CCR5 Antagonists as Anti-HIV-1 Agents. 1. Synthesis and Biological Evaluation of 5-Oxopyrrolidine-3-carboxamide Derivatives

Shinichi IMAMURA,*[,a] Yuji ISHIHARA,[a] Taeko HATTORI,[a] Osamu KURASAWA,[a] Yoshihiro MATSUSHITA,[a] Yoshihiro SUGIHARA,[a] Naoyuki KANZAKI,[a] Yuji IIZAWA,[a] Masanori BABA,[b] and Shohei HASHIGUCHI[a]

[a] *Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.; 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka 532–8686, Japan: and* [b] *Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University; 8–35–1 Sakuragaoka, Kagoshima 890–8520, Japan.*
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A novel lead compound, *N*-{3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (1), was identified as a CCR5 antagonist by high-throughput screening using [^{125}I]RANTES and CCR5-expressing CHO cells. The IC_{50} value of 1 was 1.9 μM. In an effort to improve the binding affinity of 1, a series of 5-oxopyrrolidine-3-carboxamides was synthesized. Introduction of 3,4-dichloro substituents to the central phenyl ring (10i, IC_{50}=0.057 μM; 11b, IC_{50}=0.050 μM) or replacing the 1-methyl group of the 5-oxopyrrolidine moiety with a 1-benzyl group (12e, IC_{50}=0.038 μM) was found to be effective for improving CCR5 affinity. Compound 10i, 11b, and 12e also inhibited CCR5-using HIV-1 envelope-mediated membrane fusion with IC_{50} values of 0.44, 0.19, and 0.49 μM, respectively.

Key words CCR5 antagonist; chemokine; human immunodeficiency virus type 1 (HIV-1); 5-oxopyrrolidine-3-carboxamide

The development of combination antiretroviral therapy with human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors and protease inhibitors has provided a clinically effective method of suppressing viral load in HIV-1-infected individuals, and has resulted in dramatic reductions in HIV-associated morbidity and mortality.[1)] However, no current therapies are curative,[2)] and HIV-1 replicates again rapidly when treatment ceases.[3)] The complexity of the dosing regimens and the toxicity of the current anti-HIV-1 therapy make it difficult to maintain patient compliance.[4)] In addition, resistance to the currently available drugs is increasing.[5)] Therefore, there remains a need to identify new classes of agents with improved efficacy and less toxicity.

The process of HIV-1 entry into host cells is one of the attractive targets for inhibition of HIV-1 replication.[6)] Recent successful studies with enfuvirtide (T-20), a peptide inhibitor of gp41-mediated HIV-1 entry, have confirmed this process as a clinically relevant target.[7)] It has been reported that HIV-1 strains that cause the initial infection predominantly utilize CC chemokine receptor 5 (CCR5) as a coreceptor.[8)] CCR5-using (R5) HIV-1 is isolated exclusively during the asymptomatic stage, which usually persists for 5 to 10 years.[9)] CCR5 is a member of the seven-transmembrane G protein-coupled receptor superfamily.[10)] The natural ligands for CCR5 are 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*.[11)] Individuals homozygous for a defect in CCR5 expression have been identified as being highly resistant to HIV-1 infection, while this defect does not cause a significant health problem.[12—14)] In addition, infected individuals heterozygous for the defective gene appear to exhibit delayed disease progression.[15)] These observations suggest that appropriate, small-molecule CCR5 antagonists functioning as HIV-1 entry inhibitors could be promising anti-HIV-1 therapeutic agents.

Several research groups have reported structurally diverse CCR5 antagonists.[16—22)] Our laboratories have previously described the discovery of TAK-779, an anilide derivative with a quaternary ammonium moiety, as a small-molecule CCR5 antagonist.[23,24)] Continued screening of Takeda compound libraries using [^{125}I]RANTES and Chinese hamster ovary (CHO) cells expressing human CCR5 has now identified a novel lead compound, *N*-{3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (**1**), as a CCR5 antagonist (Fig. 1). In this paper, we describe the discovery of the lead compound and the subsequent optimization, focused on a series of 5-oxopyrrolidine-3-carboxamides, to obtain potent CCR5 antagonists which can inhibit the HIV-1 cell entry.

Chemistry

Target compounds were prepared by two general methods as outlined in Charts 2 and 3. The first method (Chart 2) was utilized to investigate structure–activity relationships (SARs) of alkyl linker length (Fig. 1, C) and piperidine moiety modifications (Fig. 1, D). The starting carboxylic acid **2a** was prepared by condensation of itaconic acid and methylamine (Chart 1).[25)] Coupling of the carboxylic acid **2a** with aniline using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) gave anilide **3**. Treatment of **3** with sodium hydride followed by the appropriate bromochloroalkane produced chlorides **4a**—**c**. The 2-chloroethyl derivative **4d** was prepared in a different manner as follows. *N*-Alkylation of the anilide **3** with ethyl bromoacetate followed by hydrolysis gave the carboxylic acid. The reduction of the mixed anhydride of the acid gave the alcohol, which on reaction with carbon tetrachloride and triphenylphosphine yielded **4d**. The obtained chlorides **4a**—**d** were coupled with a variety of amines in the presence of

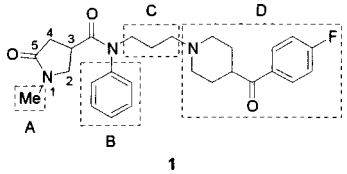

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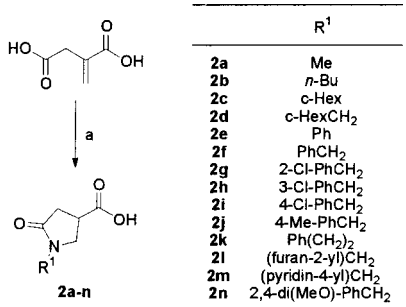
Fig. 1. Lead Compound

* To whom correspondence should be addressed. e-mail: Imamura_Shin-ichi@takeda.co.jp

potassium iodide and potassium carbonate to provide the target compounds **5a**—**i**. Alternatively, compounds **7a**—**e** were obtained by reductive amination of aldehyde **6** with amines using sodium triacetoxyborohydride. The aldehyde **6** was prepared from the anilide **3** by *N*-alkylation with 2-(2-bromoethyl)-1,3-dioxolane followed by hydrolysis with hydrochloric acid. Benzoylpiperazine derivative **5j** was prepared by hydrogenolysis of benzylpiperazine **5i** followed by benzoylation.

In order to explore the effect of substitutions on the central phenyl ring (Fig. 1, B) and 5-oxopyrrolidine moiety (Fig. 1, A), we investigated an alternate method starting from piperidines **8a**, **b** (Chart 3). The piperidines **8a**, **b** were treated with acrolein in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) to afford β-aminoaldehydes *in situ*,[26] which were converted to amine derivatives **9a**—**t** by reductive amination with various aryl or aralkyl amines using sodium triacetoxyborohydride. Coupling reactions of the amines **9a**—**q**, **s**, **t** with 5-oxopyrrolidine-3-carboxylic acids **2a**—**n** were carried out *via* the corresponding acid chlorides to afford the targets **10a**—**p**, **11a**, **b**, **12a**—**m**, **15a**, **b**. Compound **10q** was prepared by the carbodiimide-mediated coupling of the amine **9r** with the acid **2a**. The carboxylic acids **2b**—**n** were prepared by literature methods[25] from the corresponding amines (Chart 1). Removal of the 2,4-dimethoxybenzyl group of compound **12m** with trifluoroacetic acid (TFA) gave compound **13**, which on *N*-alkylation led to compound **14a**, **b**.

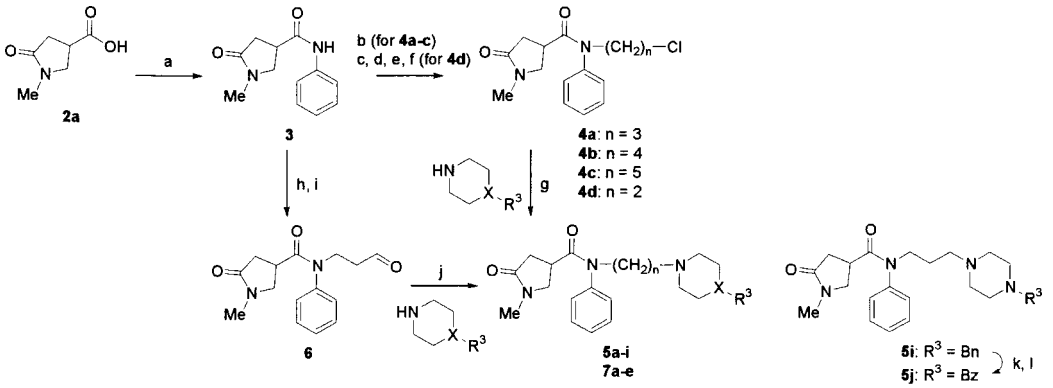
All compounds described were prepared and tested as racemates.



	R^1
2a	Me
2b	*n*-Bu
2c	c-Hex
2d	c-HexCH$_2$
2e	Ph
2f	PhCH$_2$
2g	2-Cl-PhCH$_2$
2h	3-Cl-PhCH$_2$
2i	4-Cl-PhCH$_2$
2j	4-Me-PhCH$_2$
2k	Ph(CH$_2$)$_2$
2l	(furan-2-yl)CH$_2$
2m	(pyridin-4-yl)CH$_2$
2n	2,4-di(MeO)-PhCH$_2$

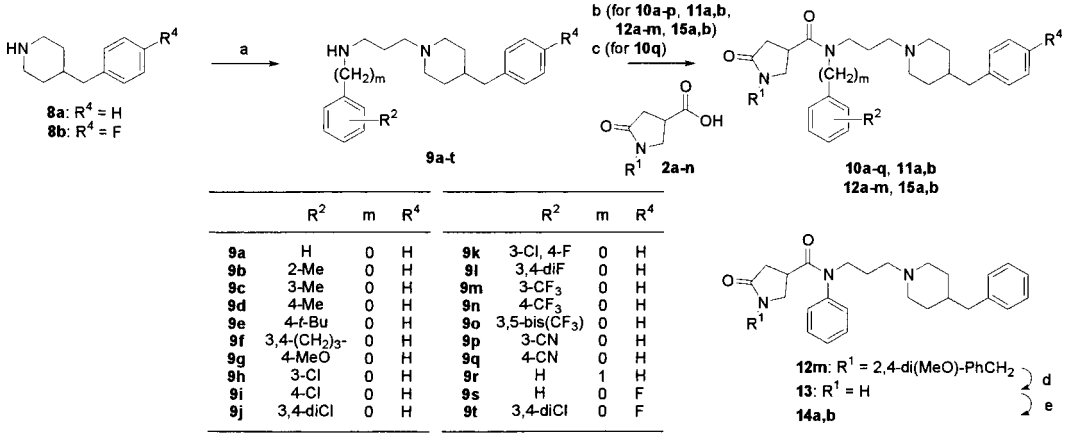
Reagents: (a) R^1-NH$_2$.

Chart 1



Reagents: (a) aniline, EDC, HOBt, DMF; (b) NaH, DMF, then Br-(CH$_2$)$_n$-Cl; (c) NaH, DMF, then BrCH$_2$CO$_2$Et; (d) aq NaOH, MeOH; (e) ClCO$_2$Et, Et$_3$N, THF, then NaBH$_4$, H$_2$O; (f) Ph$_3$P, CCl$_4$; (g) KI, K$_2$CO$_3$, MeCN; (h) NaH, DMF, then 2-(2-bromoethyl)-1,3-dioxolane; (i) aq HCl; (j) NaBH(OAc)$_3$, THF; (k) H$_2$, Pd(OH)$_2$, MeOH; (l) BzCl, Et$_3$N, THF.

Chart 2



	R^2	m	R^4		R^2	m	R^4
9a	H	0	H	**9k**	3-Cl, 4-F	0	H
9b	2-Me	0	H	**9l**	3,4-diF	0	H
9c	3-Me	0	H	**9m**	3-CF$_3$	0	H
9d	4-Me	0	H	**9n**	4-CF$_3$	0	H
9e	4-*t*-Bu	0	H	**9o**	3,5-bis(CF$_3$)	0	H
9f	3,4-(CH$_2$)$_3$-	0	H	**9p**	3-CN	0	H
9g	4-MeO	0	H	**9q**	4-CN	0	H
9h	3-Cl	0	H	**9r**	H	1	H
9i	4-Cl	0	H	**9s**	H	0	F
9j	3,4-diCl	0	H	**9t**	3,4-diCl	0	F

Reagents: (a) acrolein, cat. DBU, THF, then R^2-Ph(CH$_2$)$_m$NH$_2$, NaBH(OAc)$_3$; (b) **2**, (COCl)$_2$, cat. DMF, DCM, then added to **9**, Et$_3$N, DCM; (c) DCC, HOBt, MeCN; (d) TFA; (e) NaH, DMF, then R^1-X.

Chart 3

Results and Discussion

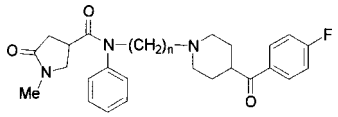
The lead compound **1** was discovered by high-throughput screening of Takeda compound libraries using a binding assay based on [^{125}I]RANTES and CHO cells expressing human CCR5. This compound was shown to have moderate affinity for CCR5 with an IC_{50} value of 1.9 μM. Our initial goal was to improve the CCR5 binding affinity. The structural feature of the lead compound **1** is 5-oxopyrrolidine-3-carboxamide moiety. Deletion of the entire 5-oxopyrrolidin-3-ylcarbonyl group, as in the intermediates **9**, resulted in complete loss of activity, suggesting that this moiety was required for interaction with CCR5. Therefore, our initial SAR studies were focused on a series of 5-oxopyrrolidine-3-carboxamides.

The lead compound **1** could be divided into four subunits (Fig. 1): 5-oxopyrrolidine substituent (A), central phenyl ring (B), alkyl linker (C), and piperidine moiety (D). We first modified the alkyl linker (C) length in order to optimize the spacing between the two halves of the molecule. As shown in Table 1, the lead compound **1** with a three-carbon chain showed the best activity. Shortening the chain of **1** to two carbons caused a marked decrease in potency (**5c**), while lengthening it led to a more gradual loss of affinity, compound **5a** and **5b** being *ca.* 2 and 3 times less potent than **1**, respectively.

With the SAR on the chain established, we then varied the piperidine moiety (D) to investigate the role of the piperidine ring and the substituent at the 4-position of the piperidine (Table 2). Replacement of the 4-fluorobenzoyl group in **1** with a 4-fluorobenzyl group showed a 6-fold enhancement in potency (**11a**, IC_{50}=0.31 μM), suggesting that the carbonyl group in the lead compound **1** was not necessary for CCR5 binding. The compound **5h** (IC_{50}=0.48 μM) having a benzyl group also exhibited improved activity comparable to **11a**. Removal of the benzyl group in **5h** resulted in a large decrease in potency (**5d**), indicating that the benzene ring was essential for potent CCR5 binding affinity. Decreasing the distance from the piperidine ring to the benzene ring (**5e**) resulted in a loss of potency, as did increasing the distance (**7c**). Constraint of the benzene ring by introduction of a double bond (**7a**) or a spiro structure (**5g**) did not improve activity. Substitution with other groups such as a phenoxy (**7d**) or benzyloxy (**7e**) provided no improvement in binding affinity. Replacement of the basic piperidine with a less basic piperazine failed to maintain activity (**5i**, **j**). Since the 4-benzylpiperidine derivatives (**5h**, **11a**) had an improved potency compared to the lead **1**, this component was utilized for further exploration.

We next turned our attention to modification of the central phenyl ring (B) (Table 3). Introduction of a methyl group at the 3- or 4-position of the phenyl ring resulted in a 3- or 5-fold improvement in the binding potency (**10b**, **10c**), while the 2-methyl derivative **10a** showed lower potency than the unsubstituted compound **5h**. The activity of 4-*tert*-butyl compound **10d** was better than **5h**. 3,4-Disubstitution as in indan-5-yl derivative **10e** also increased affinity compared to **5h**. When the electron-donating methoxy group was introduced at the 4-position of the phenyl ring (**10f**), 3-fold reduction in potency was observed. Substitution at the 4-position of the phenyl ring with electron-withdrawing groups such as trifluoromethyl (**10m**) and cyano (**10p**) also lowered potency.

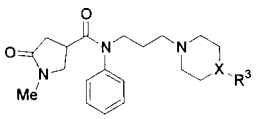
Table 1. SAR of Alkyl Linker Length

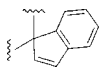
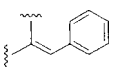


Compd.	*n*	CCR5[a] IC_{50} (μM)
1	3	1.9
5a	4	3.2
5b	5	5.0
5c	2	27%[b]

a) Inhibition of [^{125}I]RANTES binding to CCR5-expressing CHO cells. *b*) Percent inhibition at 10 μM.

Table 2. SAR of Piperidine Moiety Modifications



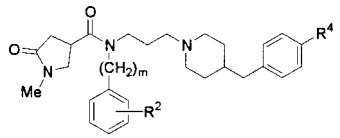
Compd.	X	R^3	CCR5[a] IC_{50} (μM)
1	CH	CO(4-F-Ph)	1.9
5d	CH	H	16%[b]
5e	CH	Ph	3.6
5f	COH	4-Cl-Ph	5.2
5g			2.1
5h	CH	CH_2Ph	0.48
5i	N	CH_2Ph	1.9
5j	N	COPh	12%[b]
7a			1.2
7b	CH	$CHPh_2$	51%[b]
7c	CH	$(CH_2)_2$Ph	1.1
7d	CH	OPh	1.6
7e	CH	OCH_2Ph	1.5
11a	CH	CH_2(4-F-Ph)	0.31

a) Inhibition of [^{125}I]RANTES binding to CCR5-expressing CHO cells. *b*) Percent inhibition at 10 μM.

Moving the trifluoromethyl group to the 3-position of the phenyl ring (**10l**) restored binding potency comparable to that of **5h**, while the bis-trifluoromethyl derivative **10n** showed lower potency. The 3-cyano compound **10o** was a poorer inhibitor, indicating that this moiety does not prefer polar substituents.

When a chlorine atom was introduced at the 4-position of the phenyl (**10h**), lower potency than the unsubstituted compound **5h** was observed, but the 3-chloro derivative **10g** exhibited 4-fold improvement in the binding affinity over **5h**. Furthermore, the 3,4-dichlorinated derivative **10i** was found to show 8-fold enhancement in inhibitory effect compared to **5h** with an IC_{50} value of 0.057 μM. Fluorinated (R^4=F) analogue of **10i** also showed good activity (**11b**, IC_{50}= 0.050 μM). Replacement of the 3,4-dichloro group by 3-chloro-4-fluoro (**10j**) or 3,4-difluoro (**10k**) group decreased the activity. Extension of the phenyl ring by a methylene unit

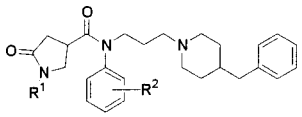
Table 3. SAR of Substitution on the Central Phenyl Ring



Compd.	R^2	m	R^4	CCR5[a] IC_{50} (μM)
5h	H	0	H	0.48
10a	2-Me	0	H	4.7
10b	3-Me	0	H	0.16
10c	4-Me	0	H	0.089
10d	4-*t*-Bu	0	H	0.16
10e	3,4-$(CH_2)_3$-	0	H	0.18
10f	4-MeO	0	H	1.5
10g	3-Cl	0	H	0.12
10h	4-Cl	0	H	1.2
10i	3,4-diCl	0	H	0.057
10j	3-Cl, 4-F	0	H	0.6
10k	3,4-diF	0	H	2.1
10l	3-CF_3	0	H	0.51
10m	4-CF_3	0	H	3.5
10n	3,5-bis(CF_3)	0	H	28%[b]
10o	3-CN	0	H	4.1
10p	4-CN	0	H	25%[b]
10q	H	1	H	0.31
11b	3,4-diCl	0	F	0.050

a) Inhibition of [^{125}I]RANTES binding to CCR5-expressing CHO cells. *b*) Percent inhibition at 10 μM.

Table 4. SAR of Substitution on the 5-Oxopyrrolidine Moiety



Compd.	R^1	R^2	CCR5[a] IC_{50} (μM)
5h	Me	H	0.48
12a	*n*-Bu	H	0.13
12b	c-Hex	H	0.11
12c	c-HexCH_2	H	0.23
12d	Ph	H	0.31
12e	$PhCH_2$	H	0.038
12f	2-Cl-$PhCH_2$	H	0.033
12g	3-Cl-$PhCH_2$	H	0.086
12h	4-Cl-$PhCH_2$	H	0.22
12i	4-Me-$PhCH_2$	H	0.33
12j	$Ph(CH_2)_2$	H	0.36
12k	(furan-2-yl)CH_2	H	0.082
12l	(pyridin-4-yl)CH_2	H	0.24
13	H	H	0.57
14a	CF_3CH_2	H	0.075
14b	2-Me-$PhCH_2$	H	0.034
15a	$PhCH_2$	3-Cl	0.044
15b	$PhCH_2$	3,4-diCl	0.043

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

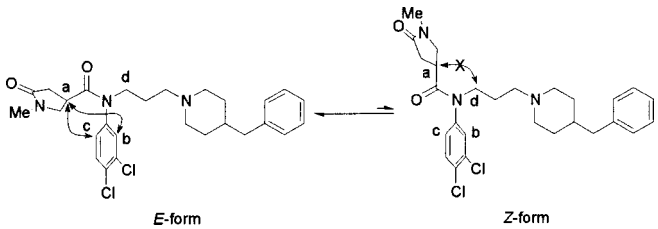


Fig. 2. NOESY Correlations of **10i**

was tolerated as seen with the benzyl derivative **10q**.

While studying the central phenyl fragment, we simultaneously investigated substitutions at the 1-position of the 5-oxopyrrolidine moiety (A) (Table 4). Removal of the 1-methyl group led to compound **13**, which was equipotent with the 1-methyl derivative **5h**. Replacing the methyl group by a butyl (**12a**) provided a 4-fold increase in potency, and replacing by a 2,2,2-trifluoroethyl group (**14a**) showed a 6-fold improvement. These results led us to explore introduction of more bulky substituents to increase potency. The 1-benzyl derivative **12e** (IC_{50}=0.038 μM) showed >10-fold enhancement in potency, whereas the 1-phenyl derivative **12d** exhibited comparable activity to the 1-methyl derivative (**5h**). Extension of the benzyl as a phenylethyl (**12j**) showed similar potency compared to phenyl (**12d**), indicating the benzyl substituent (**12e**) was optimal for CCR5 binding. Saturation of the benzene ring in **12e** affording **12c** resulted in a loss of potency, suggesting that the aromatic ring was necessary for potent activity.

Substitution on the benzyl group was then investigated. Introduction of a chlorine atom at the 2-position of the benzyl was found to be tolerated (**12f**), while 3- or 4-chloro derivatives (**12g**, **h**) showed lower potency than the unsubstituted compound **12e**. A similar trend was observed for methyl substituted analogues (**12i**, **14b**). Replacement of the benzyl with a furan-2-ylmethyl (**12k**) led to a moderate loss in binding, while the pyridin-4-ylmethyl analogue (**12l**) resulted in 6-fold reduction of activity.

The previously discussed SAR of substitutions on the central phenyl ring of the 1-methyl-5-oxopyrrolidine derivatives (Table 3) was then applied to the 1-benzyl analogues. In the case of the 1-benzyl-5-oxopyrrolidine derivatives, introduction of 3-chloro (**15a**) or 3,4-dichloro (**15b**) substituents did not significantly change the activity.

On the basis of NMR analysis, we speculated about the required conformation of the 5-oxopyrrolidine-3-carboxamide derivatives for CCR5 binding. The synthesized compounds have a central *N*,*N*-disubstituted amide moiety as a structural feature. It has been known that *N*-methylanilides prefer the *E* form in which the phenyl ring is trans to the amide oxygen.[27,28] In the *E* form, the plane of the phenyl ring is almost perpendicular to the amide plane. The ^{1}H-NMR analysis of the *N*-phenyl derivatives in this study revealed that most of the derivatives exist as an almost single rotameric form in solution at room temperature. The conformation of **10i** (free base) was determined by a NOESY experiment in $CDCl_3$ at 300 K (Fig. 2). H-a (δ 3.04) was found to correlate with H-b (δ 7.30) and H-c (δ 7.02) in the NOESY spectrum, whereas no cross peak was observed between H-a and H-d (δ 3.69). These results suggested that **10i** and probably other *N*-phenyl derivatives have an *E* form in solution. The preference of the *E* form in this series might contribute to the receptor binding.

Finally, the activities of selected compounds for inhibition of HIV-1 cell entry were examined by a HIV-1 envelope-mediated membrane fusion assay using R5 HIV-1 (JR-FL strain) envelope-expressing COS-7 cells and CCR5-expressing MOLT-4 cells. The most potent CCR5 antagonists **10i**, **11b**,

and **12e** inhibited the membrane fusion with IC_{50} values of 0.44, 0.19, and 0.49 μM, respectively. These results demonstrated that the 5-oxopyrrolidine-3-carboxamide derivatives could block R5 HIV-1 cell entry by preventing the binding of the R5 HIV-1 envelope to CCR5. The selectivity profile of compound **11b** for other chemokine receptors was evaluated using a binding assay. The IC_{50} values for CCR1, CCR2, CCR4, and CCR7 were all greater than 3 μM.

Conclusion

We have succeeded in the identification of a novel lead compound as a small-molecule CCR5 antagonist through high-throughput screening. The original lead **1** inhibited the binding of [^{125}I]RANTES to CCR5 with an IC_{50} value of 1.9 μM. Systematic modification of the lead **1**, focused on a series of 5-oxopyrrolidine-3-carboxamides, resulted in the identification of compounds with improved binding affinity. The most potent CCR5 antagonists **10i** (IC_{50}=0.057 μM), **11b** (IC_{50}=0.050 μM), and **12e** (IC_{50}=0.038 μM) inhibited HIV-1 envelope-mediated membrane fusion with IC_{50} values of 0.44, 0.19, and 0.49 μM, respectively. Further efforts directed toward additional improvement of potency will be reported in due course.

Experimental

Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out on Merck silica gel 60 (230—400 mesh) or ICN basic alumina (activity III). The yields reported 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 (200 MHz) spectrometer. Two-dimensional NOESY spectra were recorded on a Bruker DMX 600 (600 MHz) spectrometer. Chemical shifts are given in ppm with tetramethylsilane (organic solvents) or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (D_2O) as an internal standard, and coupling constants (J) are given in hertz (Hz). Mass spectra were recorded using an LC/MS system consisting of a Hewlett-Packard 1100 HPLC instrument and a Waters ZMD mass detector (ESI positive). Compound purity was checked by elemental analysis or analytical HPLC. Elemental analyses were carried out by Takeda Analytical Laboratories Ltd. Analytical HPLC was performed on a Shimadzu LC-10A system using a Shiseido CAPCELL PAK C18 UG120 column (2.0×50 mm, 3 μM). Chromatographic conditions were as follows: mobile phases, A=0.1% TFA/H_2O, B=0.1% TFA/MeCN; gradient (A/B), 0 min (90/10), 4 min (5/95), 5.5 min (5/95), 5.51 min (90/10), 8 min (90/10); flow rate, 0.5 ml/min; detection, UV 220 nm. Retention times (t_R) and purity (area percent) are reported.

5-Oxopyrrolidine-3-carboxylic Acids (2a—n) Compounds **2a**—**n** were prepared according to literature procedures.[25] **2a**[29]: Yield 35%, mp 151—152 °C (EtOH). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.04; H, 6.42; N, 6.91. **2b**: Yield 67%, oil. *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.20; H, 8.20; N, 7.36. **2c**[25]: Yield 62%, mp 186—187 °C (MeOH–Et_2O). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.41; H, 7.95; N, 6.46. **2d**: Yield 50%, mp 96—97 °C (MeOH–Et_2O). *Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.85; H, 8.22; N, 6.02. **2e**[25]: Yield 90%, mp 188—189 °C (MeOH). *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.34; H, 5.53; N, 6.91. **2f**[25]: Yield 76%, mp 144—145 °C (MeOH). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.80; H, 5.84; N, 6.48. **2g**: Yield 77%, mp 158—159 °C (MeOH). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.64; H, 4.70; N, 5.31. **2h**: Yield 69%, mp 148—149 °C (MeOH–Et_2O). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.58; H, 4.71; N, 5.31. **2i**: Yield 66%, mp 158—159 °C (MeOH–Et_2O). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.52; H, 4.66; N, 5.29. **2j**: Yield 79%, mp 154—155 °C (MeOH). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.85; H, 6.46; N, 5.86. **2k**[30]: Yield 60%, mp 185—186 °C (MeOH). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.60; H, 6.48; N, 5.74. **2l**: Yield 63%, mp 155—156 °C (EtOH). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.17; H, 5.21; N, 6.48. **2m**: Yield 15%, mp 190—191 °C (H_2O–MeOH). *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.68; H, 5.55; N, 12.46. **2n**: Yield 72%, mp 122—123 °C (*i*-PrOH–Et_2O). *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 59.96; H, 6.15; N, 5.07.

1-Methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (3) To a stirred solution of **2a** (8.59 g, 60 mmol), aniline (5.59 g, 60 mmol), and HOBt (8.92 g, 66 mmol) in *N*,*N*-dimethylformamide (DMF) (60 ml) was added EDC (17.25 g, 90 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo*, diluted with saturated aqueous $NaHCO_3$ (120 ml), and extracted with dichloromethane (DCM) (5×120 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 9/1) to afford **3** (11.04 g, yield 84%) as a white solid, mp 163—165 °C. ^{1}H-NMR ($CDCl_3$) δ 2.67 (1H, dd, J=17.1, 9.9 Hz), 2.81 (1H, dd, J=17.1, 8.4 Hz), 2.88 (3H, s), 3.15—3.31 (1H, m), 3.58 (1H, dd, J=9.6, 9.6 Hz), 3.77 (1H, dd, J=9.6, 7.0 Hz), 7.14 (1H, t, J=7.3 Hz), 7.34 (2H, dd, J=8.0, 7.3 Hz), 7.53 (2H, d, J=8.0 Hz), 7.60 (1H, br s). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.00; H, 6.44; N, 12.89.

***N*-(3-Chloropropyl)-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (4a)** To an ice-cooled stirred solution of **3** (2.00 g, 9.2 mmol) in DMF (20 ml) was added NaH (60% in oil, 733 mg, 18 mmol). After 1 h the mixture was treated with 1-bromo-3-chloropropane (1.81 ml, 18 mmol), stirred for 30 min, removed from the ice bath, and stirred for an additional 1 h. The mixture was diluted with water (100 ml) and extracted with EtOAc (3×50 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 9/1) to afford **4a** (2.43 g, yield 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 1.95—2.15 (2H, m), 2.24 (1H, dd, J=17.0, 9.3 Hz), 2.68 (1H, dd, J=17.0, 8.5 Hz), 2.77 (3H, s), 2.95—3.25 (1H, m), 3.19 (1H, t, J=8.8 Hz), 3.56 (2H, t, J=6.6 Hz), 3.65 (1H, dd, J=8.8, 7.0 Hz), 3.80—3.90 (2H, m), 7.10—7.25 (2H, m), 7.35—7.55 (3H, m).

The following compounds **4b**, **c** were prepared using a procedure similar to that described for **4a** from the corresponding bromochloroalkanes.

***N*-(4-Chlorobutyl)-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (4b)** Yield 96%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.58—1.89 (4H, m), 2.23 (1H, dd, J=16.7, 9.3 Hz), 2.60—2.80 (4H, m), 2.97—3.25 (2H, m), 3.50—3.81 (5H, m), 7.11—7.20 (2H, m), 7.36—7.53 (3H, m).

***N*-(5-Chloropentyl)-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (4c)** Yield 96%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.35—1.87 (6H, m), 2.23 (1H, dd, J=16.3, 9.3 Hz), 2.60—2.80 (4H, m), 2.95—3.24 (2H, m), 3.52 (2H, t, J=6.4 Hz), 3.59—3.77 (3H, m), 7.10—7.20 (2H, m), 7.38—7.53 (3H, m).

***N*-(2-Chloroethyl)-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (4d). Step 1: Ethyl 2-{[(1-Methyl-5-oxopyrrolidin-3-yl)carbonyl]anilino}acetate** To an ice-cooled stirred solution of **3** (2.00 g, 9.2 mmol) in DMF (20 ml) was added NaH (60% in oil, 916 mg, 23 mmol). After 1 h the mixture was treated with ethyl bromoacetate (3.05 ml, 28 mmol), stirred for 30 min, removed from the ice bath, and stirred for an additional 6 h. The mixture was poured into ice-cooled 0.5 N HCl (100 ml) and extracted with EtOAc (3×50 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 95/5) to afford the product (2.43 g, yield 87%) as a white solid, mp 72—74 °C. ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, J=7.2 Hz), 2.28 (1H, dd, J=16.4, 9.4 Hz), 2.75 (1H, dd, J=16.4, 7.8 Hz), 2.78 (3H, s), 3.10—3.35 (2H, m), 3.60—3.80 (1H, m), 4.22 (2H, q, J=7.2 Hz), 4.26 (1H, d, J=17.1 Hz), 4.45 (1H, d, J=17.1 Hz), 7.30—7.55 (5H, m).

Step 2: 2-{[(1-Methyl-5-oxopyrrolidin-3-yl)carbonyl]anilino}acetic Acid To a stirred solution of the product from step 1 (1.83 g, 6.0 mmol) in MeOH (20 ml) was added 8 N NaOH (1.5 ml), and the mixture was stirred at room temperature for 10 h. The mixture was treated with 1 N HCl (13 ml) and concentrated *in vacuo*. The residue was dissolved in EtOAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (1.54 g, yield 93%). ^{1}H-NMR ($CDCl_3$) δ 2.35 (1H, dd, J=17.0, 9.0 Hz), 2.75—2.95 (1H, m), 2.80 (3H, s), 3.10—3.35 (2H, m), 3.65—3.80 (1H, m), 4.31 (1H, d, J=17.4 Hz), 4.45 (1H, d, J=17.4 Hz), 7.30—7.55 (5H, m).

Step 3: *N*-(2-Hydroxyethyl)-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide To a stirred solution of the product from step 2 (829 mg, 3.0 mmol) and Et_3N (627 μl, 4.5 mmol) in THF (15 ml) at −15 °C was added ethyl chloroformate (430 μl, 4.5 mmol), and the mixture was stirred at from −15 to −10 °C for 30 min. Then, a solution of $NaBH_4$ (227 mg, 6.0 mmol) in water (1.5 ml) was added at −10 °C, and the mixture was stirred at from

−10 to 0 °C for 1 h. The mixture was treated with 1 N HCl at 0 °C, and the organic solvent was removed *in vacuo*. The residue was extracted with DCM, and 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 95/5) to afford the product (662 mg, yield 84%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 2.27 (1H, dd, J=16.9, 9.5 Hz), 2.71 (1H, dd, J=16.9, 8.4 Hz), 2.78 (3H, s), 3.00—3.25 (1H, m), 3.22 (1H, t, J=8.9 Hz), 3.66 (1H, dd, J=8.9, 6.6 Hz), 3.70—4.10 (4H, m), 7.15—7.30 (2H, m), 7.30—7.55 (3H, m).

Step 4: *N*-(2-Chloroethyl)-*N*-phenyl-1-methyl-5-oxo-3-pyrrolidinecarboxamide (4d) A mixture of the product from step 3 (659 mg, 2.5 mmol), triphenylphosphine (857 mg, 3.3 mmol), and carbon tetrachloride (10 ml) was stirred at reflux for 1 h. After cooling, the insoluble materials were removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 95/5) to give an oil which solidified. The solid was triturated with Et_2O and filtered to afford **4d** (366 mg, yield 52%) as a slightly brown solid, which was used immediately in the subsequent reaction. ^{1}H-NMR ($CDCl_3$) δ 2.25 (1H, dd, J=16.9, 9.3 Hz), 2.70 (1H, dd, J=16.9, 8.2 Hz), 2.78 (3H, s), 2.95—3.25 (1H, m), 3.21 (1H, t, J=8.9 Hz), 3.55—3.75 (3H, m), 4.00 (1H, dt, J=13.9, 6.2 Hz), 4.11 (1H, dt, J=13.9, 6.6 Hz), 7.20—7.30 (2H, m), 7.35—7.55 (3H, m).

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (5h)** A mixture of **4a** (400 mg, 1.4 mmol), 4-benzylpiperidine (239 μl, 1.4 mmol), KI (225 mg, 1.4 mmol), K_2CO_3 (282 mg, 2.0 mmol) in MeCN (20 ml) was stirred at reflux for 24 h. The mixture was concentrated *in vacuo*, diluted with water (15 ml), and extracted with EtOAc (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 (EtOAc/MeOH 1/0 to 9/1) to afford an oil (344 mg). The oil was dissolved in Et_2O and treated with 1 N HCl (Et_2O solution, 2 ml). The resulting precipitate was filtrated, washed with Et_2O, and dried *in vacuo* over KOH to give **5h** (282 mg, yield 44%) as an amorphous solid. ^{1}H-NMR (D_2O) δ 1.35—1.65 (2H, m), 1.75—2.10 (5H, m), 2.45 (1H, dd, J=17.7, 8.7 Hz), 2.55—2.75 (1H, m), 2.63 (2H, d, J=6.8 Hz), 2.77 (3H, s), 2.80—3.00 (2H, m), 3.00—3.70 (7H, m), 3.75—3.90 (2H, m), 7.20—7.45 (7H, m), 7.45—7.65 (3H, m). *Anal.* Calcd for $C_{27}H_{35}N_3O_2\cdot HCl\cdot 0.5H_2O$: C, 67.69; H, 7.78; Cl, 7.40; N, 8.77. Found: C, 67.58; H, 7.75; Cl, 7.17; N, 8.59.

The following compounds **5a**—**g**, **i** were prepared using a procedure similar to that described for **5h** from the chlorides **4a**—**d** and the corresponding amines.

***N*-{4-[4-(4-Fluorobenzoyl)piperidin-1-yl]butyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5a)** Compound **5a** was prepared from **4b** and 4-(4-fluorobenzoyl)piperidine hydrochloride[31] in 80% yield, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.39—1.64 (4H, m), 1.71—2.43 (9H, m), 2.60—2.80 (4H, m), 2.86—3.27 (5H, m), 3.59—3.68 (3H, m), 7.06—7.20 (4H, m), 7.35—7.53 (3H, m), 7.97 (2H, dd, J=8.9, 5.5 Hz). *Anal.* Calcd for $C_{28}H_{34}FN_3O_3\cdot C_4H_4O_4\cdot 0.5H_2O$: C, 63.56; H, 6.50; N, 6.95. Found: C, 63.36; H, 6.64; N, 6.90.

***N*-{5-[4-(4-Fluorobenzoyl)piperidin-1-yl]pentyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5b)** Compound **5b** was prepared from **4c** and 4-(4-fluorobenzoyl)piperidine hydrochloride in 91% yield, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.22—1.63 (6H, m), 1.68—1.92 (4H, m), 1.97—2.40 (5H, m), 2.60—2.80 (4H, m), 2.91—3.28 (5H, m), 3.58—3.76 (3H, m), 7.06—7.21 (4H, m), 7.35—7.53 (3H, m), 7.96 (2H, dd, J=8.8, 5.5 Hz). *Anal.* Calcd for $C_{29}H_{36}FN_3O_3\cdot C_4H_4O_4\cdot 0.5H_2O$: C, 64.06; H, 6.68; N, 6.79. Found: C, 64.17; H, 6.92; N, 6.65.

***N*-{2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5c)** Compound **5c** was prepared from **4d** and 4-(4-fluorobenzoyl)piperidine hydrochloride in 20% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.75—2.30 (4H, m), 2.43 (1H, dd, J=17.6, 9.4 Hz), 2.55—2.75 (1H, m), 2.76 (3H, s), 3.05—4.00 (10H, m), 4.05—4.30 (2H, m), 6.66 (2H, s), 7.29 (2H, t, J=8.8 Hz), 7.30—7.45 (2H, m), 7.45—7.65 (3H, m), 8.06 (2H, dd, J=8.7, 5.5 Hz). *Anal.* Calcd for $C_{26}H_{30}FN_3O_3\cdot C_4H_4O_4\cdot 1.5H_2O$: C, 60.60; H, 6.27; N, 7.07. Found: C, 60.68; H, 6.13; N, 7.15.

1-Methyl-5-oxo-*N*-phenyl-*N*-[3-(piperidin-1-yl)propyl]pyrrolidine-3-carboxamide Hydrochloride (5d) Compound **5d** was prepared from **4a** and piperidine in 48% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.30—2.10 (8H, m), 2.46 (1H, dd, J=17.2, 9.0 Hz), 2.66 (1H, dd, J=17.2, 6.0 Hz), 2.75—3.20 (4H, m), 2.78 (3H, s), 3.20—3.65 (3H, m), 3.42 (1H, t, J=10.0 Hz), 3.57 (1H, dd, J=10.0, 5.5 Hz), 3.75—3.95 (2H, m), 7.30—7.40 (2H, m), 7.50—7.70 (3H, m). *Anal.* Calcd for $C_{20}H_{29}N_3O_2\cdot HCl\cdot 0.2H_2O$: C, 62.63; H, 7.99; N, 10.96. Found: C, 62.63; H, 7.80; N, 10.99.

1-Methyl-5-oxo-*N*-phenyl-*N*-[3-(4-phenylpiperidin-1-yl)propyl]pyrrolidine-3-carboxamide Fumarate (5e) Compound **5e** was prepared from **4a** and 4-phenylpiperidine hydrochloride in 42% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.70—2.30 (6H, m), 2.45 (1H, dd, J=17.3, 9.0 Hz), 2.65 (1H, dd, J=17.3, 5.7 Hz), 2.77 (3H, s), 2.80—4.00 (12H, m), 6.67 (2H, s), 7.25—7.65 (10H, m). *Anal.* Calcd for $C_{26}H_{33}N_3O_2\cdot C_4H_4O_4\cdot 0.8H_2O$: C, 65.51; H, 7.07; N, 7.64. Found: C, 65.53; H, 6.97; N, 7.65.

***N*-{3-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5f)** Compound **5f** was prepared from **4a** and 4-(4-chlorophenyl)-4-hydroxypiperidine in 60% yield, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.44—1.95 (7H, m), 2.03—2.91 (10H, m), 2.97—3.25 (3H, m), 3.60—3.84 (3H, m), 7.13—7.54 (9H, m). *Anal.* Calcd for $C_{26}H_{32}ClN_3O_3\cdot C_4H_4O_4\cdot H_2O$: C, 59.65; H, 6.34; N, 6.96. Found: C, 59.63; H, 6.22; N, 6.83.

1-Methyl-5-oxo-*N*-phenyl-*N*-[3-(spiro[indene-1,4′-piperidin]-1′-yl)-propyl]pyrrolidine-3-carboxamide Fumarate (5g) Compound **5g** was prepared from **4a** and spiro[indene-1,4′-piperidine][32] in 43% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.45—1.65 (2H, m), 1.95—2.20 (2H, m), 2.30—2.55 (3H, m), 2.67 (1H, dd, J=17.2, 6.2 Hz), 2.77 (3H, s), 3.20—3.45 (5H, m), 3.42 (1H, t, J=9.8 Hz), 3.59 (1H, dd, J=9.8, 5.4 Hz), 3.65—3.80 (2H, m), 3.80—3.95 (2H, m), 6.63 (2H, s), 6.97 (1H, d, J=5.8 Hz), 7.02 (1H, d, J=5.8 Hz), 7.25—7.70 (9H, m). *Anal.* Calcd for $C_{28}H_{33}N_3O_2\cdot C_4H_4O_4\cdot 1.0H_2O$: C, 66.53; H, 6.80; N, 7.27. Found: C, 66.60; H, 6.62; N, 7.30.

***N*-[3-(4-Benzylpiperazin-1-yl)propyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Dihydrochloride (5i)** Compound **5i** was prepared from **4a** and 1-benzylpiperazine in 51% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.90—2.10 (2H, m), 2.44 (1H, dd, J=17.1, 9.2 Hz), 2.64 (1H, dd, J=17.1, 6.5 Hz), 2.76 (3H, s), 3.15—3.70 (13H, m), 3.70—4.00 (2H, m), 4.38 (2H, s), 7.30—7.40 (2H, m), 7.45—7.65 (8H, m). *Anal.* Calcd for $C_{26}H_{34}N_4O_2\cdot 2HCl\cdot 1.2H_2O$: C, 59.02; H, 7.31; Cl, 13.40; N, 10.59. Found: C, 59.00; H, 7.34; Cl, 13.36; N, 10.49.

***N*-[3-(4-Benzoylpiperazin-1-yl)propyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5j). Step 1: 1-Methyl-5-oxo-*N*-phenyl-*N*-[3-(piperazin-1-yl)propyl]pyrrolidine-3-carboxamide** A mixture of the free base of **5i** (463 mg, 1.1 mmol) and palladium hydroxide on carbon (20%, 93 mg) in MeOH (10 ml) was stirred under a hydrogen atmosphere at room temperature for 16 h. The catalyst was removed by filtration and washed with MeOH. The filtrate was concentrated *in vacuo* to give the product (364 mg, yield 99%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 1.60—1.85 (2H, m), 2.15—2.60 (9H, m), 2.60—2.90 (3H, m), 2.77 (3H, s), 2.95—3.20 (1H, m), 3.19 (1H, t, J=8.9 Hz), 3.64 (1H, dd, J=8.9, 6.8 Hz), 3.65—3.80 (2H, m), 7.10—7.20 (2H, m), 7.30—7.55 (3H, m).

Step 2: *N*-[3-(4-Benzoylpiperazin-1-yl)propyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (5j) To an ice-cooled stirred solution of the product from step 1 (192 mg, 0.56 mmol) and Et_3N (101 μl, 0.72 mmol) in THF (5 ml) was added benzoyl chloride (78 μl, 0.67 mmol), and the mixture was stirred for 1 h. The mixture was concentrated *in vacuo*, diluted with saturated aqueous $NaHCO_3$ (15 ml), and extracted with EtOAc (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 (EtOAc/MeOH 1/0 to 4/1) to afford the free base (221 mg, 0.49 mmol) as an oil, which was treated with fumaric acid (57 mg, 0.49 mmol) to yield **5j** (228 mg, yield 72%) as an amorphous solid. ^{1}H-NMR (D_2O) δ 1.90—2.15 (2H, m), 2.44 (1H, dd, J=17.6, 9.0 Hz), 2.65 (1H, dd, J=17.6, 6.0 Hz), 2.76 (3H, s), 3.10—4.00 (15H, m), 6.63 (2H, s), 7.30—7.40 (2H, m), 7.40—7.65 (8H, m). *Anal.* Calcd for $C_{26}H_{32}N_4O_3\cdot C_4H_4O_4\cdot 0.9H_2O$: C, 62.03; H, 6.56; N, 9.65. Found: C, 61.97; H, 6.36; N, 9.35.

1-Methyl-5-oxo-*N*-(3-oxopropyl)-*N*-phenylpyrrolidine-3-carboxamide (6). Step 1: *N*-[2-(1,3-Dioxolan-2-yl)ethyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide To an ice-cooled stirred solution of **3** (2.40 g, 11 mmol) in DMF (22 ml) was added NaH (60% in oil, 880 mg, 22 mmol). After 1 h the mixture was treated with 2-(2-bromoethyl)-1,3-dioxolane (2.58 ml, 22 mmol) and stirred at 80 °C for 12 h. The mixture was concentrated *in vacuo*, diluted with water (45 ml), and extracted with DCM (3×45 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 9/1) followed by crystallization from *i*-Pr_2O/EtOAc to give the product (2.47 g, yield 70%) as a white solid., mp 108—110 °C. ^{1}H-NMR ($CDCl_3$) δ 1.91 (2H, td, J=7.3, 4.4 Hz), 2.23 (1H, dd, J=16.9, 9.1 Hz), 2.70 (1H, dd, J=16.9, 8.0 Hz), 2.77 (3H, s), 2.95—3.15 (1H, m), 3.18 (1H, t, J=9.1 Hz), 3.66 (1H, dd, J=9.1, 6.9 Hz), 3.75—4.00 (6H, m),

4.93 (1H, t, *J*=4.4 Hz), 7.15—7.25 (2H, m), 7.35—7.55 (3H, m).

Step 2: 1-Methyl-5-oxo-*N*-(3-oxopropyl)-*N*-phenylpyrrolidine-3-carboxamide (6) The product from step 1 (1.95 g, 6.1 mmol) was dissolved in 1 N HCl (10 ml), and the mixture was stirred at room temperature for 18 h. The mixture was extracted with DCM (3×20 ml), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **6** (1.66 g, yield 99%) as an oil. ^{1}H-NMR ($CDCl_3$) δ 2.23 (1H, dd, *J*=16.6, 9.4 Hz), 2.60—2.80 (3H, m), 2.77 (3H, s), 2.95—3.15 (1H, m), 3.18 (1H, t, *J*=9.1 Hz), 3.61 (1H, dd, *J*=9.1, 6.9 Hz), 3.98 (1H, dt, *J*=14.0, 6.6 Hz), 4.14 (1H, dt, *J*=14.0, 6.9 Hz), 7.10—7.25 (2H, m), 7.35—7.55 (3H, m), 9.77 (1H, t, *J*=1.9 Hz).

***N*-[3-(4-Benzylidenepiperidin-1-yl)propyl]-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (7a)** To a stirred mixture of **6** (274 mg, 1.0 mmol), 4-benzylidenepiperidine hydrochloride[33] (231 mg, 1.1 mmol) in THF (10 ml) was added Et_3N (209 μl, 1.5 mmol) followed by $NaBH(OAc)_3$ (318 mg, 1.5 mmol), and the mixture was stirred at room temperature for 6 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (15 ml) followed by water (10 ml) and extracted with EtOAc (3×20 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 6/1) to afford an oil (376 mg). The oil was dissolved in MeOH and treated with 1 N HCl (Et_2O solution, 2 ml). The solution was concentrated *in vacuo* to give a foam, which was triturated with Et_2O, filtered, and dried *in vacuo* over KOH yielding **7a** (380 mg, yield 81%) as an amorphous solid. ^{1}H-NMR (D_2O) δ 1.90—2.15 (2H, m), 2.30—4.00 (17H, m), 2.78 (3H, s), 6.61 (1H, s), 7.25—7.65 (10H, m). *Anal.* Calcd for $C_{27}H_{33}N_3O_2\cdot HCl\cdot 0.7H_2O$: C, 67.47; H, 7.42; Cl, 7.38; N, 8.74. Found: C, 67.48; H, 7.44; Cl, 7.40; N, 8.70.

The following compounds **7b**—**e** were prepared using a procedure similar to that described for **7a** from the corresponding amines.

***N*-{3-[4-(Diphenylmethyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Fumarate (7b)** Compound **7b** was prepared from 4-(diphenylmethyl)piperidine hydrochloride[34] in 70% yield, amorphous solid. ^{1}H-NMR (DMSO-d_6) δ 1.00—1.30 (2H, m), 1.30—1.75 (4H, m), 1.95—2.55 (5H, m), 2.62 (3H, s), 2.80—3.10 (3H, m), 3.13 (1H, t, *J*=9.2 Hz), 3.37 (1H, dd, *J*=9.2, 6.1 Hz), 3.50—3.70 (4H, m), 3.54 (1H, d, *J*=11.0 Hz), 6.57 (2H, s), 7.05—7.55 (15H, m). *Anal.* Calcd for $C_{33}H_{39}N_3O_2\cdot C_4H_4O_4\cdot 0.3H_2O$: C, 70.41; H, 6.96; N, 6.66. Found: C, 70.48; H, 7.06; N, 6.67.

1-Methyl-5-oxo-*N*-phenyl-*N*-{3-[4-(2-phenylethyl)piperidin-1-yl]-propyl}pyrrolidine-3-carboxamide Hydrochloride (7c) Compound **7c** was prepared from 4-(2-phenylethyl)piperidine hydrochloride in 62% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.30—1.85 (5H, m), 1.85—2.15 (4H, m), 2.45 (1H, dd, *J*=17.7, 8.7 Hz), 2.55—3.65 (12H, m), 2.77 (3H, s), 3.75—3.95 (2H, m), 7.20—7.45 (7H, m), 7.50—7.65 (3H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_2\cdot HCl\cdot 1.0H_2O$: C, 66.98; H, 8.03; N, 8.37. Found: C, 66.99; H, 8.10; N, 8.31.

1-Methyl-5-oxo-*N*-[3-(4-phenoxypiperidin-1-yl)propyl]-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (7d) Compound **7d** was prepared from 4-phenoxypiperidine hydrochloride[35] in 78% yield, amorphous solid. ^{1}H-NMR (DMSO-d_6) δ 1.70—2.35 (7H, m), 2.35—2.55 (1H, m), 2.63 (3H, s), 2.85—3.85 (11H, m), 4.40—4.80 (1H, m), 6.90—7.10 (3H, m), 7.20—7.60 (7H, m). *Anal.* Calcd for $C_{26}H_{33}N_3O_3\cdot HCl\cdot 0.8H_2O$: C, 64.20; H, 7.38; N, 8.64. Found: C, 64.17; H, 7.50; N, 8.66.

***N*-{3-[4-(Benzyloxy)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (7e)** Compound **7e** was prepared from 4-(benzyloxy)piperidine hydrochloride in 75% yield, amorphous solid. ^{1}H-NMR (D_2O) δ 1.70—2.40 (6H, m), 2.46 (1H, dd, *J*=17.4, 8.8 Hz), 2.66 (1H, dd, *J*=17.4, 6.1 Hz), 2.78 (3H, s), 3.00—3.65 (9H, m), 3.75—4.00 (3H, m), 4.64 (2H, s), 7.30—7.45 (2H, m), 7.45 (5H, s), 7.50—7.65 (3H, m). *Anal.* Calcd for $C_{27}H_{35}N_3O_3\cdot HCl\cdot 0.6H_2O$: C, 65.27; H, 7.55; N, 8.46. Found: C, 65.27; H, 7.63; N, 8.51.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-4-methylaniline Dihydrochloride (9d)** To a stirred solution of 4-benzylpiperidine (**8a**) (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 **9d** (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 **9d** (4.52 g, yield 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 **9a**—**c**, **e**—**t** were prepared using a procedure similar to that described for **9d** from piperidines **8a**, **b**[36] and the corresponding amines.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]aniline Dihydrochloride (9a)** 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.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-2-methylaniline Dihydrochloride (9b)** Yield 69%, mp 160—165 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.40—2.25 (7H, m), 2.32 (3H, s), 2.45—3.50 (10H, m), 6.90—7.40 (9H, m). *Anal.* Calcd for $C_{22}H_{30}N_2\cdot 2HCl\cdot 1.0H_2O$: C, 63.91; H, 8.29; N, 6.78. Found: C, 64.01; H, 8.18; N, 6.74.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-methylaniline Dihydrochloride (9c)** Yield 67%, mp 173—178 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.40—2.25 (7H, m), 2.31 (3H, s), 2.45—3.50 (10H, m), 6.95—7.40 (9H, m). *Anal.* Calcd for $C_{22}H_{30}N_2\cdot 2HCl\cdot 0.2H_2O$: C, 66.22; H, 8.18; N, 7.02. Found: C, 66.30; H, 8.12; N, 6.99.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-4-*tert*-butylaniline Dihydrochloride (9e)** Yield 51%, mp 203—213 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.27 (9H, s), 1.40—1.90 (5H, m), 2.00—2.20 (2H, m), 2.45—2.60 (2H, m), 2.75—2.95 (2H, m), 3.00—3.70 (6H, m), 7.10—7.40 (7H, m), 7.44 (2H, d, *J*=8.4 Hz). *Anal.* Calcd for $C_{25}H_{36}N_2\cdot 2HCl\cdot 0.2H_2O$: C, 68.07; H, 8.77; N, 6.35. Found: C, 68.10; H, 8.80; N, 6.35.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]indan-5-amine Dihydrochloride (9f)** Yield 28%, mp 172—175 °C (dec). ^{1}H-NMR (D_2O) δ 1.42—1.50 (2H, m), 1.87—1.93 (3H, m), 2.08—2.15 (4H, m), 2.61 (2H, d, *J*=6.6 Hz), 2.82—2.94 (6H, m), 3.10—3.18 (2H, m), 3.26—3.54 (4H, m), 7.12 (1H, d, *J*=7.8 Hz), 7.24—7.41 (7H, m). *Anal.* Calcd for $C_{24}H_{32}N_2\cdot 2HCl\cdot 0.25H_2O$: C, 67.67; H, 8.25; N, 6.57. Found: C, 67.73; H, 7.97; N, 6.50.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-4-methoxyaniline Dihydrochloride (9g)** Yield 38%, mp 154—159 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.40—1.95 (5H, m), 1.95—2.20 (2H, m), 2.45—2.65 (2H, m), 2.70—3.00 (2H, m), 3.00—3.55 (6H, m), 3.76 (3H, s), 7.02 (2H, d, *J*=8.8 Hz), 7.10—7.45 (7H, m). *Anal.* Calcd for $C_{22}H_{30}N_2O\cdot 2HCl\cdot 0.4H_2O$: C, 63.12; H, 7.90; N, 6.69. Found: C, 63.12; H, 7.84; N, 6.78.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-chloroaniline Dihydrochloride (9h)** 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.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-4-chloroaniline Dihydrochloride (9i)** Yield 70%, mp 155—159 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.40—1.90 (5H, m), 1.90—2.10 (2H, m), 2.45—2.60 (2H, m), 2.70—2.95 (2H, m), 2.95—3.50 (6H, m), 6.85 (2H, d, *J*=9.2 Hz), 7.10—7.40 (7H, m). *Anal.* Calcd for $C_{21}H_{27}ClN_2\cdot 2HCl$: C, 60.66; H, 7.03; N, 6.74. Found: C, 60.85; H, 6.81; N, 6.79.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3,4-dichloroaniline Dihydrochloride (9j)** 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*=8.8, 2.8 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.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-chloro-4-fluoroaniline Dihydrochloride (9k)** Yield 40%, mp 195—197 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.53—1.75 (5H, m), 1.94—2.02 (2H, m), 2.50—2.55 (2H, m), 2.80—2.85 (2H, m), 3.07—3.10 (4H, m), 3.38—3.45 (2H, m), 6.67—6.73 (1H, m), 6.84 (1H, dd, *J*=6.0, 3.0 Hz), 7.13—7.34 (6H, m). *Anal.* Calcd for $C_{21}H_{26}ClFN_2\cdot 2HCl\cdot 0.5H_2O$: C, 56.96; H, 6.60; N, 6.33. Found: C, 57.12; H, 6.43; N, 6.46.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3,4-difluoroaniline Dihydrochloride (9l)** Yield 53%, mp 175—177 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.53—1.75 (5H, m), 1.94—1.98 (2H, m), 2.51—2.54 (2H, m), 2.66—2.84 (2H, m), 3.06—3.10 (4H, m), 3.38—3.44 (2H, m), 6.51—6.55 (1H, m),

6.67—6.77 (1H, m), 7.11—7.34 (6H, m). *Anal.* Calcd for $C_{21}H_{26}F_2N_2 \cdot 2HCl \cdot 0.2H_2O$: C, 59.92; H, 6.80; N, 6.65. Found: C, 59.93; H, 6.67; N, 6.74.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3-(trifluoromethyl)aniline Dihydrochloride (9m)** Yield 56%, mp 167—173 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 1.40—2.10 (7H, m), 2.45—2.60 (2H, m), 2.60—2.95 (2H, m), 2.95—3.30 (2H, m), 3.13 (2H, t, J=6.6 Hz), 3.41 (2H, br d, J=11.6 Hz), 6.75—6.95 (3H, m), 7.10—7.40 (6H, m). *Anal.* Calcd for $C_{22}H_{27}F_3N_2 \cdot 2HCl \cdot 0.8H_2O$: C, 56.97; H, 6.65; N, 6.04. Found: C, 56.87; H, 6.64; N, 6.10.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-4-(trifluoromethyl)aniline Dihydrochloride (9n)** Yield 36%, mp 166—168 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.56—1.75 (5H, m), 1.95—2.06 (2H, m), 2.50—2.55 (2H, m), 2.80—2.90 (2H, m), 3.04—3.18 (4H, m), 3.38—3.45 (2H, m), 6.70 (2H, d, J=8.6 Hz), 7.16—7.40 (7H, m). *Anal.* Calcd for $C_{22}H_{27}F_3N_2 \cdot 2HCl$: C, 58.80; H, 6.50; N, 6.23. Found: C, 58.64; H, 6.47; N, 6.32.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-3,5-bis(trifluoromethyl)aniline Dihydrochloride (9o)** Yield 19%, mp 182—185 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.50—1.76 (5H, m), 1.91—1.97 (2H, m), 2.50—2.55 (2H, m), 2.80—2.86 (2H, m), 3.08—3.24 (4H, m), 3.40—3.47 (2H, m), 7.05—7.34 (8H, m). *Anal.* Calcd for $C_{23}H_{26}F_6N_2 \cdot 2HCl \cdot 1.0H_2O$: C, 51.60; H, 5.65; N, 5.23. Found: C, 51.69; H, 5.54; N, 5.43.

3-{[3-(4-Benzylpiperidin-1-yl)propyl]amino}benzonitrile (9p) Yield 43%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.20—1.40 (2H, m), 1.41—1.95 (7H, m), 2.42—2.49 (2H, m), 2.56—2.60 (2H, m), 2.91—2.98 (2H, m), 3.11—3.19 (2H, m), 6.68—6.74 (2H, m), 6.89—6.93 (1H, m), 7.14—7.30 (6H, m).

4-{[3-(4-Benzylpiperidin-1-yl)propyl]amino}benzonitrile (9q) Yield 50%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.19—1.39 (2H, m), 1.45—1.96 (7H, m), 2.42—2.49 (2H, m), 2.56—2.60 (2H, m), 2.90—2.97 (2H, m), 3.15—3.24 (2H, m), 6.17—6.30 (1H, br s), 6.45 (2H, d, J=9.0 Hz), 7.14—7.42 (7H, m).

***N*-Benzyl-3-(4-benzylpiperidin-1-yl)propan-1-amine (9r)** Yield 44%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.88 (10H, m), 2.35 (2H, t, J=7.5 Hz), 2.52 (2H, d, J=6.6 Hz), 2.66 (2H, t, J=6.8 Hz), 2.88—3.00 (2H, m), 3.78 (2H, s), 7.11—7.36 (10H, m).

***N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}aniline Dihydrochloride (9s)** 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. Found: C, 61.02; H, 7.37; N, 6.76.

3,4-Dichloro-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}aniline Dihydrochloride (9t) Yield 48%, mp 203—209 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 1.35—2.05 (7H, m), 2.45—2.60 (2H, m), 2.60—3.30 (6H, m), 3.41 (2H, br d, J=10.6 Hz), 6.57 (1H, dd, J=8.8, 2.7 Hz), 6.75 (1H, d, J=2.7 Hz), 7.05—7.30 (5H, m). *Anal.* Calcd for $C_{21}H_{25}Cl_2FN_2 \cdot 2HCl \cdot 0.5H_2O$: C, 52.85; H, 5.91; N, 5.87. Found: C, 52.90; H, 6.12; N, 5.94.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-*N*-(4-methylphenyl)-5-oxopyrrolidine-3-carboxamide Hydrochloride (10c)** To an ice-cooled stirred solution of **2a** (358 mg, 2.5 mmol) and DMF (23 μl, 0.3 mmol) in DCM (10 ml) was added oxalyl chloride (256 μl, 3.0 mmol), and the mixture was stirred at 0 °C for 15 min. The mixture was removed from the ice bath and stirred for an additional 1 h. The mixture was added dropwise to a stirred solution of **9d** (395 mg, 1.0 mmol) and Et_3N (1.39 ml, 10 mmol) in DCM (15 ml) at −20 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 1 h before being quenched with saturated aqueous $NaHCO_3$ (15 ml). The organic solvent was removed *in vacuo*, and the residue was extracted with EtOAc (3×15 ml). The organic layer was 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 (442 mg) as an oil. The oil was dissolved in MeOH and treated with 1N HCl (Et_2O solution, 2 ml). The solution was concentrated *in vacuo* to give a foam, which was triturated with Et_2O, filtered, and dried *in vacuo* over KOH yielding **10c** (409 mg, yield 85%) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ 1.30—1.95 (7H, m), 2.11 (1H, dd, J=16.5, 9.9 Hz), 2.30—2.60 (3H, m), 2.35 (3H, s), 2.60—3.50 (9H, m), 2.63 (3H, s), 3.50—3.75 (2H, m), 7.10—7.40 (9H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_2 \cdot HCl \cdot 0.6H_2O$: C, 67.96; H, 7.98; Cl, 7.16; N, 8.49. Found: C, 67.99; H, 7.94; Cl, 7.45; N, 8.28.

The following compounds **10a**, **b**, **d**—**p** were prepared using a procedure similar to that described for **10c** from the anilines **9b**, **c**, **e**—**q**.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-*N*-(2-methylphenyl)-5-oxopyrrolidine-3-carboxamide Hydrochloride (10a)** Yield 59%, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.05—1.95 (9H, m), 2.05—2.35 (3H, m), 2.21 (3H, s), 2.45—3.25 (6H, m), 2.51 (2H, d, J=6.6 Hz), 2.75 (0.5×3H, s), 2.76 (0.5×3H, s), 3.40—3.80 (1H, m), 4.00—4.25 (1H, m), 7.00—7.35 (9H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_2 \cdot HCl \cdot 0.7H_2O$: C, 67.71; H, 8.00; N, 8.46. Found: C, 67.68; H, 7.97; N, 8.50.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-*N*-(3-methylphenyl)-5-oxopyrrolidine-3-carboxamide Hydrochloride (10b)** Yield 84%, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.05—1.95 (9H, m), 2.10—2.40 (3H, m), 2.38 (3H, s), 2.51 (2H, d, J=6.6 Hz), 2.55—2.90 (3H, m), 2.76 (3H, s), 2.95—3.25 (2H, m), 3.55—3.75 (3H, m), 6.85—7.00 (2H, m), 7.05—7.35 (7H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_2 \cdot HCl \cdot 0.5H_2O$: C, 68.20; H, 7.97; N, 8.52. Found: C, 68.18; H, 8.12; N, 8.63.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(4-*tert*-butylphenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10d)** Yield 75%, amorphous solid. ^{1}H-NMR (DMSO-d_6) δ 1.31 (9H, s), 1.35—1.95 (7H, m), 2.11 (1H, dd, J=16.4, 9.6 Hz), 2.35—2.60 (3H, m), 2.60—3.50 (9H, m), 2.63 (3H, s), 3.55—3.75 (2H, m), 7.10—7.40 (7H, m), 7.51 (2H, d, J=8.4 Hz). *Anal.* Calcd for $C_{31}H_{43}N_3O_2 \cdot HCl \cdot 0.6H_2O$: C, 69.34; H, 8.48; N, 7.83. Found: C, 69.27; H, 8.52; N, 7.82.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(indan-5-yl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10e)** Yield 69%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.44—1.58 (2H, m), 1.88—2.14 (7H, m), 2.44—2.49 (1H, m), 2.60—2.69 (3H, m), 2.77 (3H, s), 2.81—2.98 (6H, m), 3.06—3.14 (2H, m), 3.28—3.53 (5H, m), 3.76—3.82 (2H, m), 7.08 (1H, d, J=8.2 Hz), 7.22—7.43 (7H, m). *Anal.* Calcd for $C_{30}H_{39}N_3O_2 \cdot HCl \cdot 1.5H_2O$: C, 67.08; H, 8.07; N, 7.82. Found: C, 67.19; H, 7.97; N, 8.01.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10f)** Yield 88%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.35—1.65 (2H, m), 1.75—2.10 (5H, m), 2.45 (1H, dd, J=17.7, 9.7 Hz), 2.55—2.75 (1H, m), 2.63 (2H, d, J=7.0 Hz), 2.75—3.00 (2H, m), 2.78 (3H, s), 3.00—3.20 (2H, m), 3.20—3.65 (5H, m), 3.70—3.90 (2H, m), 3.89 (3H, s), 7.13 (2H, d, J=8.8 Hz), 7.20—7.45 (7H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_3 \cdot HCl \cdot 0.6H_2O$: C, 65.83; H, 7.73; N, 8.22. Found: C, 65.79; H, 7.70; N, 8.06.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3-chlorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10g)** Yield 79%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.40—1.55 (2H, m), 1.85—2.03 (5H, m), 2.47—2.95 (9H, m), 3.06—3.59 (7H, m), 3.71—3.85 (2H, m), 7.25—7.55 (9H, m). *Anal.* Calcd for $C_{27}H_{34}ClN_3O_2 \cdot HCl \cdot 0.7H_2O$: C, 62.71; H, 7.10; N, 8.13. Found: C, 62.77; H, 7.05; N, 8.24.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(4-chlorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10h)** Yield 86%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.35—1.65 (2H, m), 1.80—2.10 (5H, m), 2.45 (1H, dd, J=17.6, 9.6 Hz), 2.55—2.75 (1H, m), 2.64 (2H, d, J=7.2 Hz), 2.75—3.65 (9H, m), 2.78 (3H, s), 3.65—3.95 (2H, m), 7.20—7.45 (7H, m), 7.59 (2H, d, J=8.6 Hz). *Anal.* Calcd for $C_{27}H_{34}ClN_3O_2 \cdot HCl \cdot 0.6H_2O$: C, 62.93; H, 7.08; N, 8.15. Found: C, 63.04; H, 7.14; N, 8.16.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10i)** Yield 77%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.35—1.65 (2H, m), 1.75—2.10 (5H, m), 2.47 (1H, dd, J=18.0, 9.4 Hz), 2.55—2.75 (1H, m), 2.65 (2H, d, J=7.2 Hz), 2.75—3.20 (4H, m), 2.79 (3H, s), 3.20—3.70 (5H, m), 3.70—3.90 (2H, m), 7.25—7.45 (6H, m), 7.63 (1H, d, J=2.2 Hz), 7.72 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{27}H_{33}Cl_2N_3O_2 \cdot HCl \cdot 0.7H_2O$: C, 58.80; H, 6.47; N, 7.62. Found: C, 58.77; H, 6.41; N, 7.56.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3-chloro-4-fluorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10j)** Yield 68%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.40—1.58 (2H, m), 1.89—1.96 (5H, m), 2.47—2.64 (4H, m), 2.77—2.95 (5H, m), 3.01—3.13 (2H, m), 3.32—3.56 (5H, m), 3.73—3.79 (2H, m), 7.25—7.40 (6H, m), 7.55—7.60 (2H, m). *Anal.* Calcd for $C_{27}H_{33}ClFN_3O_2 \cdot HCl \cdot 0.75H_2O$: C, 60.50; H, 6.39; N, 7.84. Found: C, 60.70; H, 6.71; N, 8.16.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3,4-difluorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10k)** Yield 80%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.40—1.55 (2H, m), 1.89—2.00 (5H, m), 2.48—2.64 (4H, m), 2.77—2.94 (5H, m), 3.06—3.14 (2H, m), 3.30—3.55 (5H, m), 3.73—3.79 (2H, m), 7.20—7.46 (8H, m). *Anal.* Calcd for $C_{27}H_{33}F_2N_3O_2 \cdot HCl \cdot 0.6H_2O$: C, 62.74; H, 6.86; N, 8.13. Found: C, 62.44; H, 6.88; N, 8.27.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-5-oxo-*N*-[3-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide Hydrochloride (10l)** Yield 70%, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.05—1.95 (9H, m), 2.15—2.35 (3H, m), 2.51 (2H, d, J=6.6 Hz), 2.60—3.10 (4H, m), 2.78 (3H, s), 3.19 (1H, t, J=9.1 Hz), 3.60—3.80 (3H, m), 7.05—7.45 (7H, m), 7.55—7.75 (2H, m). *Anal.* Calcd for $C_{28}H_{34}F_3N_3O_2 \cdot HCl \cdot 0.6H_2O$: C, 61.27; H,

6.65; N, 7.66. Found: C, 61.29; H, 6.60; N, 7.69.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-methyl-5-oxo-*N*-[4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide Hydrochloride (10m)** Yield 70%, amorphous solid. ^{1}H-NMR (DMSO-d_6) δ 1.44—1.57 (2H, m), 1.70—1.85 (5H, m), 2.10—2.21 (2H, m), 2.39—2.54 (3H, m), 2.64 (3H, s), 2.70—3.05 (4H, m), 3.13—3.45 (4H, m), 3.65—3.75 (2H, m), 7.16—7.34 (5H, m), 7.65—7.69 (2H, m), 7.85—7.90 (2H, m). *Anal.* Calcd for $C_{28}H_{34}F_3N_3O_2\cdot HCl\cdot 0.5H_2O$: C, 61.47; H, 6.63; N, 7.68. Found: C, 61.43; H, 6.73; N, 7.97.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-[3,5-bis(trifluoromethyl)-phenyl]-1-methyl-5-oxopyrrolidine-3-carboxamide (10n)** Yield 50%, amorphous solid. ^{1}H-NMR (D_2O) δ 1.44—1.51 (2H, m), 1.89—2.01 (5H, m), 2.45—2.63 (4H, m), 2.69—2.96 (5H, m), 3.08—3.85 (9H, m), 7.25—7.38 (5H, m), 8.06 (2H, s), 8.26 (1H, s). *Anal.* Calcd for $C_{29}H_{33}F_6N_3O_2\cdot HCl\cdot 0.4H_2O$: C, 56.80; H, 5.72; N, 6.85. Found: C, 56.81; H, 6.07; N, 7.37.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3-cyanophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10o)** Yield 46%, amorphous solid. IR (KBr) 2232 cm^{-1}. ^{1}H-NMR (free base, $CDCl_3$) δ 1.16—2.00 (9H, m), 2.10—2.59 (5H, m), 2.78 (3H, s), 2.59—3.09 (3H, m), 3.09—3.40 (2H, m), 3.54—3.81 (3H, m), 7.09—7.32 (5H, m), 7.41—7.70 (4H, m). *Anal.* Calcd for $C_{28}H_{34}N_4O_2\cdot HCl\cdot 1.5H_2O$: C, 64.42; H, 7.34; N, 10.73. Found: C, 64.42; H, 7.18; N, 10.62.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(4-cyanophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (10p)** Yield 28%, amorphous solid. IR (KBr) 2230 cm^{-1}. ^{1}H-NMR (free base, $CDCl_3$) δ 1.21—1.99 (9H, m), 2.03—2.54 (6H, m), 2.78 (3H, s), 2.58—3.15 (4H, m), 3.58—3.78 (3H, m), 7.10—7.36 (7H, m), 7.77 (2H, d, J=8.0 Hz). *Anal.* Calcd for $C_{28}H_{34}N_4O_2\cdot HCl\cdot 1.9H_2O$: C, 63.54; H, 7.39; N, 10.59. Found: C, 63.64; H, 7.25; N, 10.32.

***N*-Benzyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-1-methyl-5-oxopyrrolidine-3-carboxamide (10q)** To a stirred mixture of **2a** (89 mg, 0.62 mmol), **9r** (200 mg, 0.62 mmol), and HOBt hydrate (104 mg, 0.68 mmol) in MeCN (6 ml) was added 1,3-dicyclohexylcarbodiimide (DCC) (141 mg, 0.68 mmol), and the mixture was stirred at 80 °C for 1 h. The mixture was concentrated *in vacuo*, diluted with EtOAc (20 ml), and filtered. The filtrate was washed with 2 N NaOH (5 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on alumina (EtOAc) to afford **10q** (125 mg, yield 45%) as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.40 (2H, m), 1.41—1.88 (7H, m), 2.19—2.78 (8H, m), 2.80 (1.5H, s), 2.88 (1.5H, s), 3.21—3.82 (5H, m), 4.48—4.73 (2H, m), 7.11—7.37 (10H, m). *Anal.* Calcd for $C_{28}H_{37}N_3O_2\cdot 0.25H_2O$: C, 74.38; H, 8.36; N, 9.29. Found: C, 74.38; H, 8.49; N, 9.09.

The following compounds **11a**, **b** were prepared using a procedure similar to that described for **10c** from the anilines **9s**, **t**.

***N*-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (11a)** Yield 43%, amorphous solid. ^{1}H-NMR (CD_3OD) δ 1.30—1.70 (2H, m), 1.75—2.10 (5H, m), 2.31 (1H, dd, J=17.2, 9.6 Hz), 2.56—2.71 (3H, m), 2.77 (3H, s), 2.92 (2H, t-like, J=12.4 Hz), 3.09—3.36 (4H, m), 3.53—3.70 (3H, m), 3.70—3.90 (2H, m), 6.97—7.10 (2H, m), 7.17—7.24 (2H, m), 7.34—7.60 (5H, m). *Anal.* Calcd for $C_{27}H_{34}FN_3O_2\cdot HCl\cdot 1.5H_2O$: C, 62.96; H, 7.44; N, 8.16. Found: C, 62.99; H, 7.44; N, 8.10.

***N*-(3,4-Dichlorophenyl)-*N*-{3-[4-(4-fluorobenzyl)piperidin-1-yl]-propyl}-1-methyl-5-oxopyrrolidine-3-carboxamide Hydrochloride (11b)** Yield 65%, amorphous solid. ^{1}H-NMR (CD_3OD) δ 1.40—1.70 (2H, m), 1.70—2.10 (5H, m), 2.36 (1H, dd, J=17.2, 9.8 Hz), 2.50—2.70 (3H, m), 2.78 (3H, s), 2.92 (2H, t-like, J=12.0 Hz), 3.08—3.60 (4H, m), 3.50—3.70 (3H, m), 3.70—3.90 (2H, m), 7.02 (2H, t, J=8.8 Hz), 7.17—7.24 (2H, m), 7.35 (1H, dd, J=8.4, 2.2 Hz), 7.68—7.72 (2H, m). *Anal.* Calcd for $C_{27}H_{32}Cl_2FN_3O_2\cdot HCl\cdot 1.7H_2O$: C, 55.19; H, 6.24; N, 7.15. Found: C, 55.14; H, 6.27; N, 7.15.

The following compounds **12a**—**m** were prepared using a procedure similar to that described for **10c** from the acids **2b**—**n** and the aniline **9a**.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-butyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12a)** Yield 46%, oil. ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, J=7.2 Hz), 1.05—1.90 (13H, m), 2.22 (1H, dd, J=16.8, 8.8 Hz), 2.28 (2H, t, J=7.4 Hz), 2.50 (2H, d, J=6.6 Hz), 2.66 (1H, dd, J=16.8, 8.8 Hz), 2.75—2.90 (2H, m), 2.94—3.45 (4H, m), 3.62—3.75 (3H, m), 7.10—7.50 (10H, m). *Anal.* Calcd for $C_{30}H_{41}N_3O_2\cdot 0.5H_2O$: C, 74.34; H, 8.73; N, 8.67. Found: C, 74.60; H, 8.77; N, 8.89.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-cyclohexyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12b)** Yield 57%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.00—1.86 (19H, m), 2.15—2.32 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.58—2.70 (1H, m), 2.67—3.06 (3H, m), 3.18 (1H, t, J=9.0 Hz), 3.56—3.94 (4H, m), 7.10—7.50 (10H, m). *Anal.* Calcd for $C_{32}H_{43}N_3O_2\cdot 0.5H_2O$: C, 75.26; H, 8.68; N, 8.23. Found: C, 75.19; H, 8.37; N, 8.32.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(cyclohexylmethyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12c)** Yield 70%, oil. ^{1}H-NMR ($CDCl_3$) δ 0.80—1.03 (2H, m), 1.04—1.38 (5H, m), 1.39—1.90 (13H, m), 2.16—2.32 (3H, m), 2.51 (2H, d, J=6.6 Hz), 2.61—3.20 (7H, m), 3.63—3.75 (3H, m), 7.10—7.50 (10H, m). *Anal.* Calcd for $C_{33}H_{45}N_3O_2$: C, 76.85; H, 8.79; N, 8.15. Found: C, 76.50; H, 8.89; N, 8.18.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-5-oxo-*N*,1-diphenylpyrrolidine-3-carboxamide (12d)** Yield 62%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—2.00 (9H, m), 2.27—2.45 (3H, m), 2.51 (2H, d, J=6.6 Hz), 2.81—2.99 (3H, m), 3.10—3.27 (1H, m), 3.62 (1H, t, J=9.0 Hz), 3.71—3.79 (2H, m), 4.18 (1H, t, J=9.0 Hz), 7.09—7.53 (15H, m). *Anal.* Calcd for $C_{32}H_{37}N_3O_2\cdot 0.5H_2O$: C, 76.16; H, 7.59; N, 8.33. Found: C, 75.91; H, 7.85; N, 8.35.

1-Benzyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (12e) Yield 68%, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.15—1.33 (2H, m), 1.40—1.86 (7H, m), 2.23—2.36 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.68—2.90 (3H, m), 2.92—3.12 (2H, m), 3.53 (1H, dd, J=7.6, 5.4 Hz), 3.64—3.72 (2H, m), 4.33 (1H, d, J=14.6 Hz), 4.43 (1H, d, J=14.6 Hz), 7.00—7.30 (15H, m). *Anal.* Calcd for $C_{33}H_{39}N_3O_2\cdot HCl\cdot 1.5H_2O$: C, 69.15; H, 7.56; N, 7.33. Found: C, 68.78; H, 7.31; N, 7.59.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(2-chlorobenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide Hydrochloride (12f)** Yield 72%, amorphous solid. ^{1}H-NMR (free base, $CDCl_3$) δ 1.10—1.35 (2H, m), 1.35—1.85 (7H, m), 2.23—2.37 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.69—2.90 (3H, m), 2.96—3.18 (2H, m), 3.58 (1H, dd, J=8.4, 6.2 Hz), 3.69 (2H, t, J=7.8 Hz), 4.48 (1H, d, J=15.2 Hz), 4.58 (1H, d, J=15.2 Hz), 7.10—7.64 (14H, m). *Anal.* Calcd for $C_{33}H_{38}ClN_3O_2\cdot HCl\cdot 0.8H_2O$: C, 66.61; H, 6.88; N, 7.06. Found: C, 66.58; H, 6.91; N, 7.06.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(3-chlorobenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12g)** Yield 81%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.90 (9H, m), 2.23—2.37 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.67—2.83 (3H, m), 2.98—3.12 (2H, m), 3.50—3.60 (1H, m), 3.69 (2H, t-like, J=7.6 Hz), 4.30 (1H, d, J=14.6 Hz), 4.41 (1H, d, J=14.6 Hz), 7.00—7.50 (14H, m). *Anal.* Calcd for $C_{33}H_{38}ClN_3O_2\cdot 0.5H_2O$: C, 71.66; H, 7.11; N, 7.60. Found: C, 71.87; H, 7.09; N, 7.36.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(4-chlorobenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12h)** Yield 78%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.90 (9H, m), 2.23—2.36 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.67—2.83 (3H, m), 2.96—3.10 (2H, m), 3.50—3.60 (1H, m), 3.69 (2H, t-like, J=7.4 Hz), 4.35 (2H, s), 7.00—7.50 (14H, m). *Anal.* Calcd for $C_{33}H_{38}ClN_3O_2\cdot 0.2H_2O$: C, 72.36; H, 7.07; N, 7.67. Found: C, 72.37; H, 7.06; N, 7.49.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(4-methylbenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12i)** Yield 40%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.37 (2H, m), 1.37—1.88 (7H, m), 2.32 (3H, s), 2.21—2.37 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.66—2.88 (3H, m), 2.95—3.15 (2H, m), 3.45—3.60 (1H, m), 3.65 (2H, t-like, J=8.0 Hz), 4.44 (2H, s), 7.05—7.60 (14H, m). MS *m/z*: 524 (MH^+). HPLC t_R 3.57 min (97%).

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-5-oxo-*N*-phenyl-1-(2-phenylethyl)pyrrolidine-3-carboxamide (12j)** Yield 59%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.12—1.37 (2H, m), 1.38—1.90 (7H, m), 2.13—2.31 (3H, m), 2.51 (2H, d, J=6.6 Hz), 2.61—2.85 (5H, m), 2.92—3.06 (2H, m), 3.44 (2H, t-like, J=7.4 Hz), 3.54—3.59 (1H, m), 3.69 (2H, t-like, J=7.4 Hz), 7.07—7.44 (15H, m). *Anal.* Calcd for $C_{34}H_{41}N_3O_2$: C, 77.98; H, 7.89; N, 8.02. Found: C, 77.78; H, 7.72; N, 7.85.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(furan-2-ylmethyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12k)** Yield 18%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.15—1.33 (2H, m), 1.40—1.86 (7H, m), 2.19—2.31 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.68 (1H, t, J=8.8 Hz), 2.81 (2H, br d, J=11.4 Hz), 2.92—3.10 (1H, m), 3.18 (1H, t, J=8.8 Hz), 3.57—3.73 (3H, m), 4.31 (1H, d, J=15.4 Hz), 4.44 (1H, d, J=15.4 Hz), 6.20—6.30 (2H, m), 7.10—7.50 (11H, m). MS *m/z*: 500 (MH^+). HPLC t_R 3.32 min (97%).

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-5-oxo-*N*-phenyl-1-(pyridin-4-ylmethyl)pyrrolidine-3-carboxamide (12l)** Yield 63%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.00—1.86 (9H, m), 2.24—2.41 (3H, m), 2.50 (2H, d, J=6.2 Hz), 2.70—2.90 (3H, m), 3.02—3.15 (2H, m), 3.50—3.74 (3H, m), 4.40 (2H, s), 7.05—7.50 (12H, m), 8.55 (2H, d, J=5.8 Hz). *Anal.* Calcd for $C_{32}H_{38}N_4O_2\cdot 0.5H_2O$: C, 73.96; H, 7.56; N, 10.78. Found: C, 73.81; H, 7.39; N, 10.74.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(2,4-dimethoxybenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (12m)** Yield 62%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.90 (9H, m), 2.15—2.35 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.60—3.20 (5H, m), 3.40—3.75 (3H, m), 3.78 (6H, s), 4.35 (2H, s), 6.35—

6.50 (2H, m), 7.00—7.50 (11H, m).

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (13)** Compound **12m** (920 mg, 1.6 mmol) was dissolved in TFA (16 ml), and the mixture was stirred at 60 °C for 3 h. The mixture was concentrated *in vacuo*, diluted with saturated 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 alumina (EtOAc/MeOH 1/0 to 4/1) to afford **13** (566 mg, yield 84%) as a white solid, mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.33 (2H, m), 1.38—1.87 (7H, m), 2.08—2.32 (3H, m), 2.51 (2H, d, J=6.6 Hz), 2.59—2.85 (3H, m), 3.09—3.28 (2H, m), 3.55—3.75 (3H, m), 5.42 (1H, br), 7.10—7.49 (10H, m). *Anal.* Calcd for $C_{26}H_{33}N_3O_2 \cdot 0.1H_2O$: C, 74.11; H, 7.94; N, 9.97. Found: C, 74.02; H, 7.93; N, 10.00.

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-5-oxo-*N*-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide (14a)** To an ice-cooled stirred solution of **13** (100 mg, 0.24 mmol) in DMF (1.5 ml) was added NaH (60% in oil, 29 mg, 0.7 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was treated with 2,2,2-trifluoroethyl triflate (172 μl, 1.2 mmol), stirred at room temperature for 1 h, and concentrated *in vacuo*. The residue was diluted with 1 N NaOH and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on alumina (hexane/EtOAc 1/1 to 0/1) to afford **14a** (36 mg, yield 30%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 1.15—1.35 (2H, m), 1.40—1.85 (7H, m), 2.22—2.36 (3H, m), 2.51 (2H, d, J=6.2 Hz), 2.65—2.90 (3H, m), 3.03—3.20 (1H, m), 3.37 (1H, t, J=8.4 Hz), 3.60—3.80 (4H, m), 3.85—4.02 (1H, m), 7.10—7.30 (8H, m), 7.32—7.50 (2H, m). MS *m/z*: 502 (MH^+). HPLC t_R 3.34 min (99%).

***N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-(2-methylbenzyl)-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (14b)** Compound **14b** was prepared using a procedure similar to that described for **14a** from 2-methylbenzylbromide. Yield 63%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.90 (9H, m), 2.25 (3H, s), 2.20—2.36 (3H, m), 2.50 (2H, d, J=6.4 Hz), 2.67—2.85 (3H, m), 2.95—3.10 (2H, m), 3.40—3.60 (1H, m), 3.67 (2H, t-like, J=7.8 Hz), 4.40 (2H, s), 7.00—7.50 (14H, m). MS *m/z*: 524 (MH^+). HPLC t_R 3.53 min (99%).

The following compounds **15a**, **b** were prepared using a procedure similar to that described for **10c** from the acid **2f** and the anilines **9h**, **j**.

1-Benzyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-(3-chlorophenyl)-5-oxopyrrolidine-3-carboxamide (15a) Yield 39%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.30 (2H, m), 1.30—1.85 (7H, m), 2.23—2.38 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.68—2.85 (3H, m), 2.96—3.13 (2H, m), 3.48—3.70 (3H, m), 4.48 (2H, s), 7.08—7.60 (14H, m). *Anal.* Calcd for $C_{33}H_{38}ClN_3O_2 \cdot 0.6H_2O$: C, 71.42; H, 7.12; N, 7.57. Found: C, 71.36; H, 7.20; N, 7.51.

1-Benzyl-*N*-[3-(4-benzylpiperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide (15b) Yield 58%, oil. ^{1}H-NMR ($CDCl_3$) δ 1.10—1.38 (2H, m), 1.38—1.86 (7H, m), 2.22—2.40 (3H, m), 2.50 (2H, d, J=6.6 Hz), 2.66—2.82 (3H, m), 2.90—3.15 (2H, m), 3.45—3.70 (3H, m), 4.34 (1H, d, J=14.8 Hz), 4.46 (1H, d, J=14.8 Hz), 6.97 (1H, dd, J=8.6, 2.6 Hz), 7.10—7.40 (11H, m), 7.49 (1H, d, J=8.6 Hz). *Anal.* Calcd for $C_{33}H_{37}Cl_2N_3O_2$: C, 68.51; H, 6.45; N, 7.26. Found: C, 68.36; H, 6.49; N, 7.23.

Receptor Binding Assays CHO-K1 and CCR5-expressing CHO cells[23] 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]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).

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 with at a ratio of 3 : 1 : 5 and co-transfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After 2 d 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).

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