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Bioorganic & Medicinal Chemistry 12 (2004) 2295–2306
Bioorganic & Medicinal Chemistry

CCR5 antagonists as anti-HIV-1 agents. Part 2: Synthesis and biological evaluation of *N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*,*N*′-diphenylureas

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Received 9 January 2004; revised 4 February 2004; accepted 5 February 2004

Abstract—We have previously reported the novel lead compound **1a** as a CCR5 antagonist for treatment of HIV-1 infection. SAR studies on incorporating various acyl groups as a replacement for the 5-oxopyrrolidine-3-carbonyl group of the lead structure resulted in the discovery of *N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*,*N*′-diphenylurea (**4a**) with significantly improved CCR5 binding affinity. Substitutions (4-Cl, **4e**,**f**; 4-Me, **4i**) on the *N*′-phenyl ring further increased the binding affinity. Introduction of polar substituents on the phenyl ring of the 4-benzylpiperidine moiety enhanced the inhibitory activity of the HIV-1 envelope-mediated membrane fusion (**4v**,**w**), suggesting that polar substituents at this position can interfere effectively with HIV-1 cell entry.

1. Introduction

Treatment with highly active antiretroviral therapy (HAART) has successfully suppressed viral replication, recovered immune function, and improved quality of life in human immunodeficiency virus type 1 (HIV-1)-infected individuals. However, the effectiveness of currently available HAART is limited by the development of viral resistance as well as the toxicity and complexity of drug regimens. Therefore, there remains a need to develop new anti-HIV-1 drugs with improved efficacy and less toxicity.

The discovery of chemokine receptors as 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.[1] HIV-1 strains that cause the initial infection predominantly utilize CC chemokine receptor 5 (CCR5),[2] and CCR5-using (R5) HIV-1 is isolated exclusively during the asymptomatic stage of the infection, which usually persists 5–10 years.[3] CCR5 is a member of 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 1α (MIP-1α), and MIP-1β], which have been reported to inhibit R5 HIV-1 infection in vitro.[4] Individuals homozygous for a defect in CCR5 expression are highly resistant to HIV-1 infection, while this defect does not represent a significant health problem.[5–7] In addition, infected individuals heterozygous for the defective CCR5 gene appear to have delayed disease progression.[8] These observations suggest that CCR5 antagonists functioning as HIV-1 entry inhibitors could be promising anti-HIV-1 therapeutic agents.

Our laboratories have previously described the discovery of TAK-779 as the first small-molecule CCR5 antagonist,[9,10] and thereafter, several research groups reported structurally diverse CCR5 antagonists.[11–15] We also continued the screening of our compound libraries using a CCR5–RANTES binding assay and identified a novel lead compound **1a** (Fig. 1). Subsequent optimization of **1a** resulted in compounds with improved

Keywords: CCR5 antagonist; Chemokine; HIV-1; *N*,*N*′-Diphenylurea.
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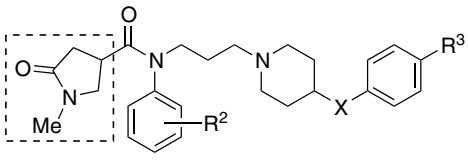
doi:10.1016/j.bmc.2004.02.004

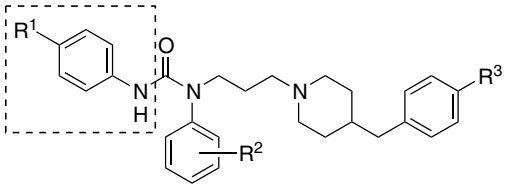
5-Oxopyrrolidine-3-carboxamide Type



1a-c

	R^2	X	R^3	CCR5 IC_{50} (nM)
1a	H	CO	F	1900
1b	H	CH_2	H	480
1c	3,4-diCl	CH_2	H	57

N,N'-Diphenylurea Type



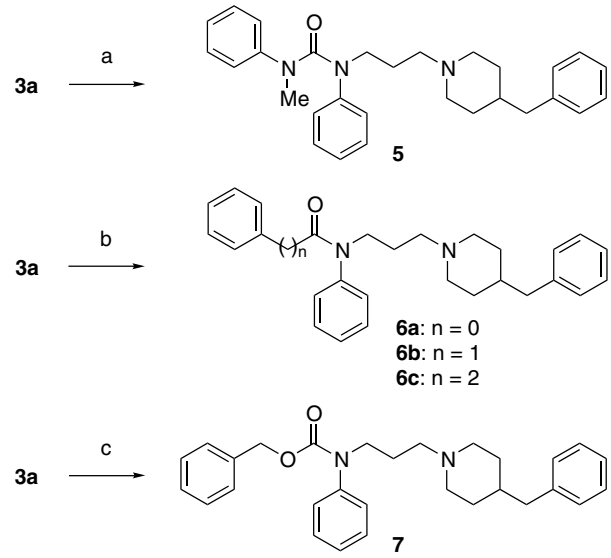
4a,e-w

Figure 1.

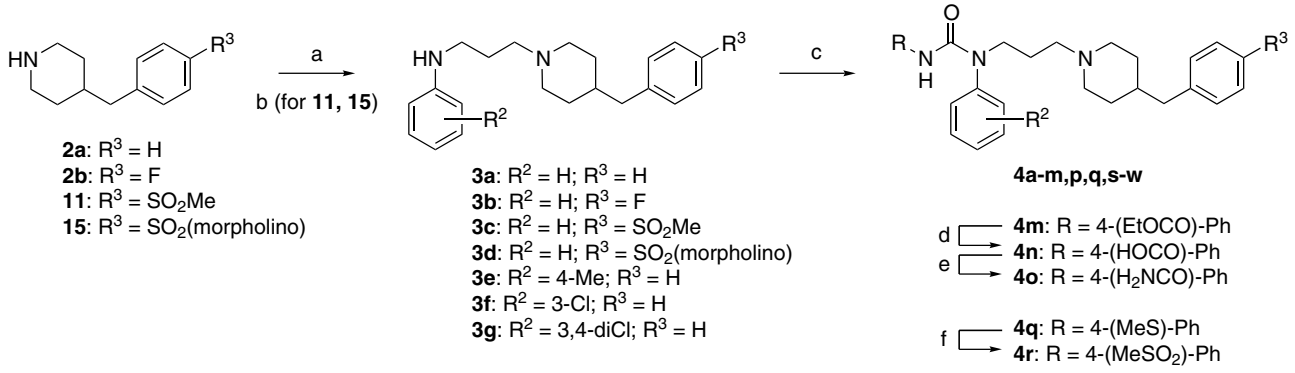
binding potency (e.g., **1c**).[16] As part of an effort to identify compounds with further improved potency, we incorporated various acyl groups as a replacement for the 5-oxopyrrolidine-3-carbonyl group in the original lead structure. In this paper, we describe the synthesis and structure-activity relationships (SAR) of *N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*,*N'*-diphenylureas, which have led to a potent series of novel CCR5 antagonists.

2. Chemistry

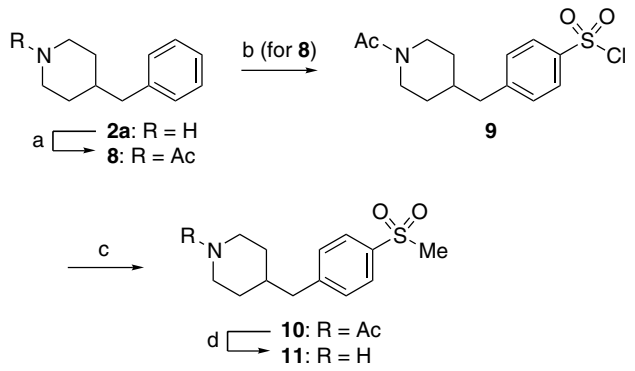
Target compounds were synthesized as outlined in Schemes 1 and 2. Treatment of 4-benzylpiperidines **2a**,**b**, **11**, **15** with acrolein in tetrahydrofuran (THF) in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided β-aminoaldehydes in situ,[17] which were subjected to reductive amination with substituted anilines using sodium triacetoxyborohydride to afford anilines **3a**–**g** (Scheme 1). The anilines **3c**,**d** were also prepared by coupling of 4-benzylpiperidines **11**, **15** with *N*-(3-chloropropyl)aniline hydrochloride in the presence of potassium iodide and potassium carbonate. Reaction of **3a**–**g** with a variety of isocyanates furnished urea derivatives **4a**–**m**,**p**,**q**,**s**–**w**. The ester group in **4m** was hydrolyzed to give carboxylic acid **4n**, which was converted to carboxamide **4o**. Methylsulfonyl derivative **4r** was obtained by oxidation of **4q** with Oxone.[18]



Scheme 2. Reagents: (a) NaH, THF, then PhN(Me)COCl; (b) $Ph(CH_2)_nCOCl$, Et_3N, DCM; (c) $PhCH_2OCOCl$, aq NaOH, THF.



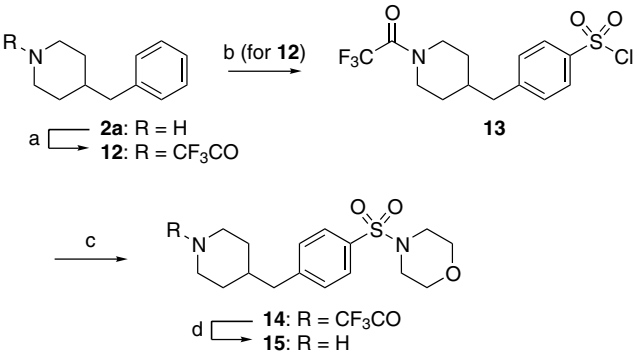
Scheme 1. Reagents: (a) acrolein, cat. DBU, THF, then R^2-$PhNH_2$, $NaBH(OAc)_3$; (b) *N*-(3-chloropropyl)aniline hydrochloride, KI, K_2CO_3, MeCN, DMF; (c) R-NCO, Et_3N, DCM; (d) aq NaOH, EtOH; (e) NH_4Cl, Et_3N, EDC, HOBt, DMF, (f) Oxone, aq H_2SO_4, MeOH.



Scheme 3. Reagents: (a) Ac_2O; (b) $ClSO_3H$, DCM; (c) Na_2SO_3, $NaHCO_3$, H_2O, then $ClCH_2CO_2H$, aq NaOH; (d) concd HCl, then aq NaOH.

N-Methyl analogue **5** was prepared from the free base of **3a** by deprotonation with sodium hydride followed by treatment with *N*-methyl-*N*-phenylcarbamoyl chloride (Scheme 2). Coupling reaction of the aniline **3a** with the appropriate acyl chloride afforded the amide derivatives **6a–c**. Carbamate derivative **7** was obtained by the reaction of **3a** with benzyl chloroformate.

The preparation of the required piperidines **11** and **15** is presented in Schemes 3 and 4, respectively. The amino group of **2a** was protected by acetylation affording **8**, which was treated with chlorosulfonic acid to give sulfonyl chloride **9** (Scheme 3). Conversion of **9** into sulfone **10** was accomplished by reduction of the chlorosulfonyl group, alkylation of the intermediate sulfinate with 2-chloroacetic acid, and decarboxylation.[19] Deprotection of the acetyl group in **10** using concentrated hydrochloric acid, followed by neutralization, provided the desired piperidine **11**. Sulfonamide analogue **15** was prepared as follows (Scheme 4). Reaction of **2a** with trifluoroacetic anhydride followed by chlorosulfonylation gave compound **13**. Treatment of **13** with morpholine provided sulfonamide **14**, which on deprotection using potassium carbonate yielded the piperidine **15**.



Scheme 4. Reagents: (a) TFAA; (b) $ClSO_3H$, DCM; (c) morpholine, Et_3N, THF; (d) K_2CO_3, H_2O, MeOH.

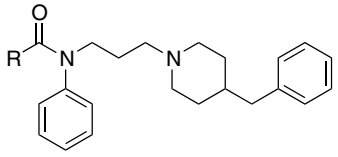
3. Results and discussion

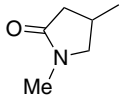
The compounds prepared were evaluated for their potency to inhibit binding of ^{125}I-labeled RANTES to Chinese hamster ovary (CHO) cells expressing human CCR5, and the results are reported as IC_{50} values. Selected compounds were further tested in an HIV-1 envelope-mediated membrane fusion assay to 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 similarly as IC_{50} values.

We have previously reported the identification of the novel lead compound **1a** ($IC_{50} = 1900$ nM) as a CCR5 antagonist (Fig. 1). Subsequent optimization, focused on a series of 5-oxopyrrolidine-3-carboxamides, resulted in compounds with increased binding affinity (e.g., **1c**, $IC_{50} = 57$ nM). To identify more potent compounds, our focus was directed toward replacement of the 5-oxopyrrolidine moiety in the lead structure.

We first replaced the 5-oxopyrrolidine moiety in **1b** ($IC_{50} = 480$ nM) with a phenyl group to obtain compound **6a**, which resulted in a 5-fold reduction in binding affinity (Table 1). Extension of the phenyl as a benzyl (**6b**) restored binding affinity comparable to **1b**, but further elongation did not improve the activity (**6c**). More promising results were obtained with urea derivatives, where replacement of the benzyl in **6b** with a phenylamino group afforded compound **4a** with significant improvement in binding affinity ($IC_{50} = 18$ nM). The marked enhancement in binding affinity of compound **4a** prompted us to explore the SAR of this class. Benzylamino derivative **4b** showed lower potency than

Table 1. Acyl modifications



Compound	R	CCR5[a] IC_{50} (nM)
1b		480
4a	PhNH	18
4b	$PhCH_2NH$	150
4c	c-HexNH	24
4d	*n*-PrNH	62
5	PhN(Me)	6600
6a	Ph	2300
6b	$PhCH_2$	450
6c	$Ph(CH_2)_2$	920
7	$PhCH_2O$	2000

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

4a, indicating the phenylamino substituent was optimal for CCR5 binding. N-Methylation of **4a** resulted in a substantial loss of potency (**5**), suggesting that a hydrogen donor NH group was critical for binding or the methyl group was not sterically tolerated. It has been reported that N-methylation of *N*,*N*′-diphenylurea causes a conformational change, in which the phenyl ring is located *trans* to the urea oxygen.[20] The conformational change might affect the binding affinity. The importance of the NH group was also confirmed by carbamate **7** showing >10-fold lower potency than the corresponding urea **4b**. Interestingly, the cyclohexyl analogue **4c** also had potent affinity comparable to **4a**, while the propyl analogue **4d** had slightly lower potency than **4c**. These results suggested that the steric bulkiness of the acyl moiety was preferable for potent binding affinity.

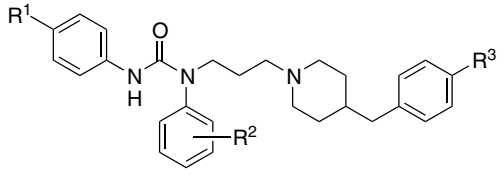
Having identified the *N*,*N*′-diphenylurea group as critical for CCR5 binding affinity, we then searched for the optimal substituent on the *N*′-phenyl ring (Table 2, R^1). Introduction of a chlorine atom at the 4-position of the *N*′-phenyl ring of **4a** resulted in about a 3-fold improvement in the binding potency (**4e**, $IC_{50} = 5.9$ nM). The presence of a fluorine substituent in the 4-benzylpiperidine moiety ($R^3 = F$) had little effect on CCR5 binding (**4e** vs **4f**). Methyl analogue **4i** also exhibited potent activity ($IC_{50} = 6.6$ nM), but incorporation of a bulky isopropyl group (**4j**) resulted in decreased binding affinity, indicating this moiety may interact with a sterically restricted pocket of the receptor. Other halogens such as fluorine (**4g**) and bromine (**4h**) showed equivalent potency to **4a**, and the small polar cyano group (**4l**) was also tolerated, but the bulky ethoxycarbonyl group (**4m**) decreased potency. Carbamoyl (**4o**), methoxy (**4p**), and methylsulfonyl (**4r**) derivatives exhibited comparable affinity to **4a**, suggesting that medium-size polar groups are allowed at this position. The selectivity profile of compound **4e** for other chemokine receptors was evaluated using a binding assay. The IC_{50} values for CCR1, CCR2, CCR4, and CCR7 were all greater than 10 μM.

We next investigated substitution on the central phenyl ring (R^2). It has been demonstrated that appropriate substitutions (e.g., 4-Me; 3-Cl; 3,4-diCl) on the central phenyl enhanced activity in the 5-oxopyrrolidine-3-carboxamide series (Fig. 1, **1b** vs **1c**).[16] In the *N*,*N*′-diphenylurea series, on the contrary, the unsubstituted derivative **4e** showed more potent activity than the 4-methyl (**4s**), 3-chloro (**4t**), and 3,4-dichloro (**4u**) derivatives (Table 2). The difference in SAR between the two series might stem from their receptor binding modes. Other substitutions (2-F, 3-F, 4-F, 2-MeO, 3-MeO, 4-MeO) on the central phenyl ring also failed to increase the activity in the *N*,*N*′-diphenylurea derivatives (data not shown).

In the exploration of the 4-benzylpiperidine moiety (R^3), sulfonyl substituents were found to be effective for increasing binding affinity. Introduction of a methylsulfonyl group at the 4-position of the benzyl showed about a 5-fold improvement (**4v**, $IC_{50} = 1.2$ nM) in the CCR5 binding potency compared to the parent compound **4e** ($IC_{50} = 5.9$ nM), and the sulfonamide analogue **4w** also had potent affinity with an IC_{50} value of 1.0 nM.

Selected compounds were evaluated in an HIV-1 envelope-mediated membrane fusion assay (Table 2). For the more potent CCR5 antagonists **4e** and **4f**, we observed a good correlation between the inhibitory activity of CCR5 binding and that of HIV-1 envelope-mediated membrane fusion. Unexpected results were obtained in the sulfone (**4v**) and sulfonamide (**4w**) derivatives, in which the inhibitory activity of CCR5 binding did not correlate with that of HIV-1 envelope-mediated membrane fusion. As mentioned above, the IC_{50} values of compounds **4v** and **4w** were about 5-fold lower than that of compound **4e** in the CCR5 binding assay. However, in the HIV-1 envelope-mediated membrane fusion assay, compound **4v** showed an IC_{50} value of 0.59 nM, which was about 16-fold lower than that of **4e** ($IC_{50} = 9.4$ nM). Furthermore, sulfonamide analogue **4w** inhibited the membrane fusion with an IC_{50} value of 0.050 nM, which was about 180-fold lower than that of **4e**. The discrepancy in the inhibitory activities for CCR5 binding and HIV-1 envelope-mediated membrane fusion probably reflects the differences in the receptor binding sites of the ligands (RANTES and effector cells expressing HIV-1 envelope). These results suggested that

Table 2. *N*,*N*′-diphenylurea derivatives



Compound	R^1	R^2	R^3	CCR5[a] IC_{50} (nM)	Fusion[b] IC_{50} (nM)
4a	H	H	H	18	64
4e	Cl	H	H	5.9	9.4
4f	Cl	H	F	7.8	13
4g	F	H	F	13	NT
4h	Br	H	F	18	NT
4i	Me	H	F	6.6	NT
4j	*i*-Pr	H	F	76	NT
4k	CF_3	H	F	14	14
4l	NC	H	F	15	10
4m	EtOCO	H	F	280	NT
4n	HOCO	H	F	350	NT
4o	H_2NCO	H	F	29	14
4p	MeO	H	F	30	33
4q	MeS	H	F	15	13
4r	$MeSO_2$	H	F	26	18
4s	Cl	4-Me	H	11	22
4t	Cl	3-Cl	H	19	52
4u	Cl	3,4-diCl	H	62	61
4v	Cl	H	SO_2Me	1.2	0.59
4w	Cl	H	SO_2(morpholino)	1.0	0.050

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

polar substituents on the phenyl ring of the 4-benzylpiperidine moiety can interfere effectively with the HIV-1 cell entry.

4. Conclusion

Replacement of the 5-oxopyrrolidine fragment in the original structure (**1b**) with a phenylamino group gave the *N*,*N*′-diphenylurea derivative **4a**, which was found to have significantly improved CCR5 binding affinity. SAR studies of this series determined that the urea group is essential for potent binding affinity. Substitutions on the *N*′-phenyl ring revealed that small hydrophobic substituents (Cl, **4e**,**f**; Me, **4i**) at the 4-position enhanced the binding affinity. Sulfone (**4v**) and sulfonamide (**4w**) derivatives showed more potent activity in HIV-1 envelope-mediated membrane fusion assay than expected from the activity in the CCR5 binding assay. This finding suggests that the polar substituents play an important role in inhibiting the HIV-1 entry process and will be helpful in designing potent HIV-1 entry inhibitors.

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), basic alumina (ICN Biomedicals, activity III), or NH silica gel (Fuji Silysia, NH-DM1020). 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 by Takeda Analytical Research Laboratories, Ltd.

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

To a stirred solution of 4-benzylpiperidine (**2a**) (3.51 g, 20 mmol) and DBU (30 μL, 0.2 mmol) in THF (40 mL) was added dropwise a solution of acrolein (90%, 1.49 mL, 20 mmol) in THF (5 mL) at −20 °C, and the mixture was stirred at −20 to −10 °C for 1 h. The mixture was treated with *p*-toluidine (2.14 g, 20 mmol) followed by $NaBH(OAc)_3$ (8.48 g, 40 mmol) at −10 °C, and allowed to warm to room temperature. After 23 h, the mixture was diluted with aqueous $NaHCO_3$ 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 (EtOAc/MeOH 1:0 to 4:1) to afford the free base of **3e** (4.07 g) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.15–1.95 (9H, s), 2.23 (3H, s), 2.42 (2H, t, $J = 6.8$ Hz), 2.55 (2H, d, $J = 6.6$ Hz), 2.85–3.00 (2H, m), 3.13 (2H, t, $J = 6.4$ Hz), 6.51 (2H, d, $J = 8.4$ Hz), 6.98 (2H, d, $J = 8.4$ Hz), 7.10–7.35 (5H, m). Treatment with 4 N HCl (EtOAc solution, 8 mL) in *i*-PrOH (20 mL) gave the HCl salt **3e** (4.52 g, 57%) as a white solid, mp 186–192 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.40–1.90 (5H, m), 2.00–2.25 (2H, m), 2.31 (3H, s), 2.45–2.60 (2H, m), 2.70–2.95 (2H, m), 2.95–3.55 (6H, m), 7.10–7.45 (9H, m). Anal. Calcd for $C_{22}H_{30}N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 65.34; H, 8.22; Cl, 17.53; N, 6.93. Found: C, 65.24; H, 8.38; Cl, 17.37; N, 6.98.

The following compounds (**3a**,**b**,**f**,**g**) were prepared using a procedure similar to that described for **3e** from **2a,b** and the appropriate aniline.

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

Yield 47%, 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.

5.3. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}aniline dihydrochloride (3b)

Yield 54%, mp 227–230 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.35–1.90 (5H, m), 1.95–2.20 (2H, m), 2.45–2.60 (2H, m), 2.83 (2H, br t, $J = 11.5$ Hz), 3.11 (2H, br t, $J = 7.4$ Hz), 3.24 (2H, br t, $J = 6.8$ Hz), 3.42 (2H, br d, $J = 10.6$ Hz), 6.90–7.20 (9H, m). Anal. Calcd for $C_{21}H_{27}FN_2 \cdot 2HCl \cdot 0.8H_2O$: C, 60.96; H, 7.45; N, 6.77; Cl, 17.14; F, 4.59. Found: C, 61.02; H, 7.37; N, 6.76; Cl, 17.04; F, 4.30.

5.4. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-chloroaniline dihydrochloride (3f)

Yield 41%, mp 199–202 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.53–2.01 (7H, m), 2.50–2.55 (2H, m), 2.66–2.92 (2H, m), 3.08–3.20 (4H, m), 3.38–3.44 (2H, m), 6.61–6.69 (3H, m), 7.07–7.30 (6H, m). Anal. Calcd for $C_{21}H_{27}ClN_2 \cdot 2HCl \cdot 0.1H_2O$: C, 60.39; H, 7.04; N, 6.71. Found: C, 60.33; H, 6.93; N, 6.84.

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

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.

5.6. *N*-(3-{4-[4-(Morpholin-4-ylsulfonyl)benzyl]piperidin-1-yl}propyl)aniline (3d)

5.6.1. Step 1: *N*-(3-chloropropyl)aniline hydrochloride. To a mixture of formanilide (100 g, 0.83 mol) and 1-bromo-3-chloropropane (156 g, 0.99 mol) in acetone (500 mL) was added Cs_2CO_3 (323 g, 0.99 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 (2×100 mL), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 1:0 to 7:3) to afford (3-chloropropyl)phenylformamide (145 g, 89%) as a pale yellow oil. This oil (144 g, 0.73 mol) was dissolved in *i*-PrOH (500 mL) and treated with concentrated HCl (120 mL). The mixture was stirred at 60 °C for 5 h, then cooled with an ice bath. The resulting precipitate was collected by filtration, washed with *i*-PrOH (2×100 mL), and dried in vacuo to give *N*-(3-chloropropyl)aniline hydrochloride (109 g, 72%) as a white solid.

5.6.2. Step 2: *N*-(3-{4-[4-(morpholin-4-ylsulfonyl)benzyl]piperidin-1-yl}propyl)aniline (3d). A mixture of *N*-(3-chloropropyl)aniline hydrochloride (1.63 g, 7.9 mmol), **15** (2.33 g, 7.2 mmol), KI (1.31 g, 7.9 mmol), and K_2CO_3 (3.97 g, 29 mmol) in MeCN/DMF (1:1, 28 mL) was stirred at 100 °C for 6 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layer was washed with brine (30 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1:0 to 4:1) to give **3d** (2.89 g, 88%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.20–2.00 (9H, m), 2.45 (2H, t, $J = 6.8$ Hz), 2.64 (2H, d, $J = 6.4$ Hz), 2.85–3.05 (6H, m), 3.17 (2H, t, $J = 6.4$ Hz), 3.70–3.80 (4H, m), 6.50–6.75 (3H, m), 7.10–7.25 (2H, m), 7.33 (2H, d, $J = 8.4$ Hz), 7.67 (2H, d, $J = 8.4$ Hz).

5.7. *N*-(3-{4-[4-(Methylsulfonyl)benzyl]piperidin-1-yl}propyl)aniline (3c)

Compound **3c** was prepared using a procedure similar to that described for **3d** from **11** in 98% yield, oil. ^{1}H NMR ($CDCl_3$) δ 1.26–1.91 (9H, m), 2.45 (2H, t, $J = 6.8$ Hz), 2.66 (2H, d, $J = 6.6$ Hz), 2.95 (2H, d, $J = 11.4$ Hz), 3.05 (3H, s), 3.17 (2H, t, $J = 6.3$ Hz), 4.65 (1H, br s), 6.58 (2H, d, $J = 7.2$ Hz), 6.68 (1H, t, $J = 7.2$ Hz), 7.17 (2H, t, $J = 8.0$ Hz), 7.35 (2H, d, $J = 8.4$ Hz), 7.86 (2H, d, $J = 8.0$ Hz).

5.8. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*′-(4-chlorophenyl)-*N*-phenylurea (4e)

To a stirred solution of **3a** (22.9 g, 60 mmol) and Et_3N (18.5 mL, 132 mmol) in dichloromethane (DCM) (500 mL) was added 4-chlorophenyl isocyanate (13.8 g, 90 mmol). After being stirred at room temperature for 12 h, the mixture was washed with saturated aqueous $NaHCO_3$ (2×400 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 recrystallization from Et_2O to afford **4e** (13.8 g, 50%) as a white solid, mp 101–103 °C. ^{1}H NMR ($CDCl_3$) δ 1.23–1.46 (2H, m), 1.46–1.90 (7H, m), 2.36 (2H, t, $J = 7.3$ Hz), 2.51 (2H, d, $J = 6.6$ Hz), 2.82–2.90 (2H, m), 3.77 (2H, t, $J = 7.3$ Hz), 6.66 (1H, br), 7.10–7.52 (14H, m). Anal. Calcd for $C_{28}H_{32}ClN_3O$: C, 72.79; H, 6.98; Cl, 7.67; N, 9.09. Found: C, 72.41; H, 6.97; Cl, 7.72; N, 8.98.

The following compounds (**4a**–**d**,**f**–**m**,**p**,**q**,**s**–**w**) were prepared using a procedure similar to that described for **4e** from **3a**–**g** and the appropriate isocyanate.

5.9. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*,*N*′-diphenylurea hydrochloride (4a)

Yield 82%, amorphous solid. ^{1}H NMR (DMSO-d_6) δ 1.30–1.95 (7H, m), 2.54–2.57 (2H, m), 2.80–2.93 (2H, m), 3.00–3.12 (2H, m), 3.42–3.80 (2H, m), 3.62–3.78 (2H, m), 6.95–7.55 (15H, m), 7.85 (1H, s). Anal. Calcd for $C_{28}H_{33}N_3O \cdot HCl \cdot 0.75H_2O$: C, 70.42; H, 7.71; N, 8.80. Found: C, 70.43; H, 7.31; N, 8.74.

5.10. *N*′-Benzyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-phenylurea hydrochloride (4b)

Yield 67%, amorphous solid. ^{1}H NMR (DMSO-d_6) δ 1.40–1.81 (7H, m), 2.53–2.56 (2H, m), 2.77–2.89 (2H, m), 2.98–3.18 (2H, m), 3.35–3.40 (2H, m), 3.65–3.70 (2H, m), 4.20 (2H, s), 7.18–7.54 (15H, m). Anal. Calcd for $C_{29}H_{35}N_3O \cdot HCl \cdot 0.5H_2O$: C, 71.51; H, 7.66; N, 8.63. Found: C, 71.60; H, 7.74; N, 8.46.

5.11. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*′-cyclohexyl-*N*-phenylurea (4c)

Yield 72%, mp 106–108 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 0.80–1.95 (19H, m), 2.30 (2H, t, $J = 7.6$ Hz), 2.50 (2H, d, $J = 6.6$ Hz), 2.83 (2H, br d, $J = 11.8$ Hz), 3.40–3.75 (1H, m), 3.68 (2H, t, $J = 7.3$ Hz), 4.15 (1H, d, $J = 8.0$ Hz), 7.05–7.50 (10H, m). Anal. Calcd for $C_{28}H_{39}N_3O$: C, 77.55; H, 9.07; N, 9.69. Found: C, 77.65; H, 8.96; N, 9.75.

5.12. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-phenyl-*N*′-propylurea (4d)

Yield 92%, oil. ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, $J = 7.3$ Hz), 1.10–1.95 (11H, m), 2.33 (2H, t, $J = 7.6$ Hz), 2.53 (2H, d, $J = 6.6$ Hz), 2.86 (2H, br d, $J = 11.6$ Hz), 3.05–3.20 (2H, m), 3.71 (2H, t, $J = 7.3$ Hz), 4.55–4.70 (1H, m), 7.10–7.50 (10H, m). Anal. Calcd for $C_{25}H_{35}N_3O \cdot 0.5H_2O$: C, 74.59; H, 9.01; N, 10.44. Found: C, 74.78; H, 9.19; N, 10.43.

5.13. *N*′-(4-Chlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-*N*-phenylurea hydrochloride (4f)

Yield 94%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.10–2.00 (9H, m), 2.36 (2H, br t, $J = 7.3$ Hz), 2.48 (2H, d, $J = 6.6$ Hz), 2.86 (2H, br d, $J = 11.6$ Hz), 3.77 (2H, t, $J = 7.1$ Hz), 6.60 (1H, br s), 6.85–7.55 (13H, m). Anal. Calcd for $C_{28}H_{31}ClFN_3O \cdot HCl \cdot 0.5H_2O$: C, 64.00; H, 6.33; N, 8.00. Found: C, 64.12; H, 6.39; N, 8.00.

5.14. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-(4-fluorophenyl)-*N*-phenylurea hydrochloride (4g)

Yield 91%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.13–1.89 (9H, m), 2.36 (2H, t, $J = 7.3$ Hz), 2.47 (2H, d, $J = 6.6$ Hz), 2.86 (2H, d, $J = 11.8$ Hz), 3.77 (2H, t, $J = 7.1$ Hz), 6.60 (1H, s), 6.87–7.10 (6H, m), 7.19–7.51 (7H, m). Anal. Calcd for $C_{28}H_{31}F_2N_3O \cdot HCl \cdot 0.7H_2O$: C, 65.60; H, 6.57; N, 8.20. Found: C, 65.63; H, 6.78; N, 8.04.

5.15. *N*′-(4-Bromophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-*N*-phenylurea (4h)

Yield 88%, mp 84–85 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.13–1.89 (9H, m), 2.36 (2H, t, $J = 7.5$ Hz), 2.48 (2H, d, $J = 6.6$ Hz), 2.86 (2H, d, $J = 11.8$ Hz), 3.76 (2H, t, $J = 7.3$ Hz), 6.62 (1H, br s), 6.90–7.10 (4H, m), 7.18–7.51 (9H, m). Anal. Calcd for $C_{28}H_{31}BrFN_3O$: C, 64.12; H, 5.96; N, 8.01. Found: C, 63.88; H, 5.95; N, 8.02.

5.16. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-(4-methylphenyl)-*N*-phenylurea hydrochloride (4i)

Yield 88%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.21–1.86 (9H, m), 2.27 (3H, s), 2.35 (2H, t, $J = 7.5$ Hz), 2.47 (2H, d, $J = 6.9$ Hz), 2.85 (2H, d, $J = 12.0$ Hz), 3.77 (2H, t, $J = 7.4$ Hz), 6.45 (1H, s), 6.94 (2H, t, $J = 8.9$ Hz), 7.02–7.09 (4H, m), 7.17 (2H, d, $J = 8.7$ Hz), 7.28–7.49 (5H, m). Anal. Calcd for $C_{29}H_{34}FN_3O \cdot HCl \cdot H_2O$: C, 67.75; H, 7.25; N, 8.17. Found: C, 67.82; H, 7.39; N, 7.92.

5.17. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-(4-isopropylphenyl)-*N*-phenylurea hydrochloride (4j)

Yield 99%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.18–1.88 (15H, m), 2.35 (2H, t, $J = 7.5$ Hz), 2.47 (2H, d, $J = 6.6$ Hz), 2.76–2.90 (2H, m), 3.77 (2H, t, $J = 7.3$ Hz), 6.45 (1H, s), 6.94–7.49 (13H, m). Anal. Calcd for $C_{31}H_{38}FN_3O \cdot HCl \cdot 0.5H_2O$: C, 69.84; H, 7.56; N, 7.88. Found: C, 69.77; H, 7.51; N, 7.67.

5.18. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*-phenyl-*N*′-[4-(trifluoromethyl)phenyl]urea hydrochloride (4k)

Yield 81%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.22–1.89 (9H, m), 2.37 (2H, t, $J = 7.4$ Hz), 2.48 (2H, d, $J = 6.9$ Hz), 2.86 (2H, d, $J = 11.7$ Hz), 3.78 (2H, t, $J = 7.1$ Hz), 6.79 (1H, br s), 6.95 (2H, t, $J = 8.7$ Hz), 7.04–7.09 (2H, m), 7.29–7.52 (9H, m). Anal. Calcd for $C_{29}H_{31}F_4N_3O \cdot HCl \cdot 0.5H_2O$: C, 62.31; H, 5.95; N, 7.52. Found: C, 62.23; H, 6.13; N, 7.48.

5.19. *N*′-(4-Cyanophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}-*N*-phenylurea hydrochloride (4l)

Yield 94%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.15–1.91 (9H, m), 2.36 (2H, t, $J = 7.3$ Hz), 2.49 (2H, d, $J = 6.6$ Hz), 2.86 (2H, d, $J = 11.8$ Hz), 3.78 (2H, t, $J = 7.3$ Hz), 6.87–7.11 (5H, m), 7.29 (2H, d, $J = 8.4$ Hz), 7.37–7.54 (7H, m). Anal. Calcd for $C_{29}H_{31}FN_4O \cdot HCl \cdot 0.6H_2O$: C, 67.26; H, 6.46; N, 10.82. Found: C, 67.38; H, 6.72; N, 10.54.

5.20. Ethyl 4-({[3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl(phenyl)amino]carbonyl}amino)benzoate (4m)

Yield 97%, mp 89–90 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$) δ 1.15–1.90 (12H, m), 2.37 (2H, t, $J = 7.5$ Hz), 2.49 (2H, d, $J = 6.6$ Hz), 2.87 (2H, d, $J = 11.6$ Hz), 3.78 (2H, t, $J = 7.4$ Hz), 4.33 (2H, q, $J = 7.2$ Hz), 6.80 (1H, br s), 6.91–7.11 (4H, m), 7.28–7.53 (7H, m), 7.92 (2H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{31}H_{36}FN_3O_3$: C, 71.93; H, 7.01; N, 8.12. Found: C, 71.95; H, 6.85; N, 8.18.

5.21. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-(4-methoxyphenyl)-*N*-phenylurea hydrochloride (4p)

Yield 97%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.12–1.89 (9H, m), 2.36 (2H, t, $J = 7.5$ Hz), 2.47 (2H, d, $J = 6.6$ Hz), 2.86 (2H, d, $J = 11.8$ Hz), 3.73–3.81 (5H, m), 6.47 (1H, s), 6.79 (2H, d, $J = 8.8$ Hz), 6.90–7.10 (4H, m), 7.19 (2H, d, $J = 8.8$ Hz), 7.28–7.50 (5H, m). Anal. Calcd for $C_{29}H_{34}FN_3O_2 \cdot HCl \cdot 0.5H_2O$: C, 66.85; H, 6.96; N, 8.06. Found: C, 67.05; H, 7.11; N, 7.76.

5.22. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-[4-(methylsulfanyl)phenyl]-*N*-phenylurea hydrochloride (4q)

Yield 100%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.15–1.89 (9H, m), 2.36 (2H, t, $J = 7.5$ Hz), 2.43 (3H, s), 2.48 (2H, d, $J = 6.6$ Hz), 2.86 (2H, d, $J = 11.8$ Hz), 3.77 (2H, t, $J = 7.1$ Hz), 6.55 (1H, br s), 6.90–7.50 (13H, m). Anal. Calcd for $C_{29}H_{34}FN_3OS \cdot HCl \cdot 0.7H_2O$: C, 64.41; H, 6.79; N, 7.77. Found: C, 64.47; H, 6.67; N, 7.59.

5.23. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*′-(4-chlorophenyl)-*N*-(4-methylphenyl)urea hydrochloride (4s)

Yield 87%, amorphous solid. ^{1}H NMR (DMSO-d_6) δ 1.20–1.95 (7H, m), 2.34 (3H, s), 2.45–2.60 (2H, m), 2.60–3.50 (6H, m), 3.68 (2H, t, $J = 6.8$ Hz), 7.10–7.35 (11H,

m), 7.44 (2H, d, $J = 9.2$ Hz), 7.93 (1H, s). Anal. Calcd for $C_{29}H_{34}ClN_3O \cdot HCl \cdot 0.5H_2O$: C, 66.79; H, 6.96; N, 8.06. Found: C, 66.84; H, 6.99; N, 7.95.

5.24. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3-chlorophenyl)-*N*′-(4-chlorophenyl)urea hydrochloride (4t)

Yield 27%, amorphous solid. ^{1}H NMR (DMSO-d_6) δ 1.40–1.91 (7H, m), 2.51–2.54 (2H, m), 2.78–2.90 (2H, m), 3.00–3.17 (2H, m), 3.37–3.43 (2H, m), 3.71–3.78 (2H, m), 7.15–7.50 (13H, m), 8.34 (1H, s). Anal. Calcd for $C_{28}H_{31}Cl_2N_3O \cdot HCl \cdot H_2O$: C, 61.04; H, 6.22; N, 7.63. Found: C, 60.80; H, 6.20; N, 7.73.

5.25. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*′-(4-chlorophenyl)-*N*-(3,4-dichlorophenyl)urea (4u)

Yield 78%, mp 128–131 °C. ^{1}H NMR ($CDCl_3$) δ 1.10–2.00 (9H, m), 2.39 (2H, t, $J = 6.8$ Hz), 2.51 (2H, d, $J = 6.2$ Hz), 2.88 (2H, br d, $J = 11.8$ Hz), 3.78 (2H, t, $J = 6.6$ Hz), 7.05–7.40 (10H, m), 7.41 (1H, d, $J = 2.6$ Hz), 7.49 (1H, d, $J = 8.4$ Hz), 7.90 (1H, br s). Anal. Calcd for $C_{28}H_{30}Cl_3N_3O$: C, 63.34; H, 5.70; N, 7.91. Found: C, 63.25; H, 5.58; N, 7.93.

5.26. *N*′-(4-Chlorophenyl)-*N*-(3-{4-[4-(methylsulfonyl)benzyl]piperidin-1-yl}propyl)-*N*-phenylurea hydrochloride (4v)

Yield 68%, amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.10–1.95 (9H, m), 2.35 (2H, t, $J = 7.5$ Hz), 2.60 (2H, d, $J = 6.6$ Hz), 2.86 (2H, br d, $J = 11.0$ Hz), 3.04 (3H, s), 3.76 (2H, t, $J = 7.3$ Hz), 6.48 (1H, br s), 7.10–7.55 (11H, m), 7.84 (2H, d, $J = 8.0$ Hz). Anal. Calcd for C_{29} $H_{34}ClN_3O_3S \cdot HCl \cdot H_2O$: C, 58.58; H, 6.27; N, 7.07. Found: C, 58.52; H, 6.25; N, 7.02.

5.27. *N*′-(4-Chlorophenyl)-*N*-(3-{4-[4-(morpholin-4-ylsulfonyl)benzyl]piperidin-1-yl}propyl)-*N*-phenylurea hydrochloride (4w)

Yield 54%, amorphous solid. ^{1}H NMR (CD_3OD) δ 1.40–2.10 (7H, m), 2.75 (2H, d, $J = 6.6$ Hz), 2.80–3.10 (6H, m), 3.18 (2H, t, $J = 7.3$ Hz), 3.45–3.75 (6H, m), 3.86 (2H, t, $J = 6.6$ Hz), 7.15–7.65 (11H, m), 7.71 (2H, d, $J = 8.6$ Hz). Anal. Calcd for $C_{32}H_{39}ClN_4O_4S \cdot HCl \cdot 1.4H_2O$: C, 57.12; H, 6.41; N, 8.33. Found: C, 57.18; H, 6.57; N, 8.02.

5.28. 4-({[{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}(phenyl)amino]carbonyl}amino)benzoic acid (4n)

To a stirred solution of **4m** (1.90 g, 3.67 mmol) in EtOH (20 mL) was added 1 N aqueous NaOH (5.50 mL), and the mixture was stirred at 80 °C for 5 h. The mixture was treated with 1 N aqueous HCl (5.50 mL) and concentrated in vacuo. The residue was partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 10:1 to 4:1) to give **4n** (0.58 g, 32%) as an amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.47–1.78 (5H, m), 1.96–2.35 (4H, m), 2.52 (2H, br s), 2.85 (2H, br s), 3.44 (2H, d, $J = 10.4$ Hz), 3.75 (2H, br s), 4.35 (1H, br s), 6.35 (1H, s), 6.89–7.13 (6H, m), 7.26–7.37 (5H, m), 7.82 (2H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{29}H_{32}FN_3O_3 \cdot H_2O$: C, 68.62; H, 6.75; N, 8.28. Found: C, 68.78; H, 6.56; N, 8.05.

5.29. 4-({[{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}(phenyl)amino]carbonyl}amino)benzamide (4o)

To a mixture of **4n** (300 mg, 0.61 mmol), HOBt (83 mg, 0.61 mmol) and NH_4Cl (43 mg, 0.80 mmol) in DMF (5 mL) were added Et_3N (0.11 mL, 0.80 mmol), and EDC (153 mg, 0.80 mmol). The mixture was stirred at room temperature for 3 h and concentrated in vacuo. The residue was diluted with saturated aqueous $NaHCO_3$ (60 mL) and extracted with EtOAc (3×60 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (EtOAc/MeOH 100:1) followed by trituration with hexane/EtOAc to give **4o** (200 mg, 77%) as a white solid, mp 198–200 °C. ^{1}H NMR ($CDCl_3$) δ 1.22–1.91 (9H, m), 2.37 (2H, t, $J = 7.5$ Hz), 2.49 (2H, d, $J = 6.2$ Hz), 2.87 (2H, d, $J = 11.2$ Hz), 3.78 (2H, t, $J = 7.4$ Hz), 5.50 (1H, br s), 5.92 (1H, br s), 6.87–7.11 (4H, m), 7.26–7.53 (7H, m), 7.72 (2H, d, $J = 8.4$ Hz). Anal. Calcd for $C_{29}H_{33}FN_4O_2$: C, 71.29; H, 6.81; N, 11.47. Found: C, 71.17; H, 6.77; N, 11.30.

5.30. *N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-*N*′-[4-(methylsulfonyl)phenyl]-*N*-phenylurea hydrochloride (4r)

To an ice-cooled solution of **4q** (498 mg, 1.01 mmol) in MeOH (5 mL) was added 1 N H_2SO_4 (1.01 mL) followed by a solution of Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (938 mg, 1.53 mmol) in water (5 mL). After being stirred at room temperature for 1 h, the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. 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 NH silica gel (hexane/EtOAc 1:1) to give an oil (400 mg). Treatment with 4 N HCl (EtOAc solution) gave **4r** (389 mg, 69%) as an amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.23–1.91 (9H, m), 2.37 (2H, t, $J = 7.3$ Hz), 2.49 (2H, d, $J = 6.4$ Hz), 2.87 (2H, d, $J = 11.4$ Hz), 3.01 (3H, s), 3.78 (2H, t, $J = 7.2$ Hz), 6.91–7.11 (5H, m), 7.27–7.55 (7H, m), 7.79 (2H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{29}H_{34}FN_3O_3S \cdot HCl \cdot 0.8H_2O$: C, 60.62; H, 6.42; N, 7.31. Found: C, 60.82; H, 6.55; N, 7.14.

5.31. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N'*-methyl-*N*,*N'*-diphenylurea hydrochloride (5)

5.31.1. Step 1: *N*-[3-(4-benzylpiperidin-1-yl)propyl]aniline. Hydrochloride salt **3a** (3.81 g, 10 mmol) was basified with 1 N aqueous NaOH (30 mL) and extracted with Et_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give the corresponding free base (2.96 g, 96%).

5.31.2. Step 2: *N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N'*-methyl-*N*,*N'*-diphenylurea hydrochloride (5). To a stirred solution of the product from step 1 (308 mg, 1.0 mmol) was added NaH (60% in oil, 120 mg, 3.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The mixture was treated with *N*-methyl-*N*-phenylcarbamoyl chloride (509 mg, 3.0 mmol) and stirred at 80 °C for 17 h. The mixture was diluted with water (15 mL) at 0 °C and extracted with Et_2O (3×15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on alumina (hexane/EtOAc 5:1 to 2:1) followed by column chromatography on silica gel (hexane/EtOAc 1:1 to 0:1) to give an oil (393 mg). The oil was dissolved in MeOH, treated with 1 N HCl (Et_2O solution, 2 mL), and concentrated in vacuo. The residue was triturated with hexane to give **5** (351 mg, 74%) as a hygroscopic amorphous solid. ^{1}H NMR (free base, $CDCl_3$) δ 1.10–1.90 (9H, m), 2.29 (2H, t, $J = 7.5$ Hz), 2.50 (2H, d, $J = 6.6$ Hz), 2.83 (2H, br d, $J = 11.8$ Hz), 3.15 (3H, s), 3.59 (2H, t, $J = 7.6$ Hz), 6.65–7.35 (15H, m). Anal. Calcd for $C_{29}H_{35}N_3O \cdot HCl \cdot 0.5H_2O$: C, 71.51; H, 7.66; N, 8.63. Found: C, 71.46; H, 7.69; N, 8.64.

5.32. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*,2-diphenylacetamide (6b)

To a stirred mixture of **3a** (381 mg, 1.0 mmol) and phenylacetyl chloride (198 μL, 1.5 mmol) in DCM (10 mL) was added Et_3N (558 μL, 4.0 mmol) at 0 °C. After being stirred at room temperature for 15 h, the mixture was treated with 1 N aqueous NaOH (6 mL) and extracted with DCM. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, hexane/EtOAc 4:1 to 2:1) to give **6b** (404 mg, 95%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.10–1.90 (9H, m), 2.20–2.40 (2H, m), 2.52 (2H, d, $J = 6.6$ Hz), 2.83 (2H, br d, $J = 11.4$ Hz), 3.42 (2H, s), 3.73 (2H, t, $J = 7.6$ Hz), 6.95–7.50 (15H, m). Anal. Calcd for $C_{29}H_{34}N_2O \cdot 0.3H_2O$: C, 80.63; H, 8.07; N, 6.48. Found: C, 80.72; H, 8.05; N, 6.49.

The following compounds (**6a**,**c**) were prepared using a procedure similar to that described for **6b** from the appropriate acid chloride.

5.33. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-phenylbenzamide hydrochloride (6a)

Yield 65%, amorphous. ^{1}H NMR (DMSO-d_6) δ 1.30–2.05 (7H, m), 2.45–2.60 (2H, m), 2.60–3.50 (6H, m), 3.89 (2H, t, $J = 6.9$ Hz), 7.05–7.40 (15H, m). Anal. Calcd for $C_{28}H_{32}N_2O \cdot HCl \cdot H_2O$: C, 72.01; H, 7.55; N, 6.00. Found: C, 72.23; H, 7.66; N, 5.96.

5.34. *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*,3-diphenylpropanamide (6c)

Yield 95%, oil. ^{1}H NMR ($CDCl_3$) δ 1.10–1.90 (9H, m), 2.20–2.35 (4H, m), 2.51 (2H, d, $J = 6.6$ Hz), 2.82 (2H, br d, $J = 11.4$ Hz), 2.89 (2H, t, $J = 7.9$ Hz), 3.68 (2H, t, $J = 7.5$ Hz), 6.90–7.40 (15H, m). Anal. Calcd for $C_{30}H_{36}N_2O \cdot 0.2H_2O$: C, 81.11; H, 8.26; N, 6.31. Found: C, 80.99; H, 8.35; N, 6.33.

5.35. Benzyl [3-(4-benzylpiperidin-1-yl)propyl]phenylcarbamate (7)

To a stirred suspension of **3a** (381 mg, 1.0 mmol) in THF (7 mL) was added 1 N aqueous NaOH (7 mL) followed by benzyl chloroformate (571 μL, 4.0 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was diluted with water (15 mL) and extracted with Et_2O (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 (hexane/EtOAc 1:1 to 1:3) to give **7** (422 mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.10–1.90 (9H, m), 2.27 (2H, t, $J = 7.5$ Hz), 2.50 (2H, d, $J = 6.2$ Hz), 2.78 (2H, br d, $J = 11.2$ Hz), 3.70 (2H, t, $J = 7.3$ Hz), 5.13 (2H, s), 7.05–7.40 (15H, m). Anal. Calcd for $C_{29}H_{34}N_2O_2 \cdot 0.2H_2O$: C, 78.06; H, 7.77; N, 6.28. Found: C, 77.98; H, 7.80; N, 6.13.

5.36. 1-Acetyl-4-benzylpiperidine (8)

Acetic anhydride (110 mL, 1.17 mol) was added dropwise to 4-benzylpiperidine (**2a**) (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 **8** (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).

5.37. 4-[(1-Acetylpiperidin-4-yl)methyl]benzenesulfonyl chloride (9)

A solution of **8** (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, 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 **9** (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).

5.38. 1-Acetyl-4-[4-(methylsulfonyl)benzyl]piperidine (10)

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 **9** (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 aqueous HCl (20 mL) at 0 °C and extracted with EtOAc (60, 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 to 9:1) to give **10** (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).

5.39. 4-[4-(Methylsulfonyl)benzyl]piperidine (11)

A mixture of **10** (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 **11** (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 1 N aqueous 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 **11** (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).

5.40. 4-Benzyl-1-(trifluoroacetyl)piperidine (12)

To a stirred solution of 4-benzylpiperidine (**2a**) (98.8 g, 0.56 mol) in EtOAc (500 mL) was added trifluoroacetic anhydride (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 aqueous 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 to 9:1) to give **12** (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).

5.41. 4-{[1-(Trifluoroacetyl)piperidin-4-yl]methyl}benzenesulfonyl chloride (13)

A solution of **12** (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, 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 to 1:1) to give **13** (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), 2.48 (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).

5.42. 4-[(4-{[1-(Trifluoroacetyl)piperidin-4-yl]methyl}-phenyl)sulfonyl]morpholine (14)

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 **13** (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), 1 N aqueous 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 to 1:1) to give **14** (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).

5.43. 4-{[4-(Piperidin-4-ylmethyl)phenyl]sulfonyl}morpholine (15)

To a stirred solution of **14** (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, 2×20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give **15** (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).

5.44. Receptor binding assays

CHO-K1 and CCR5-expressing CHO cells[9] were incubated with various concentrations of test compound in the 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 reaction was terminated by washing out the free ligand with cold phosphate-buffered saline, and the cell-associated radioactivity was counted by TopCount scintillation counter (Packard). Binding assays for other chemokine receptors were carried out in a similar manner using the following ligands: CCR1 (RANTES), CCR2 (monocyte chemoattractant protein 1), CCR4 (thymus- and activation-regulated chemokine), and CCR7 (MIP-3β).

5.45. HIV-1 envelope-mediated membrane fusion assay

COS-7 cells were maintained in Dulbecco's modified Eagle medium (D-MEM) supplemented with 10% FBS, 100 U/mL penicillin, 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, 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 3:1:5 and co-transfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After 2 days incubation, transfected COS-7 cells and MOLT-4/CCR5/Luc$^+$ cells were seeded in a 96-well plate at 10^4 cells each per well, and various concentrations of the 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, and 100 μg/mL streptomycin was used as medium for 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).

Acknowledgements

We would like to thank Mr. Kenichi Kuroshima for CCR5 binding assay. We would also like to thank Mr. Katsunori Takashima, Dr. Hiroshi Miyake, and Ms. Shikiko Shiki for membrane fusion assay.

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