 3.75−3.82 (3H, m), 4.50−4.56 (1H, m), 7.05 (1H, dd, J = 2.4, 8.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.55 (1H, d, J = 8.4 Hz). Anal. ($C_{17}H_{21}Cl_3N_2O_2$) C, H, N.

1-Acetyl-*N*-(3-chloro-4-methylphenyl)-*N*-(3-chloropropyl)piperidine-4-carboxamide (4b). To a stirred solution of **3b** (20.0 g, 78.6 mmol) in 1-methyl-2-pyrrolidone (NMP) (100 mL) was added portionwise 1-acetylpiperidine-4-carbonyl chloride[23] (44.7 g, 236 mmol), and the mixture was stirred at room temperature for 18 h. The mixture was diluted with water (300 mL) and extracted with EtOAc (3 × 200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 9:1) followed by recrystallization from EtOAc/Et_2O to afford **4b** (24.7 g, 85%) as a white solid, mp 113−114 °C. ^{1}H NMR ($CDCl_3$) δ 1.50−2.10 (6H, m), 2.05 (3H, s), 2.25−2.50 (2H, m), 2.43 (3H, s), 2.75−2.95 (1H, m), 3.53 (2H, t, J = 6.6 Hz), 3.65−3.85 (1H, m), 3.77 (2H, t, J = 7.1 Hz), 4.51 (1H, br d, J = 12.8 Hz), 6.98 (1H, dd, J = 2.2, 7.7 Hz), 7.18 (1H, d, J = 2.2 Hz), 7.31 (1H, d, J = 7.7 Hz). Anal. ($C_{18}H_{24}Cl_2N_2O_2$) C, H, N.

1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-(3-{4-[(4-fluorophenyl)sulfanyl]piperidin-1-yl}propyl)piperidine-4-carboxamide Hydrochloride (5a). A mixture of **4a** (470 mg, 1.2 mmol), **16a** (297 mg, 1.2 mmol), KI (199 mg, 1.2 mmol), and K_2CO_3 (498 mg, 3.6 mmol) in MeCN (24 mL) was stirred at 80 °C for 20 h. The mixture was concentrated in vacuo, and the residue was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 9:1) to afford the free base of **5a** (504 mg). The free base (504 mg) was dissolved in MeOH (6 mL), treated with 4 N HCl (EtOAc solution, 1.5 mL), and concentrated in vacuo. The resulting foam was triturated with Et_2O, collected by filtration, and dried in vacuo over KOH to give **5a** (445 mg, 62%) as an amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.45−2.10 (12H, m), 2.05 (3H, s), 2.20−2.50 (2H, m), 2.29 (2H, t, J = 7.1 Hz), 2.70−3.05 (4H, m), 3.65 (2H, t, J = 7.7 Hz), 3.78 (1H, br d, J = 13.2 Hz), 4.52 (1H, br d, J = 13.2 Hz), 6.99 (2H, m), 7.04 (1H, dd, J = 2.4, 8.4 Hz), 7.32 (1H, d, J = 2.4 Hz), 7.40 (2H, m), 7.53 (1H, d, J = 8.4 Hz). Anal. ($C_{28}H_{34}Cl_2FN_3O_2S$·HCl·0.5H_2O) C, H, N.

1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-(3-{4-[(4-fluorophenyl)-sulfinyl]piperidin-1-yl}propyl)piperidine-4-carboxamide (5b). Compound **5b** was prepared by a method similar to that described for **5a** from **16b**. Yield 70%, amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.40−2.10 (12H, m), 2.05 (3H, s), 2.20−2.65 (3H, m), 2.28 (2H, t, J = 7.2 Hz), 2.75−3.00 (3H, m), 3.63 (2H, m), 3.78 (1H, br d, J = 13.1 Hz), 4.53 (1H, br d, J = 13.1 Hz), 7.02 (1H, dd, J = 2.4, 8.6 Hz), 7.22 (2H, m), 7.29 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.6 Hz), 7.60 (2H, m). Anal. ($C_{28}H_{34}Cl_2FN_3O_3S$·0.75H_2O) C, H, N.

1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-(3-{4-[(4-fluorophenyl)sulfonyl]piperidin-1-yl}propyl)piperidine-4-carboxamide Hydrochloride (5c). Compound **5c** was prepared by a method similar to that described for **5a** from **16c**. Yield 42%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.50−2.10 (12H, m), 2.05 (3H, s), 2.20−2.50 (2H, m), 2.28 (2H, t, J = 7.2 Hz), 2.75−3.00 (4H, m), 3.62 (2H, t, J = 7.5 Hz), 3.78 (1H, br d, J = 13.2 Hz), 4.52 (1H, br d, J = 13.2 Hz), 7.02 (1H, dd, J = 2.2, 8.4 Hz), 7.25 (2H, m), 7.29 (1H, d, J = 2.2 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.87 (2H, m). Anal. ($C_{28}H_{34}Cl_2FN_3O_4S$·HCl·0.5H_2O) C, H, N.

***N*-{3-[4-(4-Cyanobenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (5d).** A mixture of **4c**[17] (770 mg, 1.8 mmol), **28** (355 mg, 1.5 mmol), KI (299 mg, 1.8 mmol), and K_2CO_3 (829 mg, 6.0 mmol) in MeCN/DMF (1:1, 30 mL) was stirred at 100 °C for 6 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 aqueous NaOH (3 × 5 mL) followed by brine (5 mL), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 9:1) to afford **5d** (622 mg, 70%) as an amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.10−2.05 (13H, m), 2.10−2.35 (1H, m), 2.27 (2H, t, J = 7.4 Hz), 2.45−2.65 (2H, m), 2.57 (2H, d, J = 6.6 Hz), 2.74 (3H, s), 2.82 (2H, br d, J = 11.4 Hz), 3.55−3.80 (4H, m), 7.02 (1H, dd, J = 2.5, 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.5 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz). Anal. ($C_{29}H_{36}Cl_2N_4O_3S$·0.5H_2O) C, H, N.

Methyl 4-({1-[3-((3,4-Dichlorophenyl){[1-(methylsulfonyl)-piperidin-4-yl]carbonyl}amino)propyl]piperidin-4-yl}methyl)-benzoate (5e). Compound **5e** was prepared by a method similar to that described for **5d** from **23**. Yield 62%, mp 148−151 °C (EtOAc/*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.23−1.42 (13H, m), 2.20−2.40 (3H, m), 2.52−2.59 (4H, m), 2.74 (3H, s), 2.80−2.89 (2H, m), 3.62−3.76 (4H, m), 3.90 (3H, s), 7.06 (1H, dd, J = 2.6, 8.4 Hz), 7.19 (2H, d, J = 8.4 Hz), 7.32 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.94 (2H, d, J = 8.4 Hz). Anal. ($C_{30}H_{39}Cl_2N_3O_5S$·0.75H_2O) C, H, N.

***N*-{3-[4-(4-Carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (5f).** Compound **5f** was prepared by a method similar to that described for **5d** from **22a**. Yield 52%, mp 196−197 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 1.21−1.34 (2H, m), 1.40−1.97 (11H, m), 2.10−2.30 (3H, m), 2.50−2.65 (2H, m), 2.57 (2H, d, J = 5.8 Hz), 2.74 (3H, s), 2.78−2.84 (2H, m), 3.61−3.76 (4H, m), 5.40−6.20 (2H, m), 7.02 (1H, dd, J = 2.6, 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz). Anal. ($C_{29}H_{38}Cl_2N_4O_4S$) C, H, N.

***N*-{3-[4-(3-Carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (5g).**

Compound **5g** was prepared by a method similar to that described for **5d** from **27b**. Yield 59%, mp 184−186 °C (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.10−2.00 (13H, m), 2.10−2.35 (3H, m), 2.45−2.70 (2H, m), 2.57 (2H, d, J = 6.2 Hz), 2.74 (3H, s), 2.82 (2H, br d, J = 11.0 Hz), 3.55−3.80 (4H, m), 5.50−6.20 (2H, m), 7.03 (1H, dd, J = 2.2, 8.4 Hz), 7.25−7.40 (3H, m), 7.52 (1H, d, J = 8.4 Hz), 7.55−7.65 (2H, m). Anal. ($C_{29}H_{38}Cl_2N_4O_4S$) C, H, N.

***N*-{3-[4-(2-Carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (5h).** Compound **5h** was prepared by a method similar to that described for **5d** from **27a**. Yield 73%, amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.10−2.05 (13H, m), 2.10−2.35 (3H, m), 2.45−2.65 (2H, m), 2.65−2.90 (2H, m), 2.74 (3H, s), 2.77 (2H, d, J = 6.6 Hz), 3.55−3.80 (4H, m), 5.60−5.85 (2H, m), 7.04 (1H, dd, J = 2.4, 8.4 Hz), 7.10−7.50 (5H, m), 7.52 (1H, d, J = 8.4 Hz). Anal. ($C_{29}H_{38}Cl_2N_4O_4S\cdot H_2O$) C, H, N.

***N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[4-(methylcarbamoyl)benzyl]-piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide Hydrochloride (5i).** Compound **5i** was prepared by a method similar to that described for **5d** from **22b**. Yield 55%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.20−1.40 (2H, m), 1.40−2.00 (11H, m), 2.10−2.40 (3H, m), 2.54−2.62 (2H, m), 2.55 (2H, d, J = 6.4 Hz), 2.74 (3H, s), 2.80−2.85 (2H, m), 3.01 (3H, d, J = 4.8 Hz), 3.61−3.76 (4H, m), 6.12 (1H, br q, J = 4.8 Hz), 7.03 (1H, dd, J = 2.2, 8.0 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.0 Hz). Anal. ($C_{30}H_{40}Cl_2N_4O_4S\cdot HCl\cdot 2H_2O$) C, H, N.

***N*-(3-{4-[4-(*tert*-Butylcarbamoyl)benzyl]piperidin-1-yl}propyl)-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (5j).** Compound **5j** was prepared by a method similar to that described for **5d** from **22c**. Yield 67%, mp 121−122 °C (EtOAc/*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.20−1.40 (2H, m), 1.47 (9H, s), 1.55−2.00 (11H, m), 2.20−2.30 (3H, m), 2.50−2.70 (2H, m), 2.55 (2H, d, J = 6.2 Hz), 2.74 (3H, s), 2.75−2.84 (2H, m), 3.59−3.76 (4H, m), 5.91 (1H, br s), 7.03 (1H, dd, J = 2.6, 8.4 Hz), 7.16 (2H, d, J = 8.0 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.0 Hz). Anal. ($C_{33}H_{46}Cl_2N_4O_4S\cdot 0.5H_2O$) C, H, N.

***N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[4-(dimethylcarbamoyl)benzyl]piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide Hydrochloride (5k).** Compound **5k** was prepared by a method similar to that described for **5d** from **22d**. Yield 43%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.12−1.40 (2H, m), 1.40−2.00 (11H, m), 2.10−2.40 (3H, m), 2.40−2.63 (2H, m), 2.53 (2H, d, J = 6.6 Hz), 2.74 (3H, s), 2.74−2.90 (2H, m), 3.00 (3H, br s), 3.10 (3H, br s), 3.62 (4H, m), 7.02−7.06 (1H, m), 7.15 (2H, d, J = 6.2 Hz), 7.32 (1H, d, J = 2.0 Hz), 7.34 (2H, d, J = 6.2 Hz), 7.52 (1H, d, J = 8.4 Hz). Anal. ($C_{31}H_{42}Cl_2N_4O_4S\cdot HCl\cdot 2H_2O$) C, H, N.

1-Acetyl-*N*-{3-[4-(4-carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3,4-dichlorophenyl)piperidine-4-carboxamide (5l). A mixture of **4a** (392 mg, 1.0 mmol), **22a** (280 mg, 1.1 mmol), KI (183 mg, 1.1 mmol), and K_2CO_3 (415 mg, 3.0 mmol) in MeCN/DMF (1:1, 6 mL) was stirred at 80 °C for 20 h. The mixture was concentrated in vacuo, and the residue was diluted with EtOAc (20 mL) and washed with water (2 × 20 mL), 1 N aqueous NaOH (2 × 20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 3:2) followed by trituration with Et_2O to afford **5l** (320 mg, 56%) as a white solid, mp 126−127 °C. ^{1}H NMR ($CDCl_3$) δ 1.19−1.34 (2H, m), 1.40−1.87 (11H, m), 2.05 (3H, s), 2.23−2.42 (4H, m), 2.57 (2H, d, J = 6.2 Hz), 2.79−2.92 (3H, m), 3.61−3.81 (3H, m), 4.49−4.55 (1H, m), 5.60−6.20 (2H, m), 7.03 (1H, dd, J = 2.6, 8.4 Hz), 7.20 (2H, d, J = 8.0 Hz), 7.31 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.73 (2H, d, J = 8.0 Hz). Anal. ($C_{30}H_{38}Cl_2N_4O_3\cdot 0.5H_2O$) C, H, N.

1-Acetyl-*N*-{3-[4-(4-carbamoylbenzyl)piperidin-1-yl]propyl}-*N*-(3-chloro-4-methylphenyl)piperidine-4-carboxamide (5m). A mixture of **22a** (16.5 g, 65 mmol) and K_2CO_3 (22.3 g, 161 mmol) in DMF (200 mL) was stirred at 80 °C for 1 h. To the mixture was added **4b** (20.0 g, 54 mmol) followed by KI (8.94 g, 54 mmol) and MeCN (200 mL), and the mixture was stirred at 80 °C for 14 h. The mixture was concentrated in vacuo, and the residue was partitioned between DCM (500 mL) and water (100 mL). The organic layer was separated, washed with 1 N aqueous NaOH (3 × 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 7:3) to afford **5m** (21.4 g, 72%) as an amorphous solid. Recrystallization from EtOAc/EtOH (4:1) gave **5m** as a white crystalline solid, mp 166−167 °C. ^{1}H NMR ($CDCl_3$) δ 1.15−1.35 (2H, m), 1.42−1.90 (11H, m), 2.04 (3H, s), 2.20−2.46 (2H, m), 2.26 (2H, t, J = 7.5 Hz), 2.42 (3H, s), 2.57 (2H, d, J = 6.6 Hz), 2.73−2.92 (3H, m), 3.64 (2H, t, J = 7.7 Hz), 3.76 (1H, br d, J = 13.5 Hz), 4.50 (1H, br d, J = 13.5 Hz), 5.25−6.35 (2H, m), 6.95 (1H, dd, J = 2.1, 8.1 Hz), 7.17 (1H, d, J = 2.1 Hz), 7.20 (2H, d, J = 8.3 Hz), 7.28 (1H, d, J = 8.1 Hz), 7.72 (2H, d, J = 8.3 Hz). Anal. ($C_{31}H_{41}ClN_4O_3$) C, H, N.

4-({1-[3-((3,4-Dichlorophenyl){[1-(methylsulfonyl)piperidin-4-yl]carbonyl}amino)propyl]piperidin-4-yl}methyl)benzoic Acid (6). To a solution of **5e** (113 mg, 0.18 mmol) in MeOH (3 mL) was added 1 N aqueous NaOH (0.72 mL), and the mixture was stirred at 60 °C for 3 h. The mixture was treated with 1 N aqueous HCl (0.72 mL) and concentrated in vacuo. The residue was diluted with water and extracted with DCM. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM/MeOH 1:0 to 4:1) to afford **6** (103 mg, 93%) as an amorphous solid. ^{1}H NMR (CD_3OD) δ 1.51−1.95 (11H, m), 2.20−2.40 (1H, m), 2.40−2.60 (2H, m), 2.67 (2H, d, J = 6.6 Hz), 2.73 (3H, s), 2.80−3.10 (4H, m), 3.46−4.89 (6H, m), 7.23 (2H, d, J = 8.0 Hz), 7.36 (1H, dd, J = 2.2, 8.4 Hz), 7.68 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 2.2 Hz), 7.91 (2H, d, J = 8.0 Hz). Anal. ($C_{29}H_{37}Cl_2N_3O_5S\cdot 2H_2O$) C, H, N.

1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-[3-(4-oxopiperidin-1-yl)-propyl]piperidine-4-carboxamide (7). Compound **7** was prepared by a method similar to that described for **5a** from 4-piperidone monohydrate hydrochloride. Yield 54%, mp 107−110 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.62−1.82 (6H, m), 2.06 (3H, s), 2.30−2.49 (8H, m), 2.71 (4H, q, J = 5.8 Hz), 2.81−2.94 (1H, m), 3.69−3.82 (3H, m), 4.51−4.57 (1H, m), 7.06 (1H, dd, J = 2.6, 8.4 Hz), 7.33 (1H, d, J = 2.6 Hz), 7.55 (1H, d, J = 8.4 Hz). Anal. ($C_{22}H_{29}Cl_2N_3O_3\cdot H_2O$) C, H, N.

1-Acetyl-*N*-(3,4-dichlorophenyl)-*N*-{3-[4-(4-fluoroanilino)piperidin-1-yl]propyl}piperidine-4-carboxamide Dihydrochloride (8). To an ice-cooled stirred solution of **7** (1000 mg, 2.2 mmol) and 4-fluoroaniline (269 mg, 2.4 mmol) in THF (3 mL) was added AcOH (126 μL, 2.2 mmol) followed by $NaBH(OAc)_3$ (699 mg, 3.3 mmol), and the mixture was stirred at room temperature for 20 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (100 mL), stirred for 2 h, and extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 4:1) to afford the free base of **8** (695 mg). The free base (208 mg) was converted to the hydrochloride salt using 4 N HCl (EtOAc solution) to give the dihydrochloride **8** (187 mg, 46%) as a pale purple amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.30−1.50 (2H, m), 1.50−1.87 (6H, m), 2.00−2.13 (4H, m), 2.06 (3H, s), 2.30−2.37 (4H, m), 2.78−2.93 (3H, m), 3.10−3.30 (1H, m), 3.63−3.81 (4H, m), 4.50−4.57 (1H, m), 6.52 (2H, dd, J = 4.4, 8.8 Hz), 6.87 (2H, t, J = 8.8 Hz), 7.09 (1H, dd, J = 2.2, 8.4 Hz), 7.32 (1H, d, J = 2.2 Hz), 7.53 (1H, d, J = 8.4 Hz). Anal. ($C_{28}H_{35}Cl_2FN_4O_2\cdot 2HCl\cdot 1.5H_2O$) C, H, N.

***N*-(3-{4-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}propyl)-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide (9).** A mixture of **4c**[17] (2.99 g, 7.0 mmol), 4-[(*tert*-butoxycarbonyl)amino]piperidine (1.40 g, 7.0 mmol), KI (1.16 g, 7.0 mmol), and K_2CO_3 (0.97 g, 7.0 mmol) in MeCN (35 mL) was stirred at 80 °C for 18 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc/THF (2:1, 120 mL) and water (20 mL). The organic layer was separated, washed with

water (2 × 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 1:0 to 9:1) followed by trituration with *i*-Pr_2O to afford **9** (3.21 g, 78%) as a white solid, mp 100−103 °C. ^{1}H NMR ($CDCl_3$) δ 1.20−2.10 (12H, m), 1.44 (9H, s), 2.10−2.35 (1H, m), 2.29 (2H, t, J = 7.3 Hz), 2.45−2.85 (4H, m), 2.74 (3H, s), 3.30−3.55 (1H, m), 3.60−3.80 (4H, m), 4.25−4.50 (1H, m), 7.02 (1H, dd, J = 2.4, 8.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.4 Hz). Anal. ($C_{26}H_{40}Cl_2N_4O_5S$) C, H, N.

***N*-[3-(4-Aminopiperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)-1-(methylsulfonyl)piperidine-4-carboxamide Dihydrochloride (10).** To a stirred suspension of **9** (2.99 g, 5.1 mmol) in MeOH (20 mL) was added 4 N HCl (EtOAc solution, 40 mL), and the mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo, and the residue was triturated with EtOAc, collected by filtration, and dried in vacuo to give **10** (2.70 g, 95%) as a white solid, mp 250−254 °C. ^{1}H NMR (CD_3OD) δ 1.60−2.65 (13H, m), 2.73 (3H, s), 3.00−3.30 (4H, m), 3.40−3.85 (5H, m), 3.80 (2H, t, J = 6.8 Hz), 7.41 (1H, dd, J = 2.3, 8.5 Hz), 7.70 (1H, d, J = 8.5 Hz), 7.73 (1H, d, J = 2.3 Hz). Anal. ($C_{21}H_{32}Cl_2N_4O_3S\cdot 2HCl\cdot 0.5H_2O$) C, H, N.

***N*-(3,4-Dichlorophenyl)-*N*-[3-(4-{[(4-fluorophenyl)sulfonyl]amino}piperidin-1-yl)propyl]-1-(methylsulfonyl)piperidine-4-carboxamide Hydrochloride (11a).** To a stirred suspension of **10** (564 mg, 1.0 mmol) in DCM (10 mL) was added Et_3N (502 μL, 3.6 mmol) followed by 4-fluorobenzenesulfonyl chloride (234 mg, 1.2 mmol), and the mixture was stirred at room temperature for 18 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (40 mL) and saturated aqueous $NaHCO_3$ (15 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 9/1) to afford the free base of **11a** (613 mg). The free base (613 mg) was converted to the hydrochloride salt using 4 N HCl (EtOAc solution) to give **11a** (614 mg, 90%) as an amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.25−2.05 (12H, m), 2.10−2.35 (1H, m), 2.25 (2H, t, J = 7.4 Hz), 2.45−2.80 (4H, m), 2.74 (3H, s), 3.14 (1H, m), 3.63 (2H, t, J = 7.7 Hz), 3.73 (2H, m), 4.62 (1H, br d, J = 8.0 Hz), 7.01 (1H, dd, J = 2.4, 8.5 Hz), 7.19 (2H, m), 7.29 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.5 Hz), 7.89 (2H, m). Anal. ($C_{27}H_{35}Cl_2FN_4O_5S_2\cdot HCl\cdot 0.5H_2O$) C, H, N.

***N*-(3,4-Dichlorophenyl)-*N*-(3-{4-[(4-fluorobenzoyl)amino]-piperidin-1-yl}propyl)-1-(methylsulfonyl)piperidine-4-carboxamide (11b).** Compound **11b** was prepared by a method similar to that described for **11a** from 4-fluorobenzoyl chloride. Yield 91%, mp 184−187 °C (*i*-Pr_2O/EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.40−2.40 (15H, m), 2.48−2.67 (2H, m), 2.74 (3H, s), 2.77−2.90 (2H, m), 3.62−3.80 (4H, m), 3.85−4.07 (1H, m), 5.82−5.93 (1H, m), 7.01−7.16 (3H, m), 7.32 (1H, d, J = 2.2 Hz), 7.54 (1H, d, J = 8.4 Hz), 7.70−7.80 (2H, m). Anal. ($C_{28}H_{35}Cl_2FN_4O_4S\cdot 0.75H_2O$) C, H, N.

***tert*-Butyl 4-[(4-Fluorophenyl)sulfanyl]piperidine-1-carboxylate (13). Step 1: *tert*-Butyl 4-[(Methylsulfonyl)oxy]piperidine-1-carboxylate.** To an ice-cooled stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (**12**) (20.13 g, 100 mmol) and Et_3N (16.7 mL, 120 mmol) in THF (200 mL) was added methanesulfonyl chloride (9.3 mL, 120 mmol) dropwise, and the mixture was stirred at 0 °C for 3 h. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL, 2 × 100 mL). The organic layer was washed with 1 N aqueous HCl (2 × 50 mL) followed by saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O/hexane (1:1, 200 mL), collected by filtration, and dried in vacuo to give the product (25.65 g, 92%) as a white solid, mp 89−91 °C. ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.70−2.10 (4H, m), 3.04 (3H, s), 3.30 (2H, ddd, J = 4.2, 7.9, 13.7 Hz), 3.71 (2H, ddd, J = 4.1, 6.7, 13.7 Hz), 4.89 (1H, tt, J = 3.8, 7.7 Hz).

Step 2: *tert*-Butyl 4-[(4-Fluorophenyl)sulfanyl]piperidine-1-carboxylate (13). A mixture of the product from step 1 (4.19 g, 15.0 mmol), 4-fluorobenzenethiol (2.08 mL, 19.5 mmol), and potassium carbonate (2.70 g, 19.5 mmol) in DMF (150 mL) was stirred at 70 °C for 7 h. The mixture was concentrated in vacuo, and the residue was diluted with EtOAc (80 mL) and washed with water (20 mL), 0.5 N aqueous NaOH (3 × 10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 19:1 to 9:1) to give **13** (4.04 g, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.49 (2H, m), 1.88 (2H, m), 2.88 (2H, ddd, J = 3.0, 10.6, 13.6 Hz), 3.09 (1H, tt, J = 4.0, 10.3 Hz), 3.97 (2H, m), 7.01 (2H, m), 7.43 (2H, m).

***tert*-Butyl 4-[(4-Fluorophenyl)sulfinyl]piperidine-1-carboxylate (14).** To an ice-cooled stirred solution of **13** (1.87 g, 6.0 mmol) in DCM (30 mL) was added a solution of *m*CPBA (70%, 1.48 g, 6.0 mmol) in DCM (30 mL) dropwise over 30 min, and the mixture was stirred at 0 °C for 1 h. The mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (3 × 30 mL). 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 to 1:2) to give **14** (1.39 g, 71%) as a colorless oil, which solidified on standing, mp 112−114 °C. ^{1}H NMR ($CDCl_3$) δ 1.40−1.85 (4H, m), 1.44 (9H, s), 2.55−2.80 (3H, m), 4.20 (2H, m), 7.24 (2H, m), 7.60 (2H, m).

***tert*-Butyl 4-[(4-Fluorophenyl)sulfonyl]piperidine-1-carboxylate (15).** To an ice-cooled stirred solution of **13** (1.87 g, 6.0 mmol) in DCM (30 mL) was added *m*CPBA (70%, 3.25 g, 13 mmol), and the mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The mixture was filtered, and the filtrate was washed with 5% aqueous sodium thiosulfate (2 × 10 mL) and saturated aqueous $NaHCO_3$ (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with Et_2O, collected by filtration, and dried in vacuo to give **15** (1.85 g, 90%) as a white solid, mp 167−169 °C. ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.59 (2H, m), 1.98 (2H, br d, J = 11.8 Hz), 2.66 (2H, br t, J = 12.6 Hz), 3.03 (1H, tt, J = 3.8, 12.0 Hz), 4.23 (2H, br d, J = 13.2 Hz), 7.26 (2H, m), 7.89 (2H, m).

4-[(4-Fluorophenyl)sulfanyl]piperidine Hydrochloride (16a). To a solution of **13** (1.87 g, 6.0 mmol) in MeOH (10 mL) was added 4 N HCl (EtOAc solution, 20 mL), and the mixture was stirred at room temperature for 18 h. The mixture was concentrated in vacuo, and the residue was triturated with EtOAc, collected by filtration, washed with EtOAc, and dried in vacuo to give **16a** (1.35 g, 91%) as a white solid, mp 169−172 °C. ^{1}H NMR (CD_3OD) δ 1.73 (2H, dtd, J = 4.0, 10.6, 14.5 Hz), 2.16 (2H, m), 3.05 (2H, m), 3.25−3.50 (3H, m), 7.11 (2H, m), 7.53 (2H, m).

4-[(4-Fluorophenyl)sulfinyl]piperidine Trifluoroacetate (16b). To an ice-cooled stirred solution of **14** (1.08 g, 3.3 mmol) in DCM (21 mL) was added trifluoroacetic acid (7 mL), and the mixture was stirred at 0 °C for 1 h. The mixture was concentrated in vacuo, and the residue was triturated with *i*-Pr_2O, collected by filtration, dried in vacuo to give **16b** (1.11 g, 99%) as a white solid, mp 177−178 °C. ^{1}H NMR (CD_3OD) δ 1.65−2.05 (3H, m), 2.19 (1H, m), 2.90−3.20 (3H, m), 3.50 (2H, m), 7.40 (2H, m), 7.73 (2H, m).

4-[(4-Fluorophenyl)sulfonyl]piperidine Hydrochloride (16c). Compound **16c** was prepared by a method similar to that described for **16a** from **15**. Yield 97%, mp 250−255 °C (EtOAc). ^{1}H NMR (CD_3OD) δ 1.90 (2H, m), 2.20 (2H, m), 3.01 (2H, dt, J = 3.3, 12.9 Hz), 3.40−3.65 (3H, m), 7.43 (2H, m), 7.99 (2H, m).

4-{[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]methyl}benzoic Acid (20). Step 1: Methyl 4-[(Diethoxyphosphoryl)methyl]benzoate. A mixture of methyl 4-(bromomethyl)benzoate (**17**) (25.0 g, 109 mmol) and triethyl phosphite (24.3 mL, 142 mmol) was stirred at 150 °C for 24 h. The mixture was purified by vacuum distillation to give the product (21.5 g, 69%) as a colorless oil, bp 165−172 °C/1 Torr. ^{1}H NMR ($CDCl_3$) δ 1.24 (6H, t, J = 7.0 Hz), 3.21 (2H, d, J = 22.4 Hz), 3.91 (3H, s), 4.02 (4H, qd, J = 7.0, 8.1 Hz), 7.38 (2H, dd, J = 2.4, 8.4 Hz), 7.99 (2H, d, J = 8.4 Hz).

Step 2: *tert*-Butyl 4-[4-(Methoxycarbonyl)benzylidene]piperidine-1-carboxylate (18). To an ice-cooled stirred solution of compound from step 1 (40.0 g, 140 mmol) and 15-crown-5 (2.3

mL, 12 mmol) in THF (240 mL) was added NaH (60% in oil, 5.60 g, 140 mmol), and the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (23.3 g, 117 mmol) in THF (100 mL) dropwise over 20 min at 0 °C, and the mixture was stirred at room temperature for 4 h. The mixture was poured into ice water (200 mL) and extracted with EtOAc (2 × 200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1:0 to 4:1) to give a mixture of **18** and *tert*-butyl 4-[4-(ethoxycarbonyl)benzylidene]piperidine-1-carboxylate (**18′**) (37.9 g, 98%, **18**:**18′** = ca. 2:1 by ^{1}H NMR) as a semisolid, which was used for the next step without further purification. Compound **18** could be isolated in pure form by recrystallization from hexane. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.35 (2H, t, J = 5.8 Hz), 2.47 (2H, t, J = 5.8 Hz), 3.42 (2H, t, J = 5.8 Hz), 3.52 (2H, t, J = 5.8 Hz), 3.91 (3H, s), 6.38 (1H, s), 7.25 (2H, d, J = 8.4 Hz), 7.99 (2H, d, J = 8.4 Hz).

Step 3: *tert*-Butyl 4-[4-(Methoxycarbonyl)benzyl]piperidine-1-carboxylate (19). A mixture of **18** and **18′** (37.8 g) was dissolved in MeOH/THF (1:1, 200 mL) and hydrogenated over 10% Pd/C (water ∼50%, 7.56 g) at room temperature for 18 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 1:0 to 4:1) to give a mixture of **19** and *tert*-butyl 4-[4-(ethoxycarbonyl)benzyl]piperidine-1-carboxylate (**19′**) (39.0 g, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.05−1.42 (2H, m), 1.45 (9H, s), 1.55−1.77 (3H, m), 2.59 (2H, d, J = 7.0 Hz), 2.57−2.69 (2H, m), 3.91 (3H, s), 4.04−4.18 (2H, m), 7.21 (2H, d, J = 8.0 Hz), 7.96 (2H, d, J = 8.0 Hz).

Step 4: 4-{[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]methyl}-benzoic Acid (20). To a solution of a mixture of **19** and **19′** (38.9 g) in EtOH (175 mL) was added 1 N aqueous NaOH (175 mL), and the mixture was stirred at 80 °C for 8 h. The mixture was concentrated in vacuo, and the residue was diluted with DCM (300 mL) and acidified with 1 N aqueous HCl (210 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with DCM (100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with *i*-Pr_2O/hexane, collected by filtration, and dried in vacuo to give **20** (33.8 g, 91%) as a white solid, mp 165−167 °C. ^{1}H NMR ($CDCl_3$) δ 1.08−1.26 (2H, m), 1.45 (9H, s), 1.57−1.77 (3H, m), 1.26−2.70 (2H, m), 2.61 (2H, d, J = 7.4 Hz), 4.05−4.11 (2H, m), 7.24 (2H, d, J = 8.0 Hz), 8.03 (2H, d, J = 8.0 Hz).

***tert*-Butyl 4-(4-Carbamoylbenzyl)piperidine-1-carboxylate (21a).** To an ice-cooled stirred mixture of **20** (33.73 g, 106 mmol), HOBt·H_2O (16.17 g, 106 mmol), and ammonium chloride (7.34 g, 137 mmol) in DMF (200 mL) was added Et_3N (19.1 mL, 137 mmol) followed by EDC (26.32 g, 137 mmol), and the mixture was stirred at room temperature for 20 h. The mixture was diluted with water (800 mL) and extracted with EtOAc (3 × 200 mL). The organic layer was washed with 1 N aqueous HCl (2 × 100 mL) followed by saturated aqueous $NaHCO_3$ (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 (hexane/EtOAc 1:1 to 0:1) followed by trituration with *i*-Pr_2O to give **21a** (30.52 g, 91%) as a white solid, mp 144−145 °C. ^{1}H NMR ($CDCl_3$) δ 1.05−1.25 (2H, m), 1.45 (9H, s), 1.56−1.76 (3H, m), 2.59 (2H, d, J = 2.0 Hz), 2.57−2.69 (2H, m), 4.04−4.10 (2H, m), 5.50−6.20 (2H, m), 7.22 (2H, d, J = 8.4 Hz), 7.74 (2H, d, J = 8.4 Hz).

***tert*-Butyl 4-[4-(Methylcarbamoyl)benzyl]piperidine-1-carboxylate (21b).** Compound **21b** was prepared by a method similar to that described for **21a** from methylamine hydrochloride. Yield 86%, mp 148−150 °C. ^{1}H NMR ($CDCl_3$) δ 1.04−1.25 (2H, m), 1.45 (9H, s), 1.56−1.79 (3H, m), 2.57 (2H, d, J = 6.6 Hz), 2.63−2.69 (2H, m), 3.01 (3H, d, J = 4.8 Hz), 4.04−4.10 (2H, m), 6.14 (1H, br s), 7.19 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz).

***tert*-Butyl 4-[4-(*tert*-Butylcarbamoyl)benzyl]piperidine-1-carboxylate (21c).** Compound **21c** was prepared by a method similar to that described for **21a** from *tert*-butylamine. Yield 89%, mp 168−171 °C. ^{1}H NMR ($CDCl_3$) δ 1.05−1.26 (2H, m), 1.45 (9H, s), 1.47 (9H, s), 1.55−1.80 (3H, m), 2.57 (2H, d, J = 7.0 Hz), 2.62−2.69 (2H, m), 4.04−4.11 (2H, m), 5.91 (1H, br s), 7.18 (2H, d, J = 8.0 Hz), 7.64 (2H, d, J = 8.0 Hz).

***tert*-Butyl 4-[4-(Dimethylcarbamoyl)benzyl]piperidine-1-carboxylate (21d).** Compound **21d** was prepared by a method similar to that described for **21a** from dimethylamine hydrochloride. Yield 98%, oil. ^{1}H NMR ($CDCl_3$) δ 1.10−1.30 (2H, m), 1.45 (9H, s), 1.58−1.70 (3H, m), 2.55 (2H, d, J = 7.0 Hz), 2.63−2.69 (2H, m), 3.00 (3H, br s), 3.10 (3H, br s), 4.04−4.18 (2H, m), 7.16 (2H, d, J = 8.2 Hz), 7.35 (2H, d, J = 8.2 Hz).

4-(Piperidin-4-ylmethyl)benzamide Hydrochloride (22a). To a stirred solution of **21a** (30.5 g, 96 mmol) in MeOH (100 mL) was added 4 N HCl (EtOAc solution, 200 mL), and the mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and the residue was triturated with EtOAc, collected by filtration, washed with EtOAc, and dried in vacuo to give **22a** (27.3 g, quant.) as a white solid, mp 235−238 °C. ^{1}H NMR (CD_3OD) δ 1.25−1.56 (2H, m), 1.82−2.01 (3H, m), 2.68 (2H, d, J = 6.8 Hz), 2.88−3.01 (2H, m), 3.30−3.40 (2H, m), 7.31 (2H, d, J = 8.4 Hz), 7.82 (2H, d, J = 8.4 Hz).

***N*-Methyl-4-(piperidin-4-ylmethyl)benzamide Hydrochloride (22b).** Compound **22b** was prepared by a method similar to that described for **22a** from **21b**. Yield quant., mp 218−221 °C. ^{1}H NMR (CD_3OD) δ 1.30−1.60 (2H, m), 1.82−2.00 (3H, m), 2.68 (2H, d, J = 7.0 Hz), 2.88−2.99 (2H, m), 2.91 (3H, s), 3.29−3.39 (2H, m), 7.30 (2H, d, J = 8.4 Hz), 7.76 (2H, d, J = 8.4 Hz).

***N*-(*tert*-Butyl)-4-(piperidin-4-ylmethyl)benzamide Hydrochloride (22c).** Compound **22c** was prepared by a method similar to that described for **22a** from **21c**. Yield quant., mp 220−224 °C. ^{1}H NMR (CD_3OD) δ 1.32−1.45 (2H, m), 1.45 (9H, s), 1.82−2.00 (3H, m), 2.67 (2H, d, J = 7.0 Hz), 2.86−3.00 (2H, m), 3.29−3.39 (2H, m), 7.27 (2H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.0 Hz).

***N*,*N*-Dimethyl-4-(piperidin-4-ylmethyl)benzamide (22d).** To a stirred solution of **21d** (367 mg, 1.06 mmol) in MeOH (10 mL) was added 4 N HCl (EtOAc solution, 20 mL), and the mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and the residue was diluted with water (20 mL) and basified with 1 N aqueous NaOH (5 mL) at 0 °C. The aqueous layer was treated with brine (20 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo to give **22d** (88 mg, 34%) as an amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.09−1.26 (2H, m), 1.59−1.65 (3H, m), 1.80−2.00 (1H, m), 2.49−2.60 (4H, m), 3.01−3.09 (8H, m), 7.16 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz).

Methyl 4-(Piperidin-4-ylmethyl)benzoate (23). A mixture of the free base of **22a** (2.18 g, 10 mmol) and concentrated sulfuric acid (1.1 mL) in MeOH (20 mL) was stirred at reflux for 20 h. The mixture was concentrated in vacuo, and the residue was diluted with saturated aqueous $NaHCO_3$ (100 mL) and extracted with DCM (40 mL, 4 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give **23** (2.28 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.10−1.35 (2H, m), 1.55−1.80 (3H, m), 2.45−2.70 (4H, m), 2.95−3.20 (2H, m), 3.90 (3H, s), 7.21 (2H, d, J = 8.5 Hz), 7.95 (2H, d, J = 8.5 Hz).

***tert*-Butyl 4-(2-Cyanobenzylidene)piperidine-1-carboxylate (25a). Step 1: Diethyl (2-Cyanobenzyl)phosphonate.** A mixture of 2-(bromomethyl)benzonitrile (**24a**) (24.0 g, 122 mmol) and triethyl phosphite (25.1 mL, 146 mmol) was stirred at 150 °C for 20 h. The mixture was purified by vacuum distillation to give the product (29.4 g, 95%) as a colorless oil, bp 160−170 °C/1.4 Torr. ^{1}H NMR ($CDCl_3$) δ 1.28 (6H, t, J = 7.0 Hz), 3.41 (2H, d, J = 22.2 Hz), 4.10 (4H, qd, J = 7.0, 8.0 Hz), 7.30−7.45 (1H, m), 7.50−7.60 (2H, m), 7.66 (1H, d, J = 7.6 Hz).

Step 2: *tert*-Butyl 4-(2-Cyanobenzylidene)piperidine-1-carboxylate (25a). To an ice-cooled stirred solution of compound from step 1 (27.4 g, 108 mmol) and 15-crown-5 (0.54 mL, 2.7 mmol) in THF (180 mL) was added NaH (60% in oil, 4.32 g, 108 mmol), and the mixture was stirred at room temperature for 30 min. To the mixture was added a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (17.9 g, 90 mmol) in THF (90 mL) dropwise over 10

min at 0 °C, and the mixture was stirred at room temperature for 5 h. The mixture was diluted with water (180 mL) at 0 °C and extracted with EtOAc (2 × 180 mL). The organic layer was washed with 1 N aqueous NaOH (3 × 30 mL) followed by brine (30 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 **25a** (21.7 g, 81%) as a white solid, mp 109−111 °C. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.25−2.50 (4H, m), 3.44 (2H, t, J = 5.8 Hz), 3.55 (2H, t, J = 5.8 Hz), 6.50 (1H, s), 7.20−7.40 (2H, m), 7.45−7.60 (1H, m), 7.60−7.70 (1H, m).

***tert*-Butyl 4-(3-Cyanobenzylidene)piperidine-1-carboxylate (25b).** Compound **25b** was prepared by a method similar to that described for **25a** from 3-(bromomethyl)benzonitrile (**24b**). Mp 87−88 °C. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.25−2.50 (4H, m), 3.42 (2H, t, J = 5.8 Hz), 3.52 (2H, t, J = 5.8 Hz), 6.32 (1H, s), 7.35−7.55 (4H, m).

***tert*-Butyl 4-(4-Cyanobenzylidene)piperidine-1-carboxylate (25c).** Compound **25c** was prepared by a method similar to that described for **25a** from 4-(bromomethyl)benzonitrile (**24c**). ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.36 (2H, t, J = 5.8 Hz), 2.44 (2H, t, J = 5.8 Hz), 3.42 (2H, t, J = 5.8 Hz), 3.53 (2H, t, J = 5.8 Hz), 6.36 (1H, s), 7.28 (2H, d, J = 8.3 Hz), 7.61 (2H, d, J = 8.3 Hz).

***tert*-Butyl 4-(2-Cyanobenzyl)piperidine-1-carboxylate (26a).** Compound **25a** (2.98 g, 10 mmol) was dissolved in MeOH/THF (1:1, 20 mL), and hydrogenated over 10% Pd/C (water ∼50%, 596 mg) at room temperature for 1 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 9:1 to 2:1) followed by trituration with hexane to give **26a** (2.50 g, 83%) as a white solid, mp 71−73 °C. ^{1}H NMR ($CDCl_3$) δ 1.05−1.42 (2H, m), 1.45 (9H, s), 1.55−1.77 (3H, m), 2.59 (2H, d, J = 7.0 Hz), 2.57−2.69 (2H, m), 3.91 (3H, s), 4.04−4.18 (2H, m), 7.21 (2H, d, J = 8.0 Hz), 7.96 (2H, d, J = 8.0 Hz).

***tert*-Butyl 4-(3-Cyanobenzyl)piperidine-1-carboxylate (26b).** Compound **26b** was prepared by a method similar to that described for **26a** from **25b**. Yield 35%, mp 95−97 °C (*i*-Pr_2O/hexane). ^{1}H NMR ($CDCl_3$) δ 1.00−1.30 (2H, m), 1.40−1.80 (3H, m), 1.45 (9H, s), 2.50−2.75 (2H, m), 2.58 (2H, d, J = 6.8 Hz), 3.95−4.20 (2H, m), 7.30−7.60 (4H, m).

***tert*-Butyl 4-(4-Cyanobenzyl)piperidine-1-carboxylate (26c).** Compound **26c** was prepared by a method similar to that described for **26a** from **25c**. Yield 70%. ^{1}H NMR ($CDCl_3$) δ 1.00−1.85 (5H, m), 1.45 (9H, s), 2.50−2.80 (2H, m), 2.60 (2H, d, J = 7.2 Hz), 3.95−4.25 (2H, m), 7.24 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz).

2-(Piperidin-4-ylmethyl)benzamide Hydrochloride (27a). Step 1: *tert*-Butyl 4-(2-Carbamoylbenzyl)piperidine-1-carboxylate. To a mixture of **26a** (984 mg, 3.3 mmol) and 8 N aqueous NaOH (412 μL, 3.3 mmol) in EtOH (5 mL) was added 30% H_2O_2 (2 mL), and the mixture was stirred at 50 °C for 6 h. To the mixture was added 30% H_2O_2 (10 mL), and the mixture was stirred at 50 °C for an additional 6 h. The mixture was concentrated in vacuo, diluted with water, and extracted with DCM. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1:1 to 0:1) followed by recrystallization from *i*-Pr_2O to give the product (571 mg, 55%) as a white solid, mp 125−127 °C. ^{1}H NMR ($CDCl_3$) δ 1.00−1.30 (2H, m), 1.43 (9H, s), 1.50−1.90 (3H, m), 2.45−2.70 (2H, m), 2.77 (2H, d, J = 7.0 Hz), 3.90−4.15 (2H, m), 6.13 (1H, br s), 6.30 (1H, br s), 7.10−7.50 (4H, m).

Step 2: 2-(Piperidin-4-ylmethyl)benzamide Hydrochloride (27a). Compound **27a** was prepared by a method similar to that described for **22a** using the product from step 1. Yield quant., amorphous solid. ^{1}H NMR (CD_3OD) δ 1.30−1.60 (2H, m), 1.75−2.10 (3H, m), 2.75−3.00 (2H, m), 2.82 (2H, d, J = 7.0 Hz), 3.25−3.45 (2H, m), 7.20−7.50 (4H, m).

3-(Piperidin-4-ylmethyl)benzamide Hydrochloride (27b). A mixture of **26b** (1000 mg, 3.3 mmol) and concentrated hydrochloric acid (5 mL) was stirred at 70 °C for 3 h. The mixture was concentrated in vacuo, treated with MeOH (10 mL), and concentrated again. The residue was recrystallized from *i*-PrOH to give **27b** (472 mg, 56%) as a white solid, mp 222−225 °C. ^{1}H NMR (CD_3OD) δ 1.30−1.60 (2H, m), 1.75−2.10 (3H, m), 2.69 (2H, d, J = 7.0 Hz), 2.94 (2H, dt, J = 2.9, 12.9 Hz), 3.25−3.45 (2H, m), 7.35−7.45 (2H, m), 7.65−7.80 (2H, m).

4-(Piperidin-4-ylmethyl)benzonitrile Hydrochloride (28). To a stirred solution of **26c** (32.0 g, 107 mmol) in EtOAc (50 mL) was added 4 N HCl (EtOAc solution, 50 mL), and the mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, and the residue was triturated with EtOAc, collected by filtration, washed with EtOAc, and dried in vacuo to give **28** (20.4 g, 81%) as a white solid, mp 196−198 °C. ^{1}H NMR (CD_3OD) δ 1.35−1.55 (2H, m), 1.75−2.05 (3H, m), 2.71 (2H, d, J = 7.1 Hz), 2.93 (2H, dt, J = 3.0, 13.1 Hz), 3.30−3.40 (2H, m), 7.40 (2H, d, J = 8.1 Hz), 7.67 (2H, d, J = 8.1 Hz).

Receptor Binding Assays. CHO-K1 and CCR5-expressing CHO cells[14] 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 CCR2b, eotaxin for CCR3, thymus- and activation-regulated chemokine for CCR4, and MIP-3β for CCR7.

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 cotransfected 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).

Metabolic Stability Assay. Human hepatic microsomes were purchased from Xenotech, LLC (Lenexa, KS). An incubation mixture with a final volume of 0.1 mL consisted of microsomal protein in 50 mmol/L KH_2PO_4−K_2HPO_4 phosphate buffer (pH 7.4) and 0.5 μmol/L test compound. The concentration of hepatic microsomal protein was 0.4 mg/mL. An NADPH-generating system containing 50 mmol/L $MgCl_2$, 50 mmol/L glucose-6-phosphate, 5 mmol/L beta-$NADP^+$ and 15 unit/mL glucose-6-phosphate dehydrogenase was prepared and added to the incubation mixture with a 10% volume of the reaction mixture. After the addition of the NADPH-generating system, the mixture was incubated at 37 °C for 0 and 20 min. The reaction was terminated by the addition of acetonitrile equivalent to the volume of the reaction mixture. All incubations were made in triplicate.

Test compound in the reaction mixture was measured by LC/MS. The HPLC system consisted of an Agilent 1100 series (Agilent Technologies, Inc.) equipped with a degasser, a high-pressure binary gradient pump, an autosampler, and a thermostated column compartment. The column was Cadenza CD-C18 (30 × 2 mm I.D.; Imtakt Co. Ltd., Kyoto, Japan). The column temperature and the

flow-rate were 40 °C and 0.2 mL/min, respectively. The mobile phase consisted of 0.01 mol/L ammonium formate−formic acid (1000:2, v/v) and acetonitrile. The time program for the gradient elution was as follows: the concentration of acetonitrile was 10% for 0.1 min, followed by a linear increase from 10% to 90% over 0.1 min, held at 90% until 3 min, and then the column was equilibrated at 10% for 4 min. The column effluent was analyzed using a LCQdeca mass spectrometer (Thermo Electron Corporation) equipped with an electrospray ionization source. The ion source was operated at 350 °C with the capillary voltage at 11 V. Nitrogen was used as sheath gas (flow rate = 80) and auxiliary gas (flow rate = 20). The protonated parent ion was monitored to produce mass-extracted chromatogram, which was then integrated to measure analyte response.

For metabolic stability determinations, chromatograms were analyzed for parent compound disappearance from the reaction mixtures. The parent compound peak area in the 0-min incubation sample was considered to be the 100% value and parent compound levels were expressed as percent (%) parent remaining.

Antiviral Assay, Cytotoxicity Assay, and Pharmacokinetic Analysis in Monkeys. Procedures for these studies have been reported previously.[22]

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

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