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

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The search for new small-molecule CCR5 antagonists by high-throughput screening (HTS) of the Takeda chemical library using [^{125}I]RANTES and CHO/CCR5 cells led to the discovery of lead compounds (**A**, **B**) with a quaternary ammonium or phosphonium moiety, which were synthesized to investigate new MCP-1 receptor antagonists. A series of novel anilide derivatives **1** with a quaternary ammonium moiety were designed, synthesized, and tested for their CCR5 antagonistic activity. Through the optimization of lead compounds, we have found *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (**1r,** TAK-779) as a highly potent and selective nonpeptide CCR5 antagonist with a IC_{50} value of 1.4 nM in the binding assay. Compound **1r** also inhibited the replication of macrophage (M)-tropic HIV-1 (Ba-L strain) in both MAGI-CCR5 cells and PBMCs with EC_{50} values of 1.2 and 3.7 nM, respectively. The synthesis and structure−activity relationships of **1r** and its related compounds are detailed.

Introduction

Currently, there are two types of anti-HIV-1 (human immunodeficiency virus type 1) agents: HIV-1 reverse transcriptase inhibitors and protease inhibitors. Combination chemotherapy using these two types of anti-HIV-1 agents has achieved long-term suppression of viral replication in HIV-1-infected individuals.[1] However, the development of novel anti-HIV-1 agents with different mechanisms of action is still essential, considering the low patient compliance to long-term combination chemotherapy and the emergence of resistant strains to these two types of inhibitors.[2]

The β-chemokine receptor CCR5, a G-protein-coupled seven-transmembrane domain receptor, has been shown to act as a major coreceptor for fusion and entry of macrophage-tropic (M-tropic or R5) HIV-1 into the host cells.[3−6] M-tropic strains are predominant during the asymptomatic stages of HIV-1 infection whereas T-cell line tropic (T-tropic or x4) strains become prevalent, concomitant with the decline of $CD4^+$ T cells, in the symptomatic stages.[7] A 32-base-pair deletion in the CCR5 coding region (CCR5Δ32) generates a nonfunctional receptor, and CCR5Δ32 homozygous individuals are apparently normal but resistant to infection with M-tropic HIV-1.[8−12] Thus, CCR5 is an attractive target for inhibition of M-tropic HIV-1 replication.

Although the natural ligands for CCR5 [regulated on activation, normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α and MIP-1β][13−15] and their modifications [Met-RANTES and aminooxypentane (AOP)-RANTES] are known to block M-tropic HIV-1 infection,[6,16−20] nonpeptide CCR5 antagonists have not been identified. In this report, we describe the discovery of lead compounds, design, synthesis, structure−activity relationships (SARs), and biological evaluation of *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (**1r,** TAK-779) and related compounds.

Discovery of Lead Compounds and Design

To identify CCR5 antagonists, we established Chinese hamster ovary (CHO)/CCR5 cells stably expressing CCR5 on their surface and found that [^{125}I]RANTES binds to the cells with a high affinity.[21] Lead compounds such as a quaternary ammonium salt **A** and a phosphonium salt **B**, which were synthesized to investigate new monocyte chemoattractant protein-1 (MCP-1) receptor (CCR2b) antagonists, were discovered from the Takeda chemical library by high-throughput screening (HTS) based on receptor binding assay using [^{125}I]RANTES and CHO/CCR5 cells. The similarity between CCR5 and CCR2b (76% identity)[14] might contribute to the discovery of lead compounds. A series of anilide derivatives **1** with a quaternary ammonium moiety were designed, synthesized, and tested for their CCR5 antagonistic activity (Figure 1).

Chemistry

The synthetic routes to the target anilide derivatives **1** with a quaternary ammonium moiety are outlined in Schemes 1 and 2. The synthesis of the target compounds **1** was carried out by a coupling reaction of two key intermediates, the carboxylic acids **3, 4** and the anilines

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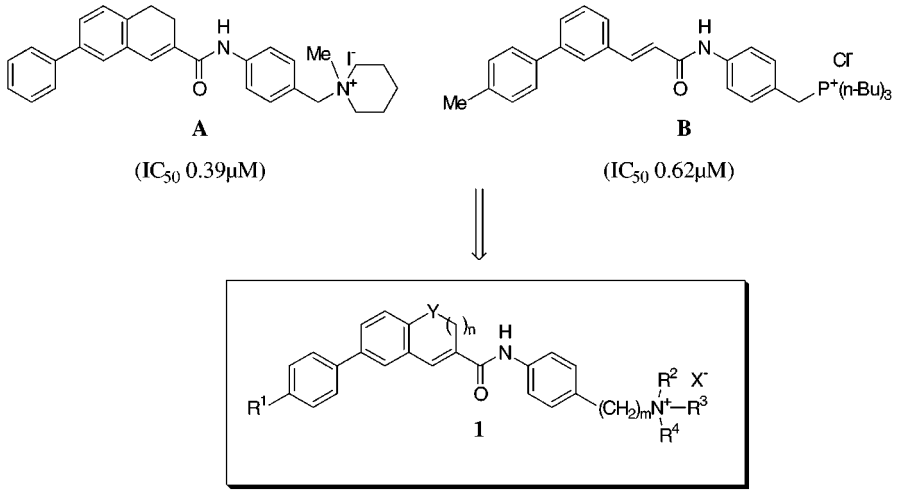
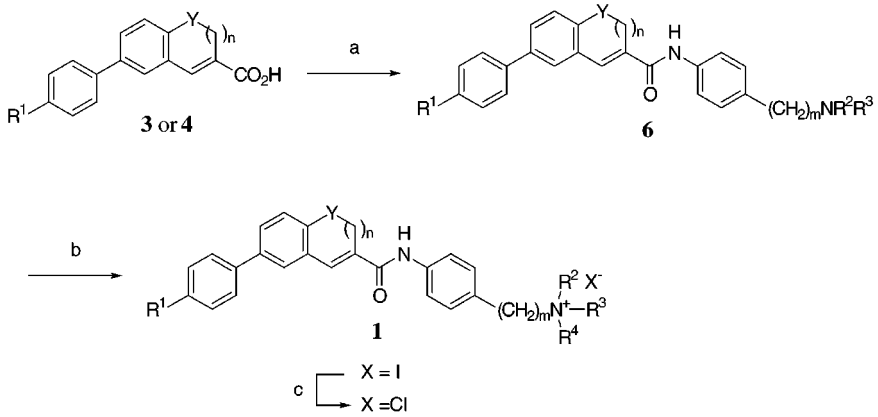


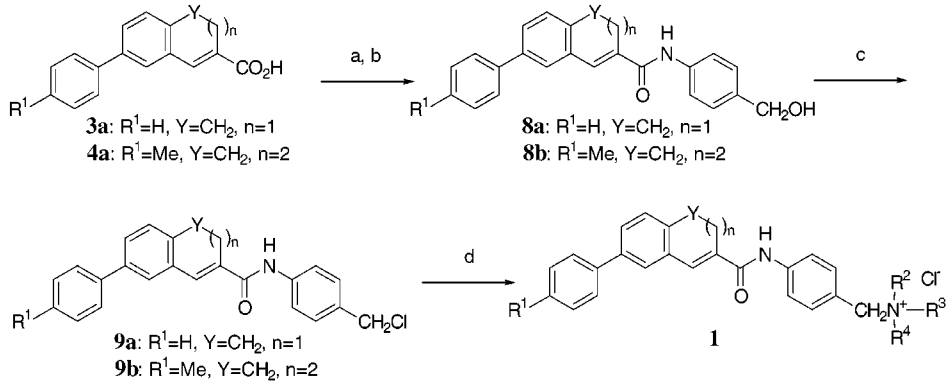
Figure 1. Structures of lead compounds (**A, B**) and design of anilide derivatives **1** with a quaternary ammonium moiety.

Scheme 1[a]



[a] (a) (1) $(COCl)_2$, cat. DMF/CH_2Cl_2, (2) **5**, NEt_3/THF or **5**, HOBt, WSC, NEt_3/DMF; (b) MeI/DMF; (c) ion-exchange resin (Cl^-)/aq MeOH.

Scheme 2[a]



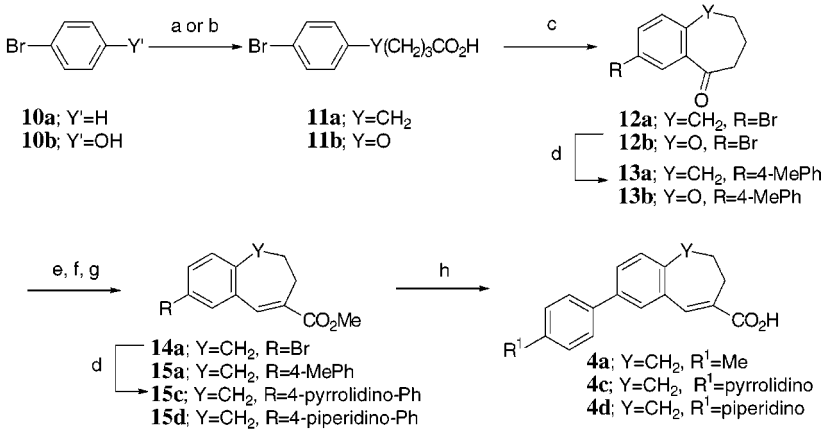
[a] (a) (1) $(COCl)_2$, cat. DMF/CH_2Cl_2, (2) **7**, NEt_3/THF; (b) HCl/acetone; (c) $SOCl_2$, pyridine/$CHCl_3$; (d) $NR^2R^3R^4$/DMF.

5, followed by quaternary ammoniation of the resulting amine derivatives **6** using iodomethane. The quaternary ammonium iodides were converted to the corresponding chlorides **1** using ion-exchange resin (Cl^-) (Method A: Scheme 1).

An alternative synthetic route was characterized by direct quaternary ammoniation of the benzyl chloride **9** and the appropriate tertiary amines. Namely, coupling of the carboxylic acids **3, 4** with the O-protected 4-aminobenzyl alcohols **7** and subsequent deprotection gave the benzyl alcohols **8**, which were converted to the benzyl chlorides **9**, followed by treatment with the amines to provide the quaternary ammonium chlorides **1** (Method B: Scheme 2).

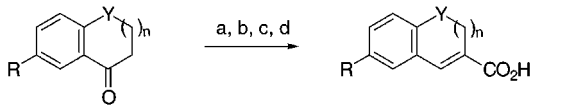
The key intermediates, the carboxylic acids **3, 4**, were prepared according to Schemes 3−7. The Friedel−Crafts reaction of bromobenzene **(10a)** with ethylglutaryl chloride, subsequent alkaline hydrolysis and reduction of the resulting keto acid using triethylsilane[22] gave the 5-(4-bromophenyl)valeric acid **(11a)**. The 4-(4-bromophenoxy)butyric acid **(11b)** was prepared by alkylation of *p*-bromophenol **(10b)** with ethyl 4-bromobutyrate and subsequent alkaline hydrolysis. The ketones **12a,b** were prepared by the intramolecular Friedel−Crafts reaction

Scheme 3[a]



[a] (a) (1) $ClCO(CH_2)_2CO_2Et$, $AlCl_3$, (2) aq NaOH/MeOH, (3) Et_3SiH/TFA; (b) (1) $Br(CH_2)_3CO_2Et$, K_2CO_3/DMF, (2) aq NaOH/MeOH; (c) PPA, 100 °C; (d) 4-R^1PhB$(OH)_2$, cat. $Pd(PPh_3)_4$, K_2CO_3/toluene, H_2O, EtOH, reflux; (e) NaOMe/$(MeO)_2CO$, reflux; (f) $NaBH_4$/MeOH, CH_2Cl_2, −10 °C; (g) MsCl, NEt_3/THF then DBU; (h) aq NaOH/MeOH, THF.

Scheme 4[a]



[a] (a) NaOMe/$(MeO)_2CO$, reflux; (b) $NaBH_4$/MeOH, CH_2Cl_2, 0 °C; (c) aq NaOH/MeOH, reflux; (d) HCl/2-methoxyethyl ether, 100 °C.

of the carboxylic acids **11a,b** using polyphosphoric acid (PPA). The Suzuki coupling reaction of the bromides **12a,b** with 4-methylphenylboronic acid and subsequent methoxycarbonylation gave the β-keto esters. Sodium borohydride reduction of these β-keto esters and subsequent dehydration by mesylation and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the α,β-unsaturated esters **14a, 15a**. The synthesis of benzocycloheptene-8-carboxylic acids **4a,c,d** was performed by the Suzuki coupling reaction of the bromide **14a** and subsequent alkaline hydrolysis (Scheme 3). The dihydronaphthalene-3-carboxylic acids **3a,b** were prepared by methoxycarbonylation of the 7-aryl-1-tetralones **16a,b**, which were obtained by the Suzuki coupling reaction of 1-tetralone 7-trifluoromethanesulfonate[23] and subsequent reduction, alkaline hydrolysis, and HCl dehydration (Scheme 4). The 7-bromo-1-benzoxepine-4-carboxylate **(14b)** was synthesized by the Dieckmann condensation of the diester **18** prepared from methyl 5-bromosalicylate **(17)**, followed by reduction, mesylation, and dehydration in the presence of excess triethylamine. The Suzuki coupling reaction of the 7-bromide **14b** and subsequent alkaline hydrolysis provided the 7-arylbenzoxepine-4-carboxylic acids **4e,f** (Scheme 5). The Dieckmann condensation of 5-bromosalicylaldehyde **(19)** and *tert*-butyl acrylate followed by the Suzuki coupling reaction and acid hydrolysis provided the 1-benzopyran-3-carboxylic acid **(3c)** (Scheme 6). The benzocycloheptene-8-carboxylic acid **(4a)** was also prepared by carboxylation of the ketone **13a** using K_2CO_3 or potassium *tert*-butoxide in DMSO in the presence of crown ether under CO_2 atmosphere[24] and subsequent reduction and dehydration (Scheme 7).

The other key intermediates, aniline derivatives **5a**−**i** were prepared by Fe reduction or hydrogenation of the nitro derivatives **24a**−**i** as shown in Schemes 8 and 9. The nitro derivatives **24a**−**d** were prepared by the amination of 4-nitrobenzyl chloride **(23a)** or 4-nitrophenethyl bromide **(23b)** with the cyclic amines (Scheme 8). The *N*-alkyl-*N*-methyl-4-nitrobenzylamines **24e**−**i** were obtained by reductive amination[25] of 4-nitrobenzylamine hydrochloride **(25a)** with the appropriate ketones or 4-nitrobenzaldehyde **(25b)** with 3-aminopropanol using sodium triacetoxyborohydride followed by reductive amination with formalin of the resulting secondary amines (Scheme 9).

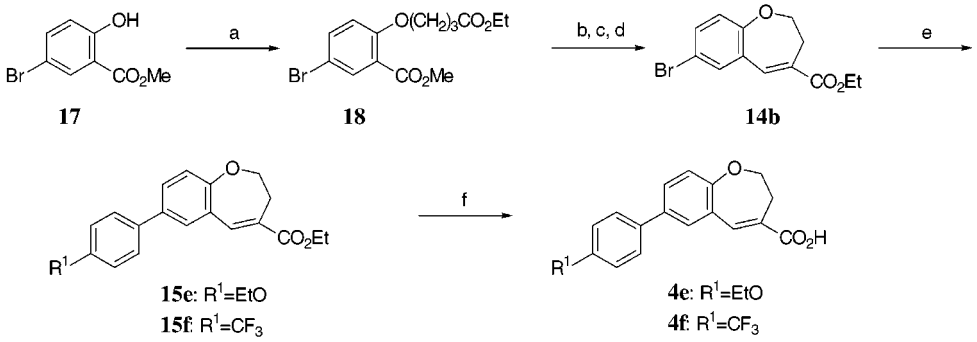
Condensation of two key intermediates, the carboxylic acids and the anilines, was carried out by the usual acid-chloride and activated-ester methods. Conversion of the carboxylic acids **3a**−**c, 4a,b,e,f** into the corresponding acid chlorides and subsequent condensation with the anilines **5a**−**i** gave the tertiary amine derivatives **6a,b,d,g**−**m,o**−**t,w**. The carboxylic acids **4c**−**d** were coupled with the aniline **5e** using 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC) to provide the amine derivatives **6u,v**. The ketone **6n** was prepared by deprotection of the ethylene acetal **6w**. The tertiary amine derivatives **6a,b,d,g**−**v** were methylated using iodomethane to afford the quaternary ammonium iodides **1a,b,d,g**−**q,s**−**v, 2**. The quaternary ammonium chloride **1r** was prepared by conversion of the corresponding iodide **1w** using ion-exchange resin (Cl^-) (Scheme 1).

The coupling reaction of the dihydronaphthalenecarboxylic acid **(3a)** or the benzocycloheptenecarboxylic acid **(4a)** with the O-protected 4-aminobenzyl alcohol **7** followed by deprotection gave the benzyl alcohols **8a,b**, which were converted into the benzyl chlorides **9a,b**. Treatment of the benzyl chlorides **9a,b** with triethylamine, 2-picoline, or *N*,*N*-dimethyl-*N*-(tetrahydropyran-4-yl)amine **(26)** provided the quaternary ammnoium chlorides **1e,f,r**, respectively. Coupling of the benzyl chloride **9a** and hexamethyleneimine and subsequent methylation afforded the quaternary ammnoium iodide **1c** (Scheme 2). Further details are to be found in Tables 1−4 and 6 and the Experimental Section.

Biological Results and Discussion

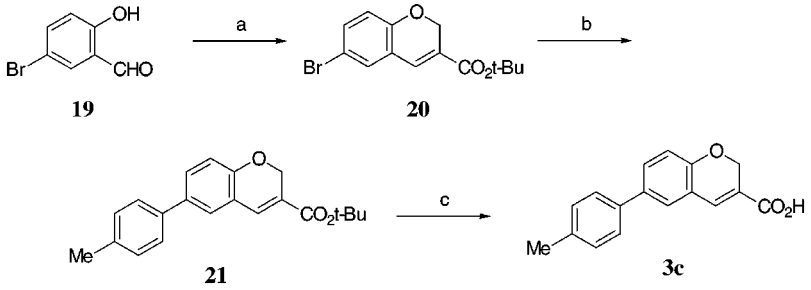
The compounds prepared were evaluated for their inhibitory effects on chemokine binding to CCR5-

Scheme 5[a]



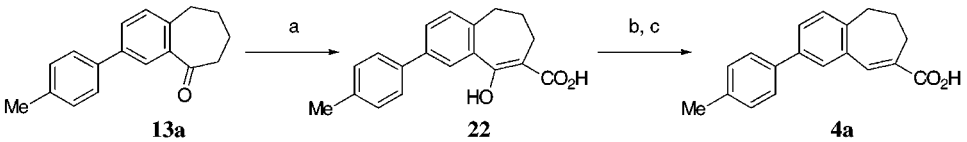
[a] (a) $Br(CH_2)_3CO_2Et$, K_2CO_3 /DMF; (b) LDA/THF, −78 °C; (c) $NaBH_4$/MeOH/CH_2Cl_2, −10 °C; (d) MsCl, NEt_3/THF; (e) 4-R^1PhB$(OH)_2$, cat. $Pd(PPh_3)_4$, K_2CO_3/toluene, H_2O, EtOH, reflux; (f) aq NaOH/MeOH, THF.

Scheme 6[a]



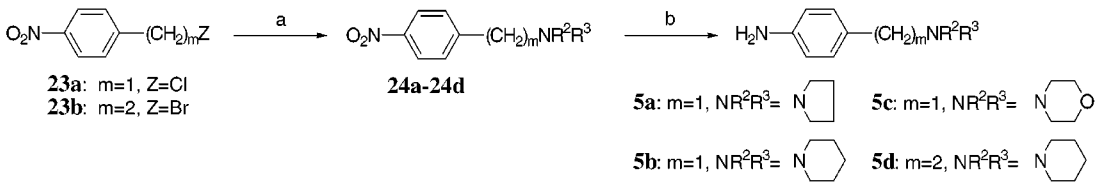
[a] (a) *tert*-Butyl acrylate, *t*-BuOK/*t*-BuOH, reflux; (b) 4-MePhB$(OH)_2$, cat. $Pd(PPh_3)_4$, K_2CO_3/toluene, H_2O, EtOH, reflux; (c) HCl/EtOAc.

Scheme 7[a]



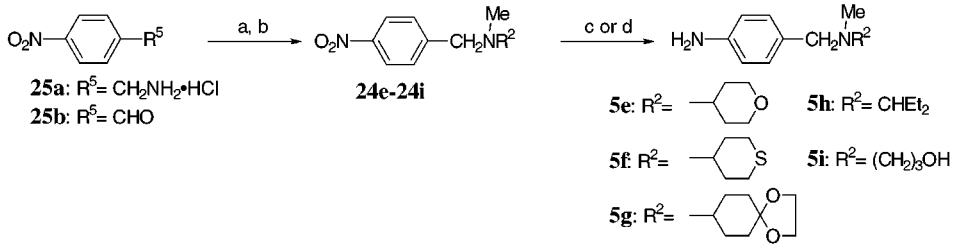
[a] (a) CO_2, 18-crown-6, K_2CO_3 or *t*-BuOK/DMSO; (b) $NaBH_4$/MeOH; (c) 80% HCO_2H, reflux.

Scheme 8[a]



[a] (a) HNR^2R^3, K_2CO_3/THF or DMF; (b) 10% Pd/C, H_2/EtOH or EtOAc.

Scheme 9[a]

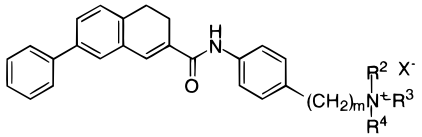


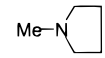
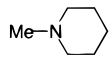
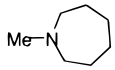
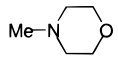
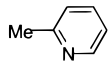
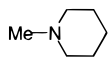
[a] (a) R′R″C=O, $NaBH(OAc)_3$, NEt_3/CH_2ClCH_2Cl or $H_2N(CH_2)_3OH$, $NaBH(OAc)_3$/CH_2ClCH_2Cl; (b) aq HCHO, $NaBH(OAc)_3$/CH_2ClCH_2Cl; (c) 10% Pd/C, H_2,/EtOH; (d) Fe/AcOH.

expressing CHO cells. Binding reactions were performed in the presence of [^{125}I]RANTES and various concentrations of the test compound. The results are summarized in Tables 1−4 as IC_{50} values (i.e., the concentration needed to inhibit the binding of [^{125}I]RANTES by 50%).

The 6-phenyl-1,2-dihydronaphthalene derivatives **1a**−**g** with a variety of quaternary ammonium moieties are listed in Table 1. In changes of the piperidinium group in the lead compound **A** (**1b**), the alicyclic ammonium groups such as pyrrolidinium (**1a**) and perhydroazepinium (**1c**) groups maintained activity, while the aromatic pyridinium group (**1f**) decreased activity. The morpholinium (**1d**) or triethylammonium (**1e**) derivative, which is considered an insertion of oxygen atom at 4-position

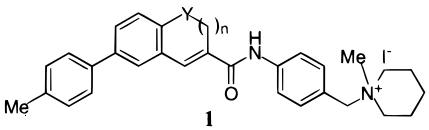
Table 1. Physical Properties and Inhibitory Effects of Dihydronaphthalenes **1a**−**g** on Chemokine Binding to CCR5



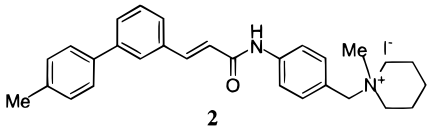
compd.	$NR^2R^3R^4$	m	X	IC_{50}[a] (μM)	mp(°C)	Recrystln. solvent	Synthetic method	Yield(%)	formula	anal.[b]
1a		1	I	0.43	156-160	MeOH-EtOAc	A	83	$C_{29}H_{31}IN_2O•1.0H_2O$	C, H, N
1b(A)		1	I	0.39	183-186	DMF-EtOAc	A	77	$C_{30}H_{33}IN_2O$	C, H, N
1c		1	I	0.38	197-199	MeOH-EtOAc	A	89	$C_{31}H_{35}IN_2O•0.5H_2O$	C, H, N
1d		1	I	1.2	166-170	DMF-EtOAc	A	96	$C_{29}H_{31}IN_2O_2•0.5H_2O$	C, H, N
1e	NEt_3	1	Cl	0.84	205-206	DMF-EtOAc	B	87	$C_{30}H_{35}ClN_2O•0.25H_2O$	C, H, N
1f		1	Cl	3.2	152-155	MeOH-EtOAc	B	70	$C_{30}H_{27}ClN_2O•1.0H_2O$	C, H, N
1g		2	I	1.1	219-220	MeOH-EtOAc	A	88	$C_{31}H_{35}IN_2O•0.25H_2O$	C, H, N

[a] The concentration required to inhibit the binding of [^{125}I]RANTES by 50%. All data represent means of duplicate separate experiments. [b] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

Table 2. Physical Properties and Inhibitory Effects of Compounds **1h**−**k** and **2** on Chemokine Binding to CCR5



1



2

compd.	Y	n	IC_{50}[a] (μM)	mp(°C)	Recrystln. solvent	Synthetic method	Yield(%)	formula	anal.[b]
1h	CH_2	1	0.24	202-204	DMF-EtOAc	A	92	$C_{31}H_{35}IN_2O•0.5H_2O$	C, H, N
1i	O	1	0.66	209-210(dec.)	$CHCl_3$-EtOH	A	70	$C_{30}H_{33}IN_2O_2•0.25H_2O$	C, H, N
1j	CH_2	2	0.025	220-221(dec.)	EtOH-EtOAc	A	86	$C_{32}H_{37}IN_2O•0.5H_2O$	C, H, N
1k	O	2	0.043	227-228(dec.)	EtOH-EtOAc	A	97	$C_{31}H_{35}IN_2O_2$	C, H, N
2	-	-	0.57	176-178	DMF-EtOAc	A	92	$C_{29}H_{33}IN_2O•1.5H_2O$	C, H, N

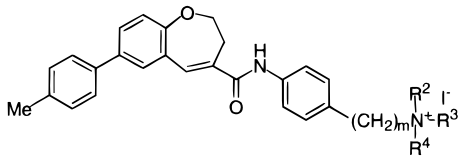
[a] The concentration required to inhibit the binding of [^{125}I]RANTES by 50%. All data represent means of duplicate separate experiments. [b] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

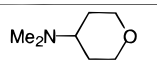
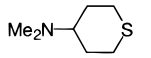
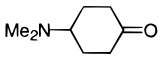
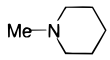
of the piperidinium ring, or a ring-opened form of the alicyclic ammonium, exhibited less potent activity in comparison with compound **1b**. Replacement of the benzylpiperidinium moiety with the phenethylpiperidinium moiety (**1g**) also resulted in a relative decrease of activity.

Next, keeping the quaternary piperidinium moiety in the lead compound **A**, changes of the dihydronaphthalene ring were investigated (Table 2). Interestingly, ring expansion of the [6,6]-fused dihydronaphthalene ring into the [6,7]-fused benzocycloheptene greatly increased potency. The benzocycloheptene **1j** was about 10 times more active than the corresponding dihydronaphthalene **1h**. However, the benzopyran **1i** and the ring-opened styryl derivative **2** were less active than the dihydronaphthalene **1h**. Replacement of the [6,6]-fused benzopyran ring with the [6,7]-fused benzoxepine ring also enhanced the activity. The benzoxepine **1k** exhibited ca. 15-fold more potent activity as compared with the benzopyran **1i**. These results indicate that the condensed ring size or shape is an important requirement for potent activity.

We investigated the effects of the quaternary ammonium groups again, keeping the 7-(4-tolyl)benzoxepine structure of compound **1k** (Table 3). Surprisingly, replacement of the piperidinium moiety with the bulkier *N*-(α-branched alkyl)-*N*-methylammonium moieties (**1l**−**o**) brought about the further increase of potency. Namely, the benzoxepines with the tetrahydropyran-4-yl (**1l**), tetrahydrothiopyran-4-yl (**1m**), and 3-pentyl (**1o**) groups as *N*-(α-branched alkyl) groups exhibited highly potent activity (IC_{50} values: 1.4−4.5 nM). In particular, the tetrahydropyran-4-aminium derivative **1l**, which was designed to decrease the molecular lipophilicity, was the most potent analogue (IC_{50} = 1.4 nM). However, compound **1o** with the *N*-(3-hydroxypropyl) group showed ca. one-fifth the activity of compound **1l** with the *N*-(α-branched alkyl) group. Furthermore, the methylene chain length between the phenyl and the quaternary ammonium groups affected the activity. The phenethyl-

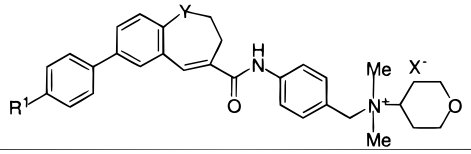
Table 3. Physical Properties and Inhibitory Effects of Benzoxepines **1l−q** on Chemokine Binding to CCR5



compd.	$NR^2R^3R^4$	m	IC_{50}[a](μM)	mp(°C)	Recrystln. solvent	Synthetic method	Yield(%)	formula	anal.[b]
1l		1	0.0014	202-204(dec.)	MeOH-EtOAc	A	88	$C_{32}H_{37}IN_2O_3$	C, H, N
1m		1	0.0031	185-186(dec.)	EtOH-hexane	A	66	$C_{32}H_{37}IN_2O_2S•1.0H_2O$	C, H, N
1n		1	0.0045	211-214(dec.)	EtOH-EtOAc	A	93	$C_{33}H_{37}IN_2O_3$	C, H, N
1o	Me_2NCHEt_2	1	0.0033	190-200	toluene-acetone	A	43	$C_{32}H_{39}IN_2O_2$	C, H, N
1p	$Me_2N(CH_2)_3OH$	1	0.0068	216-219	EtOH-EtOAc	A	85	$C_{30}H_{35}IN_2O_3•0.5H_2O$	C, H, N
1q		2	0.11	168-169	EtOH-hexane	A	quant.	$C_{32}H_{37}IN_2O_2•0.5H_2O$	C, H, N

[a] The concentration required to inhibit the binding of [^{125}I]-RANTES by 50%. All data represent means of duplicate separate experiments. [b] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

Table 4. Physical Properties and Inhibitory Effects of Compounds **1r−v** on Chemokine Binding to CCR5



compd.	R^1	Y	X	IC_{50}[a](μM)	mp(°C)	Recrystln. solvent	Synthetic method	Yield(%)	formula	anal.[b]
1r(TAK-779)	Me	CH_2	Cl	0.0014	226-232(dec.)	EtOH	A, B	80, 86	$C_{33}H_{39}ClN_2O_2$	C, H, N, Cl
1s	EtO	O	I	0.0018	152-158	EtOH-EtOAc	A	68	$C_{33}H_{39}IN_2O_4•1.0H_2O$	C, H, N
1t	CF_3	O	I	0.0015	213-214(dec.)	EtOH-Et_2O	A	69	$C_{32}H_{34}F_3IN_2O_3•0.25H_2O$	C, H, N
1u		CH_2	I	0.0038	178-179(dec.)	EtOH-EtOAc	A	28	$C_{36}H_{44}IN_3O_2•1.0H_2O$	C, H, N
1v		CH_2	I	0.0022	177-178	EtOH-hexane	A	60	$C_{37}H_{46}IN_3O_2•1.0H_2O$	C, H, N
1w	Me	CH_2	I	0.0018	157-158	EtOH-EtOAc	A	95	$C_{33}H_{39}IN_2O_2•0.5H_2O$	C, H, N

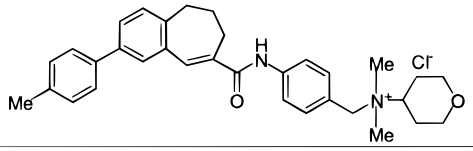
[a] The concentration required to inhibit the binding of [^{125}I]RANTES by 50%. All data represent means of duplicate separate experiments except **1r** (triplicate). [b] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

piperidinium **1q** showed less potent activity when compared with the corresponding benzylpiperidinium **1k**.

Finally, we determined the effects of substituents on the phenyl group on the benzocycloheptene or benzoxepine ring, keeping the *N*,*N*-dimethyl-*N*-tetrahydropyran-4-aminium moiety (Table 4). The (4-methylphenyl)benzocycloheptene **(1r)** was as highly active as the corresponding benzoxepine **1l**. Substitution of the ethoxy (**1s**) or trifluoromethyl group (**1t**) for the methyl group (**1r**) retained activity, whereas the pyrrolidino (**1u**) and piperidino (**1v**) derivatives exhibited relative weaker activity. Among anilide derivatives with a quaternary ammonium moiety synthesized, compounds **1l,r** exhibited the most potent CCR5 antagonistic activity. Actually, both compounds **1l,r** were about 280 times more active than lead compound **A**. The results of SAR study of anilide derivatives **1** suggested that a proper shape of molecule in addition to a strong basicity, suitable bulkiness and good location of quaternary ammonium moiety is essential for optimal CCR5 antagonistic activity. From these results and the other factors including cytotoxicity, physicochemical properties, and ease of synthesis, compound **1r** was selected for further biological evaluation.

Biological properties of **1r** are listed in Table 5. To determine whether the inhibitory effect of **1r** on chemokine binding is specific to CCR5, the activities of **1r** were examined in CHO cells stably expressing the chemokine receptors CCR1, CCR3, and CCR4 in a manner similar to CCR5. Compound **1r** had no effect on the binding of [^{125}I]RANTES, [^{125}I]eotaxin, and [^{125}I]thymus and activation-regulated chemokine (TARC) to CCR1, CCR3,

Table 5. Selectivity to the Chemokine Receptors and Anti-HIV-1 Activity of **1r** (TAK-779)



	IC_{50}[a](μM) or EC_{50}[b](μM)
CCR5[c]	0.0014
CCR1[c]	>10
CCR2b[c]	0.027
CCR3[c]	>10
CCR4[c]	>10
Anti HIV-1; MAGI-CCR5[d]	0.0012 ± 0.0001
Anti HIV-1; PBMCs[d]	0.0037 ± 0.0006

[a] 50% inhibitory concentration. [b] 50% antiviral effective concentration. [c] Inhibitory effects on the binding of [^{125}I]RANTES, [^{125}I]RANTES, [^{125}I]MCP-1, [^{125}I]eotaxin, or [^{125}I]-TARC to CCR5-, CCR1-, CCR2b-, CCR3-, or CCR4-expressing CHO cells, respectively. [d] Inhibitory effects on HIV-1 (Ba-L) replication were evaluated in MAGI-CCR5 cells or PBMCs. All data represent means ± SEM of at least 3 separate experiments.

and CCR4, respectively. Although compound **1r** inhibited the binding of [^{125}I]MCP-1 to CCR2b in CHO/CCR2b cells with an IC_{50} value of 27 nM, the value was about 20-fold higher than that for CCR5. The inhibition of CCR2b by compound **1r** might be caused by the similarity between CCR2b and CCR5. High specificity of **1r** seems to be very important from a chemotherapeutic viewpoint, since individuals having a defect in CCR5 are apparently normal. Nonspecific inhibition of other β-chemokine receptors may generate serious side effects associated with chemokine dysregulation. These results indicate that compound **1r** preferentially inhibits CCR5. In addition, we evaluated the inhibitory effects of **1r** on M-tropic HIV-1 (Ba-L strain) replication in MAGI-CCR5 cells and peripheral blood mononuclear cells (PBMCs). Compound **1r** greatly inhibited the replication in both MAGI-CCR5 cells and PBMCs. Its 50% effective concentrations (EC_{50} values) were 1.2 and 3.7 nM, respectively. The 50% cytotoxic concentrations (CC_{50} values) of **1r** for MAGI-CCR5 cells and PBMCs were 51 and >20 μM, respectively (data not shown). Thus, the selectivity indexes (ratio of CC_{50} to EC_{50}) were high, indicating that compound **1r** is an extremely potent inhibitor of M-tropic HIV-1 replication.

In summary, the search for new small-molecule CCR5 antagonists by HTS using [^{125}I]RANTES and CHO/CCR5 cells led to the discovery of lead compounds (**A, B**) with a quaternary ammonium or phosphonium moiety. Designed anilide derivatives **1** with a quaternary ammonium moiety were synthesized by a coupling reaction using two key intermediates, the carboxylic acids **3, 4** and the anilines **5**, followed by quaternary ammoniation. An alternative synthetic route is characterized by direct quaternary ammoniation of the benzyl chloride **9** and the tertiary amine.

Changes of the dihydronaphthalene ring in the lead compound **A** to the benzocycloheptene or benzoxepine ring and of the piperidinium moiety to the *N*-methyl-*N*-tetrahydropyran-4-aminium moiety greatly enhanced CCR5 antagonistic activity. Consequently, we have found a highly potent and selective small-molecule nonpeptide CCR5 antagonist *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (**1r,** TAK-779). Compound **1r** also displayed significant inhibition of R5 HIV-1 (Ba-L strain) replication in both MAGI-CCR5 cells and PBMCs. This compound seems to be a promising agent for treatment and prophylaxis of HIV-1 infection and was selected as a clinical candidate.

Experimental Section

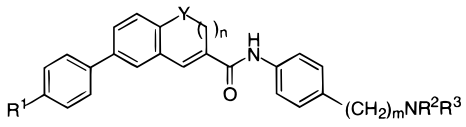
Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz), with tetramethylsilane as the internal standard. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within ±0.4% of the theoretical values unless otherwise noted. Chromatographic purification was carried out on silica gel columns (Kieselgel 60, 0.063−0.200 mm; Merck). Yields were not maximized.

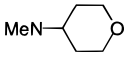
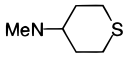
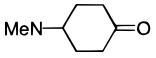
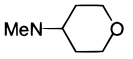
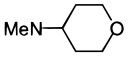
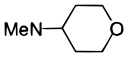
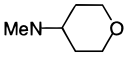
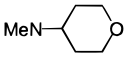
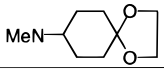
5-(4-Bromophenyl)valeric Acid (11a). To a mixture of $AlCl_3$ (40.0 g, 0.300 mol) in bromobenzene (150 mL) was added dropwise ethylglutaryl chloride (25.0 g, 0.140 mol) under ice cooling. The mixture was stirred at room temperature for 3.5 h and then poured into ice and HCl (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. To a solution of the residue in MeOH (200 mL) was added 2 N NaOH (125 mL), and the mixture was refluxed for 1.5 h. The mixture was concentrated in vacuo, and the residue was acidified using HCl and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 30.8 g (81%) of 4-(4-bromobenzoyl)butyric acid as colorless prisms. To a solution of 4-(4-bromobenzoyl)butyric acid (30.5 g, 0.113 mol) in trifluoroacetic acid (61 mL) was added dropwise triethylsilane (32.7 g, 0.281 mol) under nitrogen atmosphere. The reaction mixture was stirred at 55 °C for 2 days. The solvent was evaporated in vacuo, and the residue was extracted with 1 N NaOH. After being washed with Et_2O, the aqueous layer was acidified using 1 N HCl and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 21.2 g (73%) of **11a** as colorless prisms: mp 91−93 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−1.69 (4H, m), 2.34−2.41 (2H, m), 2.55−2.62 (2H, m), 7.05 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz). Anal. ($C_{11}H_{13}BrO_2$) C, H.

4-(4-Bromophenoxy)butyric Acid (11b). A mixture of *p*-bromophenol (55.3 g, 0.320 mol), ethyl 4-bromobutyrate (68.7 g, 0.352 mol) and K_2CO_3 (88.5 g, 0.640 mol) in DMF (200 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo, and water was added to the residue. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. To a solution of the residue in MeOH (180 mL) was added 3 N NaOH (320 mL), and the mixture was refluxed for 30 min. The mixture was concentrated in vacuo, and the residue was extracted with water. After being washed with Et_2O, the aqueous layer was acidified using HCl and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 76.0 g (92%) of **11b** as colorless prisms: mp 135−136 °C; ^{1}H NMR ($CDCl_3$) δ 2.05−2.18 (2H, m), 2.58 (2H, t, J = 7.3 Hz), 3.99 (2H, t, J = 6.1 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.8 Hz). Anal. ($C_{10}H_{11}BrO_3$) C, H.

3-Bromo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (12a). A mixture of **11a** (27.1 g, 0.105 mol) and polyphosphoric acid (630 g) was heated at 100 °C for 12 h. The mixture was poured into ice and water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with 1 N NaOH, water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column

Table 6. Physical Properties of Amine Derivatives **6**



compd.	R^1	Y	n	m	NR^2R^3	mp(°C)	Recrystln. solvent	Yield(%)	formula	anal.[a]
6a	H	CH_2	1	1		186-187	EtOAc-IPE	13	$C_{28}H_{28}N_2O•0.25H_2O$	C, H, N
6b	H	CH_2	1	1		163-164	EtOAc-IPE	68	$C_{29}H_{30}N_2O•0.25H_2O$	C, H, N
6c	H	CH_2	1	1		168-170	EtOAc-hexane	73	$C_{30}H_{32}N_2O$	C, H, N
6d	H	CH_2	1	1		186-187	EtOAc-hexane	78	$C_{28}H_{28}N_2O_2$	C, H, N
6g	H	CH_2	1	2		157-159	EtOAc-IPE	66	$C_{30}H_{32}N_2O$	C, H, N
6h	Me	CH_2	1	1		187-189	EtOAc-IPE	75	$C_{30}H_{32}N_2O$	C, H, N
6i	Me	O	1	1		196-197	EtOH-EtOAc	65	$C_{29}H_{30}N_2O_2•0.25H_2O$	C, H, N
6j	Me	CH_2	2	1		192-193	CH_2Cl_2-hexane	89	$C_{31}H_{34}N_2O•0.25H_2O$	C, H, N
6k	Me	O	2	1		188-189	EtOAc-hexane	90	$C_{30}H_{32}N_2O_2$	C, H, N
6l	Me	O	2	1		162-163	EtOAc-hexane	76	$C_{31}H_{34}N_2O_3•0.25H_2O$	C, H, N
6m	Me	O	2	1		180-181	EtOAc-hexane	88	$C_{31}H_{34}N_2O_2S$	C, H, N
6n	Me	O	2	1		149-150	EtOAc-hexane	76	$C_{32}H_{34}N_2O_3$	C, H, N
6o	Me	O	2	1	$MeNCHEt_2$	133-134	EtOAc-hexane	72	$C_{31}H_{36}N_2O_2$	C, H, N
6p	Me	O	2	1	$MeN(CH_2)_3OH$	119-120	EtOAc-hexane	60	$C_{29}H_{32}N_2O_3•0.25H_2O$	C, H, N
6q	Me	O	2	2		201-202	EtOH-EtOAc	76	$C_{31}H_{34}N_2O_2$	C, H, N
6r	Me	CH_2	2	1		161-162	EtOAc-hexane	quant.	$C_{32}H_{36}N_2O_2$	C, H, N
6s	EtO	O	2	1		174-176	EtOAc-hexane	79	$C_{32}H_{36}N_2O_4$	C, H, N
6t	CF_3	O	2	1		205-209	EtOAc-hexane	43	$C_{31}H_{31}F_3N_2O_3$	C, H, N
6u		CH_2	2	1		124-125	EtOAc-hexane	39	$C_{35}H_{41}N_3O_2•0.25H_2O$	C, H, N
6v		CH_2	2	1		170-171	EtOAc-hexane	62	$C_{36}H_{43}N_3O_2•0.25H_2O$	C, H, N
6w	Me	O	2	1		192-193	EtOAc	52	$C_{34}H_{38}N_2O_4$	C, H, N

[a] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

chromatography (hexane:EtOAc = 4:1) to give 16.8 g (67%) of **12a** as a pale brown oil: ^{1}H NMR ($CDCl_3$) δ 1.78−1.90 (4H, m), 2.70−2.76 (2H, m), 2.85−2.91 (2H, m), 7.08 (1H, d, J = 8.1 Hz), 7.52 (1H, dd, J = 2.2, 8.1 Hz), 7.84 (1H, d, J = 2.2 Hz).

12b. This compound was prepared by a manner similar to that used for **12a**, yield 70%: ^{1}H NMR ($CDCl_3$) δ 2.15−2.29 (2H, m), 2.89 (2H, t, J = 7.0 Hz), 4.24 (2H, t, J = 6.6 Hz), 6.97 (1H, d, J = 8.8 Hz), 7.50 (1H, dd, J = 2.6, 8.1 Hz), 7.87 (1H, d, J = 2.6 Hz).

3-(4-Methylphenyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (13a). A mixture of **12a** (15.2 g, 63.6 mmol), 4-methylphenylboronic acid (9.50 g, 69.9 mmol), EtOH (100 mL), and 2 M K_2CO_3 (100 mL) in toluene (300 mL) was stirrred at room temperature under argon atmosphere for 30 min. Tetrakis(triphenylphosphine)palladium (2.90 g, 2.51 mmol) was added, and the mixture was refluxed overnight under argon atmosphere. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed successively with water and brine,

dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 8:1) to give 15.6 g (98%) of **13a** as a red oil: ^{1}H NMR ($CDCl_3$) δ 1.82−1.94 (4H, m), 2.39 (3H, s), 2.74−2.80 (2H, m), 2.93−2.99 (2H, m), 7.24 (2H, d, J = 8.0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.0 Hz), 7.64 (1H, dd, J = 2.0, 8.0 Hz), 7.96 (1H, d, J = 2.0 Hz).

The following compounds (**13b, 15c−f, 16a,b, 21**) were prepared by a manner similar to that used for **13a**.

13b: yield 82%; mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 2.18−2.31 (2H, m), 2.39 (3H, s), 2.94 (2H, t, J = 7.0 Hz), 4.28 (2H, t, J = 6.6 Hz), 7.14 (1H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.48 (2H, d, J = 8.2 Hz), 7.66 (1H, dd, J = 2.4, 8.8 Hz), 8.00 (1H, d, J = 2.4 Hz). Anal. ($C_{17}H_{16}O_2$) C, H.

15c: yield 77%; mp 135−136 °C; ^{1}H NMR ($CDCl_3$) δ 1.99−2.10 (6H, m), 2.66 (2H, t, J = 6.4 Hz), 2.81−2.86 (2H, m), 3.30−3.37 (4H, m), 3.83 (3H, s), 6.63 (2H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.0 Hz), 7.41 (1H, dd, J = 2.0, 8.0 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.51 (1H, s), 7.78 (1H, s). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

15d: yield 70%; mp 129−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.57−1.73 (6H, m), 2.04−2.13 (2H, m), 2.66 (2H, t, J = 6.6 Hz), 2.81−2.87 (2H, m), 3.19−3.24 (4H, m), 3.83 (3H, s), 7.00 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 8.0 Hz), 7.42 (1H, dd, J = 2.2, 8.2 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.51 (1H, s), 7.78 (1H, s). Anal. ($C_{24}H_{27}NO_2$) C, H, N.

15e: yield 82%; mp 124−127 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 1.44 (3H, t, J = 7.0 Hz), 3.00 (2H, t, J = 4.0 Hz), 4.08 (2H, q, J = 7.0 Hz), 4.28 (2H, q, J = 7.2 Hz), 4.30 (2H, t, J = 4.0 Hz), 6.96 (2H, dd, J = 6.6, 2.2 Hz), 7.02 (1H, d, J = 8.4 Hz), 7.41 (1H, d, J = 2.6 Hz), 7.44−7.51 (3H, m), 7.65 (1H, s). Anal. ($C_{21}H_{22}O_4$) C, H.

15f: yield 80%; mp 107−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.2 Hz), 2.99−3.05 (2H, m), 4.29 (2H, q, J = 7.2 Hz), 4.33 (2H, t, J = 4.8 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.49 (1H, dd, J = 8.4, 2.4 Hz), 7.58 (1H, d, J = 2.4 Hz), 7.62−7.73 (5H, m). Anal. ($C_{20}H_{17}F_3O_3$) C, H.

16a: yield 86%; ^{1}H NMR ($CDCl_3$) δ 2.10−2.25 (2H, m), 2.65−2.75 (2H, m), 2.96−3.05 (2H, m), 7.31−7.50 (4H, m), 7.57−7.67 (2H, m), 7.73 (1H, dd, J = 2.2, 8.0 Hz), 8.30(1H, d, J = 2.2 Hz).

16b: yield 72%; mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 2.10−2.24 (2H, m), 2.39 (3H, s), 2.69 (2H, t, J = 6.6 Hz), 3.00 (2H, t, J = 6.6 Hz), 7.21−7.35 (3H, m), 7.52 (2H, d, J = 8.4 Hz), 7.71 (1H, dd, J = 2.2, 8.2 Hz), 8.27(1H, d, J = 2.2 Hz). Anal. ($C_{17}H_{16}O$) C, H.

21: yield 74%; mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (9H, s), 2.39 (3H, s), 4.98 (2H, d, J = 1.4 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.33 (1H, d, J = 2.2 Hz), 7.36−7.45 (4H, m). Anal. ($C_{21}H_{22}O_3$) C, H.

Methyl 2-Bromo-6,7-dihydro-5*H*-benzocycloheptene-8-carboxylate (14a). To a solution of **12a** (35.4 g, 0.148 mol) in dimethyl carbonate (500 mL) was added sodium methoxide (40.0 g, 0.740 mol), and the mixture was refluxed under nitrogen atmosphere for 8 h. The reaction mixture was poured into 1 N HCl under ice cooling, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 9:1) to give 28.3 g (64%) of colorless prisms. To a solution of the prisms (22.5 g, 75.7 mmol) in CH_2Cl_2 (200 mL) was added a mixture of $NaBH_4$ (3.70 g, 97.8 mmol) in MeOH below −20 °C, and the mixture was stirred at −10 °C for 1h. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 4:1) to give 19.4 g (86%) of a yellow oil. To a solution of the oil (19.4 g, 64.8 mmol) and triethylamine (27.0 mL, 0.194 mol) in CH_2Cl_2 (200 mL) was added dropwise methanesulfonyl chloride (7.50 mL, 96.9 mmol) under ice cooling. After being stirred overnight at room temperature, DBU (35.0 mL, 0.234 mol) was added dropwise under ice cooling. The reaction mixture was stirred 30 min at room temperature, washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 4:1) to give 13.5 g (74%) of **14a** as pale yellow prisms: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.97−2.10 (2H, m), 2.62 (2H, t, J = 6.6 Hz), 2.72−2.78 (2H, m), 3.82 (3H, s), 7.02 (1H, d, J = 8.0 Hz), 7.32 (1H, dd, J = 2.2, 8.0 Hz), 7.45 (1H, d, J = 2.2 Hz), 7.60 (1H, s). Anal. ($C_{13}H_{13}BrO_2$) C, H.

15a. This compound was prepared by a manner similar to that used for **14a**, yield 77%: mp 80−81 °C; ^{1}H NMR ($CDCl_3$) δ 2.02−2.14 (2H, m), 2.40 (3H, s), 2.67 (2H, t, J = 6.6 Hz), 2.82−2.88 (2H, m), 3.83 (3H, s), 7.19−7.27 (3H, m), 7.41−7.54 (4H, m), 7.78 (1H, s). Anal. ($C_{20}H_{20}O_2$) C, H.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxylic Acid (4a). A solution of **15a** (11.9 g, 40.7 mmol) and 1 N NaOH (200 mL) in MeOH (100 mL) and THF (200 mL) was stirred overnight at room temperature. The mixture was concentrated and extracted with EtOAc after being acidified using 1 N HCl. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 10.2 g of **4a** (90%) as colorless prisms: mp 185−186 °C; ^{1}H NMR ($CDCl_3$) δ 2.07−2.16 (2H, m), 2.40 (3H, s), 2.70 (2H, t, J = 6.6 Hz), 2.86−2.91 (2H, m), 7.21−7.28 (3H, m), 7.44−7.56 (4H, m), 7.91 (1H, s). Anal. ($C_{19}H_{18}O_2$) C, H.

The following compounds **(4c−f)** were prepared by a manner similar to that used for **4a**.

4c: yield quant.; mp 242−243 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.93−2.00 (6H, m), 2.56 (2H, t, J = 5.8 Hz), 2.76−2.82 (2H, m), 3.23−3.35 (4H, m), 6.60 (2H, d, J = 8.8 Hz), 7.20 (1H, d, J = 8.2 Hz), 7.44 (1H, dd, J = 1.0, 8.2 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.56 (1H, d, J = 1.0 Hz), 7.69 (1H, s). Anal. ($C_{22}H_{23}NO_2$) C, H.

4d: yield quant.; mp 219−220 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.53−1.62 (6H, m), 1.91−1.98 (2H, m), 2.56 (2H, t, J = 6.4 Hz), 2.77−2.82 (2H, m), 3.14−3.25 (4H, m), 6.99 (2H, d, J = 8.7 Hz), 7.23 (1H, d, J = 8.0 Hz), 7.47 (1H, dd, J = 1.9, 8.0 Hz), 7.54 (2H, d, J = 8.7 Hz), 7.60 (1H, d, J = 1.9 Hz), 7.70 (1H, s). Anal. ($C_{23}H_{25}NO_2 \cdot 0.25H_2O$) C, H, N.

4e: yield 95%; mp 269−271 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (3H, t, J = 7.0 Hz), 2.81−2.94 (2H, m), 4.06 (2H, q, J = 7.0 Hz), 4.18−4.31 (2H, m), 6.94−7.00 (3H, m), 7.49−7.79 (5H, m). Anal. ($C_{19}H_{18}O_4$) C, H.

4f: yield 97%; mp 273−276 °C; ^{1}H NMR (DMSO-d_6) δ 2.89 (2H, t, J = 4.4 Hz), 4.28 (2H, t, J = 4.4 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.61−7.70 (2H, m), 7.78 (2H, d, J = 8.4 Hz), 7.92−7.96 (3H, m). Anal. ($C_{18}H_{13}F_3O_3$) C, H.

7-(4-Methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic Acid (4b). To a solution of **13b** (3.60 g, 14.3 mmol) in dimethyl carbonate (50 mL), was added sodium methoxide (3.85 g, 71.3 mmol), and the mixture was refluxed under nitrogen atmosphere for 8 h. The reaction mixture was poured into 1 N HCl under ice cooling, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 3.50 g (80%) of colorless prisms. To a solution of the prisms (1.80 g, 5.80 mmol) in CH_2Cl_2 (25 mL) was added $NaBH_4$ (0.60 g, 15.9 mmol) in MeOH under ice cooling, and the mixture was stirred for 30 min under ice cooling. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated in vacuo. A mixture of the residue and 1 N NaOH (50 mL) in MeOH (25 mL) and Et_2O (20 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated, and extracted with water. The aqueous layer was washed with Et_2O, and extracted with EtOAc after acidified using 1 N HCl. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. A solution of the residue and HCl (5 mL) in 2-methoxyethyl ether (25 mL) was heated at 100 °C for 40 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 1.23 g (76%) of **4b** as colorless prisms: mp 255−256 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 3.02 (2H, t, J = 4.6 Hz), 4.33 (2H, t, J = 4.6 Hz), 7.05 (1H, d, J = 8.6 Hz), 7.24 (2H, d, J = 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 7.47−7.56 (2H, m), 7.78 (1H, s). Anal. ($C_{18}H_{16}O_3$) C, H.

The following compounds **(3a,b)** were prepared by a manner similar to that used for **4b**.

3a: yield 44%; mp 204−208 °C; ^{1}H NMR ($CDCl_3$) δ 2.61−2.73 (2H, m), 2.88−3.00 (2H, m), 7.23−7.60 (8H, m), 7.74 (1H, s).

3b: yield 36%; mp 230−231 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 2.61−2.71 (2H, m), 2.89−2.98 (2H, m), 7.22−7.28 (3H, m), 7.45−7.51 (4H, m), 7.73 (1H, s). Anal. ($C_{18}H_{16}O_2$) C, H.

Methyl 5-Bromo-2-[3-(ethoxycarbonyl)propyloxy]benzoate (18). A mixture of methyl 5-bromosalicylate (5.00 g, 21.6 mmol), ethyl 4-bromobutyrate(4.22 g, 21.6 mmol) and K_2CO_3 (7.50 g, 54.3 mmol) in DMF (50 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo, and water was added to the residue. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 1:5) to give 6.50 g (87%) of **18** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz), 2.07−2.20 (2H, m), 2.57 (2H, t, J = 7.1 Hz), 3.89 (3H, s), 3.98−4.19 (5H, m), 6.85 (1H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 2.6, 8.8 Hz), 7.90 (1H, d, J = 2.6 Hz).

Ethyl 7-Bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (14b). To a solution of diisopropylamine (3.20 mL, 22.8 mmol) in THF (50 mL) was added dropwise 1.6 M *n*-butyllithium in hexane (13.0 mL, 20.8 mmol) at −78 °C under argon atmosphere. The mixture was stirred for 30 min under ice cooling, and then a solution of **18** (6.50 g, 18.8 mmol) in THF (20 mL) was added dropwise at −78 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight, and then poured into water. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. To a solution of the residue in CH_2Cl_2 (100 mL) was added a mixture of $NaBH_4$ (2.00 g, 52.8 mmol) in MeOH (40 mL) at −15 °C, and the mixture was stirred for 1 h at −10 °C. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated in vacuo. To a solution of the residue and triethylamine (7.90 mL, 56.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise methanesulfonyl chloride (2.20 mL, 28.4 mmol) under ice cooling. The reaction mixture was stirred overnight at room temperature, and then poured into water. The mixture was concentrated, and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 5:1) to give 2.28 g (41%) of **14b** as colorless prisms: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t, J = 7.2 Hz), 2.98 (2H, t, J = 4.7 Hz), 4.23−4.33 (4H, m), 6.86 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.6, 8.8 Hz), 7.46−7.47 (2H, m). Anal. ($C_{13}H_{13}BrO_3$) C, H.

***tert*-Butyl 6-Bromo-2*H*-1-benzopyran-3-carboxylate (20).** To a solution of 5-bromosalicylaldehyde (10.0 g, 49.7 mmol) and *tert*-butyl acrylate (17.5 mL, 0.119 mol) in *tert*-BuOH (100 mL) was added potassium *tert*-butoxide (1.70 g, 15.1 mmol), and the mixture was refluxed for 66 h. The mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water, 1 N NaOH and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 9:1) to give 11.0 g (70%) of **20** as pale yellow prisms: mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (9H, s), 4.95 (2H, d, J = 0.8 Hz), 6.72 (1H, d, J = 8.4 Hz), 7.21−7.30 (3H, m). Anal. ($C_{14}H_{15}BrO_3$) C, H.

6-(4-Methylphenyl)-2*H*-1-benzopyran-3-carboxylic Acid (3c). A mixture of **21** (3.00 g, 9.31 mmol) and 4 N HCl in EtOAc (10.0 mL, 40.0 mmol) was stirred for 16 h at room temperature. Hexane was added to the mixture, and the resulting precipitate was filtered to give 2.10 g (86%) of **3c** as pale yellow prisms: mp 236−237 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 5.05 (2H, d, J = 1.4 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.23−7.27 (2H, m), 7.37 (1H, d, J = 2.2 Hz), 7.41−7.52 (3H, m), 7.63 (1H, s). Anal. ($C_{17}H_{14}O_3$) C, H.

2-(4-Methylphenyl)-9-hydroxy-6,7-dihydro-5*H*-benzocycloheptene-8-carboxylic Acid (22). To a solution of **13a** (0.50 g, 2.0 mmol) and 18-crown-6 (1.1 g, 4.0 mmol) in DMSO (15 mL) was added potassium *tert*-butoxide (1.7 g, 15 mmol) under cooling, and the mixture was stirred for 3 h at room temperature under carbon dioxide (CO_2) atmosphere. The reaction mixture was poured into water, and acidified using 1 N HCl. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 0.47 g(80%) of **22** as pale yellow prisms: mp 113−117 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.12−2.23 (4H, m), 2.40 (3H, s), 2.70 (2H, t, J = 6.4 Hz), 7.26 (2H, d, J = 8.4 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.59 (1H, dd, J = 2.2, 8.0 Hz), 7.86 (1H, d, J = 2.2 Hz), 12.46 (1H, s). Anal. ($C_{19}H_{18}O_3$) C, H.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxylic Acid (4a). To a solution of **22** (0.47 g, 1.6 mmol) in EtOH (40 mL) was added $NaBH_4$ (0.58 g, 15 mmol) at room temperature. The mixture was stirred for 1 h, and then 1 N HCl was added, and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 0.46 g of prisms. A solution of the prisms in formic acid (80%, 10 mL) was refluxed for 1.5 h, and the mixture was poured into water. The aqueous mixture was extracted with EtOAc. After being washed with water, the organic layer was extracted with 1 N NaOH. The aqueous layer was acidified using 1 N HCl and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 0.22 g (51%) of **4a** as colorless prisms.

1-(4-Nitrobenzyl)piperidine (24b). To a solution of 4-nitrobenzyl chloride (5.00 g, 29.1 mmol) in THF (50 mL), was added piperidine (6.20 g, 72.8 mmol) under ice cooling. The mixture was stirred overnight at room temperature, and poured into water. The aqueous mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 3:2) to give 6.40 g (quant.) of **24b** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.38−1.70 (6H, m), 2.30−2.45 (4H, m), 3.55 (2H, s), 7.51 (2H, d, J = 8.8 Hz), 8.17 (2H, d, J = 8.8 Hz).

The following compounds (**24a,c,d**) were prepared by a manner similar to that used for **24b**.

24a: yield 99%; ^{1}H NMR ($CDCl_3$) δ 1.75−1.85 (4H, m), 2.43−2.58 (4H, m), 3.71 (2H, s), 7.51 (2H, d, J = 8.6 Hz), 8.18 (2H, d, J = 8.6 Hz).

24c: yield 99%; mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 2.37−2.55 (4H, m), 3.59 (2H, s), 3.65−3.80 (4H, m), 7.53 (2H, d, J = 8.4 Hz), 8.18 (2H, d, J = 8.4 Hz). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

24d: yield 97%; ^{1}H NMR ($CDCl_3$) δ 1.39−1.75 (6H, m), 2.35−2.65 (6H, m), 2.85−3.00 (2H, m), 7.36 (2H, d, J = 8.8 Hz), 8.14 (2H, d, J = 8.8 Hz).

***N*-(4-Nitrobenzyl)-*N*-(tetrahydropyran-4-yl)methylamine (24e).** To a mixture of *p*-nitrobenzylamine hydrochloride (16.7 g, 88.5 mmol), tetrahydro-4*H*-pyran-4-one (8.90 g, 88.9 mmol) and triethylamine (12.5 mL, 89.7 mmol) in 1,2-dichloroethane (200 mL) was added sodium triacetoxyborohydride (26.3 g, 0.124 mol) under ice cooling. The mixture was stirred for 8 h at room temperature under nitrogen atmosphere, and then 37% formaldehyde (7.90 mL, 97.3 mmol) and sodium triacetoxyborohydride (26.3 g, 0.124 mol) were added successively under ice cooling. The reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. The solvent was evaporated in vacuo, and the residue was neutralized using 1 N NaOH. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 22.2 g (quant.) of **24e** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.56−1.79 (4H, m), 2.21 (3H, s), 2.58−2.73 (1H, m), 3.38 (2H, dt, J = 3.2, 11.2 Hz), 3.68 (2H, s), 4.02−4.09 (2H, m), 7.51 (2H, d, J = 8.8 Hz), 8.18 (2H, d, J = 8.8 Hz).

The following compounds **24f**−**i** were prepared by a manner similar to that used for **24e**.

24f: yield quant.; ^{1}H NMR ($CDCl_3$) δ 1.65−1.85 (2H, m), 2.09−2.17 (2H, m), 2.21 (3H, s), 2.46 (1H, tt, J = 3.1, 11.6 Hz), 2.67−2.74 (4H, m), 3.68 (2H, s), 7.50 (2H, d, J = 8.8 Hz), 8.17 (2H, d, J = 8.8 Hz).

24g: yield 95%; mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−1.86 (8H, m), 2.20 (3H, s), 2.47−2.57 (1H, m), 3.66 (2H, s), 3.95 (4H, s), 7.51 (2H, d, J = 8.8 Hz), 8.17 (2H, d, J = 8.8 Hz). Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

24h: yield 97%; ^{1}H NMR ($CDCl_3$) δ 0.95 (6H, t, J = 7.3 Hz), 1.26−1.60 (4H, m), 2.14 (3H, s), 2.25−2.32 (1H, m), 3.67 (2H, s), 7.53 (2H, d, J = 8.4 Hz), 8.17 (2H, d, J = 8.4 Hz).

24i: yield 67%; ^{1}H NMR ($CDCl_3$) δ 1.75−1.82 (2H, m), 2.26 (3H, s), 2.66 (2H, t, J = 7.1 Hz), 3.63 (2H, s), 3.79 (2H, t, J = 5.3 Hz), 7.49 (2H, d, J = 8.8 Hz), 8.20 (2H, d, J = 8.8 Hz).

1-(4-Aminobenzyl)piperidine (5b). A solution of **24b** (10.5 g, 47.7 mmol) in EtOAc (1000 mL) was hydrogenated over 10% Pd−C (50% wet, 0.7 g) for 2 h at room temperature under atmospheric pressure. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give 6.70 g (75%) of **5b** as colorless crystals: mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.35−1.65 (6H, m), 2.28−2.45 (4H, m), 3.37 (2H, s), 3.61 (2H, br), 6.64 (2H, d, J = 8.6 Hz), 7.09 (2H, d, J = 8.6 Hz). Anal. ($C_{12}H_{18}N_2$) C, H, N.

The following compounds (**5a,c,d**) were prepared by a manner similar to that used for **5b**.

5a: yield 43%; ^{1}H NMR ($CDCl_3$) δ 1.60−1.90 (4H, m), 2.35−2.55 (4H, m), 3.45−3.70 (4H, m), 6.64 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.4 Hz).

5c: yield 1.9%; mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 2.32−2.52 (4H, m), 3.39 (2H, s), 3.45−3.80 (6H, m), 6.64 (2H, d, J = 8.2 Hz), 7.09 (2H, d, J = 8.2 Hz). Anal. ($C_{11}H_{16}N_2O$)

5d: yield quant.; ^{1}H NMR ($CDCl_3$) δ 1.40−1.80 (6H, m), 2.35−2.60 (6H, m), 2.60−2.80 (2H, m), 3.40−3.70 (2H, br), 6.62 (2H, d, J = 8.4 Hz), 7.00 (2H, d, J = 8.4 Hz).

4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]-aniline (5e). To a solution of **24e** (22.3 g, 88.9 mmol) in acetic acid (500 mL) was added reduced iron (20.0 g, 0.358 mol), and the mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo, and EtOAc was added to the residue. The precipitate was removed by filtration, and the filtrate was washed successively with 1 N NaOH, water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 15.4 g (79%) of **5e** as colorless prisms: mp 93−94 °C; ^{1}H NMR ($CDCl_3$) δ 1.65−1.76 (4H, m), 2.19 (3H, s), 2.58−2.68 (1H, m), 3.36 (2H, dt, J = 3.2, 11.3 Hz), 3.48 (2H, s), 3.60 (2H, br), 4.00−4.05 (2H, m), 6.65 (2H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz). Anal. ($C_{13}H_{20}N_2O$) C, H, N.

The following compounds **(5f−i)** were prepared by a manner similar to that used for **5e**.

5f: yield 86%; mp 88−89 °C; ^{1}H NMR ($CDCl_3$) δ 1.65−1.84 (2H, m), 2.10−2.18 (2H, m), 2.19 (3H, s), 2.45 (1H, tt, J = 3.2, 13.0 Hz), 2.65−2.71 (4H, m), 3.47 (2H, s), 3.61 (2H, br), 6.64 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.4 Hz). Anal. ($C_{13}H_{20}N_2S$) C, H, N.

5g: yield 86%; ^{1}H NMR ($CDCl_3$) δ 1.36−1.93 (8H, m), 2.17 (3H, s), 2.43−2.57 (1H, m), 3.46 (2H, s), 3.60 (2H, br), 3.94 (4H, s), 6.64 (2H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz).

5h: yield 82%; ^{1}H NMR ($CDCl_3$) δ 0.92 (6H, t, J = 7.3 Hz), 1.20−1.59 (4H, m), 2.10 (3H, s), 2.18−2.29 (1H, m), 3.44 (2H, s), 3.57 (2H, br), 6.64 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.4 Hz).

5i: yield 72%; ^{1}H NMR ($CDCl_3$) δ 1.67−1.78 (2H, m), 2.21 (3H, s), 2.62 (2H, t, J = 5.5 Hz), 3.41 (2H, s), 3.65 (2H, br), 3.77 (2H, t, J = 5.1 Hz), 6.65 (2H, d, J = 8.4 Hz), 7.07 (2H, d, J = 8.4 Hz).

***N*-[4-[*N*-Methyl-*N*-(4-tetrahydropyranyl)aminomethyl]-phenyl]-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxamide (6r).** To a solution of **4a** (8.50 g, 30.5 mmol) in CH_2Cl_2 (100 mL) was added oxalyl chloride (8.00 mL, 91.7 mmol) and DMF (cat. amount) under ice cooling; the mixture was stirred for 2 h at room temperature. The solvent was evaporated in vacuo. A solution of the residue in THF (75 mL) was added dropwise to a solution of **5e** (7.50 g, 34.0 mmol) and triethylamine (16.8 mL, 0.121 mol) in THF (50 mL) under ice cooling, and the reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. The solvent was evaporated in vacuo, and then water was addded. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 14.6 g (quant.) of **6r** as colorless prisms: ^{1}H NMR ($CDCl_3$) δ 1.59−1.77 (4H, m), 2.13−2.21 (2H, m), 2.21 (3H, s), 2.40 (3H, s), 2.55−2.75 (3H, m), 2.86−2.92 (2H, m), 3.37 (2H, dt, J = 2.8, 10.9 Hz), 3.57 (2H, s), 4.01−4.07 (2H, m), 7.21−7.33 (4H, m), 7.41−7.58 (7H, m), 7.63 (1H, s).

The following compounds (**6a,b,d,g−m,o−q,s,t,w**) were prepared by a manner similar to that used for **6r**.

6a: ^{1}H NMR ($CDCl_3$) δ 1.75−1.85 (4H, m), 2.45−2.55 (4H, m), 2.65−2.80 (2H, m), 2.90−3.05 (2H, m), 3.60 (2H, s), 7.25−7.60 (14H, m).

6b: ^{1}H NMR ($CDCl_3$) δ 1.35−1.70 (6H, m), 2.30−2.45 (4H, m), 2.65−2.80 (2H, m), 2.92−3.04 (2H, m), 3.46 (2H, s), 7.23−7.62 (14H, m).

6d: ^{1}H NMR ($CDCl_3$) δ 2.38−2.47 (4H, m), 2.66−2.78 (2H, m), 2.92−3.03 (2H, m), 3.48 (2H, s), 3.67−3.75 (4H, m), 7.25−7.60 (14H, m).

6g: ^{1}H NMR ($CDCl_3$) δ 1.40−1.80 (6H, m), 2.40−2.60 (6H, m), 2.65−2.85 (4H, m), 2.90−3.00 (2H, m), 7.15−7.60 (14H, m).

6h: ^{1}H NMR ($CDCl_3$) δ 1.38−1.65 (6H, m), 2.32−2.42 (7H, m), 2.65−2.77 (2H, m), 2.92−3.02 (2H, m), 3.46 (2H, s), 7.20−7.34 (6H, m), 7.40−7.58 (7H, m).

6i: ^{1}H NMR ($CDCl_3$) δ 1.41−1.71 (6H, m), 2.34−2.43 (7H, m), 3.46 (2H, s), 5.12 (2H, d, J = 1.4 Hz), 6.95 (1H, d, J = 8.0 Hz), 7.14 (1H, br s), 7.23−7.29 (3H, m), 7.31−7.38 (2H, m), 7.40−7.46 (6H, m).

6j: ^{1}H NMR ($CDCl_3$) δ 1.38−1.50 (2H, m), 1.50−1.63 (4H, m), 2.13−2.22 (2H, m), 2.35−2.39 (4H, m), 2.40 (3H, s), 2.72 (2H, t, J = 6.4 Hz), 2.85−2.91 (2H, m), 3.46 (2H, s), 7.21−7.33 (5H, m), 7.41−7.57 (6H, m), 7.63 (1H, s).

6k: ^{1}H NMR ($CDCl_3$) δ 1.40−1.47 (2H, m), 1.52−1.60 (4H, m), 2.34−2.39 (4H, m), 2.39 (3H, s), 3.07 (2H, t, J = 4.4 Hz), 3.46 (2H, s), 4.36 (2H, t, J = 4.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 7.22−7.33 (5H, m), 7.43−7.58 (6H, m).

6l: ^{1}H NMR ($CDCl_3$) δ 1.59−1.74 (4H, m), 2.20 (3H, s), 2.39 (3H, s), 2.58−2.66 (1H, m), 3.07 (2H, t, J = 4.5 Hz), 3.37 (2H, dt, J = 2.8, 11.0 Hz), 3.56 (2H, s), 4.01−4.06 (2H, m), 4.35 (2H, t, J = 4.5 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.22−7.33 (4H, m), 7.43−7.56 (6H, m), 7.62 (1H, s).

6m: ^{1}H NMR ($CDCl_3$) δ 1.60−1.85 (2H, m), 2.10−2.15 (2H, m), 2.21 (3H, s), 2.39 (3H, s), 2.40−2.50 (1H, m), 2.66−2.72 (4H, m), 3.08 (2H, t, J = 4.6 Hz), 3.57 (2H, s), 4.36 (2H, t, J = 4.6 Hz), 7.06 (1H, d, J = 8.4 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.43−7.57 (7H, m).

6o: ^{1}H NMR ($CDCl_3$) δ 0.94 (6H, t, J = 7.5 Hz), 1.26−1.53 (4H, m), 2.13 (3H, s), 2.24−2.31 (1H, m), 2.40 (3H, s), 3.09 (2H, t, J = 4.4 Hz), 3.55 (2H, s), 4.37 (2H, t, J = 4.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 7.17−7.36 (4H, m), 7.44−7.54 (7H, m).

6p: ^{1}H NMR ($CDCl_3$) δ 1.68−1.80 (2H, m), 2.24 (3H, s), 2.39 (3H, s), 2.65 (2H, t, J = 5.8 Hz), 3.07 (2H, t, J = 4.6 Hz), 3.52 (2H, s), 3.77 (2H, t, J = 5.2 Hz), 4.35 (2H, t, J = 4.6 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.22−7.31 (3H, m), 7.43−7.52 (5H, m), 7.57 (2H, d, J = 8.4 Hz), 7.78 (1H, s).

6q: ^{1}H NMR ($CDCl_3$) δ 1.45−1.48 (2H, m), 1.50−1.65 (4H, m), 2.39 (3H,s), 2.47−2.58 (6H, m), 2.76−2.84 (2H, m), 3.07 (2H, t, J = 4.4 Hz), 4.36 (2H, t, J = 4.4 Hz), 7.05 (1H, d, J = 8.0 Hz), 7.17−7.26 (4H, m), 7.43−7.51 (7H, m).

6s: ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 7.0 Hz), 1.62−1.82 (4H, m), 2.21 (3H, s), 2.55−2.72 (1H, m), 3.08 (2H, t, J = 4.8 Hz), 3.31−3.44 (2H, m), 3.57 (2H, s), 3.97−4.10 (2H, m), 4.08 (2H, q, J = 7.0 Hz), 4.36 (2H, *t*, J = 4.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.24−7.58 (10H, m).

6t: ^{1}H NMR ($CDCl_3$) δ 1.69−1.82 (4H, m), 2.21 (3H, s), 2.55−2.74 (1H, m), 3.10 (2H, t, J = 4.7 Hz), 3.31−3.44 (2H, m), 3.58 (2H, s), 3.99−4.11 (2H, m), 4.39 (2H, t, J = 4.7 Hz), 7.11 (1H, d, J = 8.4 Hz), 7.25−7.34 (3H, m), 7.46−7.58 (5H, m), 7.62−7.71 (4H, m).

6w: ^{1}H NMR ($CDCl_3$) δ 1.48−1.86 (8H, m), 2.20 (3H, s), 2.39 (3H, s), 2.45−2.60 (1H, m), 3.08 (2H, t, J = 4.5 Hz), 3.56 (2H, s), 3.95 (4H, s), 4.36 (2H, t, J = 4.5 Hz), 7.06 (1H, d, J = 8.4 Hz), 7.23−7.33 (4H, m), 7.44−7.56 (7H, m).

***N*-[4-[*N*-(4-Oxocyclohexyl)-*N*-methylaminomethyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (6n).** A solution of **6w** (17.1 g, 31.7 mmol) in acetic acid (100 mL) and 1 N HCl (200 mL) was heated at 100 °C for 1.5 h, and then the mixture was concentrated. The residue was neutralized using 1 N NaOH, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give crude prisms. Recrystallized from EtOAc−hexane to give 12.0 g (76%) of **6n** as colorless prisms: ^{1}H NMR($CDCl_3$) δ 1.78−2.13 (4H, m), 2.23 (3H, s), 2.25−2.35 (2H, m), 2.39 (3H, s), 2.45−2.57 (2H, m), 2.84−2.94 (1H, m), 3.08 (2H, t, J = 4.4 Hz), 3.59 (2H, s), 4.35 (2H, t, J = 4.4 Hz), 7.06 (1H, d, J = 8.0 Hz), 7.22−7.34 (4H, m), 7.43−7.57 (6H, m), 7.65 (1H, s).

***N*-[4-[*N*-Methyl-*N*-(4-tetrahydropyranyl)aminomethyl]-phenyl]-2-[4-(1-pyrrolidinyl)phenyl]-6,7-dihydro-5*H*-benzocycloheptene-8-carboxamide (6u).** To a solution of **4c** (0.45 g, 1.3 mmol), **5e** (0.33 g, 1.5 mmol) and 1-hydroxybenzotriazole (0.18 g, 1.3 mmol) in DMF (20 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.39 g, 2.0 mmol) under ice cooling. After being allowed to warm to room temperature, 4-(dimethylamino)pyridine (cat. amount) and triethylamine (0.56 mL, 3.9 mmol) were added, and the reaction mixture was stirred overnight at room temperature. The mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (5% MeOH and 0.5% NEt_3 in EtOAc) to give crude prisms. Recrystallized from EtOAc and hexane to give 0.28 g (39%) of **6u** as colorless prisms: ^{1}H NMR ($CDCl_3$) δ 1.66−1.77 (4H, m), 1.99−2.06 (4H, m), 2.11−2.18 (2H, m), 2.21 (3H, s), 2.55−2.75 (3H, m), 2.84−2.90 (2H, m), 3.30−3.44 (6H, m), 3.58 (2H, s), 4.00−4.14 (2H, m), 6.64 (2H, d, J = 9.0 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.5 Hz), 7.39−7.51 (4H, m), 7.57 (2H, d, J = 8.5 Hz), 7.64 (1H, s).

6v. This compound was prepared by a manner similar to that used for **6u**: ^{1}H NMR ($CDCl_3$) δ 1.59−1.65 (2H, m), 1.65−1.80 (8H, m), 2.05−2.21 (2H, m), 2.21 (3H, s), 2.55−2.68 (1H, m), 2.71 (2H, t, J = 6.3 Hz), 2.84−2.90 (2H, m), 3.19−3.24 (4H, m), 3.37 (2H, dt, J = 2.8, 11.2 Hz), 3.57 (2H, s), 4.01−4.11 (2H, m), 7.00 (2H, d, J = 8.8 Hz), 7.20 (1H, d, J = 7.6 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.41−7.51 (4H, m), 7.56 (2H, d, J = 8.4 Hz), 7.63 (1H, s).

***tert*-Butyldimethyl-4-nitrobenzyloxysilane.** To a mixture of 4-nitrobenzyl alcohol (10.0 g, 65.3 mmol) and imidazole (11.2 g, 0.165 mol) in DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (11.8 g, 78.3 mmol). The mixture was stirred at room temperature for 1.5 h and then poured into water. The aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane:EtOAc = 7:1) to give 17.5 g (quant.) of *tert*-butyldimethyl-4-nitrobenzyloxysilane as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.13 (6H, s), 0.96 (9H, s), 4.83 (2H, s), 7.48 (2H, d, J = 8.6 Hz), 8.20 (2H, d, J = 8.6 Hz).

***tert*-Butyldimethyl-4-aminobenzyloxysilane (7).** This compound was prepared from *tert*-butyldimethyl-4-nitrobenzyloxysilane by a manner similar to that used for **5b**, yield 94%: ^{1}H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.92 (9H, s), 3.50−3.70 (2H, br), 4.62 (2H, s), 6.65 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.4 Hz).

***N*-(4-Hydroxymethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxamide (8b).** To a mixture of **4a** (0.42 g, 1.5 mmol) in CH_2Cl_2 (7 mL) were added successively oxalyl chloride (0.40 mL, 4.6 mmol) and DMF (cat. amount) under ice cooling. The mixture was stirred for 1.5 h at room temperature, and the solvent was evaporated in vacuo. A solution of the residue in THF (10 mL) was added dropwise to a solution of **7** (0.37 g, 1.6 mmol) and triethylamine (0.62 mL, 4.5 mmol) in THF (5 mL) under ice cooling. The reaction mixture was stirred for 30 min at room temperature under N_2. The solvent was evaporated in vacuo. Water was addded to the residue, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. A solution of the residue and 6 N HCl (0.19 mL) in acetone (5 mL) was stirred for 45 min at room temperature. The mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo to give 0.40 g of **8b** (52%) as colorless prisms: mp 179−181 °C; ^{1}H NMR ($CDCl_3$) δ 2.10−2.20 (2H, m), 2.40 (3H, s), 2.72 (2H, t, J = 6.2 Hz), 2.85−2.91 (2H, m), 4.67 (2H, s), 7.21−7.27 (2H, m), 7.36 (2H, d, J = 8.4 Hz), 7.42−7.50 (5H, m), 7.61 (2H, d, J = 8.4 Hz), 7.67 (1H, s). Anal. ($C_{26}H_{25}NO_2 \cdot 0.25H_2O$) C, H, N.

8a. This compound was prepared by a manner similar to that used for **8b**, yield 91%: mp 207−210 °C; ^{1}H NMR (DMSO-d_6) δ 2.50−2.66 (2H, m), 2.80−2.95 (2H, m), 4.46 (2H, s), 7.73−7.72 (13H, m), 9.91 (1H, s). Anal. ($C_{24}H_{21}NO_2 \cdot 0.5H_2O$) C, H, N.

***N*-(4-Chloromethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxamide (9b).** To a solution of **8b** (10.0 g, 26.1 mmol) and pyridine (0.1 mL) in $CHCl_3$ (150 mL) was added dropwise a solution of thionyl chloride (3.40 mL, 46.6 mmol) in $CHCl_3$ (90 mL), and the mixture was stirred for 17 h at room temperature under N_2. The mixture was poured into water, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give 10.2 g (97%) of **9b** as colorless prisms: mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 2.05−2.21 (2H, m), 2.40 (3H, s), 2.71 (2H, t, J = 6.4 Hz), 2.84−2.91 (2H, m), 4.58 (2H, s), 7.20−7.27 (2H, m), 7.35−7.52 (7H, m), 7.59−7.65 (2H, m), 7.71 (1H, s). Anal. Calcd. for ($C_{26}H_{24}ClNO \cdot 0.25H_2O$) C, H, N.

9a. This compound was prepared by a manner similar to that used for **9b**, yield 83%: mp 176−177 °C; ^{1}H NMR (DMSO-d_6) δ 2.55−2.68 (2H, m), 2.85−2.95 (2H, m), 4.74 (2H, s), 7.30−7.80 (13H, m), 10.05 (1H, s). Anal. ($C_{24}H_{20}ClNO$) C, H, N.

***N*-[4-(1-Perhydroazepinylmethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (6c).** A mixture of **9a** (0.30 g, 0.80 mmol) and hexamethyleneimine (0.27 mL, 2.4 mmol) in THF (10 mL) was stirred at room temperature for 19 h and refluxed for additional 3.5 h. The mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc:NEt_3 = 40:2) to give crude prisms. Recrystallized from EtOAc and hexane to give 0.26 g (73%) of **6c** as colorless prisms: ^{1}H NMR ($CDCl_3$) δ 1.61 (8H, s), 2.56−2.76 (6H, m), 2.92−3.03 (2H, m), 3.61 (2H, s), 7.23−7.61 (14H, m).

***N,N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium Iodide (1w): Method A.** A solution of **6r** (57.5 g, 0.120 mol) and iodomethane (18.6 mL, 0.299 mol) in DMF (500 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo, and then EtOAc was added to the residue. The precipitate was filtered, washed with EtOAc and MeOH. Recrystallized from EtOH and EtOAc to give 71.0 g (95%) of **1w** as colorless prisms: ^{1}H NMR (DMSO-d_6) δ 1.80−2.20 (6H, m), 2.35 (3H, s), 2.64 (2H, t, J = 6.6 Hz), 2.80−2.88 (2H, m), 2.88 (6H, s), 3.33−3.40 (2H, m), 3.50−3.65 (1H, m), 4.02−4.09 (2H, m), 4.47 (2H, s), 7.26−7.37 (4H, m), 7.50−7.60 (5H, m), 7.66 (1H, s), 7.88 (2H, d, J = 8.8 Hz), 10.22 (1H, s).

The following compounds (**1a**−**d**,**g**−**q**,**s**−**v**, **2**) were prepared by a manner similar to that used for **1w**.

1a: ^{1}H NMR ($CDCl_3$) δ 2.05−2.40 (4H, m), 2.65−2.76 (2H, m), 2.82−2.95 (2H, m), 3.05 (3H, s), 3.43−3.57 (2H, m), 3.80−4.00 (2H, m), 4.98 (2H, s), 7.18 (1H, d, J = 8.0 Hz), 7.30−7.56 (9H, m), 7.70 (1H, s), 7.80−7.90 (2H, m), 8.74 (1H, s).

1b: ^{1}H NMR (DMSO-d_6) δ 1.40−2.00 (6H, m), 2.55−2.70 (2H, m), 2.80−3.00 (5H, m), 3.20−3.45 (4H, m), 4.53 (2H, s), 7.30−7.70 (11H, m), 7.89 (2H, d, J = 8.6 Hz), 10.18 (1H, s).

1c: ^{1}H NMR (DMSO-d_6) δ 1.50−1.70 (4H, m), 1.80−1.96 (4H, m), 2.55−2.68 (2H, m), 2.83−2.97 (5H, m), 3.22−3.36 (2H, m),

3.40−3.60 (2H, m), 4.50 (2H, s), 7.30−7.70 (11H, m), 7.89 (2H, d, J = 8.4 Hz), 10.19 (1H, s).

1d: ^{1}H NMR ($CDCl_3$) δ 2.60−2.75 (2H, m), 2.75−2.90 (2H, m), 3.22 (3H, s), 3.35−3.50 (2H, m), 3.55−3.75 (2H, m), 3.80−4.05 (4H, m), 5.13 (2H, s), 7.12 (1H, d, J = 7.6 Hz), 7.25−7.55 (9H, m), 7.71 (1H, s), 7.80−7.87 (2H, m), 8.95 (1H, s).

1g: ^{1}H NMR (DMSO-d_6) δ 1.45−1.90 (6H, m), 2.55−2.70 (2H, m), 2.80−3.17 (7H, m), 3.25−3.60 (6H, m), 7.25−7.80 (13H, m), 9.95 (1H, s).

1h: ^{1}H NMR (DMSO-d_6) δ 1.40−2.00 (6H, m), 2.35 (3H, s), 2.55−2.67 (2H, m), 2.82−2.95 (5H, m), 3.22−3.35 (4H, m), 4.53 (2H, s), 7.24−7.35 (3H, m), 7.46−7.60 (7H, m), 7.89 (2H, d, J = 8.8 Hz), 10.15 (1H, s).

1i: ^{1}H NMR ($CDCl_3$) δ 1.62−2.01 (4H, m), 2.36 (3H, s), 3.06 (3H, br s), 3.34−3.49 (2H, m), 3.60−3.76 (2H, m), 4.97 (2H, br s), 5.04 (2H, br s), 6.85 (1H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.2 Hz), 7.37−7.42 (3H, m), 7.47−7.52 (3H, m), 7.83−7.91 (3H, m), 9.00 (1H, br s).

1j: ^{1}H NMR (DMSO-d_6) δ 1.45−1.65 (2H, m), 1.80−1.94 (4H, m), 1.99−2.09 (2H, m), 2.35 (3H, s), 2.64 (2H, t, J = 6.1 Hz), 2.83−2.88 (2H, m), 2.91 (3H, s), 3.23−3.29 (4H, m), 4.53 (2H, s), 7.26−7.38 (4H, m), 7.48−7.68 (6H, m), 7.87 (2H, d, J = 8.6 Hz), 10.23 (1H, s).

1k: ^{1}H NMR (DMSO-d_6) δ 1.45−1.70 (2H, m), 1.70−1.95 (4H, m), 2.34 (3H, s), 2.91 (3H, s), 3.00 (2H, br), 3.24−3.34 (4H, m), 4.31 (2H, br), 4.53 (2H, s), 7.06 (1H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.36 (1H, s), 7.48−7.59 (5H, m), 7.75 (1H, s), 7.86 (2H, d, J = 8.8 Hz), 10.19 (1H, s).

1l: ^{1}H NMR (DMSO-d_6) δ 1.80−2.00 (2H, m), 2.10−2.25 (2H, m), 2.35 (3H, s), 2.88 (6H, s), 2.95−3.05 (2H, m), 3.15−3.45 (2H, m), 3.45−3.70 (1H, m), 4.00−4.15 (2H, m), 4.25−4.35 (2H, m), 4.46 (2H, s), 7.06 (1H, d, J = 8.4 Hz), 7.27 (2H, d, J = 7.6 Hz), 7.36 (1H, s), 7.50−7.60 (5H, m), 7.70−7.80 (1H, m), 7.86 (2H, d, J = 8.8 Hz), 10.20 (1H, s).

1m: ^{1}H NMR (DMSO-d_6) δ 1.75−2.00 (2H, m), 2.34 (3H, s), 2.55−2.75 (4H, m), 2.75−2.85 (2H, m), 2.90 (6H, s), 3.00 (2H, br), 3.14−3.25 (1H, m), 4.31 (2H, br), 4.47 (2H, s), 7.07 (1H, d, J = 8.4 Hz), 7.27 (2H, d, J = 7.8 Hz), 7.36 (1H, s), 7.50−7.59 (5H, m), 7.74 (1H, d, J = 2.2 Hz), 7.86 (2H, d, J = 8.8 Hz), 10.19 (1H, s).

1n: ^{1}H NMR (DMSO-d_6) δ 2.09−2.24 (2H, m), 2.34 (3H, s), 2.41−2.61 (6H, m), 2.97 (6H, s), 2.97−3.00 (2H, m), 3.79−3.90 (1H, m), 4.31 (2H, t, J = 4.4 Hz), 4.56 (2H, s), 7.07 (1H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.2 Hz), 7.37 (1H, s), 7.55−7.60 (5H, m), 7.75 (1H, d, J = 2.2 Hz), 7.88 (2H, d, J = 8.8 Hz), 10.20 (1H, s).

1o: ^{1}H NMR ($CDCl_3$) δ 1.09 (6H, t, J = 7.0 Hz), 1.60−1.80 (2H, m), 2.00−2.30 (2H, m), 2.36 (3H, s), 3.00 (6H, s), 3.00−3.10 (2H, m), 3.30−3.40 (1H, m), 4.20−4.35 (2H, m), 4.81 (2H, s), 6.98 (1H, d, J = 8.8 Hz), 7.20 (2H, d, J = 7.4 Hz), 7.35−7.60 (6H, m), 7.70−7.80 (1H, m), 7.83 (2H, d, J = 8.8 Hz), 8.83 (1H, s).

1p: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.00−2.20 (2H, m), 2.40 (3H, s), 3.06−3.10 (2H, m), 3.10 (6H, s), 3.51−3.61 (2H, m), 3.73 (2H, t, J = 5.4 Hz), 4.37 (2H, t, J = 4.6 Hz), 4.61 (2H, s), 7.07 (1H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.46−7.59 (7H, m), 7.81 (2H, d, J = 8.2 Hz), 9.54 (1H, s).

1q: ^{1}H NMR ($CDCl_3$) δ 1.65−1.95 (6H, m), 2.35 (3H, s), 2.95−3.05 (4H, m), 3.25 (3H, s), 3.61−3.85 (6H, m), 4.29 (2H, *t*, J = 4.2 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.17−7.26 (4H, m), 7.40−7.50 (4H, m), 7.58 (2H, d, J = 8.4 Hz), 7.70 (1H, d, J = 2.2 Hz), 8.49 (1H, br).

1s: ^{1}H NMR (DMSO-d_6) δ 1.41 (3H, t, J = 7.0 Hz), 1.68−1.98 (2H, m), 2.10−2.26 (2H, m), 2.94 (6H, s), 2.98−3.08 (2H, m), 3.35−3.59 (3H, m), 3.96−4.16 (2H, m), 4.03 (2H, q, J = 7.0 Hz), 4.19−4.31 (2H, m), 4.84 (2H, s), 6.91 (2H, d, J = 8.8 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.38 (1H, dd, J = 8.4, 2.2 Hz), 7.44−7.57 (5H, m), 7.69 (1H, d, J = 2.2 Hz), 7.80 (2H, d, J = 8.4 Hz), 8.01 (1H, s).

1t: ^{1}H NMR (DMSO-d_6) δ 1.42−1.66 (2H, m), 1.75−1.88 (2H, m), 2.55 (6H, s), 2.62−2.72 (2H, m), 2.94−3.35 (3H, m), 3.68−3.81 (2H, m), 3.96−4.08 (2H, m), 4.13 (2H, s), 6.80 (1H, d, J = 8.8 Hz), 7.05 (1H, s), 7.21 (2H, d, J = 8.4 Hz), 7.34−7.40 (1H, m), 7.44−7.63 (7H, m), 9.89 (1H, s).

1u: ^{1}H NMR (DMSO-d_6) δ 1.80−2.20 (10H, m), 2.63 (2H, t, J = 5.6 Hz), 2.81−2.84 (2H, m), 2.88 (6H, s), 3.24−3.44 (6H, m), 3.54−3.65 (1H, m), 4.02−4.11 (2H, m), 4.46 (2H, s), 6.62 (2H, d, J = 9.0 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.36−7.60 (7H, m), 7.88 (2H, d, J = 8.4 Hz), 10.22 (1H, s).

1v: ^{1}H NMR (DMSO-d_6) δ 1.50−1.70 (6H, m), 1.80−1.95 (2H, m), 2.00−2.10 (2H, m), 2.10−2.20 (2H, m), 2.60−2.70 (2H, m), 2.75−2.87 (2H, m), 2.88 (6H, s), 3.14−3.24 (6H, m), 3.53−3.65 (1H, m), 4.00−4.15 (2H, m), 4.46 (2H, s), 7.00 (2H, d, J = 8.8 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.36 (1H, s), 7.46−7.62 (6H, m), 7.87 (2H, d, J = 8.8 Hz), 10.22 (1H, s).

2: ^{1}H NMR (DMSO-d_6) δ 1.62 (2H, m), 1.88 (4H, m), 2.37 (3H, s), 2.93 (3H, s), 3.36 (4H, m), 4.55 (2H, s), 6.97 (1H, d, J = 15.8 Hz), 7.31 (2H, d, J = 7.6 Hz), 7.50−7.90 (11H, m), 10.44 (1H, s).

***N,N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium Chloride (1r).** A solution of **1w** (75.0 g, 0.120 mol) in MeOH and water was subjected to an ion exchange column chromatography (Dowex SBR, 20−50 mesh, Cl^- form) to give crude prisms. Recrystallized from EtOH to give 50.6 g (80%) of **1r** as colorless prisms: ^{1}H NMR (DMSO-d_6) δ 1.80−2.25 (6H, m), 2.35 (3H, s), 2.65 (2H, t, J = 6.4 Hz), 2.80−2.89 (2H, m), 2.89 (6H, s), 3.24−3.43 (2H, m), 3.61 (1H, t, J = 11.0 Hz), 4.04−4.10 (2H, m), 4.49 (2H, s), 7.26−7.32 (3H, m), 7.42 (1H, s), 7.50−7.61 (5H, m), 7.69 (1H, d, J = 1.8 Hz), 7.91 (2H, d, J = 8.6 Hz), 10.32 (1H, s).

1r: Method B. To a solution of **26** (4.50 g, 34.8 mmol) in DMF (50 mL) was added a solution of **9b** (9.40 g, 23.4 mmol) in DMF (50 mL), and the mixture was stirred for 23 h at room temperature under nitrogen atmosphere. The solvent was evaporated in vacuo, and the crude prisms were filtered, washed with acetone. Recrystallized from EtOH to give 10.6 g (86%) of **1r** as colorless prisms.

The following compounds **(1e,f)** were prepared by a manner similar to that used for **1r** (Method B).

1e: ^{1}H NMR ($CDCl_3$) δ 1.37 (9H, t, J = 6.9 Hz), 2.72−2.96 (4H, m), 3.22 (6H, q, J = 6.9 Hz), 4.62 (2H, s), 7.15−7.45 (7H, m), 7.50−7.60 (3H, m), 7.99 (1H, s), 8.12 (2H, d, J = 8.6 Hz), 10.19 (1H, s).

1f: ^{1}H NMR ($CDCl_3$) δ 2.60−2.90 (7H, m), 6.07 (2H, s), 7.04−7.15 (3H, m), 7.25−7.50 (7H, m), 7.65 (1H, d, J = 7.8 Hz), 7.72−7.92 (4H, m), 8.12−8.22 (1H, m), 9.63 (1H, d, J = 6.2 Hz), 9.86 (1H, s).

***(E)*-Tri-*n*-butyl[4-[[3-(4-methylphenyl)cinnamoyl]amino]benzyl]phosphonium Chloride (B).** To a solution of (*E*)-*N*-[4-(chloromethyl)phenyl]-3-(4-methylphenyl)cinnamamide (0.30 g, 0.83 mmol) in toluene (10 mL) was added tri-*n*-butylphosphine (0.25 mL, 1.0 mmol), and the mixture was heated for 3 days at 80 °C. After cooled to room temperature, the resulting precipitate was filtered. Recrystallized from MeOH and EtOAc to give 0.39 g (83%) of **B** as colorless prisms: mp 216−217 °C; ^{1}H NMR (DMSO-d_6) δ 0.85−1.00 (9H, m), 1.30−1.60 (12H, m), 2.05−2.25 (6H, m), 2.37 (3H, s), 3.79 (2H, d, J = 15.2 Hz), 7.05 (1H, d, J = 15.8 Hz), 7.25−7.35 (4H, m), 7.48−7.90 (9H, m), 10.61 (1H, s). Anal. ($C_{35}H_{47}ClNOP$) C, H, N.

***N,N*-Dimethyl-*N*-(tetrahydropyran-4-yl)amine (26).** To a solution of tetrahydropyran-4*H*-one (60.0 g, 0.599 mol), water (5.00 mL) and DMF (70.0 mL, 0.904 mol) was added formic acid (46.0 mL, 1.22 mol), and the mixture was heated at 140 °C for 23 h. The solvent was evaporated in vacuo, and the residue was distilled under reduced pressure to give a crude liquid. The crude liquid was dissolved in aq HCl and washed with CH_2Cl_2; the aqueous layer was basified using 1 N NaOH and extracted with CH_2Cl_2 after being saturated with NaCl. The organic layer was dried over K_2CO_3, and evaporated in vacuo. The residue was purified by distillation to give 10.4 g (29%) of **26** as a colorless liquid: bp_{29} 75−82 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−1.82 (4H, m), 2.28 (6H, s), 2.25−2.40 (1H, m), 3.37 (2H, ddd, J = 2.2, 11.8, 11.8 Hz), 3.97−4.05 (2H, m).

Binding Assays. CHO-K1 and CHO/CCR5 cells (5×10^4 cells/100 μL) were cultured in a microtiter tray. After a 24-h incubation at 37 °C, culture medium was replaced with the

binding buffer (Ham's F-12 medium containing 20 mM Hepes and 0.5% bovine serum albumin; pH 7.2). Binding reactions were performed at room temperature for 40 min in the presence of [^{125}I]RANTES (specific activity: 2000 Ci/mmol; Amersham Pharmacia, Buckinghamshire, U.K.) and various concentration of the test compound. The binding reaction was terminated by washing out the free ligand with cold PBS, and the cell-associated radioactivity was counted by Top-count scintillation counter (Packard Japan, Tokyo, Japan). Binding assays for other receptors, CCR1, CCR2, CCR3 and CCR4, were carried out in a similar way.

Antiviral Assays.[26,27] The anti HIV-1 activities of the test compounds were based on the inhibition of virus-induced infectious focus formation in MAGI-CCR5 cells and the reduction of p24 antigen production in PBMCs. MAGI-CCR5 cells (1×10^4 cells/well) were cultured in a microtiter tray. After a 24-h incubation at 37 °C, the culture supernatants were replaced with fresh culture media containing R5 HIV-1 (Ba-L strain, approximately 300 focus forming units/well) and various concentrations of the test compounds. After a 2-day incubation, the cells were fixed and stained with 5-bromo-4-chloro-3-indolyl-β-D-galactosidase (X-Gal). The number of infected (blue) cells was counted microscopically. For the PBMC assays, phytochemagglutinin-stimulated PBMCs (2.5×10^5 cells/500 μL) were infected with HIV-1 in the presence of various concentrations of the test compounds. The amounts of the virus used for infection were, depending on the replicability of each strain, generally 1−10 ng of p24 per 2.5×10^5 cells. After an overnight incubation at 37 °C, the cells were washed extensively to remove unadsorbed viral particles and were incubated further with culture media containing the same concentrations of the compounds as those used during viral adsorption. On day 6 after viral infection, the culture supernatants were collected and determined for their p24 antigen levels with a sandwich ELISA kit (Cellular Products, Buffalo, NY).

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

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