Highly Potent and Orally Active CCR5 Antagonists as Anti-HIV-1 Agents: Synthesis and Biological Activities of 1-Benzazocine Derivatives Containing a Sulfoxide Moiety

Masaki Seto,*,† Katsuji Aikawa,† Naoki Miyamoto,† Yoshio Aramaki,† Naoyuki Kanzaki,† Katsunori Takashima,† Yoji Kuze,† Yuji Iizawa,† Masanori Baba,‡ and Mitsuru Shiraishi†

Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan, and Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1, Sakuragaoka, Kagoshima 890-8544, Japan

Received September 29, 2005

Chemical modification has been performed on an orally bioavailable and potent CCR5 antagonist, sulfoxide compound **4**, mainly focusing on replacement of the [6,7]-fused 1-benzazepine nucleus. We designed, synthesized, and evaluated the biological activities of ring-expanded [6,8]-, [6,9]-, and [6,10]-fused compounds containing *S*-sulfoxide moieties, which led to the discovery of 1-benzazocine and 1-benzazonine compounds that exhibited potent inhibitory activities (equivalent to compound **4**) in a binding assay. In addition, 1-benzazocine compounds possessing the *S*-sulfoxide moiety ((***S***)-(−)-**5a**,**b**,**d**,**e**) showed greater potency than compound **4** in a fusion assay. From further investigation in a multi-round infection assay, it was found that 1-isobutyl-1-benzazocine compound (***S***)-(−)-**5b**, containing the *S*-{[(1-propyl-1*H*-imidazol)-5-yl]methyl}sulfinyl group, showed the most potent anti-HIV-1 activity (IC_{90} = 0.81 nM, in MOLT4/CCR5 cells). Compound (***S***)-(−)-**5b** (TAK-652) also inhibited the replication of six macrophage-tropic (CCR5-using or R5) HIV-1 clinical isolates in peripheral blood mononuclear cells (PBMCs) (mean IC_{90} = 0.25 nM). It was also absorbed after oral administration in rats, dogs, and monkeys and was thus selected as a clinical candidate. The synthesis and biological activity of the 1-benzazocine compound (***S***)-(−)-**5b** and its related derivatives are described.

Introduction

Human immunodeficiency virus type 1 (HIV-1) infectious disease remains a serious health problem around the world, and efforts to develop anti-HIV-1 agents are being made by many pharmaceutical companies. The discovery of HIV-1 protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors, and nonnucleoside transcriptase inhibitors has had a great impact on the treatment of HIV-1 infection. Combination chemotherapy using these three types of anti-HIV-1 agents, called HAART (highly active antiretroviral therapy), has led to the achievement of long-term, virtually complete suppression of viral replication in HIV-1 infected individuals and reduction of mortality.[1] Furthermore, a new anti-HIV-1 drug called enfuvirtide, a member of the entry inhibitor class of drugs,[2] was approved by the FDA in March 2003. However, difficult dosing regimens, the emergence of drug resistant HIV-1,[3] and long-term adverse effects[4] are reported as significant problems with HAART. In addition, it has been found that viral eradication is unfeasible even with combination chemotherapy,[5] and this has led to the need for novel anti-HIV-1 agents with new mechanisms of action.

CC chemokine receptor 5 (CCR5) belongs to the super family of seven-transmembrane G-protein coupled receptors (GPCRs), and its natural ligands are known to be RANTES (regulated on activation normal T-cell expressed and secreted) and macrophage inflammatory proteins (MIP)-1α and MIP-1β. First, it was reported that natural ligands for CCR5 act on blocking R5 HIV-1 infection,[6] and then it was discovered that CCR5 is a coreceptor for entry of macrophage-tropic (CCR5-using or R5) HIV-1 into host cells.[7−11] Furthermore, it has been found that individuals with a 32-base-pair deletion in the CCR5 coding region (CCR5Δ32-homozygotes) are highly resistant to R5 HIV-1 infection and that R5 HIV-1 infected CCR5Δ32-heterozygotes have been identified with a delay in disease progression.[12−16] In addition, these individuals do not appear to have any significant health problems. From these observations, CCR5 antagonists have attracted a great deal of attention as novel anti-HIV-1 candidates, and many pharmaceutical companies have started to search for CCR5 antagonists.[17,18] We discovered the first nonpeptide, small-molecule CCR5 antagonist **1** as an anti-HIV-1 candidate for injection in 1999 (Figure 1).[19,20] In the area of orally bioavailable CCR5 antagonists, it has been reported that Schering-Plough's SCH-C[21] and SCH-D,[22] Pfizer's UK-427857,[23] and Ono/Glaxo-SmithKline's ONO4128/AK602/GW873140[24] were selected as clinical candidates; SCH-D and UK-427857 are now in clinical trials. In addition, our colleagues at Takeda have discovered an orally bioavailable clinical candidate, TAK-220.[25]

Compound **1** was found to exhibit poor oral absorption due to its polar quaternary ammonium moiety. To develop orally active CCR5 antagonists, we previously reported chemical modification of [6,7]-fused 1-benzoxepine, 1-benzthiepine 1,1-dioxide, or 1-benzazepine compounds containing tertiary amine, pyridine *N*-oxide, or sulfoxide moieties as polar substituents in place of the quaternary ammonium moiety, which led to the discovery of potent, orally bioavailable tertiary amine (**2**), pyridine *N*-oxide (**3**), and *S*-sulfoxide (**4**) compounds (Figure 1).[26−29] Through optimization of the tertiary amine compounds, it was found that 1-benzazepine compounds containing bulky alkyl groups at the 1-position, such as propyl, isobutyl, and (1-methyl-1*H*-pyrazol-4-yl)methyl groups, showed potent CCR5 antagonism and potent inhibition of HIV-1 envelope (Env)-mediated membrane fusion.[27] In addition, we found that the

* Corresponding author. Tel: +81-6-6300-6651. Fax: +81-6-6300-6306. E-mail: Seto_Masaki@takeda.co.jp.
† Takeda Pharmaceutical Company Limited.
‡ Kagoshima University.

10.1021/jm0509703 CCC: $33.50
Published on Web 03/01/2006

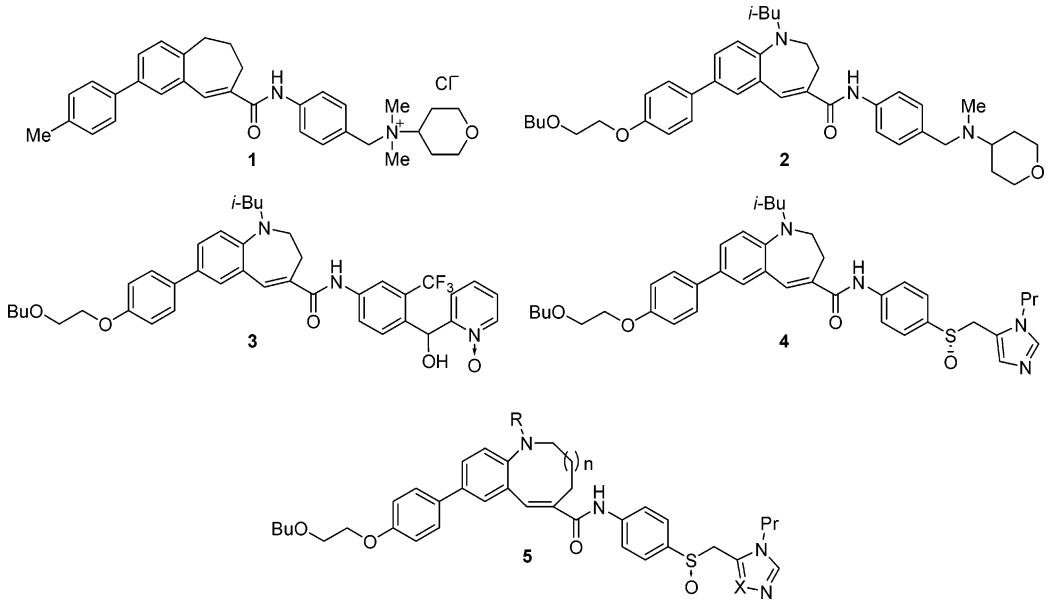
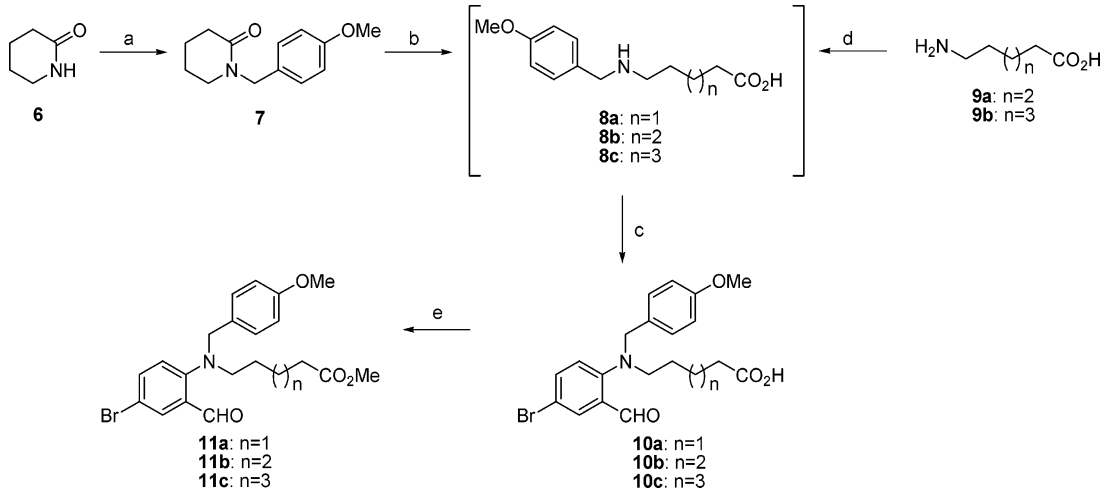


Figure 1. Structure of CCR5 antagonists **1**−**4** and design of new compounds **5** containing a sulfoxide moiety.

Scheme 1. Synthesis of Cyclization Precursors **11**[a]



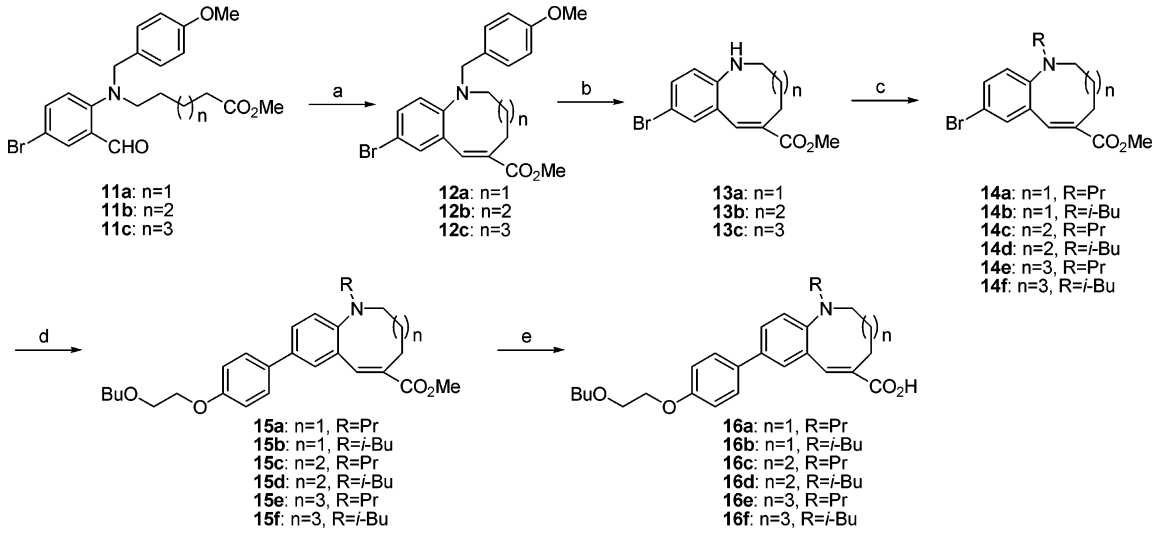
[a] Reagents: (a) 4-methoxybenzyl chloride, KOH, $(n\text{-Bu})_4NBr$, tolune; (b) 4 N NaOH and then concentrated HCl; (c) 5-bromo-2-fluorobenzaldehyde, Na_2CO_3, DMSO, water; (d) 10% Pd−C, 4-methoxybenzaldehyde, 1 N NaOH, MeOH, H_2; and (e) MeI, K_2CO_3, DMF.

incorporation of a 4-[2-(butoxy)ethoxy] group on the 7-phenyl group of the [6,7]-fused nucleus led to both enhanced binding affinity and improved pharmacokinetic properties in rats.[27] Further investigation of the 1-benzazepine compounds containing both the sulfoxide moiety and the heteroaryl groups led to the discovery that the presence of a methylene group between the sulfoxide moiety and the heteroaryl group was necessary for the appearance of potent binding affinity and that *S*-sulfoxide compounds were more active than the corresponding *R*-isomers in the binding and fusion assays.[29] Compounds **2**−**4** exhibited potent inhibition in the fusion assay, comparable to compound **1** for injection; however, the plasma level of the tertiary amine compound **2** after oral administration to rats was lower than those of the pyridine *N*-oxide (**3**) and sulfoxide (**4**) compounds.[27−29] On the basis of these results, ease of synthesis, and structural novelty, we selected the sulfoxide moiety as the key polar substituent in our search for orally active and potent CCR5 antagonists as anti-HIV-1 agents. In our first paper concerning quaternary ammonium compounds,[20] we reported that replacement of the [6,6]-fused ring with a [6,7]-fused ring increased the activity about 10-fold, suggesting sensitive SAR effects in this region of the molecule. Considering these results, we investigated chemical modification of the sulfoxide compounds, focusing primarily on replacement of the 1-benzazepine nucleus with a [6,8]-, [6,9]-, or [6,10]-fused ring. This led to the discovery of the remarkably potent and orally bioavailable CCR5 antagonist (***S***)-(−)-**5b** as an anti-HIV-1 agent. In this paper, we describe the design, synthesis, and biological evaluation of sulfoxide compounds containing [6,8]- to [6,10]-fused ring nuclei.

Chemistry

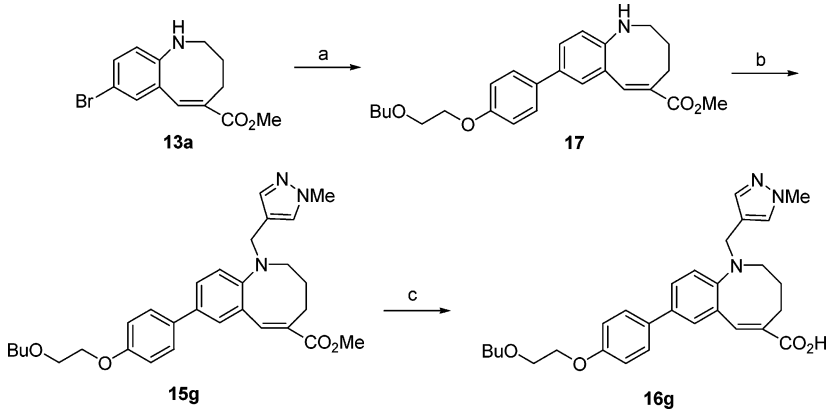
The synthetic route to the cyclization precursors **11a**−**c** is illustrated in Scheme 1. Alkylation of piperidin-2-one **6** with 4-methoxybenzyl chloride gave 1-(4-methoxybenzyl) piperidin-2-one (**7**). Conversion of piperidin-2-one **7** into carboxylic acid **10a** was carried out in a one-pot reaction. Thus, hydrolysis of **7** with 4 N aqueous NaOH under reflux and subsequent reaction of the resulting amino acid **8a** with 5-bromo-2-fluorobenzaldehyde gave carboxylic acid **10a**. Intermediate **11a** was synthesized by esterification of the carboxylic acid **10a** using iodomethane and potassium carbonate (K_2CO_3). Other precursors (**11b**,**c**) were prepared by an alternative method. Reaction of the amino acids **8b**,**c**, prepared by the reductive amination

Scheme 2. Synthesis of Carboxylic Acids **16**[a]



[a] Reagents: (a) 28% NaOMe in MeOH, $CO(OMe)_2$; (b) trifluoroacetic acid, toluene; (c) propionaldehyde or isobutyraldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; (d) 4-[2-(butoxy)ethoxy]phenylboronic acid, K_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH, water; and (e) 1 N NaOH, THF, MeOH.

Scheme 3. Synthesis of Carboxylic Acid **16g**[a]



[a] Reagents: (a) 4-[2-(butoxy)ethoxy]phenylboronic acid, K_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH, water; (b) 1-methylpyrazol-4-carbaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; and (c) 1 N NaOH, THF, MeOH.

of **9a**,**b** with 4-methoxybenzaldehyde and Pd-C/H_2, with 5-bromo-2-fluorobenzaldehyde and subsequent esterification, afforded compounds **11b**,**c**.

The key intermediates, carboxylic acids **16a**−**f** with [6,8]-, [6,9]-, or [6,10]-fused rings, were synthesized according to Scheme 2. Synthesis of the [6,8]-fused 1-benzazocine compound **12a** was accomplished by an intramolecular Claisen−Schmidt type cyclization of compound **11a** using sodium methoxide (NaOMe) in dimethyl carbonate.[30] Removal of the 4-methoxybenzyl group using trifluoroacetic acid (TFA) gave the 1-unsubstituted 1-benzazocine **13a**. Reductive amination of **13a** gave the 1-alkyl-1-benzazocines **14a**,**b**. The key 1-benzazocine-5-carboxylic acids **16a**,**b** were prepared by Suzuki coupling of the 8-bromides **14a**,**b** and subsequent alkaline hydrolysis of the resulting **15a**,**b**. The other key carboxylic acids **16c**−**f**, with [6,9]- or [6,10]-fused rings, were obtained by synthetic methods similar to those described for the 1-benzazocine-5-carboxylic acid **16a**.

The 1-benzazocine-5-carboxylic acid **16g** with a 1-[(1-methyl-1*H*-pyrazol-4-yl)methyl] group was prepared according to Scheme 3. The Suzuki coupling reaction of 1-unsubstituted 1-benzazocine **13a** and subsequent reductive amination of the resulting compound **17** gave 1-[(1-methyl-1*H*-pyrazol-4-yl)-methyl]-1-benzazocine **15g**. Alkaline hydrolysis of the ester **15g** gave the key carboxylic acid **16g**.

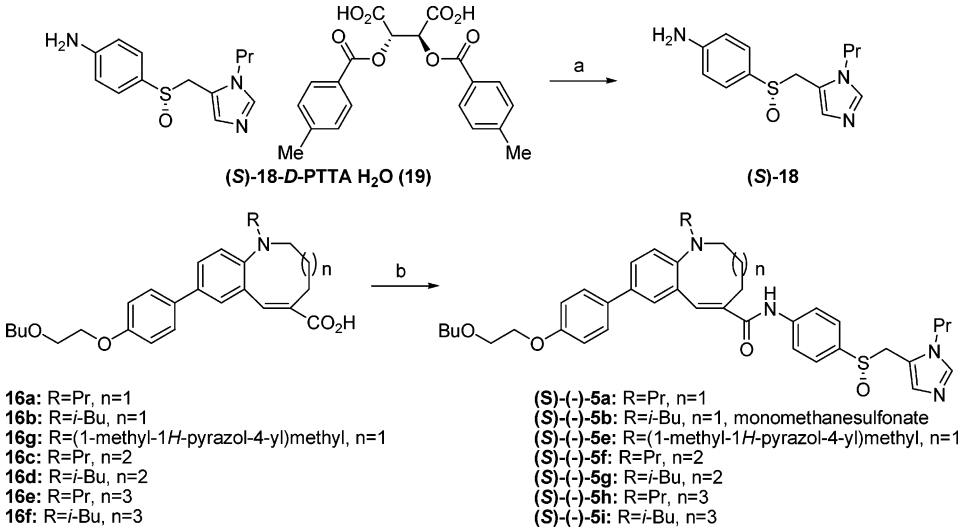
The synthetic route used for the *S*-sulfoxide compounds (***S***)-(−)-**5a**,**b**,**e**−**i** is shown in Scheme 4. The di-*p*-toluoyl-D-tartaric acid (D-PTTA) salt monohydrate of the aniline (***S***)-**18** (compound **19**)[31] was converted into the free base (***S***)-**18** and condensed with carboxylic acids **16a**−**g** via acid chloride formation to give the target *S*-sulfoxide compounds (***S***)-(−)-**5a**,**e**−**i** and the free base of (***S***)-(−)-**5b**. Compound (***S***)-(−)-**5b** was obtained as the monomethanesulfonate salt.

The synthetic route to the target sulfoxide triazole compounds (***S***)-(−)-**5c**,**d** is illustrated in Scheme 5. Conversion of carboxylic acids **16a**,**b** into their acid chlorides and coupling with *S*-(4-aminophenyl)-*O*-benzylthiocarbonate[29] was followed by removal of the *S*-carboxybenzyl (Cbz) group and subsequent alkylation with 3-(chloromethyl)-4-propyl-4*H*-1,2,4-triazole to afford the sulfide compounds **20a**,**b**. The target *S*-sulfoxide compounds (***S***)-(−)-**5c**,**d** were prepared by *m*-chloroperbenzoic acid (*m*CPBA) oxidation of **20a**,**b** and subsequent optical resolution utilizing chiral high-performance liquid chromatography (HPLC).

Biological Results and Discussion

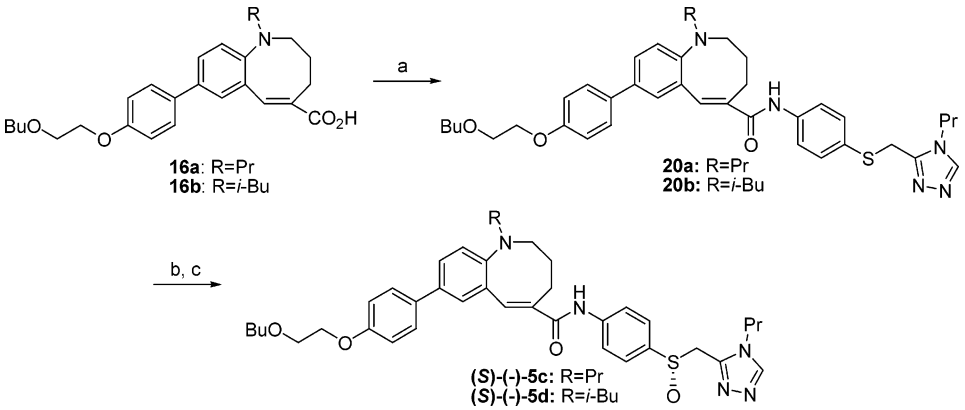
In a previous paper on 1-benzazepine compounds,[29] we reported that *S*-sulfoxide compounds were more active than the corresponding *R*-sulfoxide, sulfide, or sulfone compounds and that the presence of a methylene group between the sulfoxide moiety and the heteroaryl group was necessary to exhibit potent

Scheme 4. Synthesis of *S*-Sulfoxides (***S***)-(−)-**5**[a]



[a] Reagents: (a) 1 N HCl and then 25% aqueous K_2CO_3; (b) (1) $SOCl_2$, cat. DMF, THF and (2) (***S***)-**18**, Et_3N THF.

Scheme 5. Synthesis of *S*-Sulfoxides (***S***)-(−)-**5c**,**d**[a]



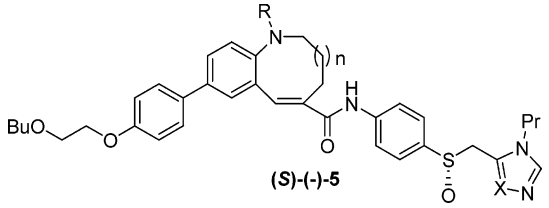
[a] Reagents: (a) (1) $SOCl_2$, cat. DMF, THF, (2) *S*-(4-aminophenyl)-*O*-benzylthiocarbonate, Et_3N, THF and then 1 N NaOH, 3-(chloromethyl)-4-propyl-4*H*-1,2,4-triazole hydrochloride, MeOH; (b) *m*CPBA, CH_2Cl_2; and (c) optical resolution by HPLC.

binding affinity. In addition, we found that compounds with 1-propylimidazol-5-yl or 4-propyl-4*H*-1,2,4-triazol-3-yl groups exhibited potent CCR5 antagonistic activity. Representative 1-benzazepine compound **4** showed significantly potent CCR5 antagonistic activity. It inhibited R5 HIV-1 replication with an IC_{50} value of 5.3 nM in a multi-round infection assay, but its IC_{90} value was 860 nM, as shown in Table 2. Previously, in the search for compound **1**, we found that the fused ring size and shape affected CCR5 activity.[20] Therefore, to discover CCR5 antagonists with greater anti-HIV-1 potency, we investigated the inhibitory effects of fused ring compounds **5** containing the (1-propylimidazol-5-yl)- or (4-propyl-1,2,4-triazol-3-yl)methylsulfinyl group.

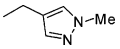
First of all, the compounds prepared were evaluated for their inhibitory effects on chemokine binding to CCR5-expressing CHO cells. Binding reactions were performed in the presence of [^{125}I]-RANTES at various concentrations of test compounds; the results are summarized in Table 1 as IC_{50} values. The [6,8]-fused 1-benzazocine compounds were first investigated. The 1-isobutyl-1-benzazocine (***S***)-(−)-**5b**, containing the 1-propylimidazol-5-yl group, was as highly active as the corresponding 1-isobutyl-1-benzazepine **4**, and replacement of the 1-isobutyl group of (***S***)-(−)-**5b** with the 1-propyl ((***S***)-(−)-**5a)** or 1-[(1-methyl-1*H*-pyrazol-4-yl)methyl] group ((***S***)-(−)-**5e)** also retained potent activity. Compounds (***S***)-(−)-**5c**,**d**, containing the 4-propyl-1,2,4-triazol-3-yl group, also exhibited high activity, comparable to the 1-propylimidazol-5-yl compounds (***S***)-(−)-**5a,b**. These results suggested that the 1-benzazocine ring was a promising nucleus for the synthesis of compounds with high binding affinity for CCR5. We next investigated ring expansion of the bicyclic ring into [6,9]- and [6,10]-fused ring compounds. Whereas the [6,9]-fused benzazonines (***S***)-(−)-**5f**,**g** exhibited potent inhibition, comparable to 1-benzazepine **4**, the [6,10]-fused 1-benzazecines (***S***)-(−)-**5h**,**i** showed reduced activity. On the basis of these results, the optimal scaffold size for receptor binding is believed to be compounds containing [6,7]- to [6,9]-fused rings.

Second, compounds with potent binding affinity were evaluated for inhibition of HIV-1 Env-mediated membrane fusion. The membrane fusion assay was carried out using R5 HIV-1 (JR-FL strain) Env-expressing COS-7 cells and MOLT-4/CCR5 cells. The results are summarized in Table 1 as IC_{50} values. The 1-benzazocine compounds (***S***)-(−)-**5a**−**d** showed potent inhibitory activity. In particular, compounds (***S***)-(−)-**5a**,**b**,**d** exhibited higher potency than the 1-benzazepine compound **4** and quaternary ammonium compound **1** in the fusion assay, while maintaining a similar level of potency in the binding assay. The 1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-1-benzazocine (***S***)-(−)-**5e** possessed the same level of high activity as the corresponding 1-isobutyl compound (***S***)-(−)-**5b**. Enlarging the ring size from a [6,8]-ring ((***S***)-(−)-**5b**) to a [6,9]-ring ((***S***)-(−)-**5g**) retained potent activity, although (***S***)-(−)-**5g** showed a

Table 1. Inhibitory Effects of Compounds **5** on Chemokine Binding to CCR5-Expressing CHO Cells and on HIV-1 Env-Mediated Membrane Fusion

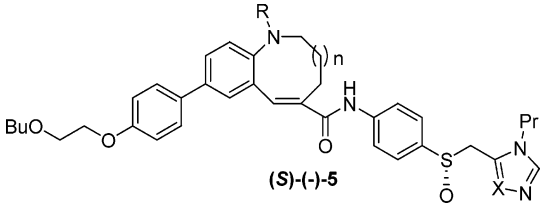


(*S*)-(-)-5

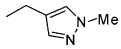
compd.	*n*	R	X	CCR5 IC_{50}[a] (nM)	fusion IC_{50}[b] (nM)	formula	anal.[c]
(***S***)-(−)-**5a**	1	Pr	CH	1.7	0.24	$C_{40}H_{50}N_4O_4S\cdot0.25H_2O$	CHN
(***S***)-(−)-**5b**	1	*i*-Bu	CH	3.1	0.10	$C_{41}H_{52}N_4O_4S\cdot CH_3SO_3H$	CHN
(***S***)-(−)-**5c**	1	Pr	N	2.2	0.95	$C_{39}H_{49}N_5O_4S\cdot H_2O$	CHN
(***S***)-(−)-**5d**	1	*i*-Bu	N	2.4	0.19	$C_{40}H_{51}N_5O_4S\cdot0.5H_2O$	CHN
(***S***)-(−)-**5e**	1		CH	1.7	0.21	$C_{42}H_{50}N_6O_4S\cdot0.5H_2O$	CHN
(***S***)-(−)-**5f**	2	Pr	CH	4.7		$C_{41}H_{52}N_4O_4S$	CHN
(***S***)-(−)-**5g**	2	*i*-Bu	CH	6.8	0.48	$C_{42}H_{54}N_4O_4S\cdot0.25H_2O$	CHN
(***S***)-(−)-**5h**	3	Pr	CH	25		$C_{42}H_{54}N_4O_4S\cdot0.25H_2O$	CHN
(***S***)-(−)-**5i**	3	*i*-Bu	CH	67		$C_{43}H_{56}N_4O_4S\cdot0.25H_2O$	CHN
1				1.4	1.4		
4	0	*i*-Bu	CH	1.9	1.0		

[a] The concentration required to inhibit the binding of [^{125}I]-RANTES to CCR5-expressing CHO cells by 50%. Data for new compounds were compared to positive control compound **4** (IC_{50} for **4**: 1.4−2.6 nM, a result of four experiments). [b] The concentration required to inhibit the membrane fusion between HIV-1 Env-expressing COS-7 cells and MOLT-4/CCR5 cells by 50%. Data represent mean IC_{50} values from triplicate measurements. [c] All compounds gave satisfactory elemental analysis (±0.4%) for C, H, and N.

Table 2. Anti-HIV-1 Activity of Compounds **4** and **5** in MOLT4/CCR5 Cells



(*S*)-(-)-5

compd.	*n*	R	X	CCR5 IC_{50}[a] (nM)	fusion IC_{50}[b] (nM)	Anti-HIV IC_{50}[c] (nM)	IC_{90}[c] (nM)
(***S***)-(−)-**5a**	1	Pr	CH	1.7	0.24	1.4	72%[d]
(***S***)-(−)-**5b**	1	*i*-Bu	CH	3.1	0.10	0.20	0.81
(***S***)-(−)-**5d**	1	*i*-Bu	N	2.4	0.19	<1.6	10
(***S***)-(−)-**5e**	1		CH	1.7	0.21	2.3	11
(***S***)-(−)-**5g**	2	*i*-Bu	CH	6.8	0.48	2.1	19
4	0	*i*-Bu	CH	1.9	1.0	5.3	860

[a] [b]See corresponding footnotes in Table 1. [c] The concentration required to inhibit the replication of R5 HIV-1 (Ba-L) in MOLT-4/CCR5 cells by 50 or 90%. IC_{50} or IC_{90} values shown are the means of duplicate measurements. [d] Percent inhibition at 5 nM.

slightly lower IC_{50} value of 0.48 nM. The previously mentioned results suggested that the [6,8]-fused 1-benzazocine ring was the optimal nucleus for obtaining potent fusion inhibition. In general, compounds (***S***)-(−)-**5a**,**b**,**d**,**e**,**g** show greater potency in the fusion assay than in the binding assay. It has been reported that the binding site for β-chemokines on CCR5 does not completely overlap with that for either recombinant gp120 or virions.[32] While we do not yet have detailed structural information on the binding sites for these compounds, it appears likely that they may be binding in a region that provides more efficient inhibition of gp120 binding than of chemokine binding. This would lead to the differences in potency observed for (***S***)-(−)-**5a**,**b**,**d**,**e**,**g** in the fusion and binding assays.

In addition, compounds (***S***)-(−)-**5a**,**b**,**d**,**e**,**g** with high potency in the inhibition of HIV-1 Env-mediated membrane fusion were investigated for their inhibitory effects on R5 HIV-1 (Ba-L strain) replication in MOLT-4/CCR5 cells. The results are illustrated in Table 2. The 1-isobutyl-1-benzazocine compound (***S***)-(−)-**5b** containing the imidazol-5-yl moiety strongly inhibited R5 HIV-1 replication with IC_{50} and IC_{90} values of 0.20 and 0.81 nM, respectively, and its activity was significantly more potent than 1-benzazepine compound **4**. IC_{50} values for the corresponding 1-propyl ((***S***)-(−)-**5a**) and 1-[(1-methyl-1*H*-pyrazol-4-yl)methyl] ((***S***)-(−)-**5e**) compounds were 1.4 and 2.3 nM, respectively, and these compounds were found to be less active than the 1-isobutyl derivative (***S***)-(−)-**5b**. The [6,9]-fused 1-isobutyl-1-benzazonine compound (***S***)-(−)-**5g** with an imidazole moiety was also less active than the 1-isobutyl-1-benzazocine (***S***)-(−)-**5b**. Triazole compound (***S***)-(−)-**5d** exhibited potent inhibition with an IC_{50} value of <1.6 nM, but its IC_{90} value (IC_{90} = 10 nM) was larger than that of the corresponding imidazole compound (***S***)-(−)-**5b**. These results suggested that the 1-benzazocine ring is optimal and that both the 1-isobutyl group and the 1-propyl-1*H*-imidazol-5-yl group are essential for highly potent anti-HIV-1 activity in the multiround infection assay. From these results, we selected compound (***S***)-(−)-**5b** as a candidate for further biological evaluation.

Table 3. Inhibitory Effects of **(*S*)-(−)-5b** on Replication of HIV-1

HIV-1 strain	IC_{50}[a] (nM)	IC_{90}[a] (nM)
KK	0.043	0.19
CTV	0.070	0.31
HKW	0.049	0.16
HNK	0.087	0.36
HTN	0.089	0.32
HHA	0.024	0.13
mean	0.061	0.25

[a] The concentration required to inhibit the viral replication in PBMCs by 50 or 90%. Assays were performed in triplicate and repeated 3 or 4 times using PBMCs obtained from different donors. Data represent mean values.

Further biological evaluation of compound (***S***)-(−)-**5b** is summarized in Table 3. Compound (***S***)-(−)-**5b** was found to greatly inhibit the replication of six R5 HIV-1 clinical isolates (KK, CTV, HKW, HNK, HTN, HHA) in human peripheral

Table 4. Inhibitory Effects of (*S*)-(−)-**5b** on Ligand Binding to Chemokine Receptors

	IC_{50}[a] (nM)					
	CCR5[b]	CCR1[b]	CCR2b[b]	CCR3[b]	CCR4[b]	CCR7[b]
(*S*)-(−)-**5b**	3.1	>10000	5.9	2400	1100	>10000

[a] The concentration required to inhibit the ligand binding to chemokine receptor by 50%. [b] Inhibitory effects on the binding of [^{125}I]-RANTES, [^{125}I]-RANTES, [^{125}I]-MCP-1, [^{125}I]-eotaxin, [^{125}I]-TARC, or [^{125}I]-MIP-3β to CCR5-, CCR1-, CCR2b-, CCR3-, CCR4-, or CCR7-expressing CHO cells, respectively. Data represent the mean IC_{50} values from triplicate measurements.

blood mononuclear cells (PBMCs), and its activity appeared to be greater than that of compound **1**. The mean IC_{50} and IC_{90} values were 0.061 and 0.25 nM, respectively.[33] Compound (*S*)-(−)-**5b** did not affect the viability and proliferation of uninfected PBMCs at concentrations up to 10 000 nM[33] and thus is thought to possess low cytotoxicity. To evaluate the biological activity of compound (*S*)-(−)-**5b** against other chemokine receptors, binding inhibition was measured in CHO cells stably expressing the chemokine receptors CCR1, CCR2b, CCR3, CCR4, and CCR7 (in a manner similar to that for the examination of CCR5 inhibition).[33] The results are shown in Table 4. The IC_{50} values of compound (*S*)-(−)-**5b** for CCR1 and CCR7 were over 10 μM. Compound (*S*)-(−)-**5b** modestly inhibited the binding of [^{125}I]-eotaxin to CCR3 and [^{125}I]-thymus and activation-regulated chemokine (TARC) to CCR4 with IC_{50} values of 2400 and 1100 nM, respectively, and these IC_{50} values were over 350 times greater than that for CCR5. Thus, compound (*S*)-(−)-**5b** exhibited high selectivity for CCR5 over CCR1, CCR3, CCR4, and CCR7. However, the IC_{50} value of compound (*S*)-(−)-**5b** for CCR2b was 5.9 nM, which is comparable to that for CCR5. We next confirmed that (*S*)-(−)-**5b** abrogated RANTES-induced Ca^{2+} mobilization in CCR5-expressing HeLa cells.[33] On the other hand, (*S*)-(−)-**5b** did not affect RANTES-induced Ca^{2+} mobilization in CCR1-expressing HeLa cells.[33] These results indicate that (*S*)-(−)-**5b** interacts with CCR5 but not with RANTES and is thus an antagonist for CCR5. Furthermore, we performed studies with anti-CCR5 monoclonal antibodies (MAbs) in an attempt to determine the binding site of (*S*)-(−)-**5b**. It was found that (*S*)-(−)-**5b** did not affect the binding of the anti-CCR5 MAbs 45531.111 and 2D7, which recognize different regions of the second extracellular loop (ECL2) of CCR5, nor did it affect the binding of 3A9, which is specific to the N-terminus of CCR5.[33] In addition, unlike RANTES, (*S*)-(−)-**5b** did not induce CCR5 internalization. It is possible that (*S*)-(−)-**5b** could induce a conformational change in the gp120 binding site upon binding to a domain of CCR5 other than ECL2 or the N terminus, leading to inhibition of the HIV-1 gp 120 and CCR5 interaction.

Finally, we investigated the pharmacokinetic profile of compound (*S*)-(−)-**5b** in animals. The [^{14}C]-labeled analogue of compound (*S*)-(−)-**5b**[34] was intravenously administered at 1 mg/kg and orally administered at 3 mg/kg to SD (IGS) rats, beagle dogs, and cynomolgus monkeys; the results are indicated in Table 5. The C_{max} values for (*S*)-(−)-**5b** after oral administration in rats, dogs, and monkeys were 0.485, 0.570, and 0.116 μg/mL, and the AUC_{0-24h} values were 2.32, 6.01, and 0.67 μg h/mL, respectively. The oral bioavailabilities were 10.2, 88.5, and 15.6% in rats, dogs, and monkeys, respectively.

Conclusion

We performed the chemical modification of orally bioavailable 1-benzazepine compound **4** containing the *S*-sulfoxide moiety. Ring-expansion of the [6,7]-fused ring to [6,8]-, [6,9]-, or [6,10]-fused rings led to the discovery that the [6,8]-fused 1-benzazocine and [6,9]-fused 1-benzazonine compounds exhibited potent RANTES binding inhibition, equivalent to the [6,7]-fused 1-benzazepine **4**, while providing superior potency for the [6,8]-fused 1-benzazocine compounds in an HIV-1 Env-mediated membrane fusion assay. Furthermore, the 1-isobutyl-1-benzazocine (*S*)-(−)-**5b** containing the *S*-[(1-propyl-1*H*-imidazol-5yl)methyl]sulfinyl group was found to exhibit the most potent inhibition of R5 HIV-1 replication in MOLT4/CCR5 cells. Compound (*S*)-(−)-**5b** also greatly inhibited replication of six R5 HIV-1 clinical isolates in PBMCs, and its mean IC_{90} value was found to be 0.25 nM. In addition, compound (*S*)-(−)-**5b** was absorbed after oral administration in rats, dogs, and monkeys despite its relatively high molecular weight. From these results, compound (*S*)-(−)-**5b** (TAK-652) is thought to be a promising anti-HIV-1 agent and was selected as a clinical candidate for development.

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer or Varian Mercury-300 (300 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J* values) are given in Hertz (Hz). Optical resolutions were recorded with a Jasco DIP-370 or P-1030 digital polarimeter. Elemental analyses were carried out by Takeda Analytical Research Laboratories, Ltd., and results obtained were within ±0.4% of the theoretical values. Column chromatography was carried out on a silica gel column (Kieselgel 60, 63−200 mesh, Merck or Chromatorex NH-DM1020, 100−200 mesh, Fuji Silysia Chemical). Yields were not optimized.

1-(4-Methoxybenzyl)piperidin-2-on (7). A mixture of 85% KOH (18.6 g, 282 mmol) and tetrabutylammonium bromide (4.88 g, 15.1 mmol) in toluene (250 mL) was refluxed using a Dean−Stark apparatus overnight under a nitrogen atmosphere. To the mixture was added a solution of **6** (25.0 g, 252 mmol) and 4-methoxybenzyl chloride (51.3 g, 328 mmol) in toluene (50 mL) at 80 °C. After being refluxed for 8 h, the mixture was cooled to room temperature. The mixture was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=1:1) to give 28.8 g (52%) of **7** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70−1.85 (4H, m), 2.40−2.50 (2H, m), 3.15−3.25 (2H, m), 3.80 (3H, s), 4.53 (2H, s), 6.85 (2H, d, J = 8.8 Hz), 7.19 (2H, d, J = 8.8 Hz).

5-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]pentanoic Acid (10a). A mixture of **7** (50.0 g, 228 mmol) and 4 N NaOH (228 mL) was refluxed for 24 h. The mixture was neutralized using concentrated HCl under ice cooling. To the mixture was added Na_2CO_3 (53.8 g, 508 mmol) and DMSO (600 mL) at room temperature. Then 5-bromo-2-fluorobenzaldehyde (38.6 g, 190 mmol) was added dropwise to the mixture at 135 °C. After being refluxed for 5 h, the mixture was neutralized using 3 N HCl under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give 77.2 g (97%) of **10a** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.65 (4H, m), 2.25−2.33 (2H, m), 3.00−3.10 (2H, m), 3.78 (3H, s), 4.21 (2H, s), 6.79 (2H, d, J = 8.7 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz), 7.53 (1H, dd, J = 8.7, 2.4 Hz), 7.89 (1H, d, J = 2.4 Hz), 10.30 (1H, s).

6-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]hexanoic Acid (10b). A mixture of **9a** (20.0 g, 152 mmol), 4-methoxybenzaldehyde (20.8 g, 153 mmol), and 10% Pd−C (50% wet, 4.15 g) in 1 N NaOH (152.5 mL) and MeOH (240 mL) was stirred at room temperature for 24 h under a hydrogen atmosphere. Pd−C was removed by filtration. The filtrate was neutralized using 6 N

Table 5. Pharmacokinetic Parameters of Compound **(*S*)-(−)-5b**

	IV (1 mg/kg)			PO (3 mg/kg)			
	C_{5min} (μg/mL)[a]	AUC_{0-24h} (μg·h/mL)[b]	$T_{1/2}\beta$ (h)[c]	C_{max} (μg/mL)[d]	T_{max} (h)[e]	AUC_{0-24h} (μg·h/mL)[b]	BA(%)[f]
rat	8.019	7.61	4.85	0.485	1.3	2.32	10.2
dog	2.315	2.31	5.04	0.570	2.7	6.01	88.5
monkey	3.114	1.45	6.09	0.116	2.0	0.67	15.6

[a] Plasma concentration at 5 min after dosing. [b] Area under the plasma concentration−time curve for 0−24 h after dosing. [c] Half-life of compound **(*S*)-(−)-5b** in the plasma. [d] Maximum plasma concentration after oral dosing. [e] Time to reach C_{max}. [f] Bioavailability.

HCl under ice cooling and concentrated in vacuo. To a mixture of the residue and Na_2CO_3 (40.4 g, 381 mmol) in DMSO (170 mL) and water (114 mL) was added dropwise a solution of 5-bromo-2-fluorobenzaldehyde (25.8 g, 127 mmol) in DMSO (52 mL) at 135 °C. After being stirred at 135 °C overnight, the mixture was neutralized using 6 N HCl under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 2:1 → 1:1) to give 32.5 g (49%) of **10b** as a brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.70 (6H, m), 2.30 (2H, t, J = 7.4 Hz), 3.06 (2H, t, J = 7.4 Hz), 3.78 (3H, s), 4.22 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.54 (1H, dd, J = 8.8, 2.6 Hz), 7.90 (1H, d, J = 2.6 Hz), 10.31 (1H, s).

7-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]heptanoic Acid (10c). This compound was prepared in 72% yield from **9b**, 4-methoxybenzaldehyde, and 5-bromo-2-fluorobenzaldehyde by a method similar to that described for **10b**, brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−1.65 (8H, m), 2.31 (2H, t, J = 7.8 Hz), 3.05 (2H, t, J = 7.4 Hz), 3.78 (3H, s), 4.22 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.8 Hz), 7.54 (1H, dd, J = 8.8, 2.2 Hz), 7.89 (1H, d, J = 2.2 Hz), 10.30 (1H, s).

Methyl 5-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]pentanoate (11a). To a mixture of **10a** (77.2 g, 184 mmol), K_2CO_3 (30.5 g, 221 mmol) in *N*,*N*-dimethylformamide (DMF) (500 mL) was added a solution of iodomethane (36.5 g, 257 mmol) in DMF (100 mL) under ice cooling. After being stirred at room temperature for 2 h under a nitrogen atmosphere, water was added to the mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 9:1 → 4:1) to give 45.7 g (57%) of **11a** as a brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50−1.65 (4H, m), 2.20−2.30 (2H, m), 3.05−3.15 (2H, m), 3.64 (3H, s), 3.78 (3H, s), 4.22 (2H, s), 6.80 (2H, d, J = 8.6 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.6 Hz), 7.54 (1H, dd, J = 8.4, 2.6 Hz), 7.90 (1H, d, J = 2.6 Hz), 10.32 (1H, s).

The following compounds (**11b**,**c**) were prepared from the carboxylic acids **10b**,**c** and iodomethane by a method similar to that described for **11a**.

Methyl 6-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]hexanoate (11b). Yield 92%, brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.35 (2H, m), 1.40−1.65 (4H, m), 2.25 (2H, t, J = 7.4 Hz), 3.06 (2H, t, J = 7.8 Hz), 3.65 (3H, s), 3.78 (3H, s), 4.22 (2H, s), 6.81 (2H, d, J = 8.4 Hz), 6.97 (1H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.54 (1H, dd, J = 8.8, 2.6 Hz), 7.90 (1H, d, J = 2.6 Hz), 10.31 (1H, s).

Methyl 7-[(4-Bromo-2-formylphenyl)(4-methoxybenzyl)amino]heptanoate (11c). Yield 96%, brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.35 (4H, m), 1.40−1.65 (4H, m), 2.26 (2H, t, J = 7.6 Hz), 3.05 (2H, t, J = 7.2 Hz), 3.65 (3H, s), 3.78 (3H, s), 4.22 (2H, s), 6.81 (2H, d, J = 8.4 Hz), 6.97 (1H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.53 (1H, dd, J = 8.8, 2.4 Hz), 7.89 (1H, d, J = 2.4 Hz), 10.30 (1H, s).

Methyl 8-Bromo-1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (12a). To a solution of **11a** (45.7 g, 105 mmol) in dimethyl carbonate (900 mL) was added a solution of NaOMe in MeOH (28%, 26.4 g, 137 mmol) at room temperature. After being stirred at 50 °C for 6 h, water was added to the mixture under ice cooling. The mixture was neutralized using 1 N HCl under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow solid. Recrystallization from EtOAc−hexane gave 32.2 g (74%) of **12a** as yellow crystals, mp 130.5−132 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40−1.50 (2H, m), 2.57 (2H, t, J = 4.0 Hz), 3.47 (2H, t, J = 3.8 Hz), 3.80 (3H, s), 3.81 (3H, s), 4.39 (2H, s), 6.54 (1H, d, J = 6.0 Hz), 6.88 (2H, d, J = 7.8 Hz), 7.07−7.13 (3H, m), 7.26 (1H, d, J = 1.6 Hz), 7.74 (1H, s). Anal. ($C_{21}H_{22}BrNO_3$) C, H, N.

The following compounds (**12b**,**c**) were prepared from **11b**,**c** by a method similar to that described for **12a**.

Methyl 9-Bromo-1-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (12b). Yield 45%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.68 (2H, m), 1.70−1.85 (2H, m), 2.25 (2H, t, J = 6.3 Hz), 3.16 (2H, t, J = 6.3 Hz), 3.80 (3H, s), 3.85 (3H, s), 4.14 (2H, s), 6.83 (2H, d, J = 8.1 Hz), 6.91 (1H, d, J = 7.8 Hz), 7.06 (2H, d, J = 8.1 Hz), 7.24−7.27 (2H, m), 7.58 (1H, s).

Methyl 10-Bromo-1-(4-methoxybenzyl)-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (12c). Yield 26%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.35 (2H, m), 1.40−1.65 (4H, m), 2.11 (2H, t, J = 6.4 Hz), 2.87 (2H, t, J = 6.2 Hz), 3.78 (3H, s), 3.82 (2H, s), 3.84 (3H, s), 6.77 (2H, d, J = 8.8 Hz), 6.98−7.02 (3H, m), 7.17 (1H, d, J = 2.2 Hz), 7.36 (1H, dd, J = 8.8, 2.2 Hz), 7.45 (1H, s).

Methyl 8-Bromo-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (13a). To a solution of **12a** (10.0 g, 24.0 mmol) in toluene (50 mL) was added TFA (50 mL) at room temperature. After being stirred at 65 °C for 2 h, the mixture was concentrated in vacuo, and water was added to the residue under ice cooling. The mixture was neutralized using K_2CO_3 and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 9:1) to give 6.59 g (93%) of **13a** as yellow crystals. Compound **13a** was used in the next reaction without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38−1.50 (2H, m), 2.72 (2H, t, J = 6.2 Hz), 3.43−3.53 (2H, m), 3.78 (3H, s), 3.90 (1H, br s), 6.34 (1H, d, J = 8.4 Hz), 7.06−7.11 (2H, m), 7.63 (1H, s).

The follwing compounds (**13b**,**c**) were prepared from **12b**,**c** by a method similar to that described for **13a**.

Methyl 9-Bromo-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (13b). Yield 82%, yellow crystals. Compound **13b** was used in the next reaction without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60−1.80 (4H, m), 2.15−2.25 (2H, m), 3.15−3.30 (2H, m), 3.65−3.80 (1H, m), 3.83 (3H, s), 6.88 (1H, d, J = 8.8 Hz), 7.10 (1H, d, J = 2.2 Hz), 7.28 (1H, dd, J = 8.8, 2.2 Hz), 7.54 (1H, s).

Methyl 10-Bromo-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (13c). Yield 99%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45−1.85 (6H, m), 2.10−2.25 (2H, m), 3.25−3.40 (2H, m), 3.68 (1H, br s), 3.82 (3H, s), 6.76 (1H, d, J = 8.8 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 8.8, 2.0 Hz), 7.46 (1H, s).

Methyl 8-Bromo-1-propyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (14a). To a solution of **13a** (500 mg, 1.72 mmol) and propionaldehyde (490 mg, 8.44 mmol) in 1,2-dichloroethane (20 mL) was added sodium triacetoxyborohydride ($NaBH(OAc)_3$) (1.08 g, 5.10 mmol) at room temperature. The mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic

layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=9:1) to give 531 mg (91%) of **14a** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.6 Hz), 1.30−1.50 (2H, m), 1.55−1.80 (2H, m), 2.51 (2H, t, J = 6.2 Hz), 3.00−3.20 (2H, m), 3.42 (2H, t, J = 6.2 Hz), 3.78 (3H, s), 6.56 (1H, d, J = 9.6 Hz), 7.15−7.21 (2H, m), 7.68 (1H, s).

The following compounds (**14b**−**f**) were prepared from **13a**−**c** and the appropriate aldehydes by a method similar to that described for **14a**.

Methyl 8-Bromo-1-isobutyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (14b). Yield quant., yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (6H, d, J = 6.6 Hz), 1.35−1.50 (2H, m), 2.00−2.20 (1H, m), 2.49 (2H, t, J = 6.2 Hz), 2.99 (2H, d, J = 7.2 Hz), 3.42 (2H, t, J = 6.0 Hz), 3.79 (3H, s), 6.62 (1H, d, J = 9.2 Hz), 7.16−7.22 (2H, m), 7.69 (1H, s).

Methyl 9-Bromo-1-propyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (14c). Yield 95%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.40−1.90 (6H, m), 2.25 (2H, t, J = 6.6 Hz), 2.95 (2H, t, J = 8.0 Hz), 3.13 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 6.88 (1H, d, J = 8.8 Hz), 7.23−7.32 (2H, m), 7.60 (1H, s).

Methyl 9-Bromo-1-isobutyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (14d). Yield 91%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (6H, d, J = 6.6 Hz), 1.50−1.75 (5H, m), 2.19 (2H, t, J = 5.7 Hz), 2.64 (2H, d, J = 7.2 Hz), 3.06 (2H, t, J = 5.7 Hz), 3.81 (3H, s), 7.05 (1H, d, J = 8.4 Hz), 7.21 (1H, d, J = 2.1 Hz), 7.34 (1H, dd, J = 8.4, 2.1 Hz), 7.57 (1H, s).

Methyl 10-Bromo-1-propyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (14e). Yield 86%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78 (3H, t, J = 7.2 Hz), 1.20−1.65 (8H, m), 2.09 (2H, t, J = 6.4 Hz), 2.69−2.76 (2H, m), 2.97 (2H, t, J = 4.8 Hz), 3.80 (3H, s), 7.08 (1H, d, J = 8.4 Hz), 7.17 (1H, d, J = 2.2 Hz), 7.38 (1H, dd, J = 8.4, 2.2 Hz), 7.55 (1H, s).

Methyl 10-Bromo-1-isobutyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (14f). Yield 94%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (6H, d, J = 6.6 Hz), 1.10−1.75 (7H, m), 2.12 (2H, t, J = 6.2 Hz), 2.60 (2H, d, J = 7.0 Hz), 2.93 (2H, t, J = 5.6 Hz), 3.79 (3H, s), 7.09−7.14 (2H, m), 7.38 (1H, dd, J = 8.8, 2.4 Hz), 7.60 (1H, s).

Methyl 8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (15a). A mixture of **14a** (700 mg, 2.07 mmol), 4-[2-(butoxy)ethoxy]phenylboronic acid[27] (640 mg, 2.69 mmol), and K_2CO_3 (744 mg, 5.38 mmol) in toluene (15 mL), EtOH (1.5 mL), and water (1.5 mL) was stirred at room temperature for 0.5 h under an argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (120 mg, 0.104 mmol), and the mixture was stirred at 100 °C for 3 h under an argon atmosphere. Water was added to the mixture, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=10:1) to give 294 mg (31%) of **15a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91−1.00 (6H, m), 1.30−1.50 (4H, m), 1.55−1.75 (4H, m), 2.56 (2H, t, J = 6.0 Hz), 3.18 (2H, t, J = 7.8 Hz), 3.47 (2H, t, J = 6.0 Hz), 3.55 (2H, t, J = 6.9 Hz), 3.78−3.81 (5H, m), 4.14 (2H, t, J = 5.1 Hz), 6.76 (1H, d, J = 8.7 Hz), 6.95 (2H, d, J = 9.0 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.38 (1H, dd, J = 8.7, 2.4 Hz), 7.43 (2H, d, J = 9.0 Hz), 7.87 (1H, s).

The following compounds (**15b**−**f**) were prepared from **14b**−**f** by a method similar to that described for **15a**.

Methyl 8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (15b). Yield 82%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−1.01 (9H, m), 1.30−1.70 (6H, m), 2.05−2.25 (1H, m), 2.50−2.60 (2H, m), 3.06 (2H, d, J = 7.4 Hz), 3.40−3.60 (4H, m), 3.77−3.82 (5H, m), 4.14 (2H, t, J = 5.2 Hz), 6.80 (1H, d, J = 8.4 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.32−7.46 (4H, m), 7.88 (1H, s).

Methyl 9-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (15c). Yield 79%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−0.97 (6H, m), 1.30−1.95 (10H, m), 2.33 (2H, t, J = 6.2 Hz), 3.00−3.08 (2H, m), 3.21 (2H, t, J = 6.2 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.77−3.83 (5H, m), 4.15 (2H, t, J = 5.0 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.03 (1H, d, J = 8.4 Hz), 7.32 (1H, d, J = 2.2 Hz), 7.39−7.48 (3H, m), 7.77 (1H, s).

Methyl 9-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylate (15d). Yield 98%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86−0.97 (9H, m), 1.30−1.80 (9H, m), 2.20−2.30 (2H, m), 2.73 (2H, d, J = 7.4 Hz), 3.09−3.15 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78−3.82 (5H, m), 4.16 (2H, t, J = 4.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.6 Hz), 7.26−7.29 (1H, m), 7.42−7.50 (3H, m), 7.72 (1H, s).

Methyl 10-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (15e). Yield 91%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.4 Hz), 0.93 (3H, t, J = 7.2 Hz), 1.20−1.67 (12H, m), 2.10−2.20 (2H, m), 2.74−2.82 (2H, m), 2.95−3.05 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78−3.83 (5H, m), 4.16 (2H, t, J = 4.6 Hz), 6.97 (2H, d, J = 9.2 Hz), 7.22−7.26 (2H, m), 7.45−7.51 (3H, m), 7.71 (1H, s).

Methyl 10-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylate (15f). Yield 90%, yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84−0.97 (9H, m), 1.15−1.80 (11H, m), 2.10−2.25 (2H, m), 2.65 (2H, d, J = 7.0 Hz), 2.90−3.05 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78−3.83 (5H, m), 4.16 (2H, t, J = 4.6 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 1.8 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.45−7.51 (3H, m), 7.76 (1H, s).

8-[4-{2-(Butoxy)ethoxy}phenyl]-1-propyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylic Acid (16a). To a solution of **15a** (294 mg, 0.65 mmol) in THF (21 mL) and MeOH (21 mL) was added 1 N NaOH (7.0 mL) at room temperature. The mixture was stirred at 70 °C for 2 h. To the mixture was added water, and then it was neutralized using 1 N HCl under ice cooling. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow solid. Recrystallization from EtOAc−hexane gave 200 mg (70%) of **16a** as yellow crystals, mp 173−174 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−1.02 (6H, m), 1.30−1.80 (8H, m), 2.50−2.63 (2H, m), 3.11−3.27 (2H, m), 3.45−3.58 (4H, m), 3.80 (2H, t, J = 4.8 Hz), 4.15 (2H, t, J = 4.6 Hz), 6.77 (1H, d, J = 9.0 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.32−7.46 (4H, m), 7.99 (1H, s). Anal. ($C_{27}H_{35}NO_4$) C, H, N.

The following compounds (**16b**−**f**) were prepared from **15b**−**f** by a method similar to that described for **16a**.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylic Acid (16b). Yield 20%, yellow crystals (EtOAc−hexane), mp 121−122 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−1.01 (9H, m), 1.30−1.68 (6H, m), 2.10−2.20 (1H, m), 2.50−2.65 (2H, m), 3.07 (2H, d, J = 7.2 Hz), 3.45−3.58 (4H, m), 3.80 (2H, t, J = 4.8 Hz), 4.15 (2H, t, J = 4.8 Hz), 6.82 (1H, d, J = 8.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.33−7.46 (4H, m), 8.01 (1H, s). Anal. ($C_{28}H_{37}NO_4$) C, H, N.

9-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylic Acid (16c). Yield 52%, yellow crystals (EtOAc−hexane), mp 111−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91−0.97 (6H, m), 1.33−1.93 (10H, m), 2.36 (2H, t, J = 6.3 Hz), 3.05−3.10 (2H, m), 3.24 (2H, t, J = 6.3 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.1 Hz), 4.16 (2H, t, J = 5.1 Hz), 6.97 (2H, d, J = 8.7 Hz), 7.04 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 2.1 Hz), 7.42−7.49 (3H, m), 7.92 (1H, s). Anal. ($C_{28}H_{37}NO_4$) C, H, N.

9-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxylic Acid (16d). Yield 97%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86−0.96 (9H, m), 1.30−1.85 (9H, m), 2.25−2.35 (2H, m), 2.75 (2H, d, J = 7.2 Hz), 3.14 (2H, t, J = 5.7 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.20 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.45−7.50 (3H, m), 7.86 (1H, s).

10-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylic Acid (16e). Yield quant., yellow

oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.4 Hz), 0.93 (3H, t, J = 6.8 Hz), 1.23−1.80 (12H, m), 2.10−2.22 (2H, m), 2.75−2.83 (2H, m), 3.00−3.10 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.24−7.28 (2H, m), 7.46−7.51 (3H, m), 7.84 (1H, s).

10-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxylic Acid (16f). Yield 97%, yellow crystals (EtOAc−hexane), mp 111−113 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85−0.97 (9H, m), 1.20−1.80 (11H, m), 2.15−2.27 (2H, m), 2.67 (2H, d, J = 7.0 Hz), 2.90−3.05 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.20 (1H, d, J = 2.2 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.47−7.51 (3H, m), 7.91 (1H, s). Anal. ($C_{30}H_{41}NO_4$) C, H, N.

Methyl 8-{4-[2-(Butoxy)ethoxy]phenyl}-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylate (17). This compound was prepared in 39% yield from **13a** and 4-[2-(butoxy)ethoxy]phenyl)boronic acid by a method similar to that described for **15a**, yellow crystals (EtOAc−hexane), mp 106−107 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.30−1.70 (6H, m), 2.77 (2H, t, J = 6.2 Hz), 3.51−3.58 (4H, m), 3.77−3.82 (5H, m), 3.93 (1H, br s), 4.14 (2H, t, J = 4.2 Hz), 6.52 (1H, d, J = 8.0 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.21−7.29 (2H, m), 7.41 (2H, d, J = 8.8 Hz), 7.81 (1H, s). Anal. ($C_{25}H_{31}NO_4$) C, H, N.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-1,2,3,4-tetrahydro-1-benzazocine-5-carboxylic Acid (16g). To a solution of **17** (500 mg, 1.22 mmol), 1-methyl-1*H*-pyrazole-4-carbaldehyde (672 mg, 6.10 mmol), and acetic acid (0.35 mL, 6.11 mmol) in 1,2-dichloroethane (20 mL) was added $NaBH(OAc)_3$ (776 mg, 3.66 mmol) at room temperature. The mixture was stirred at room temperature overnight. Water was added to the mixture, and it was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 1:1 → 1:3) to give **15g** as a yellow oil. To a solution of **15g** in THF (36 mL) and MeOH (36 mL) was added 1 N NaOH (12 mL) at room temperature. The mixture was stirred at room temperature overnight. Water was added to the mixture. It was then neutralized using 1 N HCl under ice cooling and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 495 mg (83%) of **16g** as yellow crystals, mp 162−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 1.24−1.70 (6H, m), 2.55−2.65 (2H, m), 3.50−3.60 (4H, m), 3.80 (2H, t, J = 4.8 Hz), 3.87 (3H, s), 4.14 (2H, t, J = 4.8 Hz), 4.34 (2H, s), 6.87 (1H, d, J = 9.9 Hz), 6.95 (2H, d, J = 9.3 Hz), 7.24 (1H, s), 7.35−7.44 (5H, m), 7.98 (1H, s). Anal. ($C_{29}H_{35}N_3O_4$) C, H, N.

(*S*)-(−)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*S*)-(−)-5a). The 1 N HCl (160 mL) was added to **19**[31] (35.68 g, 53.4 mmol), and the mixture was extracted with EtOAc. To the aqueous layer was added 25% aqueous K_2CO_3 (160 mL), and the mixture was extracted with a mixture of EtOAc and *i*-PrOH (4:1). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give (***S*)-18**. To a solution of **16a** (18.0 g, 41.1 mmol) and DMF (0.5 mL) in THF (180 mL) was added thionyl chloride ($SOCl_2$) (4.50 mL, 61.7 mmol) at room temperature. After being stirred at room temperature for 1.5 h, the reaction mixture was concentrated in vacuo. A solution of the residue in THF (200 mL) was added dropwise to a mixture of (***S*)-18** and triethylamine (Et_3N) (35.0 mL, 251 mmol) in THF (150 mL) under ice cooling. After being stirred at room temperature for 4 h, water was added to the reaction mixture. The mixture was washed with 10% aqueous AcOH, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on a NH silica gel (hexane/EtOAc = 1:5 → 1:8 → 1:9) to give 21.14 g (75%) of (***S*)-(−)-5a** as a yellow amorphous powder, $[\alpha]_D$ = −132.5° (C = 0.507%, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87−1.03 (9H, m), 1.34−1.49 (2H, m), 1.50−1.85 (8H, m), 2.55−2.65 (2H, m), 3.15−3.25 (2H, m), 3.52−3.58 (4H, m), 3.75−3.83 (4H. m), 4.02 (1H, d, J = 13.8 Hz), 4.08−4.17 (3H, m), 6.56 (1H, d, J = 1.0 Hz), 6.80 (1H, d, J = 8.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.31−7.46 (7H, m), 7.55 (1H, s), 7.76 (2H, d, J = 8.8 Hz), 7.98 (1H, s). Anal. ($C_{40}H_{50}N_4O_4S\cdot0.25H_2O$) C, H, N.

(*S*)-(−)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide methanesulfonate ((*S*)-(−)-5b). The free base of (***S*)-(−)-5b** was prepared in 80% yield from **16b** and **19** by a method similar to that described for (***S*)-(−)-5a**. To a solution of the free base of (***S*)-(−)-5b** (64.91 g, 93.1 mmol) in EtOAc (600 mL) was added dropwise a solution of methanesulfonic acid (8.95 g, 93.1 mmol) in EtOAc (160 mL) at room temperature. After being stirred at room temperature for 4 h, the crystals were collected by filtration and washed with EtOAc to give 69.09 g (94%) of (***S*)-(−)-5b** as yellow crystals. The crystals (68.0 g) were purified by recrystallization from 2-butanone to give 58.9 g (85%) of (***S*)-(−)-5b** as yellow crystals, mp 145.5−147.5 °C, $[\alpha]_D$ = −191.2° (c = 0.508%, EtOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82−0.97 (12H, m), 1.29−1.39 (2H, m), 1.40−1.55 (4H, m), 1.65−1.85 (2H, m), 2.00−2.25 (1H, m), 2.29 (3H,s), 2.38−2.60 (2H, m), 3.10 (2H, d, J = 7.8 Hz), 3.30−3.60 (4H, m), 3.70 (2H, t, J = 4.8 Hz), 3.98 (2H, t, J = 6.6 Hz), 4.10 (2H, t, J = 4.8 Hz), 4.34 (1H, d, J = 15.0 Hz), 4.68 (1H, d, J = 15.0 Hz), 6.87 (1H, d, J = 8.7 Hz), 6.99 (2H, d, J = 8.7 Hz), 7.16 (1H, s), 7.42−7.60 (8H, m), 7.93 (2H, d, J = 8.7 Hz), 9.05 (1H, s), 10.18 (1H, s). Anal. ($C_{42}H_{56}N_4O_7S_2$) C, H, N.

The following compound ((***S*)-(−)-5e−i**) were prepared from carboxylic acids **16c−g** and **19** by a method similar to that described for (***S*)-(−)-5a**.

(*S*)-(−)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]-sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*S*)-(−)-5e). Yield 19%, yellow amorphous powder. $[\alpha]_D$ = −123.2° (c = 0.451%, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−0.95 (6H, m), 1.35−1.43 (2H, m), 1.50−1.70 (6H, m), 2.60−2.65 (2H, m), 3.52−3.57 (4H, m), 3.76−3.81 (4H, m), 3.87 (3H, m), 4.01 (1H, d, J = 14.1 Hz), 4.04−4.16 (3H, m), 4.35 (2H, s), 6.54 (1H, s), 6.89 (1H, d, J = 8.7 Hz), 6.95 (2H, d, J = 8.7 Hz), 7.33−7.45 (9H, m), 7.55 (1H, s), 7.75 (2H, d, J = 8.7 Hz), 8.06 (1H, s). Anal. ($C_{42}H_{50}N_6O_4S\cdot0.5H_2O$) C, H, N.

(*S*)-(−)-9-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxamide ((*S*)-(−)-5f). Yield 39%, yellow amorphous powder. $[\alpha]_D$ = −93.7° (c = 0.460%, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88−0.98 (9H, m), 1.25−2.00 (12H, m), 2.38−2.50 (2H, m), 2.95−3.10 (2H, m), 3.15−3.25 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78−3.85 (4H, m), 4.03 (1H, d, J = 14.2 Hz), 4.09−4.18 (3H, m), 6.57 (1H, s), 6.98 (2H, d, J = 9.2 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.34−7.52 (8H, m), 7.76 (2H, d, J = 8.8 Hz), 7.84 (1H, s). Anal. ($C_{41}H_{52}N_4O_4S$) C, H, N.

(*S*)-(−)-9-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazonine-6-carboxamide ((*S*)-(−)-5g). Yield 35%, yellow amorphous powder. $[\alpha]_D$ = −121.0° (c = 0.486%, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−0.95 (12H, m), 1.26−1.85 (11H, m), 2.30−2.42 (2H, m), 2.74 (2H, d, J = 7.2 Hz), 3.05−3.18 (2H, m), 3.55 (2H, t, J = 7.6 Hz), 3.81−3.85 (4H, m), 4.00−4.18 (4H, m), 6.59 (1H, s), 6.99 (2H, d, J = 8.8 Hz), 7.30−7.51 (9H, m), 7.75 (2H, d, J = 8.4 Hz), 7.82 (1H, s). Anal. ($C_{42}H_{54}N_4O_4S\cdot0.25H_2O$) C, H, N.

(*S*)-(−)-10-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxamide ((*S*)-(−)-5h). Yield 22%, yellow amorphous powder. $[\alpha]_D$ = −125.0° (c = 0.488%, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85−0.97 (9H, m), 1.25−1.81 (14H, m), 2.25−2.40 (2H, m), 2.83 (2H, t, J = 7.0 Hz), 2.90−3.10 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.75−3.85 (4H, m), 4.03 (1H, d, J = 14.0 Hz), 4.08−4.19 (3H, m), 6.58 (1H, s), 6.99 (2H, d, J = 8.8 Hz), 7.27−7.55 (9H, m), 7.77 (2H, d, J = 8.8 Hz), 7.89 (1H, s). Anal. ($C_{42}H_{54}N_4O_4S\cdot0.25H_2O$) C, H, N.

(*S*)-(−)-10-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4,5,6-hexahydro-1-benzazecine-7-carboxamide ((*S*)-(−)-5i). Yield 18%, yellow amorphous powder. $[\alpha]_D = -125.3°$ ($c = 0.472\%$, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89−0.99 (12H, m), 1.25−1.85 (13H, m), 2.30−2.40 (2H, m), 2.69 (2H, d, $J = 7.0$ Hz), 2.90−3.00 (2H, m), 3.55 (2H, t, $J = 7.0$ Hz), 3.78−3.85 (4H, m), 4.03 (1H, d, $J = 14.2$ Hz), 4.08−4.19 (3H, m), 6.59 (1H, s), 6.99 (2H, d, $J = 8.8$ Hz), 7.24−7.60 (9H, m), 7.74 (2H, d, $J = 8.8$ Hz), 7.83 (1H, s). Anal. ($C_{43}H_{56}N_4O_4S\cdot 0.25H_2O$) C, H, N.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfanyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide (20a). To a solution of **16a** (0.80 g, 1.83 mmol) and DMF (cat. amount) in THF (10 mL) was added $SOCl_2$ (0.20 mL, 2.74 mmol) at room temperature. After being stirred at room temperature for 1.5 h, the mixture was concentrated in vacuo. A solution of the residue in THF (30 mL) was added to a solution of *S*-(4-aminophenyl)-*O*-benzylthiocarbonate[29] (0.47 g, 1.81 mmol) and Et_3N (1.50 mL, 10.8 mmol) in THF (15 mL) under ice cooling. After being stirred at room temperature for 20 h, MeOH (30 mL) and 1 N NaOH (12.0 mL) were added to the mixture. The mixture was stirred at room temperature for 0.5 h under an argon atmosphere. To this was added 3-(chloromethyl)-4-propyl-4*H*-1,2,4-triazole hydrochloride[29] (0.39 g, 1.99 mmol) at room temperature. The mixture was stirred at room temperature for 2 h under an argon atmosphere, and then it was concentrated in vacuo. Water was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (EtOAc) and recrystallization from EtOAc-diisopropyl ether (*i*-Pr_2O) to give 894 mg (73%) of **20a** as yellow crystals mp 166−169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91−1.01 (9H, m), 1.36−1.43 (2H, m), 1.46−1.87 (8H, m), 2.53−2.62 (2H, m), 3.12−3.24 (2H, m), 3.48−3.57 (4H, m), 3.80 (2H, t, $J = 4.9$ Hz), 3.91 (2H, t, $J = 7.1$ Hz), 4.15 (2H, t, $J = 4.9$ Hz), 4.17 (2H, s), 6.78 (1H, d, $J = 8.7$ Hz), 6.96 (2H, d, $J = 8.7$ Hz), 7.23−7.44 (6H, m), 7.48 (1H, s), 7.56 (2H, d, $J = 9.0$ Hz), 7.87 (1H, s), 8.05 (1H, s). Anal. ($C_{39}H_{49}N_5O_3S$) C, H, N.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfanyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide (20b). This compound was prepared from **16b**, *S*-(4-aminophenyl)-*O*-benzylthiocarbonate, and 3-(chloromethyl)-4-propyl-4*H*-1,2,4-triazole hydrochloride in 72% yield by a method similar to that described for **20a**, yellow crystals (EtOAc-*i*-Pr_2O), mp 122−126 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.96 (3H, t, $J = 7.4$ Hz), 0.99 (6H, d, $J = 6.6$ Hz), 1.34−1.49 (2H, m), 1.52−1.85 (6H, m), 2.02−2.29 (1H, m), 2.50−2.63 (2H, m), 3.06 (2H, d, $J = 7.4$ Hz), 3.44−3.54 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.78−3.89 (4H, m), 4.11 (2H, s), 4.15 (2H, t, $J = 5.0$ Hz), 6.83 (1H, d, $J = 8.8$ Hz), 6.95 (2H, d, $J = 8.8$ Hz), 7.16−7.17 (1H, m), 7.27−7.45 (6H, m), 7.58 (2H, d, $J = 8.8$ Hz), 8.03 (1H, s), 8.18 (1H, s). Anal. ($C_{40}H_{51}N_5O_3S\cdot 0.25H_2O$) C, H, N.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide (5c). To a solution of **20a** (0.70 g, 1.05 mmol) in CH_2Cl_2 (10 mL) was added a solution of 70% *m*CPBA (0.39 g, 1.58 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After being stirred at −78 °C for 1 h, aqueous $Na_2S_2O_3$ was added to the mixture, and the mixture was stirred at room temperature for 0.5 h. The mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (EtOAc → EtOAc/EtOH = 19:1) and recrystallization from EtOAc-*i*-Pr_2O to give 579 mg (81%) of **5c** as yellow crystals, mp 167−170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−1.02 (9H, m), 1.34−1.46 (2H, m), 1.52−1.76 (8H, m), 2.53−2.63 (2H, m), 3.15−3.24 (2H, m), 3.47−3.58 (4H, m), 3.62−3.82 (4H, m), 3.98 (1H, d, $J = 14.1$ Hz), 4.12−4.16 (3H, m), 6.78 (1H, d, $J = 9.0$ Hz), 6.93−6.96 (3H, m), 7.33−7.39 (6H, m), 7.85 (2H, d, $J = 9.0$ Hz), 8.07 (1H, s), 8.67 (1H, s). Anal. ($C_{39}H_{49}N_5O_4S\cdot 0.25H_2O$) C, H, N.

8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide (5d). This compound was prepared from **20b** in 68% yield by a method similar to that described for **5c**, yellow crystals (EtOAc-*i*-Pr_2O), mp 105−110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 7.4$ Hz), 0.94 (3H, t, $J = 7.2$ Hz), 1.00 (6H, d, $J = 6.6$ Hz), 1.32−1.45 (2H, m), 1.50−1.73 (6H, m), 2.08−2.26 (1H, m), 2.52−2.62 (2H, m), 3.08 (2H, d, $J = 6.9$ Hz), 3.46−3.58 (4H, m), 3.61−3.82 (4H, m), 3.96 (1H, d, $J = 13.8$ Hz), 4.11−4.16 (3H, m), 6.83 (1H, d, $J = 9.0$ Hz), 6.93−6.96 (3H, m), 7.32−7.39 (6H, m), 7.85 (2H, d, $J = 9.0$ Hz), 8.07 (1H, s), 8.71 (1H, s). Anal. ($C_{40}H_{51}N_5O_4S\cdot 0.25H_2O$) C, H, N.

(*R*)-(+)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*R*)-(+)-5c) and (*S*)-(−)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-tri azol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*S*)-(−)-5c). The racemate **5c** (400 mg) was resolved with HPLC to afford optically pure (*R*)-(+)-**5c** (185 mg) and (*S*)-(−)-**5c** (196 mg) [column, CHIRAL PAK AD (50 mm×500 mm), column temperature, 30 °C; mobile phase, EtOH; flow rate 80 mL/min; UV detection, 254 nm, amount injected 125 mg]. Compound (*R*)-(+)-**5c**; yellow crystals (EtOAc-*i*-Pr_2O), mp 97−98 °C, $[\alpha]_D = +127.5°$ ($C = 0.498\%$, EtOH). Anal. ($C_{39}H_{49}N_5O_4S\cdot H_2O$) C, H, N. Compound (*S*)-(−)-**5c**; yellow crystals (EtOAc-*i*-Pr_2O), mp 98−99 °C, $[\alpha]_D = -126.1°$ ($C = 0.537\%$, EtOH). Anal. ($C_{39}H_{49}N_5O_4S\cdot H_2O$) C, H, N. ^{1}H NMR data of the chiral compounds were identical with those of **5c**.

(*R*)-(+)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*R*)-(+)-5d) and (*S*)-(−)-8-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide ((*S*)-(−)-5d). The racemate **5d** (350 mg) was resolved with HPLC to afford optically pure (*R*)-(+)-**5d** (161 mg) and (*S*)-(−)-**5d** (167 mg) [column, CHIRAL PAK AD (50 mm × 500 mm), column temperature, 30 °C; mobile phase, EtOH; flow rate 80 mL/min; UV detection, 254 nm, amount injected 105 mg]. Compound (*R*)-(+)-**5d**; yellow crystals (EtOAc-*i*-Pr_2O), mp 99−101 °C, $[\alpha]_D = +131.2°$ ($C = 0.4985\%$, EtOH). Anal. ($C_{40}H_{51}N_5O_4S\cdot H_2O$) C, H, N. Compound (*S*)-(−)-**5d**; yellow crystals (EtOAc-*i*-Pr_2O), mp 98−100 °C, $[\alpha]_D = -131.1°$ ($C = 0.517\%$, EtOH). Anal. ($C_{40}H_{51}N_5O_4S\cdot 0.5H_2O$) C, H, N. ^{1}H NMR data of the chiral compounds were identical with those of **5d**.

Receptor Binding Assays. The binding activities were determined according to the protocol previously reported.[20] Binding assays for other chemokine receptors were carried out in a similar manner using the following ligands: [^{125}I]-RANTES for CCR1, [^{125}I]-MCP-1 for CCR2b, [^{125}I]-eotaxin for CCR3, [^{125}I]-TARC for CCR4, and [^{125}I]-MIP-3β for CCR7.

HIV-1 Envelope-Mediated Membrane Fusion Assay. COS-7 cells were maintained in Dulbecco's modified Eagle medium (D-MEM), supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 U/mL penicillin G and 100 μg/mL streptomycin). MOLT-4/CCR5/Luc$^+$ cells, a lymphoblastoid cell line that expresses human CCR5 and that has an integrated copy of the HIV-1 long terminal repeat-driven luciferase reporter gene, were maintained in RPMI 1640 medium supplemented with 10% FBS, antibiotics, 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. Expression vectors encoding Tat, Rev, and envelope were mixed at a ratio of 5:1:3 and cotransfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After a 2-day incubation, transfected COS-7 cells and MOLT-4/CCR5/Luc$^+$ cells were seeded in a 96-well plate at 10^4 cells in each well, and various concentrations of 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 and antibiotics 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).

Antiviral Assay in MOLT-4/CCR5 cells. RPMI 1640 medium supplemented with 10% FBS and antibiotics was used in viral replication assay. MOLT-4/CCR5 cells were inoculated with 5000 $CCID_{50}$ of R5 HIV-1 BaL per 1×10^6 cells and incubated for 6 h. The cells were washed to remove unadsorbed viral particles and seeded into a 96-well plate (5×10^5 cells/well) with culture medium containing various concentrations of test compounds. On day 3 after infection, the cells were subcultured at 1:5 with culture medium containing the same concentration of the test compounds. On day 5 after infection, the culture supernatants were collected and determined for their p24 antigen levels by a p24 antigen ELISA kit (ZeptoMetrix).

Antiviral Assay in PBMCs. PHA-stimulated PBMCs were inoculated with 11− 55 ng of p24 of HIV-1 clinical isolates (KK, CTV, HKW, HNK, HTN, HHA) per 4×10^6 cells and incubated for 4 h. The cells were washed with culture medium to remove unadsorbed viral particles and seeded into a 96-well plate (2×10^5 cells/ well) with culture medium containing various concentrations of test compounds. On day 4 after infection, the cells were subcultured at 1:2 with culture medium containing the same concentration of the test compounds. On day 7 after infection, the culture supernatants were collected and determined for their p24 antigen levels by an ELISA kit.

Pharmacokinetic Study. The animals used in this study were three male Crj:CD(SD)IGS rats (weight 260− 346 g; Charles River Japan Inc., Kanagawa, Japan), three male beagle dogs (weight 9.0− 9.5 kg; Kitayama Labes Co., Ltd., Nagano, Japan), and three male cynomolgus monkeys (weight 2.96− 3.60 kg; Keari Co. Ltd., Osaka, Japan). They were given laboratory chow and water ad libitum and were housed in a temperature- and humidity-controlled room (20− 26 °C and 40− 80%, respectively) with a 12-h light− dark cycle.

[^{14}C]-Labeled (***S***)-(−)-**5b** was dissolved in 0.5% (w/v) methylcellulose solution, to which was added 0.1% (v/v) methanesulfonic acid and 1% (v/v) Tween 80 for oral administration (PO) at a dose of 3 mg/kg, and was dissolved in a mixture of *N*,*N*-dimethyl acetamide and poly(ethylene glycol)-400 (1:1 by vol) for intravenous injection (IV) at a dose of 1 mg/kg. Compound (***S***)-(−)-**5b** was orally administered to fasted animals and injected to fed animals.

After dosing, blood was collected from the tail vein of rats, the cephalic vein of dogs, or the femoral vein of monkeys at the designated time points. The blood was subsequently centrifuged to obtain the plasma sample. The samples were kept frozen at −20 °C until analysis.

The plasma concentrations of compound (***S***)-(−)-**5b** were quantified by HPLC , and the column used was not one for separation of optically active compounds. The HPLC system consisted of an LC-10AD pump, an SPD-10A UV detector, a CBM-10A interface module, a CTO-10AC column oven, a DGU-14A degasser, and a CLASS LC-10 data processor (Shimadzu Corp., Kyoto, Japan). The column was an XTerra MS C8 (150 × 4.6 mm i.d.; Waters, MA). The column temperature and the flow rate were 40 °C and 1.0 mL/min, respectively. The mobile phase (A) (MP (A)) was 10 mmol/L ammonium acetate−acetonitrile (9:1, v/v, pH 5.5), and the mobile phase (B) (MP (B)) was 10 mmol/L ammonium acetate−acetonitrile (1:9, v/v, pH 5.5). The time program for the gradient elution involved the following steps: 0−8 min, linear gradient 50−60% MP (B); 8−25 min, isocratic at 60% MP (B); 25−30 min, linear gradient 60−100% MP (B); and 30−40 min, isocratic at 100% MP (B). Under these conditions, compound (***S***)-(−)-**5b** was eluted at about 23 min. The column effluent was collected at 1 min intervals into scintillation-counting vials, and the radioactivity was measured by a liquid scintillation counter (LSC-5100; Aloka, MA).

Acknowledgment. We thank Mr. Kenichi Kuroshima for the CCR5 binding assay; Dr. Hiroshi Miyake and Ms. Shikiko Shiki for the membrane fusion assay and anti-HIV-1 assay; Mr. Atsutoshi Furuta for the pharmacokinetic analysis; and Mr. Mitsutaka Tanaka for optical resolution by HPLC. We also thank Dr. Kiminori Tomimatsu and his group for the synthesis of intermediate **19**.

Supporting Information Available: Elemental analysis results for compounds **12a**, **16a**−**c**,**f**,**g**, **17**, **20a**,**b**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Carpenter, C. C.; Fischl, M. A.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J. S.; Richman, D. D.; Saag, M. S.; Schooley, R. T.; Thompson, M. A.; Vella, S.; Yeni, P. G.; Volberding, P. A. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society-USA Panel. *J. Am. Med. Assoc.* **1998**, *280*, 78−86.

(2) Wild, C.; Greenwell, T.; Matthews, T. A synthetic peptide from HIV-1, gp41 is a potent inhibitor of virus-mediated cell−cell fusion. *AIDS Res. Hum. Retroviruses* **1993**, *9*, 1051−1053.

(3) Pomerantz, R. J. Primary HIV-1 resistance. *J. Am. Med. Assoc*. **1999**, *282*, 1177−1178.

(4) Deeks, S. G.; Smith, M.; Holodniy, M.; Kahn, J. O. HIV-1 protease inhibitors. A review for clinicians. *J. Am. Med. Assoc.* **1997**, *277*, 145−153.

(5) Finzi, D.; Blankson, J.; Siliciano, J. D.; Margolick, J. B.; Chadwick, K.; Pierson, T.; Smith, K.; Lisziewicz, J.; Lori, F.; Flexner, C.; Quinn, T. C.; Chaisson, R. E.; Rosenberg, E.; Walker, B.; Gange, S.; Gallant, J.; Siliciano, R. F. Latent infection of CD4+ T-cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat. Med.* **1999**, *5*, 512−517.

(6) Cocchi, F.; DeVico, A. L.; Garzino-Demo, A.; Arya, S. K.; Gallo, R. C.; Lusso, P. Identification of RANTES, MIP-1α, and MIP-1*β* as the major HIV-suppressive factors produced by CD8+ T-cells. *Science* **1995**, *270*, 1811−1815.

(7) Deng, H.; Liu, R.; Ellmeier, W.; Choe, S.; Unutmaz, D.; Burkhart, M.; Di Marzio, P.; Marmon, S.; Sutton, R. E.; Hill, C. M.; Davis, C. B.; Peiper, S. C.; Schall, T. J.; Littman, D. R.; Landau, N. R. Identification of a major coreceptor for primary isolates of HIV-1. *Nature* **1996**, *381*, 661−666.

(8) Dragic, T.; Litwin, V.; Allaway, G. P.; Martin, S. R.; Huang, Y.; Nagashima, K. A.; Cayanan, C.; Maddon, P. J.; Koup, R. A.; Moore, J. P.; Paxton, W. A. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* **1996**, *381*, 667−673.

(9) Alkhatib, G.; Combadiere, C.; Broder, C. C.; Feng, Y.; Kennedy, P. E.; Murphy, P. M.; Berger, E. A. CC CKR5: a RANTES, MIP-1α, MIP-1*β* receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* **1996**, *272*, 1955−1958.

(10) Choe, H.; Farzan, M.; Sun, Y.; Sullivan, N.; Rollins, B.; Ponath, P. D.; Wu, L.; Mackay, C. R.; LaRosa, G.; Newman, W.; Gerard, N.; Gerard, C.; Sodroski, J. The *β*-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* **1996**, *85*, 1135−1148.

(11) Doranz, B. J.; Rucker, J.; Yi, Y.; Smyth, R. J.; Samson, M.; Peiper, S. C.; Parmentier, M.; Collman, R. G.; Doms, R. W. A dual-tropic primary HIV-1 isolate that uses fusin and the *β*-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell* **1996**, *85*, 1149−1159.

(12) Liu, R.; Paxton, W. A.; Choe, S.; Ceradini, D.; Martin, S. R.; Horuk, R.; MacDonald, M. E.; Stuhlmann, H.; Koup, R. A.; Landau, N. R. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* **1996**, *86*, 367−377.

(13) Samson, M.; Libert, F.; Doranz, B. J.; Rucker, J.; Liesnard, C.; Farber, C.; Saragosti, S.; Lapoumeroulie, C.; Cognaux, J.; Forceille, C.; Muyldermans, G.; Verhofstede, C.; Burtonboy, G.; Georges, M.; Imai, T.; Rana, S.; Yi, Y.; Smith, R. J.; Collman, R. G.; Doms, R. W.; Vassart, G.; Parmentier, M. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* **1996**, *382*, 722−725.

(14) Dean, M.; Carrington, M.; Winkler, C.; Huttley, G. A.; Smith, M. W.; Allikmets, R.; Goedert, J. J.; Buchbinder, S. P.; Vittinghoff, E.; Gomperts, E.; Donfield, S.; Vlahov, D.; Kaslow, R.; Saah, A.; Rinaldo, C.; Detels, R. Hemophilia growth and development study; Multicenter AIDS cohort study; Multicenter hemophilia cohort study; San Francisco city cohort, ALIVE study; O'Brien, S. J. genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. *Science* **1996**, *273*, 1856−1862.

(15) Huang, Y.; Paxton, W. A.; Wolinsky, S. M.; Neumann, A. U.; Zhang, L.; He, T.; Kang, S.; Ceradini, D.; Jin, Z.; Yazdanbakhsh, K.; Kunstman, K.; Erickson, D.; Dragon, E.; Landau, N. R.; Phair, J.; Ho, D. D.; Koup, R. A. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat. Med.* **1996**, *2*, 1240−1243.
(16) Michael, N. L.; Chang, G.; Louie, L. G.; Mascola, J. R.; Dondero, D.; Birx, D. L.; Sheppard, H. W. The role of viral phenotype and CCR-5 gene defects in HIV-1 transmission and disease progression. *Nat. Med.* **1997**, *3*, 338−340.
(17) Kazmierski, W.; Bifulco, N.; Yang, H.; Boone, L.; DeAnda, F.; Watson, C.; Kenakin, T. Recent progress in discovery of small-molecule CCR5 chemokine receptor ligands as HIV-1 inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 2663−2676.
(18) Maeda, K.; Nakata, H.; Ogata, H.; Koh, Y.; Miyakawa, T.; Mitsuya, H. The current status of, and challenges in, the development of CCR5 inhibitors as therapeutics for HIV-1 infection. *Curr. Opin. Pharmacol.* **2004**, *4*, 447−452.
(19) Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5698−6703.
(20) Shiraishi, M.; Aramaki, Y.; Seto, M.; Imoto, H.; Nishikawa, Y.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Nishimura, O.; Baba, M.; Fujino, M. Discovery of novel, potent, and selective small-molecule CCR5 antagonists as Anti-HIV-1 agents: Synthesis and biological evaluation of anilide derivatives with a quaternary ammonium moiety. *J. Med. Chem.* **2000**, *43*, 2049−2063.
(21) Strizki, J. M.; Xu, S.; Wagner, N. E.; Wojcik, L.; Liu, J.; Hou, Y.; Endres, M.; Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Tagat, J. R.; McCombie, S.; Cox, K.; Fawzi, A. B.; Chou, C. C.; Pugliese-Sivo, C.; Davies, L.; Moreno, M. E.; Ho, D. D.; Trkola, A.; Stoddart, C. A.; Moore, J. P.; Reyes, G. R.; Baroudy, B. M. SCH-C (SCH 351125), an orally bioavailable, small-molecule antagonist of the chemokine receptor CCR5, is a potent inhibitor of HIV-1 infection in vitro and in vivo. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 12718−12723.
(22) Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S. I.; Neustadt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. Piperazine-based CCR5 antagonists as HIV-1 inhibitors. IV. Discovery of 1-[(4,6-dimethyl-5-pyrimidinyl)carbonyl]-4-[4-[2-methoxy-1(*R*)-4-(trifluoromethyl)phenyl]ethyl-3(*S*)-methyl-1-piperazinyl]-4-methylpiperidine (Sch-417690/Sch-D), a potent, highly selective, and orally bioavailable CCR5 antagonist. *J. Med. Chem.* **2004**, *47*, 2405−2408.
(23) Wood, A.; Armour, D. The Discovery of the CCR5 receptor antagonist, UK-427,857, a new agent for the treatment of HIV infection and AIDS. *Prog. Med. Chem.* **2005**, *43*, 239−271.
(24) Maeda, K.; Nakata, H.; Koh, Y.; Miyakawa, T.; Ogata, H.; Takaoka, Y.; Shibayama, S.; Sagawa, K.; Fukushima, D.; Moravek, J.; Koyanagi, Y.; Mitsuya, H. Spirodiketopiperazine-based CCR5 inhibitor, which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro. *J. Virol.* **2004**, *78*, 8654−8662.
(25) Takashima, K.; Miyake, H.; Kanzaki, N.; Tagawa, Y.; Wang, X.; Sugihara, Y.; Iizawa, Y.; Baba, M. Highly potent inhibition of human immunodeficiency virus type 1 replication by TAK-220, an orally bioavailable small molecule CCR5 antagonist. *Antimicrob. Agents Chemother.* **2005**, *49*, 3474−3482.
(26) Aramaki, Y.; Seto, M.; Okawa, T.; Oda, T.; Kanzaki, N.; Shiraishi, M. Synthesis of 1-benzothiepine and 1-benzazepine derivatives as orally active CCR5 antagonists. *Chem. Pharm. Bull.* **2004**, *52*, 254−258.
(27) Seto, M.; Aramaki, Y.; Okawa, T.; Miyamoto, N.; Aikawa, K.; Kanzaki, N.; Niwa, S.; Iizawa, Y.; Baba, M.; Shiraishi, M. Orally active CCR5 antagonists as anti-HIV-1 agents: synthesis and biological activity of 1-benzothiepine 1,1-dioxide and 1-benzazepine derivatives containing a tertiary amine moiety. *Chem. Pharm. Bull.* **2004**, *52*, 577−590.
(28) Seto, M.; Aramaki, Y.; Imoto, H.; Aikawa, K.; Oda, T.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Shiraishi, M. Orally active CCR5 antagonists as anti-HIV-1 agents 2: synthesis and biological activities of anilide derivatives containing a pyridine *N*-oxide moiety. *Chem. Pharm. Bull.* **2004**, *52*, 818−829.
(29) Seto, M.; Miyamoto, N.; Aikawa, K.; Aramaki, Y.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Shiraishi, M. Orally active CCR5 antagonists as anti-HIV-1 agents. Part 3: Synthesis and biological activities of 1-benzazepine derivatives containing a sulfoxide moiety. *Bioorg. Med. Chem.* **2005**, *13*, 363−386.
(30) Ikemoto, T.; Ito, T.; Nishiguchi, A.; Tomimatsu, K. Facile synthesis of seven- to 10-membered rings by intramolecular condensation using dialkyl carbonate as solvent. *Tetrahedron Lett.* **2004**, *45*, 9335−9339.
(31) Ikemoto, T.; Nishiguchi, A.; Ito, T.; Tawada, H. Unusual asymmetric oxidation of sulfide; the diastereoselective oxidation of prochiral sulfide-chiral acid salt with hydrogen peroxide without metal. *Tetrahedron* **2005**, *61*, 5043−5048.
(32) Wu, L.; LaRosa, G.; Kassam, N.; Gordon, C. J.; Heath, H.; Ruffing, N.; Chen, H.; Humblias, J.; Samson, M.; Parmentier, M.; Moore, J. P.; Mackay, C. R. Interaction of chemokine receptor CCR5 with its ligands: Multiple domains for HIV-1 gp120 binding and a single domain for chemokine binding. *J. Exp. Med.* **1997**, *186*, 1373−1381.
(33) Baba, M.; Takashima, K.; Miyake, H.; Kanzaki, N.; Teshima, K.; Wang, X.; Shiraishi, M.; Iizawa, Y. TAK-652 inhibits CCR5-mediated HIV-1 infection in vitro and has favorable pharmacokinetics in humans. *Antimicrob. Agents Chemother.* **2005**, *49*, 4584−4591.
(34) [^{14}C]-Labeled compound (***S***)-(−)-**5b** was prepared by Amersham Pharmacia Biotech UK, Ltd. (Buckinghamshire, UK). The synthetic method was similar to that described for nonlabeled (***S***)-(−)-**5b** from [^{14}C]-labeled 5-bromo-2-fluorobenzaldehyde synthesized by the formylation of 1-bromo-4-fluorobenzene.

JM0509703