Synthesis of 1-Benzothiepine and 1-Benzazepine Derivatives as Orally Active CCR5 Antagonists

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Quaternary ammonium benzocycloheptene compound 1 has previously been reported as a clinical candidate for an injectable CCR5 antagonist. In order to develop an orally active CCR5 antagonist, derivatives of tertiary amine benzocycloheptene 2, the chemical precursor to 1, were investigated. The benzocycloheptene ring was converted to benzothiepine and benzazepine rings and it was found that these changes could enhance the potency of tertiary amine derivatives. In particular, the 1-benzothiepine-1,1-dioxide 11b and the *N*-methyl-1-benzazepine 18 showed increased activity and good preliminary pharmacokinetic properties. The synthesis of 1-benzothiepine and 1-benzazepine derivatives and their activity are described.

Key words CCR5 antagonist; quaternary ammonium salt; tertiary amine moiety; 1-benzazapine; 1-benzothiepine

The β-chemokine receptor CCR5, a G-protein-coupled seven-transmembrane domain receptor, has been shown to act as a major co-receptor for fusion and entry of macrophage-tropic (M-tropic or R5) HIV-1 into the host cells.[1—4] Although combination chemotherapy and Highly Active Anti-Retroviral Therapy (HAART) have achieved long-term suppression of viral replication in HIV-1-infected individuals,[5] CCR5 presents an attractive target for the inhibition of M-tropic HIV-1 replication.

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 **1** has previously been reported as a novel and highly potent non-peptide CCR5 antagonist with a IC_{50} value of 1.4 nM in the binding assay.[6,7] Compound **1** has been selected as a clinical candidate for development as a subcutaneous injectable agent since it exhibited poor oral absorption owing to the quaternary ammonium moiety. However, in the course of the investigation of quaternary ammonium derivatives, it was found that the chemical precursor of **1**, benzocycloheptene derivative **2** containing a tertiary amine moiety, exhibited CCR5 antagonistic activity with an IC_{50} value of 0.95 μM in the binding assay. In addition, since **2** exhibited considerably better oral absorption than quaternary ammonium derivative **1**, **2** was used as a starting point to develop orally active small molecule CCR5 antagonists. In order to improve the potency of tertiary amine derivatives, conversion of the benzocycloheptene ring of lead compound **2** to other condensed-heterocycle rings such as 1-benzothiepine and 1-benzazepine was investigated, and the synthesis of these derivatives is described.

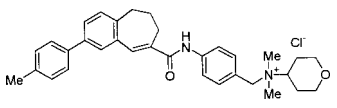
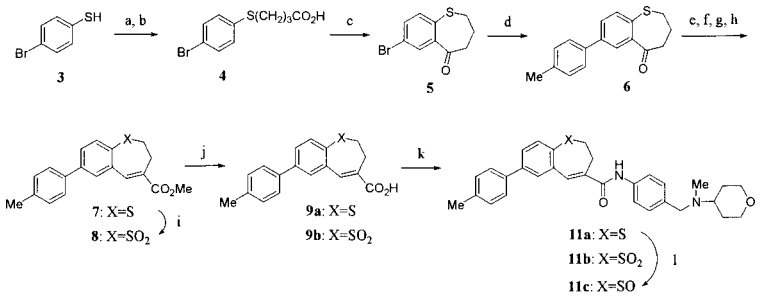


Fig. 1

Chemistry

The synthetic routes to the 1-benzothiepine, 1-benzothiepine-1-oxide and 1-benzothipine-1,1-dioxide derivatives are outlined in Chart 1. The benzothiepine ring was constructed by intramolecular Friedel-Crafts reaction of **4**, which was prepared by the alkylation of *p*-bromothiophenol **3** with ethyl 4-bromobutyrate and subsequent alkaline hydrolysis. The resulting bromide **5** was condensed with 4-methylphenylboronic acid by Suzuki coupling reaction to give the ketone **6**. Subsequent methoxycarbonylation gave the β-keto-ester, which was reduced using sodium borohydride, and dehydrated *via* mesylation to give the α,β-unsaturated esters **7**. Benzothiepine-1,1-dioxide **8** was obtained by *m*-chloroper-



Reagents: (a)$Br(CH_2)_3CO_2Et$, K_2CO_3; (b) NaOH; (c) PPA; (d) 4-MePhB$(OH)_2$, $Pd(PPh_3)_4$, (e) $(MeO)_2CO$, NaOMe; (f)$NaBH_4$; (g) MsCl. NEt_3; (h) DBU; (i) *m*CPBA; (j) NaOH, (k) 1) $(COCl)_2$, DMF, 2) **10**, NEt_3; (l) *m*CPBA.

Chart 1

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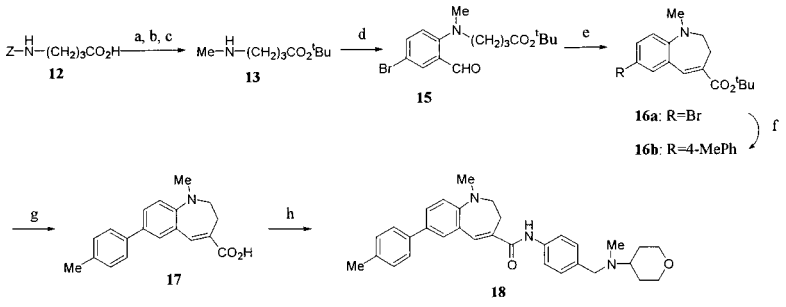


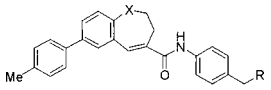
Reagents: (a) MeI, NaH; (b) *t*BuOH, H_2SO_4, $MgSO_4$; (c) H_2/Pd-C; (d) **14**, K_2CO_3; (e) *t*BuOK; (f) 4-$MePhB(OH)_2$, $Pd(PPh_3)_4$; (g) HCl; (h) 1) $SOCl_2$, DMF, 2) **10**, NEt_3.

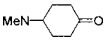
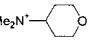
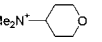
Chart 2

benzoic acid (*m*CPBA)-oxidation of **7**. Alkaline hydrolysis of the esters (**7**, **8**) afforded carboxylic acids (**9a**, **9b**), which were coupled with 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)-aminomethyl]aniline **10**[7] to provide the desired products (**11a**, **11b**). Oxidation of benzothiepine **11a** using *m*CPBA gave benzothiepine-1-oxide derivative **11c**.

Next, the synthesis of 1-methyl-1-benzazepine derivative **18** was carried out according to Chart 2. 4-{[(Benzyloxy)carbonyl]amino}butanoic acid **12** was *N*-methylated, *tert*-butyl-esterified, and deprotected by hydrogenation to give *tert*-butyl 4-(methylamino)butanoate **13**. The condensation of ester **13** with 5-bromo-2-fluorobenzaldehyde **14** gave substituted 2-aminobenzaldehyde **15**. The benzazepine ring **16a** was constructed by Dieckmann-type condensation of aldehyde **15**, using potassium *tert*-butoxide in good yeild (77%). Suzuki coupling reaction of **16a** with 4-methylphenylboronic acid gave **16b** which was converted to **17** by acid hydrolysis. Condensation of **17** with aniline **10** gave the desired anilide **18**. Further details are to be found in Table 2 and the Experimental Section.

Table 1.



Compound	X	R	IC_{50} (μM)[a]
2	CH_2		0.95
20	CH_2		2.6
21	O		4.0
22	O		1.6
23	O		0.63
24	O	$MeNCHEt_2$	0.64
25	O	$MeN(CH_2)_3OH$	0.73
19	O		0.53
1	CH_2		0.0014
26	O		0.0014

a) Inhibitory effects on the binding of [^{125}I]-RANTES to CCR5-expressing CHO cells.

Results and Discussion

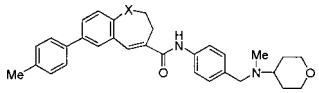
The synthesized compounds, benzocycloheptene **2**, the benzoxepine **19**, and a variety of tertiary amine derivatives **20**—**25**[7] were evaluated for their inhibitory effects on chemokine binding to CCR5-expressing CHO cells. Binding assays were performed in the presence of [^{125}I]-RANTES and the results are summarized in Tables 1 and 2 as IC_{50} values. The effect of changing the tertiary amine group of lead compound **2** for benzocycloheptene and 1-benzoxepine derivatives is shown in Table 1. Generally, the SAR of the tertiary amine moiety was similar to those of the corresponding quaternary ammonium moiety previously reported.[7] The piperidines (**20**, **21**) were less active compared with the bulkier *N*-(α-branched alkyl)-*N*-methylamines (**2**, **19**, **22**—**25**). The 4-oxocyclohexyl **23** and 3-pentyl **24** derivatives were comparable to tetrahydropyran-4-yl **19**, which was about twice as active as the benzocycloheptene **2**. Since quaternary ammonium compound **1** exhibited similar potency to the corresponding 1-benzoxepine compound **26** (IC_{50}=1.4 nM),[7] differences in the atom at the 5-postion of the benzocycloheptene ring were considered to have little effect on CCR5 antagonistic activity. However, in contrast, changes in the atom at the 5-postion of the tertiary amine derivatives, was found to affect activity.

Therefore, while retaining the tertiary amine moiety of **2**, other changes in the benzocycloheptene ring were investigated (Table 2). Replacement of the benzocycloheptene ring with the 1-benzothiepine ring **11a** slightly increased activity, and the 1-benzothiepine-1,1-dioxide **11b** and the 1-benzothiepine-1-oxide **11c** showed 3 to 5-fold more potent activity (IC_{50} values: 0.20 and 0.30 μM, respectively). In addition, the 1-benzazepine ring was examined and *N*-methyl-1-benzazepine **18** was found to exhibit more than 10-fold greater potency (IC_{50} value=0.13 μM), than benzocycloheptene **2**.

The pharmacokinetic parameters were determined for compounds **2**, **11b**, and **18** in rats (1 mg/kg, i.v.; 10 mg/kg, *p.o.*).[8] The $AUCs_{(0—24\,h)}$ of compounds **2**, **11b** and **18** were 1.03, 1.55, and 1.56 μg·h/ml, respectively (10 mg/kg, *p.o.*), and the corresponding bioavailabilities were 48%, 52%, and 67%. These results indicate that compounds **11b** and **18** possess good oral bioavailability (>50%) in rats, similar to that of compound **2**.

The quaternary ammonium compound **1** is a highly potent CCR5 antagonist. Since the tertiary amine **2** showed *ca.* 700-fold less potency, the quaternary ammonium moiety was considered to be essential for good activity. However, the results reported herein indicate potency for the tertiary amine series can be increased by changes in the benzocycloheptene

Table 2.



Compound	X	IC_{50} (μM)[a]	mp (°C)	Formula	Anal.[b]
11a	S	0.80	234—235	$C_{31}H_{34}N_2O_2S \cdot 0.25H_2O$	C, H, N
11b	SO_2	0.20	234—235	$C_{31}H_{34}N_2O_4S$	C, H, N
11c	SO	0.30	191—192	$C_{31}H_{34}N_2O_3S \cdot 0.25H_2O$	C, H, N
18	NMe	0.13	178—181	$C_{32}H_{37}N_3O_2$	C, H, N

a) Inhibitory effects on the binding of [^{125}I]RANTES to CCR5-expressing CHO cells. *b*) Analytical results were within 0.4% of the theoretical value.

ring. In particular, 1-benzothiepine-1,1-dioxide **11b** and the *N*-methyl-1-benzazepine **18** were found to have increased activity, and exhibited good preliminary pharmacokinetic properties. Further modifications of 1-benzothiepine-1,1-dioxides and 1-benzazepines are under investigation to find orally active CCR5 antagonists with improved profiles.

Experimental

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 optimized.

4-[(4-Bromophenyl)thio]butanoic Acid (4) A mixture of **3** (125 g, 0.66 mol), ethyl 4-bromobutyrate (135 g, 0.69 mol) and K_2CO_3 (109 g, 0.79 mol) in DMF (1.2 l) was stirred at room temperature for 2 h. Water was added, and the aqueous mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. To a solution of the residue in EtOH (1.5 l) was added 1 N NaOH (800 ml), and the mixture was stirred for 3 h. The mixture was concentrated *in vacuo*, and the residue was extracted with water. After being washed with EtOAc, the aqueous layer was acidified using HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 172 g (96%) of **4** as colorless crystals: mp 118—119 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.87—2.02 (2H, m), 2.53 (2H, t, J=7.1 Hz), 2.96 (2H, t, J=7.2 Hz), 7.21 (2H, d, J=8.8 Hz), 7.41 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1699. *Anal.* Calcd for $C_{10}H_{11}BrO_2S$: C, 43.65; H, 4.03. Found: C, 43.70; H, 3.93.

7-Bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (5) A mixture of **4** (58 g, 0.21 mol) and polyphosphoric acid (830 g) was heated at 110 °C for 1.5 h. The mixture was poured into ice and water, and the aqueous mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=2 : 1) to give 37.2 g (69%) of **5** as pale brown crystals: ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.35 (2H, m), 2.94—3.08 (4H, m), 7.33 (1H, d, J=8.0 Hz), 7.44 (1H, dd, J=8.0, 2.6 Hz), 7.96 (1H, d, J=2.6 Hz). IR (KBr) cm^{-1}: 1682. *Anal.* Calcd for $C_{10}H_9BrOS$: C, 46.71; H, 3.53. Found: C, 46.71; H, 3.45.

7-(4-Methylphenyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6) A mixture of **5** (17.8 g, 69.2 mmol), 4-methylphenylboronic acid (10.0 g, 73.6 mmol), EtOH (100 ml) and 2 M K_2CO_3 (100 ml) in toluene (300 ml) was stirred at room temperature under argon atmosphere for 30 min. Tetrakis(triphenylphosphine)palladium (3.2 g, 2.77 mmol) was added, and the mixture was refluxed for 3.5 h under argon atmosphere. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed 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 17.9 g (99%) of **6** as colorelss crystals: mp 108—109 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.23—2.37 (2H, m), 2.39 (3H, s), 2.98—3.12 (4H, m), 7.24 (2H, d, J=7.0 Hz), 7.48—7.59 (4H, m), 8.07 (1H, d, J=1.8 Hz). IR (KBr) cm^{-1}: 1678. *Anal.* Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01. Found: C, 75.78; H, 6.07.

16b: This compound was prepared in a similar manner to that used for **6**, yield 72%: Yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s), 2.38 (3H, s), 2.83 (2H, t, J=4.9 Hz), 3.06 (3H, s), 3.28 (2H, t, J=4.9 Hz), 6.85 (1H, d, J=8.4 Hz), 7.23 (2H, d, J=8.0 Hz), 7.45 (1H, dd, J=8.6, 2.4 Hz), 7.46 (2H, d, J=8.2 Hz), 7.53 (1H, d, J=2.2 Hz), 7.67 (1H, s).

Methyl 7-(4-Methylphenyl)-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate To a solution of **6** (17.9 g, 66.7 mmol) in dimethyl carbonate (300 ml), was added sodium methoxide (18.0 g, 330 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 with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was washed with EtOAc and hexane to give 19.8 g (92%) of the title compound as colorless crystals: mp 109—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 2.44—2.90 (3H, m), 3.17—3.30 (2H, m), 3.75 (3H, s), 4.56—4.65 (1H, m), 7.25 (2H, d, J=8.0 Hz), 7.49—7.53 (3H, m), 7.60 (1H, dd, J=8.2, 2.0 Hz), 8.10 (1H, d, J=2.0 Hz), 8.07 (1H, d, J=1.8 Hz). IR (KBr) cm^{-1}: 1748, 1682. *Anal.* Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56. Found. C, 70.33; H, 5.66.

Methyl 7-(4-Methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (7) To a solution of methyl 7-(4-methylphenyl)-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate (13.9 g, 42.6 mmol) in CH_2Cl_2 (250 ml), was added a mixture of $NaBH_4$ (2.4 g, 63.4 mmol) in MeOH below −10 °C, and the mixture was stirred at −10 °C for 1 h. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. To a solution of the residue and triethylamine (18.0 ml, 0.13 mol) in CH_2Cl_2 (250 ml), was added dropwise methanesulfonyl chloride (7.50 ml, 45.2 mmol) under ice cooling. After overnight stirring at room temperature, 1,8-diazabicyclo[5.4.0]undec-7-ene (28.0 ml, 0.187 mol) was added dropwise with ice cooling. The reaction mixture was stirred for 1 h 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 6.7 g (51%) of **7** as colorless crystals: mp 108—109 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.01 (2H, t, J=5.9 Hz), 3.22 (2H, t, J=5.9 Hz), 3.84 (3H, s), 7.26 (2H, d, J=7.8 Hz), 7.41 (1H, dd, J=8.0, 1.8 Hz), 7.46—7.54 (3H, m), 7.59 (1H, d, J=1.8 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1709. *Anal.* Calcd for $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84. Found. C, 73.60; H, 5.63.

Methyl 7-(4-Methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-dioxide (8) To a solution of **7** (1.5 g, 4.8 mmol) in CH_2Cl_2 (25 ml), *m*CPBA (70%, 2.4 g, 9.7 mmol) was added under ice cooling, and the mixture was stirred at room temperature for 1 h. After aqueous $Na_2S_2O_3$ was added, the mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 1.6 g (97%) of **8** as colorless crystals: mp 203—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.15 (2H, t, J=6.6 Hz), 3.65 (2H, t, J=6.6 Hz), 3.88 (3H, s), 7.31 (2H, d, J=8.3 Hz), 7.52 (2H, d, J=8.3 Hz), 7.69—7.74 (2H, m), 7.92 (1H, s), 8.22 (1H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1713. *Anal.* Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found. C, 66.47; H, 5.33.

7-(4-Methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic Acid (9a) A mixture of **7** (2.5 g, 8.1 mmol) and 1 N NaOH (100 ml) in MeOH (200 ml) and diethylether (100 ml) was stirred overnight at room temperature. The mixture was concentrated, acidified using 1 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 2.3 g (95%) of **9a** as colorless crystals: mp 245—246 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.05 (2H, t, J=5.4 Hz), 3.24 (2H, t, J=5.4 Hz), 7.26 (2H, d, J=8.0 Hz), 7.41—7.56 (4H, m), 7.62 (1H, d, J=2.0 Hz), 8.01 (1H, s). IR (KBr) cm^{-1}: 1680. *Anal.* Calcd for $C_{19}H_{16}O_2S$: C, 72.94; H, 5.44. Found. C, 72.71; H, 5.34.

9b: This compound was prepared in a similar manner to that used for **9a**,

yield 92% (purity about 70%); ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.14 (2H, t, J=6.6 Hz), 3.66 (2H, t, J=6.6 Hz), 7.26—7.33 (2H, m), 7.47—7.57 (2H, m), 7.70—7.74 (2H, m), 7.95 (1H, s), 8.21 (1H, d, J=8.8 Hz).

7-(4-Methylphenyl)-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (11a) To a mixture of **9a** (0.3 g, 1.0 mmol) in CH_2Cl_2 (10 ml), was added oxalyl chloride (0.27 ml, 2.8 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 (15 ml) was added dropwise to a solution of **10** (0.25 g, 1.1 mmol) and triethylamine (0.42 ml, 3.0 mol) in THF (15 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 with water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 0.45 g (90%) of **11a** as colorless crystals. Recrystallized from EtOAc and hexane: mp 234—235 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.77 (4H, m), 2.21 (3H, s), 2.40 (3H, s), 2.57—2.70 (1H, m), 3.08 (2H, t, J=5.8 Hz), 3.26—3.44 (4H, m), 3.57 (2H, s), 4.01—4.11 (2H, m), 7.24—7.34 (3H, m), 7.40—7.57 (8H, m), 7.70 (1H, s). IR (KBr) cm^{-1}: 2949, 2845, 1651, 1597, 1516. *Anal.* Calcd for $C_{31}H_{34}N_2O_2S\cdot 0.25H_2O$: C, 74.00; H, 6.91; N, 5.57. Found. C, 73.98; H, 6.86; N, 5.77.

11b: This compound was prepared in a similar manner to that used for **11a**, yield 46%, mp 234—235 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.67—1.75 (4H, m), 2.21 (3H, s), 2.42 (3H, s), 2.57—2.70 (1H, m), 3.17 (2H, t, J=6.8 Hz), 3.37 (2H, t, J=2.6, 11.2 Hz), 3.58 (2H, s), 3.73 (2H, t, J=6.8 Hz), 4.01—4.11 (2H, m), 7.27—7.36 (4H, m), 7.49—7.57 (4H, m), 7.65 (1H, s), 7.70 (1H, dd, J=2.0, 8.2 Hz), 7.94 (1H, s), 8.21 (1H, d, J=8.2 Hz). IR (KBr) cm^{-1}: 2946, 2845, 2845, 1667, 1597, 1518. *Anal.* Calcd for $C_{31}H_{34}N_2O_4S$: C, 70.16; H, 6.46; N, 5.28. Found. C, 69.95; H, 6.22; N, 5.16.

7-(4-Methylphenyl)-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1-oxide (11c) To a solution of **11a** (0.2 g, 0.4 mmol) in CH_2Cl_2 (50 ml), *m*CPBA (70%, 0.1 g, 0.4 mmol) was added below −10 °C, and the mixture was stirred at that temperature for 1 h. After aqueous $Na_2S_2O_3$ was added, the mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (10% MeOH/CH_2Cl_2) to give 0.04 g (18%) of **11c** as colorless crystals. Recrystallized from EtOAc and hexane: mp 191—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.80 (4H, m), 2.22 (3H, s), 2.41 (3H, s), 2.55—290 (2H, m), 3.10—3.25 (1H, m), 3.35—3.50 (3H, m), 3.58 (2H, s), 3.81—3.95 (1H, m), 4.01—4.11 (2H, m), 7.25 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.5 Hz), 7.45 (2H, d, J=8.0 Hz), 7.52 (1H, s), 7.61 (2H, d, J=8.5 Hz), 7.70 (1H, dd, J=2.0, 8.2 Hz), 7.97 (1H, d, J=8.0 Hz), 8.26 (1H, s). IR (KBr) cm^{-1}: 2948, 2845, 1663, 1599, 1516. *Anal.* Calcd. for $C_{31}H_{34}N_2O_3S\cdot 0.25H_2O$: C, 71.72; H, 6.70; N, 5.40. Found. C, 71.79; H, 6.82; N, 5.66.

4-[[(Benzyloxy)carbonyl](methyl)amino]butanoic Acid To a solution of **12** (25.0 g, 105 mmol) and methyl iodide (37.4 g, 263 mmol) in THF (500 ml) was added sodium hydride (60% dispersion, 10.5 g, 263 mmol) under ice cooling. The mixture was stirred at room temperature under nitrogen for 24 h and then poured into ice and 1 N NaOH. After being washed with Et_2O, the aqueous layer was acidified using conc. HCl and extracted with EtOAc. The organic layer was washed with 1 M $Na_2S_2O_3$, dried over $MgSO_4$, and evaporated *in vacuo* to give 26.3 g (quant.) of the title compound as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 1.88 (2H, m), 2.35—2.37 (2H, m), 2.93 (3H, s), 3.36 (2H, t, J=6.6 Hz), 5.13 (2H, s), 7.35 (5H, s).

***tert*-Butyl 4-[[(Benzyloxy)carbonyl](methyl)amino]butanoate** To a mixture of $MgSO_4$ (50.6 g, 420 mmol) in CH_2Cl_2 (1 l), H_2SO_4 (6.0 ml, 105 mmol) was added with vigorous stirring. After 15 min, 4-[[(benzyloxy)carbonyl](methyl)amino]butanoic acid (26.3 g, 105 mmol) and *tert*-BuOH (50.5 ml, 528 mmol) were added successively. The mixture was tightly sealed, and stirred for 18 h at room temperature. Aqueous $NaHCO_3$ was added, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=5 : 1) to give 17.2 g (53%) of title compound as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.82 (2H, quintet, J=6.6 Hz), 2.21 (2H, t, J=6.2 Hz), 2.93 (3H, s), 3.31 (2H, t, J=7.1 Hz), 5.13 (2H, s), 7.35 (5H, s).

***tert*-Butyl 4-(Methylamino)butanoate (13)** A solution of *tert*-butyl 4-[[(benzyloxy)carbonyl](methyl)amino]butanoate (6.06 g, 19.7 mmol) in MeOH (70 ml) was hydrogenated over 10% Pd-C (580 mg) for 3 h at room temperature under atmospheric pressure. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to give 3.35 g (98%) of **13** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.72 (1H, br s), 1.77 (2H, quintet, J=7.2 Hz), 2.27 (2H, t, J=7.3 Hz), 2.43 (3H, s), 2.61 (2H, t, J=7.1 Hz).

***tert*-Butyl 4-[(4-Bromo-2-formylphenyl)(methyl)amino]butanoate (15)** To a solution of **13** (1.05 g, 6.06 mmol) in DMF (5.0 ml), a solution of 5-bromo-2-fluorobenzaldehyde (**14**) (1.03 g, 5.05 mmol) in DMF (1.0 ml) and K_2CO_3 (0.84 g, 6.06 mmol) was added. The mixture was stirred at 70 °C for 60 h. Water (50 ml) was added, and the aqueous mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=10 : 1) to give 1.62 g (90%) of **15** as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.88 (2H, quintet, J=7.4 Hz), 2.22 (2H, t, J=7.3 Hz), 2.88 (3H, s), 3.14 (2H, t, J=7.3 Hz), 7.01 (1H, d, J=8.6 Hz), 7.55 (1H, dd, J=8.7, 2.5 Hz), 7.88 (1H, d, J=2.6 Hz), 10.19 (1H, s).

***tert*-Butyl 7-Bromo-1-methyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (16a)** A mixture of **15** (4.54 g, 12.7 mmol) and potassium *tert*-butoxide (1.43 g, 12.7 mmol) in *tert*-BuOH (250 ml) was stirred at reflux for 1 h. The mixture was poured into water, 1 N HCl was added, and the aqueous mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=from 10 : 1 to 1 : 1) to give 3.33 g, (77%) of **16** as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H, s), 2.80 (2H, t, J=4.8 Hz), 3.00 (3H, s), 3.21 (2H, t, J=4.7 Hz), 6.65 (1H, d, J=8.8 Hz), 7.25 (1H, dd, J=8.8, 2.2 Hz), 7.39 (1H, d, J=2.6 Hz), 7.46 (1H, s).

1-Methyl-7-(4-methylphenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid Hydrochloride (17) A mixture of **16b** (490 mg, 1.40 mmol) and 2 N HCl in EtOAc (14 ml) was stirred at room temperature for 20 h. The solvent was evaporated *in vacuo* to give 443 mg (96%) of **17** as pale yellow crystals: mp 249—252 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 2.75 (2H, t, J=4.6 Hz), 3.03 (3H, s), 3.25 (2H, t, J=4.9 Hz), 6.92 (1H, d, J=8.6 Hz), 7.22 (2H, d, J=8.2 Hz), 7.53 (1H, dd, J=8.8, 2.4 Hz), 7.55 (2H, d, J=8.2 Hz), 7.65 (1H, d, J=2.4 Hz), 7.68 (1H, s). IR (KBr) cm^{-1}: 3021, 2469, 1707, 1466, 1190, 1107, 810, 530. *Anal.* Calcd for $C_{19}H_{19}NO_2\cdot HCl\cdot 0.3H_2O$: C, 68.08; H, 6.19; N, 4.18. Found. C, 67.97; H, 6.13; N, 4.05.

1-Methyl-7-(4-methylphenyl)-*N*-[4-[[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (18) Thionyl chloride (0.26 ml, 3.57 mmol) was added to a solution of **17** (386 mg, 1.17 mmol) in DMF (12 ml) at room temperature. The mixture was stirred at room temperature for 30 min, evaporated *in vacuo*. A solution of the residue in CH_2Cl_2 (10 ml) was added dropwise to a solution of **10** (310 mg, 1.41 mmol) and triethylamine (0.82 ml, 5.88 mmol) in CH_2Cl_2 (4.0 ml) under ice cooling. The reaction mixture was stirred at room temperature for 22 h. The mixture was poured into water, and the aqueous mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (EtOh : EtOAc=1 : 9) to give crystals. Recrystallized from ethanol to give 250 mg (43%) of **18** as yellow crystals: mp 178—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.76 (4H, m), 2.21 (3H, s), 2.38 (3H, s), 2.66 (1H, septet, J=5.3 Hz), 2.96 (2H, t, J=4.4 Hz), 3.09 (3H, s), 3.30—3.43 (4H, m), 3.58 (2H, s), 4.01—4.06 (2H, m), 6.88 (1H, d, J=8.6 Hz), 7.23 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.4 Hz), 7.42, (1H, s), 7.46 (2H, d, J=8.2 Hz), 7.47 (1H, dd, J=8.3, 2.3 Hz), 7.535 (2H, d, J=8.4 Hz), 7.539 (1H, d, J=2.6 Hz), 7.58 (1H, s). IR (KBr) cm^{-1}: 3337, 2949, 2851, 1653, 1516, 1501, 1341, 1304, 1238, 818, 521. *Anal.* Calcd for $C_{32}H_{37}N_3O_2$: C, 77.54; H, 7.52; N, 8.48. Found. C, 77.51; H, 7.43; N, 8.44.

Binding Assays CHO-K1 and CHO/CCR5 cells (5×10^4 cells per 100 μl) were cultured in a microtiter tray. After a 24 h incubation at 37 °C, the 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^{TM} scintillation counter (Packard Japan, Tokyo, Japan).

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