Orally Active CCR5 Antagonists as Anti-HIV-1 Agents: Synthesis and Biological Activity of 1-Benzothiepine 1,1-Dioxide and 1-Benzazepine Derivatives Containing a Tertiary Amine Moiety

Masaki SETO,*[,a] Yoshio ARAMAKI,[a] Tomohiro OKAWA,[a] Naoki MIYAMOTO,[a] Katsuji AIKAWA,[a] Naoyuki KANZAKI,[b] Shin-ichi NIWA,[c] Yuji IIZAWA,[d] Masanori BABA,[e] and Mitsuru SHIRAISHI[a]

[a] *Medicinal Chemistry Research Laboratries, Pharmaceutical Research Division, Takeda Chemical Industries Ltd.;* [b] *Pharmaceutical Discovery Center, Pharmaceutical Research Division, Takeda Chemical Industries Ltd.;* [c] *Drug Analysis & Pharmacokinetics Research Laboratories, Pharmaceutical Research Division, Takeda Chemical Industries Ltd.;* [d] *Pharmacology Research Laboratories I, Pharmaceutical Research Division, Takeda Chemical Industries Ltd.; 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka 532–8686, Japan: and* [e] *Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University; 8–35–1, Sakuragaoka, Kagoshima 890–8520, Japan.*

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The search for orally active CCR5 antagonists was performed by chemical modification of the 1-benzothiepine 1,1-dioxide 3 and 1-benzazepine 4 lead compounds containing a tertiary amine moiety. Replacement of methyl group with a 2-($C_{2—4}$ alkoxy)ethoxy group at the 4-position on the 7-phenyl group of the 1-benzothiepine ring resulted in both enhanced activity and significant improvement in the pharmacokinetic properties upon oral administration in rats. Introduction of $C_{2—4}$ alkyl, phenyl or (hetero)arylmethyl groups as the 1-substituent on the 1-benzazepine ring together with the 2-(butoxy)ethoxy group led to further increase of activity. Among the 1-benzazepine derivatives, the isobutyl (6i), benzyl (6o) or 1-methylpyrazol-4-ylmethyl (6s) compounds were found to exhibit highly potent inhibitory effects, equivalent to the injectable CCR5 antagonist 1, in the HIV-1 envelope-mediated membrane fusion assay. In particular, compound 6s showed the most potent CCR5 antagonistic activity (IC_{50}=2.7 nM) and inhibitory effect (IC_{50}=1.2 nM) on membrane fusion, together with good pharmacokinetic properties in rats. The synthesis of 1-benzothiepine 1,1-dioxide and 1-benzazepine derivatives and their biological activity are described.

Key words CCR5 antagonist; HIV-1; 1-benzazepine; 1-benzothiepine 1,1-dioxide; 2-(alkoxy)ethoxy group

In 1996, it was found that the CC chemokine receptor 5 (CCR5) is a coreceptor for the entry of macrophage-tropic (CCR5-using or R5) human immunodeficiency virus type 1 (HIV-1) into host cells.[1—5] CCR5 is a member of the G-protein coupled seven-transmembrane domain receptors and its natural ligands [regulated on activation normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α and MIP-1β] are known to block R5 HIV-1 infection.[6] It has been found that individuals with a 32-base-pair deletion in the CCR5 coding region (CCR5Δ32) are highly resistant to R5 HIV-1 infection, and interestingly, these individuals don't appear to have any significant health problems.[7—9]

Recently, combination chemotherapy using HIV-1 protease inhibitors and reverse transcriptase inhibitors, called highly active antiretroviral therapy (HAART), has achieved high level and long-term suppression of viral replication in HIV-1 infected individuals.[10] However, eradication of HIV-1 is impossible even by HAART,[11] and there are several problems with HAART, such as the emergence of drug resistance, side-effect profiles and difficult dosing regimens.[12,13] Therefore, the discovery of novel anti-HIV-1 agents with new mechanisms of action is still needed and CCR5 antagonists as HIV-1 entry inhibitors are considered to be a new and attractive target.[14,15]

We previously discovered a small-molecule, nonpeptide CCR5 antagonist **1** as an anti-HIV-1 agent for injection.[16,17] Benzocycloheptene compound **1** exhibited highly potent CCR5 antagonistic and anti-HIV activities but poor oral absorption because of its polar quaternary ammonium moiety. We then reported that replacement of the benzocycloheptene ring in the tertiary amine compound **2** (the chemical precursor of **1**) with the 1-benzothiepine 1,1-dioxide (**3**) or 1-benzoazepine (**4**) ring moieties enhanced the activity.[18] We selected the orally active 1-benzothiepine 1,1-dioxide (**3**) and 1-benzazepine (**4**) compounds as new leads, and carried out their chemical modification in order to enhance the activity and to improve the pharmacokinetic profiles. In this paper, we describe the design, synthesis and structure–activity relationships (SAR) of the 1-benzothiepine 1,1-dioxide (**5**) and 1-benzazepine (**6**) derivatives.

Chemistry

The syntheses of the target compounds (**5**, **6**) are shown in Charts 1 and 2. Coupling reaction of the carboxylic acids **7** with 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline **8**[17] afforded the desired compounds (**5**, **6**) (Chart 1, Method A). An alternative synthetic method is outlined in Chart 2. The target compounds (**5**, **6**) were prepared by the Suzuki coupling reaction of the anilide derivatives **9** with the phenylboronic acids **10** (Chart 2, Method B).

The 1-benzothiepine-4-carboxylic acid key intermediates **7a**—**e** were synthesized according to Chart 3. Methoxycarbonylation of the ketone **11**[18] gave the β-keto ester, which was then transformed by reduction and subsequent dehydration *via* methanesulfonylation to afford the 1-benzothiepine-4-carboxylate **12**. The 1-benzothiepine 1,1-dioxide **13a** was obtained by oxidation of **12** using 30% aqueous H_2O_2. The carboxylic acids **7a**—**e** were prepared by the Suzuki coupling reaction of the 7-bromide **13a** followed by acid or alkaline hydrolysis.

The syntheses of the 1-benzazepines **13c**—**f** are illustrated

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

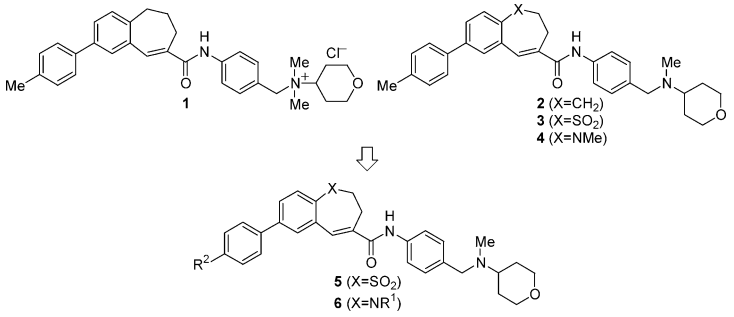
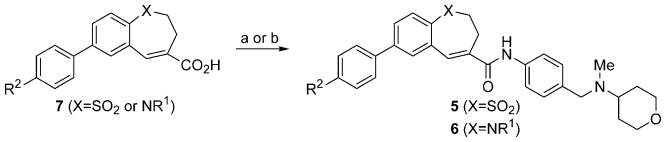
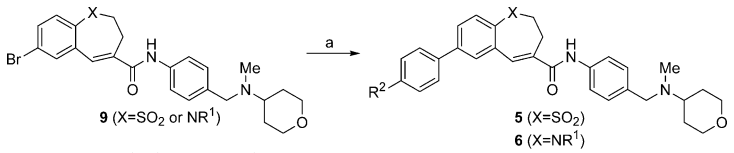


Fig. 1. Compound **1** and Lead Compounds of Orally Active CCR5 Antagonists



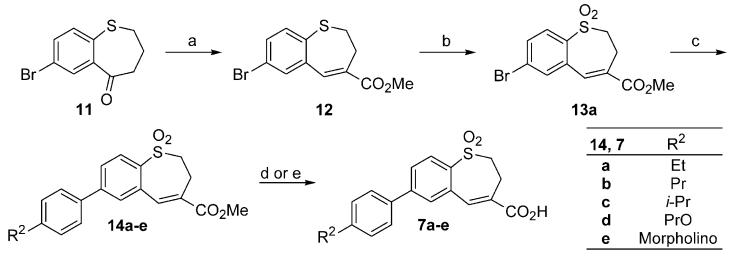
Reagents: (a) (1) $(COCl)_2$ or $SOCl_2$, cat. DMF, THF, (2) **8**, Et_3N, THF; (b) **8**, EDC, HOBt, Et_3N, DMF.

Chart 1



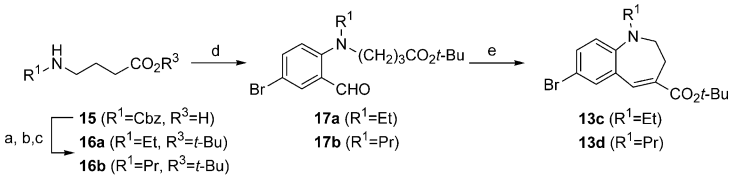
Reagents: (a) **10**, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, H_2O.

Chart 2



Reagents: (a) (1) NaOMe, $(MeO)_2CO$, (2) $NaBH_4$, MeOH, THF, (3) MsCl, Et_3N, THF, then DBU; (b) 30% aq. H_2O_2, AcOH; (c) **10**, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, H_2O; (d) 6N HCl, 1,2-dimethoxyethane; (e) 1N NaOH, EtOH, THF.

Chart 3



Reagents: (a) EtI or PrI, NaH, THF; (b) Boc_2O, DMAP, *t*-BuOH; (c) 10%Pd-C, H_2, conc. HCl, MeOH; (d) 5-bromo-2-fluorobenzaldehyde, K_2CO_3, DMF; (e) *t*-BuOK, *t*-BuOH.

Chart 4

in Charts 4 and 5. *N*-Alkylation of the *N*-Cbz protected 4-aminobutyric acid **15**, esterification[19] and subsequent removal of the Cbz group afforded the *tert*-butyl 4-(alkylamino)butyrates **16a**, **b**. Reaction of the amines **16a**, **b** with 5-bromo-2-fluorobenzaldehyde gave the cyclization precursors **17a**, **b**. The synthesis of 1-benzazepine derivatives **13c**, **d** was accomplished by the intramolecular Claisen–Schmidt type cyclization reaction of **17a**, **b** using potassium *tert*-butoxide. The 1-benzazepines **13e**, **f** were prepared by an alternative method (Chart 5). The 1-benzazepine-5-one **19** was obtained by the one-pot alkylation of **18**[20] with ethyl 4-bromobutyrate and Dieckmann-type condensation, followed by removal of the tosyl group and decarboxylation reaction using sulfuric acid and acetic acid.[21] The 1-benzazepine-4-carboxylate **20** was synthesized by a synthetic method similar to that used for 1-benzothiepine-4-carboxylate **12** after *N*-Boc protection of **19**. Removal of the *N*-Boc group of **20** gave the 1-unsubstituted 1-benzazepine **21**. Reductive amina-

tion of **21** with appropriate aldehydes afforded the 1-alkyl-1-benzazepines **13e**, **f**.[22]

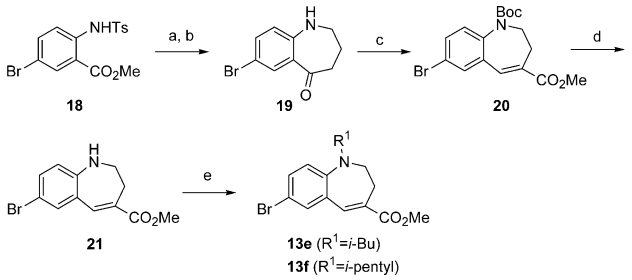
The key imtermediates **7f**—**o** were prepared according to Chart 6. Suzuki coupling reaction of **21** and subsequent reductive amination of **22** with appropriate aldehydes gave **14g**—**i**, **14k**—**o**.[22] The 1-phenyl-1-benzazepine **14j** was synthesized by phenylation of **22** using triphenylbismuth diacetate and copper(II) pivalate.[23] The ester **14f** was obtained by the Suzuki coupling reaction of **13e**. The 1-benzazepine-4-carboxylic acids **7f**—**o** were prepared by alkaline hydrolysis of the esters **14f**—**o**.

The synthetic route to the 1-acetyl-1-benzazepine-4-carboxylic acid **7p** is shown in Chart 7. Suzuki coupling reaction of **20** and subsequent deprotection of the *N*-Boc group gave the 1-benzazepine **24**. The carboxylic acid **7p** was prepared by acetylation of **24** and subsequent alkaline hydrolysis.

The other key intermediates, the anilide derivatives **9a**—**e**, were prepared according to Chart 8. Acid or alkaline hydrolysis of the compounds **13a**—**d**, **13f** provided the corresponding carboxylic acids **25a**—**e**. Conversion of the carboxylic acids **25a**—**e** into the acid chlorides and subsequent condensation with the aniline **8** gave the key intermediates **9a**—**e**.

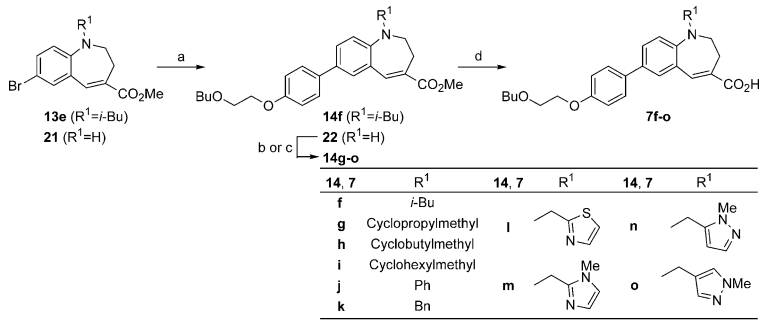
The requisite phenylboronic acids **10** utilized in the Suzuki coupling reaction were available commercially or synthesized according to Chart 9. The alkoxybromobenzenes **27a**—**f** were obtained by alkylation of the 4-bromophenol (**26a**) or 2-(4-bromophenoxy)ethanol (**26b**). Reaction of the Grignard reagents, generated by reaction of magnesium metal and the corresponding bromobenzenes **27b**—**f**, or phenyllithium, generated by halogen–metal exchange reaction of the bromobenzene **27a**, with trimethyl borate gave the 4-substituted phenylboronic acids **10a**—**f**.

The target compounds (**5a**—**d**, **6e**, **6i**, **6k**—**s**) were prepared by condensation of the acid chlorides, generated from the carboxylic acids (**7a**—**d**, **7f**—**p**), with the aniline **8** in the presence of triethylamine (Et_3N) (Chart 1, Method A). The compound **5e** was synthesized by an activated-ester method using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) (Chart 1, Method A). The other target compounds (**5f**—**k**, **6a**—**d**, **6f**—**h**, **6j**) were prepared by the Suzuki coupling re-



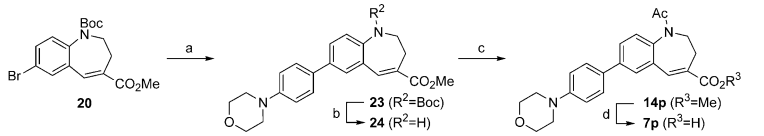
Reagents:(a) (1) NaH, NaI, $Br(CH_2)_3CO_2Et$, DMF, then NaH; (b) H_2SO_4, AcOH; (c) (1) Boc_2O, DMAP, THF, (2) MeONa, $(MeO)_2CO$, (3) $NaBH_4$, MeOH, THF, (4) MsCl, Et_3N, THF then DBU; (d) 6N HCl, EtOAc; (e) appropriate aldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane.

Chart 5



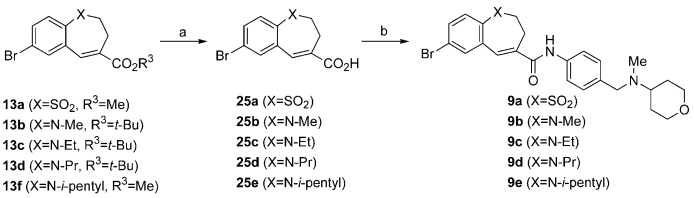
Reagents: (a) **10d**, K_2CO_3, toluene, EtOH, H_2O; (b) appropriate aldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; (c) $Ph_3Bi(OAc)_2$, cat. $Cu(OPiv)_2$, CH_2Cl_2; (d) 1N NaOH, MeOH, THF.

Chart 6



Reagents: (a) 4-(morpholino)phenylboronic acid, K_2CO_3, toluene, EtOH, H_2O; (b) 6N HCl, EtOAc; (c) AcCl, pyridine, THF; (d) 1N NaOH, MeOH, THF.

Chart 7



Reagents: (a) 6N HCl, 1,2-dimethoxyethane or 4N HCl/EtOAc, EtOAc or 1N NaOH, MeOH, THF; (b) (1) $SOCl_2$, cat. DMF, THF, (2) **8**, Et_3N, THF.

Chart 8

action of the bromides **9a**—**e** with the phenylboronic acids **10** (Chart 2, Method B).

Biological Results and Discussion

The compounds prepared were evaluated for their inhibitory effects on chemokine binding to CCR5-expressing CHO cells. Binding reactions were performed in the presence of [^{125}I]RANTES and various concentrations of the test compounds. The results are summarized in Tables 1 and 2 as IC_{50} values. The compounds with potent binding inhibitory activity were further evaluated for their inhibitory effects on an HIV-1 envelope (Env)-mediated membrane fusion. The membrane fusion assay was carried out using R5 HIV-1 (JR-FL strain) Env-expressing COS-7 cells and CCR5-expressing MOLT-4 cells. The results are summarized in Table 3 as IC_{50} values.

First, keeping the 1,1-dioxo-1-benzothiepine moiety in the lead compound **3**, the effect of the substituent at the 4-position on the 7-phenyl group was investigated (Table 1). As the size of the alkyl group was increased, the activity was found to become more potent (**5a**, **b**). Thus, the propyl compound **5b** had about 6 times greater activity than the methyl one **3**. Replacement of the propyl group (**5b**) with the propoxy group (**5d**) retained activity, but substitution with the bulkier isopropyl group (**5c**) decreased the activity compared with **5b**. These results suggested that the linear alkyl or alkoxy group was necessary for potent activity. Interestingly, the bulky morpholino-substituted compound **5e** exhibited relatively potent activity. Therefore, we examined the inhibitory effect of compound **5g** with the linear 2-(ethoxy)ethoxy group, which represents a ring-opened morpholino group after replacing the nitrogen atom with oxygen atom. The 2-(ethoxy)ethoxy-substituted compound **5g** was as highly active as compound **5d**. Furthermore, we investigated the effects of several alkoxyalkoxy groups in place of the 2-(ethoxy)ethoxy group. Replacement of the 2-(ethoxy)ethoxy group (**5g**) with the 2-(propoxy)ethoxy (**5h**) or 2-(butoxy)ethoxy (**5i**) group retained activity, whereas substitution of the smaller 2-(methoxy)ethoxy (**5f**) or longer 2-(pentyloxy)ethoxy (**5j**) group resulted in a relative decrease of activity. Replacement of the 2-(propoxy)ethoxy group (**5h**) with the 3-(ethoxy)propoxy group (**5k**) decreased the activity by about half. From these results, it was suggested that the length of alkoxyalkoxy group and position of the oxygen atom were important to exhibit potent activity. Secondly, we examined the inhibitory effects of the potent compounds **5h**, **i** in the binding assay on the HIV-1 Env-mediated membrane fusion. As shown in Table 3, their inhibitory effects were greatly weaker than their binding inhibitory activities (IC_{50}=420, 410 nM, respectively).

As described in our previous paper,[18] change at the 5-position (X) of the benzocycloheptene ring was considered to influence the activity (Fig. 1). Therefore, we targeted another lead compound, 1-benzazepine derivative **4**, in order to enhance the activity. On the basis of the above-mentioned results in the 1-benzothiepine 1,1-dioxides, we mainly modified the 1-substituent on the 1-benzazepine ring. The effect of the 4-substituent on the 7-phenyl group was verified, keeping the 1-methyl-1-benzazepine moiety (**6a**—**c**), and the 2-(butoxy)ethoxy-substituted compound **6c** was found to exhibit the most potent activity, followed by the 1-benzothiepine derivative **5i**. Replacement of the 1-methyl group of **6a** with the 1-ethyl group (**6d**) retained activity whereas the 1-acetyl-1-benzazepine derivative **6e**, which was considered as an introduction of an oxygen atom at the 1-position of the ethyl group of **6d**, decreased the activity. The 1-ethyl-1-benzazepines with the 2-(propoxy)ethoxy (**6f**) and 2-(butoxy)-

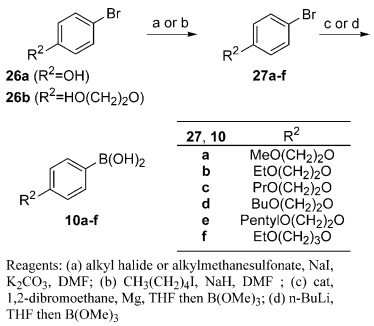
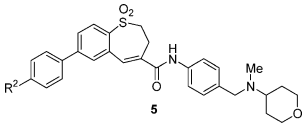


Chart 9

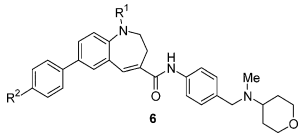
Table 1. Physical Properties and Inhibitory Effects of Compounds **5** on Chemokine Binding to CCR5-Expressing CHO Cells



Compd.	R^2	IC_{50}[a] (nM)	mp (°C)	Recrystln. solvent[b]	Method	Yield (%)	Formula	*Anal.*[c]
3	Me	200						
5a	Et	60	257—260	ET	A	61	$C_{32}H_{36}N_2O_4S$	CHN
5b	Pr	33	247—250	ET	A	69	$C_{33}H_{38}N_2O_4S$	CHN
5c	*i*-Pr	120	240—247	ET	A	67	$C_{33}H_{38}N_2O_4S$	CHN
5d	PrO	35	244—247	ET	A	56	$C_{33}H_{38}N_2O_5S$	CHN
5e	Morpholino	70	280—282	ET–E	A	24	$C_{34}H_{39}N_3O_5S\cdot 1.5H_2O$	CHN
5f	MeO(CH$_2$)$_2$O	140	227—231	ET	B	72	$C_{33}H_{38}N_2O_6S$	CHN
5g	EtO(CH$_2$)$_2$O	34	215—217	ET	B	75	$C_{34}H_{40}N_2O_6S$	CHN
5h	PrO(CH$_2$)$_2$O	35	195—197	ET	B	45	$C_{35}H_{42}N_2O_6S$	CHN
5i	BuO(CH$_2$)$_2$O	27	194—196	ET	B	68	$C_{36}H_{44}N_2O_6S$	CHN
5j	PentylO(CH$_2$)$_2$O	720	188—189	ET	B	49	$C_{37}H_{46}N_2O_6S$	CHN
5k	EtO(CH$_2$)$_3$O	68	214—215	ET	B	29	$C_{35}H_{42}N_2O_6S$	CHN

a) The concentration required to inhibit the binding of [^{125}I]RANTES to CCR5-expressing CHO cells by 50%. *b*) ET=ethanol, E=diethyl ether. *c*) All compounds gave satisfactory elemental analysis (±0.4%) for C, H and N.

Table 2. Physical Properties and Inhibitory Effects of Compounds **6** on Chemokine Binding to CCR5-expressing CHO Cells

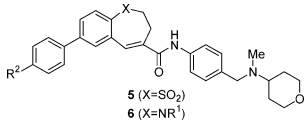


Compd.	R^1	R^2	IC_{50} [a] (nM)	mp (°C)	Recrystln. solvent[b]	Method	Yield (%)	Formula	*Anal.*[c]
4	Me	Me	130						
6a	Me	Morpholino	49	209—211	ET	B	86	$C_{35}H_{42}N_4O_3$	CHN
6b	Me	$PrO(CH_2)_2O$	68	136—138	ET	B	35	$C_{36}H_{45}N_3O_4 \cdot 0.25H_2O$	CHN
6c	Me	$BuO(CH_2)_2O$	21	107—110	EA–IPE	B	53	$C_{37}H_{47}N_3O_4 \cdot 0.1H_2O$	CHN
6d	Et	Morpholino	51	193—194	ET	B	37	$C_{36}H_{44}N_4O_3$	CHN
6e	Ac	Morpholino	200	141—145	EA–H	A	21	$C_{36}H_{42}N_4O_4$	CHN
6f	Et	$PrO(CH_2)_2O$	17	106—108	EA–IPE	B	46	$C_{37}H_{47}N_3O_4 \cdot 0.25H_2O$	CHN
6g	Et	$BuO(CH_2)_2O$	5.6	102—106	EA–IPE	B	42	$C_{38}H_{49}N_3O_4 \cdot 0.2H_2O$	CHN
6h	Pr	$BuO(CH_2)_2O$	3.5	118—121	EA–IPE	B	50	$C_{39}H_{51}N_3O_4$	CHN
6i	*i*-Bu	$BuO(CH_2)_2O$	3.6	74—75	EA–H	A	56	$C_{40}H_{53}N_3O_4$	CHN
6j	*i*-Pentyl	$BuO(CH_2)_2O$	32	Amorphous	—	B	9	$C_{41}H_{55}N_3O_4$	CHN
6k		$BuO(CH_2)_2O$	4.5	92—94	EA–H	A	86	$C_{40}H_{51}N_3O_4$	CHN
6l		$BuO(CH_2)_2O$	12	Amorphous	—	A	61	$C_{41}H_{53}N_3O_4 \cdot 2HCl \cdot 1.5H_2O$	CHN
6m		$BuO(CH_2)_2O$	14	115—117	E–EA–H	A	78	$C_{43}H_{57}N_3O_4$	CHN
6n	Ph	$BuO(CH_2)_2O$	5.6	Amorphous	—	A	58	$C_{42}H_{49}N_3O_4 \cdot 0.25H_2O$	CHN
6o	Bn	$BuO(CH_2)_2O$	5.3	127—131	EA–H	A	61	$C_{43}H_{51}N_3O_4 \cdot 0.25H_2O$	CHN
6p		$BuO(CH_2)_2O$	12	Amorphous	—	A	57	$C_{40}H_{48}N_4O_4S$	CHN
6q		$BuO(CH_2)_2O$	12	Amorphous	—	A	33	$C_{41}H_{51}N_5O_4 \cdot 0.5H_2O$	CHN
6r		$BuO(CH_2)_2O$	10	Amorphous	—	A	21	$C_{41}H_{51}N_5O_4 \cdot 0.25H_2O$	CHN
6s		$BuO(CH_2)_2O$	2.7	113—115	EA–H	A	13	$C_{41}H_{51}N_5O_4$	CHN

a) The concentration required to inhibit the binding of [^{125}I]RANTES to CCR5-expressing CHO cells by 50%. *b*) ET=ethanol, EA=ethyl acetate, IPE=diisopropyl ether, H=hexane, E=diethyl ether. *c*) All compounds gave satisfactory elemental analysis (±0.4%) for C, H and N.

ethoxy (**6g**) groups were more active than the corresponding 1-methyl-1-benzazepines **6b** and **6c**. These results suggested that the 2-(butoxy)ethoxy group was optimal as the 4-substituent on the 7-phenyl group and that enlarging the size of the 1-alkyl group led to enhancement of activity. Therefore, we investigated the effects of various alkyl groups at the 1-position on the 1-benzazepine ring, while retaining the 2-(butoxy)ethoxy group (**6h**—**m**). Introduction of the propyl (**6h**) or isobutyl (**6i**) group further increased the binding inhibitory activity. However, replacement with the bulkier isopentyl group (**6j**) resulted in a relative reduction of activity. The cyclopropylmethyl compound **6k**, which represents a cyclized isobutyl group, retained the potent activity. Enlarging the ring size from cyclopropylmethyl group (**6k**) to cyclobutylmethyl (**6l**) or cyclohexylmethyl (**6m**) groups decreased the activity by about a third. In addition, we determined the effects of 1-phenyl and 1-(substituted)methyl groups such as benzyl and 5-membered heteroarylmethyl groups, considering the propyl, isobutyl and cyclopropylmethyl groups with appropriate bulkiness were most active (**6n**—**s**). The phenyl (**6n**), benzyl (**6o**) and 1-methylpyrazol-4-ylmethyl (**6s**) compounds were as highly active as the isobutyl (**6i**) and cyclopropylmethyl (**6k**) compounds, whereas the thiazol-2-ylmethyl (**6p**), 1-methylimidazol-2-ylmethyl (**6q**) and 1-methylpyrazol-5-ylmethyl (**6r**) compounds, the isomer of **6s**, exhibited relatively weak activity. Among the 1-benzazepine derivatives **6**, the propyl (**6h**), isobutyl (**6i**) and 1-methylpyrazol-4-ylmethyl (**6s**) compounds showed most potent CCR5 antagonistic activity, comparable to compound **1**. From the results of the SAR study, it was suggested that there might be 3 pockets in the binding sites on CCR5 [for the tertiary amine moiety, the 1-substituent and the 7-(4-substitutedphenyl) group on the 1-benzazepine ring] and that the shape of molecules was essential for optimal CCR5 antagonistic activity.

Table 3. Inhibitory Effects of Compounds **4** and **5** on HIV-1 Env-Mediated Membrane Fusion



Compd.	X	R^2	RANTES	Fusion
			IC_{50} [a] (nM)	IC_{50} [b] (nM)
1	—	—	1.4	1.4
5h	SO_2	$PrO(CH_2)_2O$	35	420
5i	SO_2	$BuO(CH_2)_2O$	27	410
6g	N–Et	$BuO(CH_2)_2O$	5.6	1000
6h	N–Pr	$BuO(CH_2)_2O$	3.5	54
6i	N–*i*-Bu	$BuO(CH_2)_2O$	3.6	1.7
6k		$BuO(CH_2)_2O$	4.5	150
6n	N–Ph	$BuO(CH_2)_2O$	5.6	19
6o	N–Bn	$BuO(CH_2)_2O$	5.3	2.3
6s		$BuO(CH_2)_2O$	2.7	1.2

a) The concentration required to inhibit the binding of [^{125}I]RANTES to CCR5 expressing CHO cells by 50%. *b*) The concentration required to inhibit the membrane fusion between HIV-1 Env-expressing COS-7 cells and CCR5-expressing MOLT-4 cells by 50%.

We finally evaluated the inhibitory effects of the highly potent 1-benzazepines in the RANTES binding assay on the HIV-1 Env-mediated membrane fusion (Table 3). The effects

of the isobutyl (**6i**), benzyl (**6o**) and 1-methylpyrazol-4-ylmethyl (**6s**) compounds in the fusion assay were similar to those in the receptor binding assay. Additionally, the compounds (**6i**, **o**, **s**) greatly increased the anti-HIV-1 potency as compared with the ethyl (**6g**) and cyclopropylmethyl (**6k**) compounds, which remarkably reduced activity. The propyl (**6h**) and phenyl (**6n**) compounds showed moderate activity. From these results, it was found that isobutyl or (hetero)arylmethyl groups with suitable bulkiness, such as benzyl or 1-methylpyrazol-4-ylmtehyl, were necessary as the 1-substituent on the 1-benzazepine ring for highly potent inhibitory activity in the membrane fusion assay.

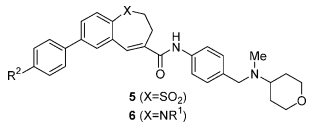
Pharmacokinetic Studies

Preliminary pharmacokinetic studies of typical compounds with potent activity were investigated in rats. The compounds were orally administered at 10 mg/kg to SD (IGS) rats and the results are summarized in Table 4. The 1-benzothiepine 1,1-dioxide **5d** with a propoxy group showed about 6 times higher plasma level than the methyl-substituted compound **3**, whereas plasma level of the ethyl compound **5a** was similar to that of **3**. Reduction of the molecular lipophilicity was considered to lead to the improvement in the pharmacokinetic profiles. However, introduction of the polar morpholino group (**5e**) resulted in only slight improvement of pharmacokinetic profiles in comparison with compound **3** owing to its probably low solubility. Surprisingly, replacing the rigid morpholino group with the flexible 2-(alkoxy)ethoxy group (**5g**—**i**) brought about remarkable improvement in the pharmacokinetic profiles together with increase of activity. Especially, the 2-(propoxy)ethoxy (**5h**) and 2-(butoxy)ethoxy (**5i**) compounds had significantly increased oral plasma levels. Thus, the 2-(butoxy)ethoxy compound **5i** showed about 75-fold C_{max} and 160-fold *AUC* values, when compared with the methyl compound **3**. Next, the 1-benzazepine derivatives with the 2-(butoxy)ethoxy group were examined. The 1-propyl-1-benzazepine **6h** exhibited about 10 times higher plasma level after oral administration compared with the lead compound **4**. On the other hand, the plasma level of the 1-isobutyl compound **6i** was not very high, probably due to its high lipophilicity. The 1-methylpyrazol-4-ylmethyl compound **6s** had reduced lipophilicity and exhibited a *ca.* 5-fold increase in both C_{max} and *AUC* values when compared with the lead compound **4**.

Conclusion

The search for orally active CCR5 antagonists was performed by chemical modification of the 1-benzothiepine 1,1-dioxide **3** and 1-benzazepine **4** lead compounds containing a tertiary amine moiety. Replacement of the methyl group with a 2-(butoxy)- or 2-(propoxy)ethoxy group at the 4-position on the 7-phenyl group of the 1-benzothiepine ring, not only resulted in enhanced activity but also significantly improved the pharmacokinetic properties upon oral administration in rats. Introduction of $C_{2—4}$ alkyl, phenyl or (hetero)arylmethyl groups as the 1-substituent on the 1-benzazepine ring together with the 2-(butoxy)ethoxy group led to further increase in activity. Among the 1-benzazepine derivatives, the isobutyl (**6i**), benzyl (**6o**) or 1-methylpyrazol-4-ylmethyl (**6s**) compounds exhibited highly potent inhibitory effects, equivalent to the injectable CCR5 antagonist **1**, in the HIV-1 Env-mediated membrane fusion assay. In particular, compound **6s** showed the most potent CCR5 antagonistic activity (IC_{50}=2.7 nM) and inhibitory effect (IC_{50}=1.2 nM) on the membrane fusion, together with good pharmacokinetic properties in rats.

Table 4. Pharmacokinetic Parameters of Compounds **5** and **6** in Rats



5 (X=SO_2)
6 (X=NR^1)

Compd.	X	R^2	Oral administration[a] C_{max}[b] (μg/ml)	T_{max}[c] (h)	$AUC_{0—24\,h}$[d] (μg h/ml)
3	SO_2	Me	0.16	3.3	1.55
4	N–Me	Me	0.11	4.0	1.56
5a	SO_2	Et	0.17	5.3	2.23
5d	SO_2	PrO	1.02	5.3	13.0
5e[e]	SO_2	Morpholino	0.26	1.7	2.55
5g	SO_2	$EtO(CH_2)_2O$	4.48	5.3	64.1
5h	SO_2	$PrO(CH_2)_2O$	13.6	4.0	213
5i	SO_2	$BuO(CH_2)_2O$	11.8	10.7	244
6h	N–Pr	$BuO(CH_2)_2O$	1.15	5.3	17.2
6i	N–*i*-Bu	$BuO(CH_2)_2O$	0.08	5.3	1.03
6s		$BuO(CH_2)_2O$	0.59	5.3	8.35

a) Compounds (10 mg/kg) suspended in 0.5% methylcellulose were orally administered to SD (IGS) rats (male, 8 weeks old, n=3). *b*) Maximum plasma concentration after 10 mg/kg oral dosing. *c*) Time to C_{max}. *d*) Area under the concentration time curve for 0—24 h after 10 mg/kg oral dosing. *e*) **5e** hydrochloride was used.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J* values) are given in Hertz (Hz). Elemental analyses were carried out by Takeda Analytical Research Laboratories, Ltd., and results obtained were within ±0.4% of the theoretical values. Column chromatography was carried out on a silica gel column (Kieselgel 60, 63—200 mesh, Merck). Yields were not optimized.

Methyl 7-Bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (12) To a solution of **11**[18] (96.0 g, 373 mmol) in dimethyl carbonate (684 ml) was added sodium methoxide (101 g, 1870 mmol) at room temperature, and the mixture was refluxed for 5 h under a nitrogen atmosphere. The mixture was acidified using 3 N HCl under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 103 g (88%) of methyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate as a pale brown solid. To a solution of methyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate (71.2 g, 226 mmol) in tetrahydrofuran (THF) was added $NaBH_4$ (8.15 g, 215 mmol) at −40 °C. MeOH (100 ml) was added to the mixture at −40 °C, and the mixture was stirred at −10—−20 °C for 1 h. Water was added to the reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. To a solution of the residue and Et_3N (60.0 ml, 430 mmol) in THF (500 ml) was added methanesulfonyl chloride (MsCl) (25.0 ml, 323 mmol) under ice cooling. The mixture was stirred under ice cooling for 0.5 h and at room temperature for 1 h. To the mixture was added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (51.6 g, 339 mmol) at room temperature. After being stirred at room temperature for 10 min, water was added to the mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=4 : 1) to give 37.2 g (55%) of **12** as pale yellow crystals, mp 94—95 °C. ^{1}H-NMR ($CDCl_3$) δ 2.94—3.00 (2H, m), 3.15—3.21 (2H, m), 3.83 (3H, s), 7.28—7.33 (2H, m), 7.51 (1H, d, J=1.2 Hz), 7.70 (1H, s). *Anal.* Calcd for $C_{12}H_{11}BrO_2S$: C, 48.17; H, 3.71. Found: C, 48.37; H, 3.77.

Methyl 7-Bromo-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (13a) To a mixture of **12** (3.00 g, 10.0 mmol) and acetic acid (30 ml) was added 30% aqueous H_2O_2 (4.50 ml) at room temperature. After being refluxed for 1 h, the reaction mixture was poured into water. The precipitated colorless crystals were collected by filtration, washed with water and diisopropyl ether (*i*-Pr_2O) to give 3.06 g (90%) of **13a** as colorless crystals, mp 162—164 °C. ^{1}H-NMR ($CDCl_3$) δ 3.11 (2H, t, J=6.5 Hz), 3.62 (2H, t, J=6.5 Hz), 3.87 (3H, s), 7.64—7.76 (3H, m), 8.03 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{12}H_{11}BrO_4S$: C, 43.52; H, 3.35. Found: C, 43.52; H, 3.18.

Methyl 7-(4-Ethylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (14a) A mixture of **13a** (0.80 g, 2.42 mmol), 4-ethylphenylboronic acid (0.40 g, 2.67 mmol) and K_2CO_3 (0.67 g, 4.85 mmol) in toluene (30 ml), EtOH (3.0 ml) and water (3.0 ml) was stirred at room temperature under an argon atmosphere for 1 h. Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (0.14 g, 0.12 mmol) was added, and the mixture was refluxed for 15 h under an argon atmosphere. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=1 : 1) to give 732 mg (85%) of **14a** as pale yellow crystals, mp 173—176 °C. ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, t, J=7.5 Hz), 2.72 (2H, q, J=7.5 Hz), 3.11—3.18 (2H, m), 3.62—3.68 (2H, m), 3.87 (3H, s), 7.33 (2H, d, J=8.1 Hz), 7.54 (2H, d, J=8.1 Hz), 7.66—7.74 (2H, m), 7.92 (1H, br s), 8.21 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.36; H, 5.63.

The following compounds (**14b**—**e**) were prepared from **13a** by a method similar to that described for **14a**.

Methyl 7-(4-Propylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (14b) Yield 62%, mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, t, J=7.4 Hz), 1.63—1.77 (2H, m), 2.66 (2H, t, J=7.6 Hz), 3.11—3.18 (2H, m), 3.61—3.68 (2H, m), 3.87 (3H, s), 7.30 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.69—7.73 (2H, m), 7.92 (1H, br s), 8.22 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{21}H_{22}O_4S$: C, 68.08; H, 5.99. Found: C, 68.13; H, 5.89.

Methyl 7-(4-Isopropylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (14c) Yield 86%, mp 142—144 °C. ^{1}H-NMR ($CDCl_3$) δ 1.30 (6H, d, J=6.6 Hz), 2.90—3.06 (1H, m), 3.12—3.18 (2H, m), 3.62—3.68 (2H, m), 3.87 (3H, s), 7.36 (2H, d, J=8.2 Hz), 7.55 (2H, d, J=8.2 Hz), 7.69—7.73 (2H, m), 7.92 (1H, br s), 8.22 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{21}H_{22}O_4S$: C, 68.08; H, 5.99. Found: C, 68.04; H, 6.15.

Methyl 7-(4-Propoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (14d) Yield 76%, mp 153—155 °C. ^{1}H-NMR ($CDCl_3$) δ 1.07 (3H, t, J=7.5 Hz), 1.76—1.93 (2H, m), 3.11—3.17 (2H, m), 3.61—3.68 (2H, m), 3.87 (3H, s), 3.99 (2H, t, J=6.6 Hz), 7.01 (2H, d, J=9.0 Hz), 7.55 (2H, d, J=9.0 Hz), 7.66—7.70 (2H, m), 7.91 (1H, br s), 8.20 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{21}H_{22}O_5S$: C, 65.27; H, 5.74. Found: C, 65.35; H, 5.63.

Methyl 7-(4-Morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate 1,1-Dioxide (14e) Yield 71%, mp 215—217 °C. ^{1}H-NMR ($CDCl_3$) δ 3.10—3.17 (2H, m), 3.23—3.28 (4H, m), 3.61—3.67 (2H, m), 3.87 (3H, s), 3.84—3.95 (4H, m), 7.00 (2H, d, J=8.8 Hz), 7.56 (2H, d, J=8.8 Hz), 7.66—7.74 (2H, m), 7.91 (1H, s), 8.18 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{22}H_{23}NO_5S$: C, 63.90; H, 5.61; N, 3.39. Found: C, 63.89; H, 5.74; N, 3.51.

7-(4-Ethylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic Acid 1,1-Dioxide (7a) To a solution of **14a** (600 mg, 1.68 mmol) in 1,2-dimethoxyethane (20 ml) was added 6 N HCl (10 ml) at room temperature, and the mixture was refluxed for 24 h. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The precipitated crystals were collected by filtration, washed with hexane to give 501 mg (87%) of **7a** as pale yellow crystals, mp 263—265 °C. ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, t, J=7.6 Hz), 2.73 (2H, q, J=7.6 Hz), 3.17 (2H, t, J=6.6 Hz), 3.67 (2H, t, J=6.6 Hz), 7.34 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.70—7.78 (2H, m), 8.02 (1H, s), 8.24 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found: C, 66.47; H, 5.41.

The following compounds (**7b**—**d**) were prepared from the corresponding esters (**14b**—**d**) by a method similar to that described for **7a**.

7-(4-Propylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic Acid 1,1-Dioxide (7b) Yield 90%. ^{1}H-NMR (DMSO-d_6) δ 0.92 (3H, t, J=7.3 Hz), 1.58—1.69 (2H, m), 2.58—2.66 (2H, m), 2.93—3.01 (2H, m), 3.72—3.79 (2H, m), 7.34 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.2 Hz), 7.88—7.93 (2H, m), 8.06—8.09 (2H, m).

7-(4-Isopropylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic Acid 1,1-Dioxide (7c) Yield 96%, mp 281—282 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ 1.30 (6H, d, J=7.0 Hz), 2.92—3.05 (1H, m), 3.13—3.20 (2H, m), 3.63—3.70 (2H, m), 7.36 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.2 Hz), 7.69—7.78 (2H, m), 8.01 (1H, br s), 8.24 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{20}H_{20}O_4S \cdot 0.2H_2O$: C, 66.72; H, 5.71. Found: C, 66.63; H, 5.79.

7-(4-Propoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic Acid 1,1-Dioxide (7d) Yield 90%, mp 270—273 °C. ^{1}H-NMR (DMSO-d_6) δ 1.00 (3H, t, J=7.5 Hz), 1.65—1.86 (2H, m), 2.93—3.00 (2H, m), 3.71—3.78 (2H, m), 4.00 (2H, t, J=6.6 Hz), 7.06 (2H, d, J=8.7 Hz), 7.78 (2H, d, J=8.7 Hz), 7.83—7.93 (2H, m), 8.03—8.07 (2H, m). *Anal.* Calcd for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41. Found: C, 64.34; H, 5.48.

7-(4-Morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboylic Acid 1,1-Dioxide (7e) To a solution of **14e** (550 mg, 1.33 mmol) in EtOH (15 ml) and THF (15 ml) was added 1 N NaOH (1.6 ml, 1.6 mmol) at room temperature. After being stirred at room temperature for 18 h, 1 N HCl (1.6 ml, 1.6 mmol) was added to the reaction mixture at room temperature. The mixture was evaporated *in vacuo*. The precipitated crystals were collected by filtration, washed with 2-propanol and *i*-Pr_2O to give 269 mg (51%) of **7e** as pale yellow crystals. ^{1}H-NMR (DMSO-d_6) δ 2.89—3.02 (2H, m), 3.15—3.26 (4H, m), 3.68—3.82 (6H, m), 7.06 (2H, d, J=9.0 Hz), 7.74 (2H, d, J=9.0 Hz), 7.83—7.91 (2H, m), 7.99—8.08 (2H, m). *Anal.* Calcd for $C_{21}H_{21}NO_5S$: C, 61.75; H, 5.43; N, 3.43. Found: C, 61.60; H, 5.65; N, 3.50.

***tert*-Butyl 4-(Ethylamino)butanoate (16a)** To a solution of **15** (25.4 g, 107 mmol) and EtI (50.0 g, 321 mmol) in THF (350 ml) was added NaH (60% dispersion in mineral oil, 12.8 g, 320 mmol) under ice cooling. The mixture was stirred at 75 °C for 13 h under a nitrogen atmosphere. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The aqueous layer was acidified using 1 N HCl under ice cooling. The mixture was extracted with EtOAc. The organic layer was washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 25.1 g (87%) of 4-{[(benzyloxy)carbonyl](ethyl)amino}butanoic acid as a yellow oil. To a solution of 4-{[(benzyloxy)carbonyl](ethyl)amino}butanoic acid (8.24 g, 31.3 mmol) and di-*tert*-butyl dicarbonate (Boc_2O) (14.3 ml, 62.2 mmol) in *tert*-BuOH (300 ml) was added 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (390 mg, 9.34 mmol) at room temperature. After being stirred at room temperature for 4 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=4 : 1) to give 4.20 g (42%) of *tert*-butyl 4-{[(benzyloxy)carbonyl](ethyl)amino}butanoate as a pale yellow oil. A mixture of *tert*-butyl 4-{[(benzyloxy)carbonyl](ethyl)amino}butanoate (3.38 g, 10.5 mmol), conc. HCl (1 drop) and 10% Pd–C (50% wet, 0.34 g) in MeOH (35 ml) was stirred at room temperature for 3 h under a hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 2.30 g (quant.) of **16a** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, t, J=7.2 Hz), 1.44 (9H, s), 1.78 (2H, quintet, J=7.2 Hz), 2.27 (2H, t, J=7.2 Hz), 2.65 (2H, t, J=7.2 Hz), 2.67 (2H, q, J=7.2 Hz).

***tert*-Butyl 4-(Propylamino)butanoate (16b)** This compound was prepared in 34% yield from **15** by a method similar to that described for **16a**. ^{1}H-NMR ($CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz), 1.45 (9H, s), 1.47—1.67 (4H, m), 1.70—1.85 (2H, m), 2.25 (2H, q, J=7.9 Hz), 2.60 (2H, dt, J=11.6, 7.2 Hz), 3.21 (1H, m).

***tert*-Butyl 4-[(4-Bromo-2-formylphenyl)(ethyl)amino]butanoate (17a)** A mixture of **16a** (2.30 g, 10.5 mmol), 5-bromo-2-fluorobenzaldehyde (2.13 g, 10.5 mmol) and K_2CO_3 (1.74 g, 12.6 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) was stirred at 70—80 °C for 73 h. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=10 : 1) to give 1.46 g (38%) of **17a** as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t, J=7.1 Hz), 1.42 (9H, s), 1.77 (2H, quintet, J=7.2 Hz), 2.21 (2H, t, J=7.1 Hz), 3.15 (2H, t, J=7.3 Hz), 3.18 (2H, q, J=7.1 Hz), 7.07 (1H, d, J=8.8 Hz), 7.58 (1H, dd, J=8.8, 2.6 Hz), 7.91 (1H, d, J=2.6 Hz), 10.25 (1H, s).

***tert*-Butyl 4-[(4-Bromo-2-formylphenyl)(propyl)amino]butanoate (17b)** This compound was prepared in 52% yield from **16b** by a method similar to that described for **17a**. ^{1}H-NMR ($CDCl_3$) δ 0.84 (3H, t, J=7.8 Hz), 1.45 (9H, s), 1.42—1.63 (2H, m), 1.81 (2H, quintet, J=7.4 Hz), 2.19 (2H, t, J=7.5 Hz), 3.09 (2H, t, J=7.6 Hz), 3.17 (2H, t, J=7.5 Hz), 7.06 (1H, d, J=8.8 Hz), 7.56 (1H, dd, J=8.7, 2.5 Hz), 7.90 (1H, d, J=2.6 Hz), 10.24 (1H, s).

***tert*-Butyl 7-Bromo-1-ethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (13c)** A mixture of **17a** (1.44 g, 3.89 mmol) and potassium *tert*-butoxide (480 mg, 4.28 mmol) in toluene (80 ml) and *tert*-BuOH (8.0 ml) was stirred at 90 °C for 3 h. 1 N HCl (6.0 ml) was added to the reaction mixture

under ice cooling and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 20 : 1) to give 964 mg (70%) of **13c** as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.53 (9H, s), 2.76 (2H, td, J=4.9, 1.4 Hz), 3.19 (2H, t, J=4.9 Hz), 3.34 (2H, q, J=7.1 Hz), 6.69 (1H, d, J=9.0 Hz), 7.23 (1H, dd, J=9.0, 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 7.47 (1H, s).

***tert*-Butyl 7-Bromo-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (13d)** This compound was prepared in 60% yield from **17b** by a method similar to that described for **13c**. ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.5 Hz), 1.53 (9H, s), 1.68 (2H, sextet, J=7.6 Hz), 2.75 (2H, t, J=4.4 Hz), 3.18—3.26 (4H, m), 6.67 (1H, d, J=9.2 Hz), 7.22 (1H, dd, J=8.8, 2.6 Hz), 7.39 (1H, d, J=2.6 Hz), 7.46 (1H, s).

Methyl 5-Bromo-2-{[(4-methylphenyl)sulfonyl]amino}benzoate (18) To a silution of methyl 5-bromo-2-aminobenzoate (28.2 g, 123 mmol) in pyridine (70 ml) was added *p*-toluenesulfonyl chloride (35.1 g, 184 mmol) at room temperature. After being stirred at 55 °C for 1 h, the mixture was concentrated *in vacuo*, poured into water, and extracted with EtOAc. The organic layer was washed with water, 1 N HCl, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 41.5 g (88%) of **18** as colorless crystals, mp 123—124 °C. ^{1}H-NMR ($CDCl_3$) δ 2.38 (3H, s), 3.89 (3H, s), 7.24 (2H, d, J=8.6 Hz), 7.53 (1H, dd, J=9.2, 2.0 Hz), 7.61 (1H, d, J=9.2 Hz), 7.73 (2H, d, J=8.6 Hz), 8.03 (1H, d, J=2.0 Hz), 10.52 (1H, s). *Anal.* Calcd for $C_{15}H_{14}BrNO_4S$: C, 46.89; H, 3.67; N, 3.65. Found: C, 46.93; H, 3.53; N, 3.67.

7-Bromo-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (19) To a solution of **18** (38.1 g, 99.3 mmol) in DMF (100 ml) was added NaH (60% dispersion in mineral oil, 4.76 g, 119 mmol) and DMF (35 ml) under ice cooling. The mixture was stirred at room temperature for 1 h under a nitrogen atmosphere. NaI (14.9 g, 99.3 mmol) and ethyl 4-bromobutyrate (21.3 g, 109 mmol) were added, and then the mixture was stirred at 80 °C for 14 h under a nitrogen atmosphere. NaH (60% dispersion in mineral oil, 4.76 g, 119 mmol) and DMF (25 ml) were added to the mixture under ice cooling. The mixture was stirred at 80 °C for 15 h under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with EtOAc. The mixture was washed successively with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 9 : 1→4 : 1) to give 25.1 g of white crystals. A mixture of the crystals (25.1 g), conc. H_2SO_4 (90 ml) and acetic acid (150 ml) was stirred at 90 °C for 2.5 h. The reaction mixture was poured into ice. The mixture was neutralized using 12 N NaOH under ice cooling. Water was added to the mixture and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 3 : 1) to give 5.01 g (21%) of **19** as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 2.18 (2H, quintet, J=7.1 Hz), 2.82 (2H, t, J=7.2 Hz), 3.25 (2H, t, J=6.6 Hz), 4.65 (1H, br s), 6.65 (1H, d, J=8.6 Hz), 7.20 (1H, dd, J=8.6, 2.2 Hz), 7.82 (1H, d, J=2.2 Hz).

Methyl 7-Bromo-1-(*tert*-butoxycarbonyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (20) To a solution of **19** (4.31 g, 18.0 mmol) and Boc_2O (13.8 g, 63.2 mmol) in THF (36 ml) was added DMAP (2.19 g, 17.9 mmol) at room temperature. The mixture was refluxed for 1.5 h. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 9 : 1) to give a yellow oil. To a solution of the oil in dimethyl carbonate (100 ml) was added sodium methoxide (4.86 g, 90.0 mmol) at room temperature, and the mixture was refluxed for 2.5 h. The reaction mixture was poured into ice water. To the mixture was added 1 M citric acid (100 ml) and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 9 : 1→4 : 1) to give 3.89 g of β-keto ester as a pale yellow amorphous. To a mixture of β-keto ester (3.89 g) and $NaBH_4$ (0.38 g, 10 mmol) in THF (100 ml) was added MeOH (10 ml) at −40 °C. The mixture was stirred at −15 °C for 1 h. To the reaction mixture was added 1 M citric acid (20 ml) and water at −40 °C, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. To a solution of the residue and Et_3N (4.1 ml, 29.4 mmol) in THF (750 ml) was added MsCl (1.15 ml, 14.9 mmol) under ice cooling. After being stirred at room temperature for 14 h, DBU (7.30 ml, 48.9 mmol) was added to the reaction mixture at room temperature. The mixture was refluxed for 10 min. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 4 : 1) to give 2.53 g (37%) of **20** as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.89 (2H, t, J=4.8 Hz), 3.61 (2H, br s), 3.83 (3H, s), 7.27 (1H, br s), 7.39 (1H, dd, J=8.4, 1.8 Hz), 7.54—7.55 (2H, m).

Methyl 7-Bromo-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (21) To a solution of **20** (5.04 g, 13.2 mmol) in EtOAc (250 ml) was added 6 N HCl (80 ml) at room temperature. The mixture was stirred at 80 °C for 0.5 h. To the reaction mixture was added 1 N NaOH (400 ml) and saturated aqueous Na_2CO_3 (300 ml). The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 3.72 g (quant) of **21** as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 2.86 (2H, t, J=5.2 Hz), 3.36 (2H, t, J=5.2 Hz), 3.80 (3H, s), 4.57 (1H, br s), 6.49 (1H, d, J=8.4 Hz), 7.15 (1H, dd, J=8.4, 2.2 Hz), 7.38 (1H, d, J=2.2 Hz), 7.53 (1H, s).

Methyl 7-Bromo-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (13e) To a solution of **21** (2.00 g, 7.09 mmol) and isobutyraldehyde (3.22 ml, 35.4 mmol) in 1,2-dichloroethane (70 ml) was added triacetoxyborohydride (5.36 g, 24.8 mmol) under ice cooling. After being stirred at room temperature for 12 h, 1 N NaOH was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 6 : 1) to give 1.82 g (76%) of **13e** as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ 0.92 (6H, d, J=6.6 Hz), 2.03 (1H, m), 2.77—2.82 (2H, m), 3.10 (2H, d, J=7.4 Hz), 3.21—3.26 (2H, m), 3.80 (3H, s), 6.71 (1H, d, J=8.8 Hz), 7.19—7.26 (1H, m), 7.42 (1H, d, J=2.6 Hz), 7.58 (1H, s).

Methyl 7-Bromo-1-(3-methylbutyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (13f) This compound was prepared in 87% yield from **21** by a method similar to that described for **13e**. ^{1}H-NMR ($CDCl_3$) δ 0.95 (6H, d, J=6.2 Hz), 1.48—1.62 (3H, m), 2.79 (2H, t, J=4.4 Hz), 3.21 (2H, t, J=4.4 Hz), 3.24—3.33 (2H, m), 3.80 (3H, s), 6.68 (1H, d, J=8.8 Hz), 7.20—7.26 (1H, m), 7.41 (1H, d, J=2.2 Hz), 7.56 (1H, s).

The following compounds (**14f**, **22**) were prepared from the corresponding bromides (**13e**, **21**) by a method similar to that described for **14a**.

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14f) Yield 62%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 0.95 (6H, d, J=6.6 Hz), 1.37—1.67 (4H, m), 1.99—2.16 (1H, m), 2.82 (2H, t, J=4.8 Hz), 3.17 (2H, d, J=7.4 Hz), 3.30 (2H, t, J=4.8 Hz), 3.55 (2H, t, J=6.6 Hz), 3.77—3.83 (5H, m), 4.13—4.18 (2H, m), 6.89 (1H, d, J=8.4 Hz), 6.97 (2H, d, J=8.8 Hz), 7.36—7.52 (4H, m), 7.77 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (22) Yield 56%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.29—1.48 (2H, m), 1.51—1.69 (2H, m), 2.88 (2H, t, J=4.6 Hz), 3.37—3.44 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.78—3.83 (2H, m), 4.16 (2H, t, J=5.0 Hz), 4.5—4.64 (1H, m), 6.67 (1H, d, J=8.2 Hz), 6.97 (2H, d, J=8.8 Hz), 7.33 (1H, dd, J=8.2, 2.2 Hz), 7.43—7.48 (3H, m), 7.71 (1H, s).

The following compounds (**14g**—**i**, **14k**—**o**) were prepared from **22** by a method similar to that described for **13e**.

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclopropylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14g) Yield quant. ^{1}H-NMR ($CDCl_3$) δ 0.24—0.32 (2H, m), 0.58—0.67 (2H, m), 0.93 (3H, t, J=7.3 Hz), 1.08—1.15 (1H, m), 1.34—1.49 (2H, m), 1.55—1.68 (2H, m), 2.86 (2H, t, J=4.4 Hz), 3.23 (2H, d, J=6.6 Hz), 3.39 (2H, t, J=4.7 Hz), 3.55 (2H, t, J=6.6 Hz), 3.73—3.83 (5H, m), 4.11—4.18 (2H, m), 6.92—7.01 (3H, m), 7.38—7.53 (4H, m), 7.77 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclobutylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14h) Yield quant. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.34—1.45 (2H, m), 1.54—2.13 (8H, m), 2.70—2.81 (3H, m), 3.26 (2H, t, J=4.8 Hz), 3.38 (2H, d, J=7.4 Hz), 3.55 (2H, t, J=6.6 Hz), 3.78—3.83 (5H, m), 4.16 (2H, t, J=4.9 Hz), 6.87 (1H, d, J=8.8 Hz), 6.97 (2H, d, J=8.8 Hz), 7.37—7.51 (4H, m), 7.75 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclohexylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14i) Yield quant. ^{1}H-NMR ($CDCl_3$) δ 0.89—1.81 (18H, m), 2.81 (2H, t, J=4.2 Hz), 3.19 (2H, d, J=6.6 Hz), 3.29 (2H, t, J=4.8 Hz), 3.55 (2H, t, J=6.6 Hz), 3.78—3.82 (5H, m), 4.15 (2H, t, J=4.9 Hz), 6.87 (H, d, J=8.8 Hz), 6.97 (2H, d, J=8.8 Hz), 7.36—7.51 (4H, m), 7.76 (1H, s).

Methyl 1-Benzyl-7-{4-[2-(butoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14k) Yield quant. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.30—1.48 (2H, m), 1.54—1.68 (2H, m), 2.77 (2H, t, J=4.7 Hz), 3.31 (2H, t, J=4.7 Hz), 3.55 (2H, t, J=6.6 Hz), 3.78—3.82 (5H,

m), 4.15 (2H, t, *J*=4.8 Hz), 4.59 (2H, s), 6.86 (1H, d, *J*=8.8 Hz), 6.97 (2H, d, *J*=8.8 Hz), 7.26—7.68 (7H, m), 7.82—7.91 (3H, m).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(thiazol-2-yl)methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14l) Yield 88%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.2 Hz), 1.34—1.45 (2H, m), 1.57—1.70 (2H, m), 2.87 (2H, t, *J*=4.4 Hz), 3.42 (2H, t, *J*=4.4 Hz), 3.55 (2H, t, *J*=6.6 Hz), 3.78—3.82 (5H, m), 4.16 (2H, t, *J*=5.6 Hz), 4.86 (2H, s), 6.95—7.00 (3H, m), 7.30 (1H, d, *J*=3.2 Hz), 7.40 (1H, dd, *J*=8.4, 2.2 Hz), 7.46 (2H, d, *J*=8.6 Hz), 7.56 (1H, d, *J*=2.6 Hz), 7.78—7.81 (2H, m).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14m) Yield 59%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.2 Hz), 1.38—1.45 (2H, m), 1.54—1.65 (2H, m), 2.41 (2H, t, *J*=4.7 Hz), 3.30 (2H, t, *J*=4.7 Hz), 3.51 (3H, s), 3.56 (2H, t, *J*=6.2 Hz), 3.79—3.83 (5H, m), 4.17 (2H, t, *J*=4.4 Hz), 4.61 (2H, s), 6.88 (1H, d, *J*=1.0 Hz), 6.97—7.06 (4H, m), 7.44—7.50 (3H, m), 7.56 (1H, d, *J*=2.2 Hz), 7.77 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-5-yl)-methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14n) Yield 67%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.4 Hz), 1.34—1.45 (2H, m), 1.55—1.70 (2H, m), 2.58 (2H, t, *J*=4.8 Hz), 3.27 (2H, t, *J*=4.8 Hz), 3.56 (2H, t, *J*=7.0 Hz), 3.79—3.83 (8H, m), 4.17 (2H, t, *J*=4.4 Hz), 4.52 (2H, s), 6.22 (1H, d, *J*=1.8 Hz), 6.92 (1H, d, *J*=8.8 Hz), 6.99 (2H, d, *J*=8.8 Hz), 7.40—7.50 (4H, m), 7.57 (1H, d, *J*=2.2 Hz), 7.79 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-4-yl)-methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14o) Yield 63%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.4 Hz), 1.34—1.45 (2H, m), 1.50—1.70 (2H, m), 2.76 (2H, t, *J*=5.0 Hz), 3.27 (2H, t, *J*=5.0 Hz), 3.56 (2H, t, *J*=7.0 Hz), 3.78—3.83 (5H, m), 3.89 (3H, s), 4.16 (2H, t, *J*=5.2 Hz), 4.42 (2H, s), 6.92—7.00 (3H, d), 7.29 (1H, s), 7.40 (1H, dd, *J*=8.4, 2.0 Hz), 7.45—7.49 (3H, m), 7.54 (1H, d, *J*=2.0 Hz), 7.78 (1H, s).

Methyl 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-phenyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14j) To a solution of **22** (500 mg, 1.26 mmol), copper(II) pivalate (70 mg, 0.26 mmol) in CH_2Cl_2 was added triphenylbismuth diacetate (780 mg, 1.40 mmol) at room temperature. After being stirred at room temperature over night, the reaction mixture was poured into 3 N HCl. The mixture was neutralized using 1 N NaOH, and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc) to give 0.42 g (71%) of **14j** as yellow crystals, mp 80—82 °C. ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, *J*=7.1 Hz), 1.31—1.49 (2H, m), 1.56—1.69 (2H, m), 2.85 (2H, t, *J*=4.4 Hz), 3.56 (2H, t, *J*=6.6 Hz), 3.79—3.84 (7H, m), 4.17 (2H, t, *J*=4.9 Hz), 6.87—7.02 (5H, m), 7.16—7.30 (3H, m), 7.40 (1H, dd, *J*=8.8, 2.2 Hz), 7.51 (2H, d, *J*=8.4 Hz), 7.64 (1H, d, *J*=2.2 Hz), 7.80 (1H, s). *Anal.* Calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.30; H, 7.17; N, 2.90.

7-{4-[2-(Butoxy)etoxy]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7f) To a solution of **14f** (750 mg, 1.66 mmol) in THF (15 ml) and MeOH (15 ml) was added 1 N NaOH (7.5 ml, 7.5 mmol) at room temperature. After being stirred at room temperature for 20 h, the reaction mixture was acidified using 1 N HCl under ice cooling. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The precipitated crystals were collected by filtration, washed with hexane : EtOAc (6 : 1) to give 610 mg (84%) of **7f** as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.0 Hz), 0.96 (6H, d, *J*=6.6 Hz), 1.34—1.47 (2H, m), 1.54—1.66 (2H, m), 1.96—2.18 (1H, m), 2.79—2.85 (2H, m), 3.19 (2H, d, *J*=6.8 Hz), 3.30—3.35 (2H, m), 3.56 (2H, t, *J*=6.6 Hz), 3.81 (2H, t, *J*=4.8 Hz), 4.16 (2H, t, *J*=4.8 Hz), 6.90 (1H, d, *J*=8.8 Hz), 6.98 (2H, d, *J*=8.8 Hz), 7.38—7.53 (4H, m), 7.89 (1H, s).

The following compounds (**7g**—**o**) were prepared from the corresponding esters (**14g**—**o**) by a method similar to that described for **7f**.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclopropylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7g) Yield 96%, mp 152—155 °C. ^{1}H-NMR ($CDCl_3$) δ 0.25—0.33 (2H, m), 0.59—0.68 (2H, m), 0.93 (3H, t, *J*=7.3 Hz), 1.05—1.20 (1H, m), 1.30—1.49 (2H, m), 1.55—1.69 (2H, m), 2.87 (2H, t, *J*=4.6 Hz), 3.25 (2H, d, *J*=6.4 Hz), 3.42 (2H, t, *J*=4.6 Hz), 3.56 (2H, t, *J*=6.6 Hz), 3.81 (2H, t, *J*=5.0 Hz), 4.16 (2H, t, *J*=5.0 Hz), 6.93—7.00 (3H, m), 7.40—7.54 (4H, m), 7.89 (1H, s). *Anal.* Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.27; H, 7.45; N, 3.21.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclobutylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7h) Yield 87%, mp 110—112 °C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.3 Hz), 1.30—2.00 (8H, m), 2.00—2.15 (2H, m), 2.71—2.80 (3H, m), 3.29 (2H, t, *J*=4.8 Hz), 3.39 (2H, d, *J*=7.0 Hz), 3.55 (2H, t, *J*=6.6 Hz), 3.80 (2H, d, *J*=5.0 Hz), 4.16 (2H, t, *J*=5.0 Hz), 6.88 (1H, d, *J*=8.0 Hz), 6.98 (2H, d, *J*=8.8 Hz), 7.39—7.51 (4H, m), 7.85 (1H, s). *Anal.* Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.51; H, 7.92; N, 2.98.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclohexylmethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7i) Yield 89%, mp 124—125 °C. ^{1}H-NMR ($CDCl_3$) δ 0.90—1.85 (18H, m), 2.83 (3H, t-like), 3.22 (2H, d, *J*=6.6 Hz), 3.32 (2H, t-like), 3.56 (2H, t, *J*=6.6 Hz), 3.81 (2H, d, *J*=5.0 Hz), 4.16 (2H, t, *J*=5.0 Hz), 6.89 (1H, d, *J*=8.8 Hz), 6.98 (2H, d, *J*=8.8 Hz), 7.39—7.53 (4H, m), 7.88 (1H, s). *Anal.* Calcd for $C_{30}H_{39}NO_4$: C, 75.44; H, 8.23; N, 2.93. Found: C, 75.46; H, 8.23; N, 2.96.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-phenyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7j) Yield 75%, mp 129—131 °C. ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, *J*=7.2 Hz), 1.34—1.49 (2H, m), 1.55—1.69 (2H, m), 2.86 (2H, t, *J*=4.4 Hz), 3.56 (2H, t, *J*=6.6 Hz), 3.79—3.84 (4H, m), 4.17 (2H, t, *J*=4.8 Hz), 6.90—7.04 (5H, m), 7.17 (1H, d, *J*=8.6 Hz), 7.23—7.31 (2H, m), 7.40 (1H, dd, *J*=8.6, 2.0 Hz), 7.50 (2H, d, *J*=7.2 Hz), 7.64 (1H, d, *J*=2.0 Hz), 7.90 (1H, s). *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.18; H, 6.85; N, 3.21.

1-Benzyl-7-{4-[2-(butoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7k) Yield 89%, mp 133—138 °C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.4 Hz), 1.34—1.45 (2H, m), 1.54—1.65 (2H, m), 2.80 (2H, br), 3.34 (2H, br), 3.56 (2H, t, *J*=6.6 Hz), 3.80 (2H, t, *J*=5.0 Hz), 4.16 (2H, t, *J*=5.0 Hz), 4.61 (2H, s), 6.88 (1H, d, *J*=8.8 Hz), 6.98 (2H, d, *J*=8.8 Hz), 7.26—7.49 (8H, m), 7.57 (1H, d, *J*=2.2 Hz), 7.94 (1H, s). *Anal.* Calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.06; H, 7.15; N, 2.68.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(thiazol-2-yl)methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7l) Yield 78%, mp 105—107 °C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.6 Hz), 1.34—1.45 (2H, m), 1.54—1.65 (2H, m), 2.89 (2H, br), 3.45 (2H, br), 3.55 (2H, t, *J*=6.6 Hz), 3.80 (2H, t, *J*=5.0 Hz), 4.16 (2H, t, *J*=5.0 Hz), 4.88 (2H, s), 6.96—7.01 (3H, m), 7.31 (1H, d, *J*=3.3 Hz), 7.46—7.49 (3H, m), 7.57 (1H, d, *J*=2.6 Hz), 7.80 (1H, d, *J*=3.3 Hz), 7.91(1H, s). *Anal.* Calcd for $C_{27}H_{30}N_2O_4S$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.76; H, 6.39; N, 5.70.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-imidazol-2-yl)-methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7m) Yield 80%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.4 Hz), 1.30—1.50 (2H, m), 1.54—1.70 (2H, m), 2.47 (2H, br), 3.32 (2H, br), 3.54—3.59 (5H, m), 3.80 (2H, t, *J*=4.9 Hz), 4.16 (2H, t, *J*=4.9 Hz), 4.68 (2H, s), 6.88 (1H, s), 6.98 (2H, d, *J*=8.4 Hz), 7.03—7.07 (2H, m), 7.45—7.49 (3H, m), 7.57 (1H, d, *J*=2.2 Hz), 7.85 (1H, s).

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-5-yl)-methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7n) Yield 77%, mp 145—148 °C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.0 Hz), 1.34—1.45 (2H, m), 1.55—1.65 (2H, m), 2.62 (2H, br s), 3.30 (2H, br s), 3.56 (2H, t, *J*=7.0 Hz), 3.79—3.84 (5H, m), 4.17 (2H, t, *J*=5.0 Hz), 4.54 (2H, s), 6.22 (1H, d, *J*=1.8 Hz), 6.93 (1H, d, *J*=8.8 Hz), 6.99 (2H, d, *J*=8.8 Hz), 7.43—7.50 (4H, m), 7.58 (1H, d, *J*=2.2 Hz), 7.89 (1H, s). *Anal.* Calcd for $C_{28}H_{33}N_3O_4$: C, 70.71; H, 6.99; N, 8.84. Found: C, 70.48; H, 6.90; N, 8.80.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-4-yl)-methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7o) Yield 69%, mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.4 Hz), 1.34—1.49 (2H, m), 1.55—1.65 (2H, m), 2.79 (2H, t, *J*=4.2 Hz), 3.30 (2H, t, *J*=4.2 Hz), 3.56 (2H, t, *J*=6.6 Hz), 3.81 (2H, t, *J*=4.8 Hz), 3.90 (3H, s), 4.16 (2H, t, *J*=5.2 Hz), 4.44 (2H, s), 6.94—7.01 (3H, m), 7.30 (1H, s), 7.40—7.50 (4H, m), 7.56 (1H, d, *J*=2.0 Hz), 7.90 (1H, s). *Anal.* Calcd for $C_{28}H_{33}N_3O_4$: C, 70.71; H, 6.99; N, 8.84. Found: C, 70.52; H, 6.90; N, 8.70.

Methyl 1-(*tert*-Butoxycarbonyl)-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (23) This compound was prepared in 82% yield from **20** by a method similar to that described for **14a**, mp 183—185 °C. ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 2.90 (2H, t, *J*=5.0 Hz), 3.19—3.24 (4H, m), 3.69 (2H, t, *J*=5.0 Hz), 3.83 (3H, s), 3.87—3.91 (4H, m), 6.98 (2H, d, *J*=9.0 Hz), 7.48 (2H, m), 7.52 (2H, d, *J*=9.0 Hz), 7.58 (1H, s), 7.73 (1H, s). *Anal.* Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.57; H, 6.76; N, 5.76.

Methyl 7-(4-Morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (24) This compound was prepared in 93% yield from **23** by a method similar to that described for **21**, mp 175—182 °C. ^{1}H-NMR ($CDCl_3$) δ 2.89 (2H, t, *J*=4.5 Hz), 3.17—3.22 (4H, m), 3.41 (2H, t, *J*=4.5 Hz), 3.81 (3H, s), 3.87—3.91 (4H, m), 6.67 (1H, d, *J*=8.3 Hz), 6.97 (2H, d, *J*=8.8 Hz), 7.33 (1H, dd, *J*=8.3, 2.0 Hz), 7.45—7.50 (3H, m), 7.73 (1H, s). *Anal.* Calcd for $C_{22}H_{24}N_2O_3 \cdot 0.2H_2O$: C, 71.80; H, 6.68; N, 7.61. Found: C, 71.51; H, 6.72; N, 7.47.

Methyl 1-Acetyl-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzaze-

pine-4-carboxylate (14p) To a solution of **24** (369 mg, 1.01 mmol) and pyridine (0.106 ml, 1.31 mmol) in THF (10 ml) was added acetyl chloride (0.086 ml, 1.2 mmol) under ice cooling. After being stirred at room temperature for 0.5 h, EtOAc was added to the reaction mixture and the mixture was washed with water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 400 mg (97%) of **14p** as a pale yellow amorphous. ^{1}H-NMR ($CDCl_3$) δ 2.05 (3H, s), 2.74—3.19 (3H, m), 3.24 (4H, t, J=4.8 Hz), 3.83 (3H, s), 3.90 (4H, t, J=4.8 Hz), 4.73—4.85 (1H, m), 7.01 (2H, d, J=8.8 Hz), 7.23 (1H, d, J=8.2 Hz), 7.54 (2H, d, J=8.8 Hz), 7.51—7.56 (1H, m), 7.67 (1H, d, J=1.8 Hz), 7.74 (1H, s).

1-Acetyl-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (7p) This compound was prepared in 98% yield from **14p** by a method similar to that described for **7f**. ^{1}H-NMR (DMSO-d_6) δ 1.95 (3H, s), 2.75 (3H, m), 3.17 (4H, t, J=4.8 Hz), 3.76 (4H, t, J=4.8 Hz), 4.54 (1H, m), 7.03 (2H, d, J=8.8 Hz), 7.46 (1H, d, J=8.2 Hz), 7.63—7.72 (4H, m), 7.88 (1H, s).

7-Bromo-2,3-dihydro-1-benzothiepine-4-carboxylic Aicd 1,1-Dioxide (25a) This compound was prepared in 95% yield from **13a** by a method similar to that described for **7a**, mp 290—300 °C. ^{1}H-NMR (DMSO-d_6) δ 2.91—2.97 (2H, m), 3.73—3.80 (2H, m), 7.73 (1H, s), 7.84 (1H, dd, J=8.4, 2.0 Hz), 7.94 (1H, d, J=8.4 Hz), 8.08 (1H, d, J=2.0 Hz). *Anal.* Calcd for $C_{11}H_9BrO_4S$: C, 41.66; H, 2.86. Found: C, 41.82; H, 3.02.

7-Bromo-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (25d) To a solution of **13d** (8.05 g, 22.0 mmol) in EtOAc (80 ml) was added 4 N HCl in EtOAc (80 ml, 320 mmol) at room temperature. After being stirred at room temperature for 12.5 h, the mixture was adjusted to pH=3 with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The oraganic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The precipitated yellow crystals were collected by filtration to give 0.98 g (14%) of **25d** as yellow crystals, mp 172—173 °C. ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz), 1.70 (2H, sextet, J=7.3 Hz), 2.81 (2H, t, J=4.6 Hz), 3.22—3.29 (4H, m), 6.70 (1H, d, J=8.8 Hz), 7.25 (1H, dd, J=8.8, 2.3 Hz), 7.43 (1H, d, J=2.3 Hz), 7.69 (1H, s). *Anal.* Calcd for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.17; H, 5.05; N, 4.42.

The following compounds (**25b**—**c**) were prepared form the corresponding esters (**13b**[18]—**c**) by a method similar to that described for **25d**.

7-Bromo-1-methyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (25b) Yield quant. ^{1}H-NMR ($CDCl_3$) δ 2.85 (2H, t, J=4.8 Hz), 3.03 (3H, s), 3.25 (2H, t, J=4.9 Hz), 6.67 (1H, d, J=9.2 Hz), 7.29 (1H, dd, J=8.8, 2.2 Hz), 7.44 (1H, d, J=2.6 Hz), 7.67 (1H, s).

7-Bromo-1-ethyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (25c) Yield 94%, mp 198—201 °C. ^{1}H-NMR (DMSO-d_6) δ 1.19 (3H, t, J=6.9 Hz), 2.69 (2H, t, J=4.4 Hz), 3.17 (2H, t, J=4.8 Hz), 3.34 (2H, q, J=6.9 Hz), 6.81 (1H, d, J=9.0 Hz), 7.28 (1H, dd, J=9.0, 2.4 Hz), 7.49 (1H, s), 7.50 (1H, d, J=1.4 Hz). *Anal.* Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.32; H, 4.72; N, 4.54.

7-Bromo-1-(3-methylbutyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (25e) This compound was prepared in 91% yield from **13f** by a method similar to that described for **14f**. ^{1}H-NMR ($CDCl_3$) δ 0.96 (6H, d, J=6.2 Hz), 1.52—1.71 (3H, m), 2.78—2.84 (2H, m), 3.21—3.26 (2H, m), 3.32 (2H, m), 6.69 (1H, d, J=8.8 Hz), 7.22—7.29 (1H, m), 7.43 (1H, d, J=2.2 Hz), 7.68 (1H, s).

7-Bromo-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (9a) To a solution of **25a** (4.47 g, 14.1 mmol) in THF (90 ml) was added $SOCl_2$ (1.03 ml, 14.1 mmol) and DMF (1.0 ml) at room temperature. The mixture was stirred at room temperature for 2 h. The mixture was added dropwise to a solution of 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)-aminomethyl]aniline (**8**) (3.41 g, 15.5 mmol) and Et_3N (7.90 ml, 56.7 mmol) in THF (30 ml) at room temperature. After being stirred at room temperature for 2 h, the mixture was concentrated *in vacuo*. To the residue was added water and precipitated colorless crystals were collected by filtration. The crystals were washed with water, EtOH, 2-propanol and *i*-Pr_2O to give 4.94 g (67%) of **9a** as colorless crystals, mp 232—235 °C. ^{1}H-NMR ($CDCl_3$) δ 1.54—1.83 (4H, m), 2.21 (3H, s), 2.54—2.73 (1H, m), 3.11—3.18 (2H, m), 3.30—3.44 (2H, m), 3.58 (2H, s), 3.66—3.73 (2H, m), 3.99—4.10 (2H, m), 7.19 (1H, s), 7.33 (2H, d, J=8.3 Hz), 7.53 (2H, d, J=8.3 Hz), 7.62—7.71 (2H, m), 7.88 (1H, br s), 8.04 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{24}H_{27}BrN_2O_4S$: C, 55.49; H, 5.24; N, 5.39. Found: C, 55.56; H, 4.98; N, 5.22.

The following compounds (**9b**—**e**) were prepared from the corresponding carboxylic acids (**25b**—**e**) by a method similar to that described for **9a**.

7-Bromo-1-methyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)-amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (9b) Yield 75%, mp 62—64 °C. ^{1}H-NMR ($CDCl_3$) δ 1.63—1.79 (4H, m), 2.21 (3H, s), 2.57—2.72 (1H, m), 2.94 (2H, t, J=4.2 Hz), 3.03 (3H, s), 3.27—3.44 (4H, m), 3.57 (2H, s), 4.00—4.07 (2H, m), 6.70 (1H, d, J=8.8 Hz), 7.20 (1H, s), 7.26—7.30 (2H, m), 7.30 (1H, dd, J=8.6, 2.4 Hz), 7.42 (1H, d, J=2.4 Hz), 7.50—7.55 (3H, m). *Anal.* Calcd. for $C_{25}H_{30}BrN_3O_2 \cdot 0.25H_2O$: C, 61.41; H, 6.29; N, 8.59. Found: C, 61.45; H, 6.25; N, 8.32.

7-Bromo-1-ethyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)-amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (9c) Yield 70%, mp 135—137 °C. ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, J=7.0 Hz), 1.63—1.76 (4H, m), 2.20 (3H, s), 2.56—2.72 (1H, m), 2.89 (2H, t, J=4.4 Hz), 3.24—3.43 (6H, m), 3.56 (2H, s), 4.01—4.07 (2H, m), 6.72 (1H, d, J=8.8 Hz), 7.18 (1H, s), 7.24 (1H, dd, J=8.8, 2.6 Hz), 7.29 (2H, d, J=8.8 Hz), 7.39 (1H, d, J=2.6 Hz), 7.53 (2H, d, J=8.8 Hz), 7.55 (1H, s). *Anal.* Calcd for $C_{26}H_{32}BrN_3O_2$: C, 62.65; H, 6.47; N, 8.43. Found: C, 62.44; H, 6.57; N, 8.22.

7-Bromo-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (9d) Yield 80%, mp 134—136 °C. ^{1}H-NMR ($CDCl_3$) δ 0.97 (3H, t, J=7.5 Hz), 1.60—1.80 (6H, m), 2.21 (3H, s), 2.57—2.70 (1H, m), 2.89 (2H, t, J=4.6 Hz), 3.22—3.30 (4H, m), 3.37 (2H, td, J=11.1, 2.8 Hz), 3.57 (2H, s), 4.01—4.07 (2H, m), 6.71 (1H, d, J=9.0 Hz), 7.19 (1H, s), 7.24 (1H, dd, J=9.0, 2.6 Hz), 7.30 (2H, d, J=8.4 Hz), 7.41 (1H, d, J=2.6 Hz), 7.50 (1H, s), 7.52 (2H, d, J=8.4 Hz). *Anal.* Calcd for $C_{27}H_{34}BrN_3O_2$: C, 63.28; H, 6.69; N, 8.20. Found: C, 63.19; H, 6.54; N, 8.05.

7-Bromo-1-(3-methylbutyl)-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (9e) Yield 54%. ^{1}H-NMR ($CDCl_3$) δ 0.96 (6H, d, J=6.2 Hz), 1.54—1.86 (7H, m), 2.21 (3H, s), 2.55—2.76 (1H, m), 2.84—2.97 (2H, m), 3.20—3.42 (6H, m) 3.57 (2H, s), 3.98—4.11 (2H, m), 6.70 (1H, d, J=8.8 Hz), 7.19—7.23 (2H, m), 7.30 (2H, d, J=8.4 Hz), 7.39 (1H, d, J=2.2 Hz), 7.54 (2H, d, J=8.4 Hz), 7.64 (1H, s).

1-Bromo-4-[2-(methoxy)ethoxy]benzene (27a) To a mixture of **26a** (15.0 g, 86.7 mmol), NaI (13.0 g, 86.7 mmol) and K_2CO_3 (14.4 g, 104.2 mmol) in DMF (200 ml) was added 2-chloroethyl methyl ether (9.00 ml, 98.5 mmol) at room temperature. The mixture was stirred at 80 °C for 3 d. Water was added to the reaction mixture and the mixture was extracted with diethyl ether (Et_2O). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 17.7 g (87%) of **27a** as an orange oil. ^{1}H-NMR ($CDCl_3$) δ 3.45 (3H, s), 3.72—3.77 (2H, m), 4.06—4.11 (2H, m), 6.81 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.9 Hz).

The following compounds (**27b**—**d**, **27f**) were prepared from **26a** by a method similar to that described for **27a**.

1-Bromo-4-[2-(ethoxy)ethoxy]benzene (27b) Yield 76%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (3H, t, J=7.0 Hz), 3.66 (2H, q, J=7.0 Hz), 3.78 (2H, t, J=4.8 Hz), 4.09 (2H, t, J=4.8 Hz), 6.77—6.84 (2H, m), 7.33—7.39 (2H, m).

1-Bromo-4-[2-(propoxy)ethoxy]benzene (27c) Yield 78%. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.55—1.71 (2H, m), 3.48 (2H, t, J=6.8 Hz), 3.74—3.79 (2H, m), 4.05—4.10 (2H, m), 6.77—6.83 (2H, m), 7.33—7.38 (2H, m).

1-Bromo-4-[2-(butoxy)ethoxy]benzene (27d) Yield 64%. ^{1}H-NMR ($CDCl_3$) δ 0.92 (3H, t, J=7.4 Hz), 1.27—1.65 (4H, m), 3.53 (2H, t, J=6.6 Hz), 3.74—3.79 (2H, m), 4.05—4.11 (2H, m), 6.81 (2H, d, J=9.0 Hz), 7.36 (2H, d, J=9.0 Hz).

1-Bromo-4-[3-(ethoxy)propoxy]benzene (27f) Yield 43%. ^{1}H-NMR ($CDCl_3$) δ 1.20 (3H, t, J=7.0 Hz), 1.98—2.08 (2H, m), 3.49 (2H, q, J=7.0 Hz), 3.58 (2H, d, J=6.0 Hz), 4.03 (2H, d, J=6.4 Hz), 6.79 (2H, d, J=9.0 Hz), 7.36 (2H, d, J=9.0 Hz).

1-Bromo-4-[2-(pentyloxy)ethoxy]benzene (27e) To a solution of **26b** (19.5 g, 89.8 mmol) in DMF (166 ml) was added sodium hydride (65% in mineral oil, 5.30 g, 143 mmol) under ice cooling. After being stirred at room temperature for 1.5 h, 1-iodopentane (17.7 ml, 135 mmol) was added to the reaction mixture at room temperature. The mixture was stirred at room temperature for 2 h, poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 10 : 1) gave 12.0 g (57%) of **27e** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t, J=6.6 Hz), 1.25—1.37 (4H, m), 1.57—1.68 (2H, m), 3.52 (2H, t, J=6.6 Hz), 3.74—3.79 (2H, m), 4.05—4.11 (2H, m), 6.78—6.83 (2H, m), 7.33—7.39 (2H, m).

{4-[2-(Methoxy)ethoxy]phenyl}boronic Acid (10a) To a solution of **27a** (17.0 g, 73.6 mmol) in THF (50 ml) and Et_2O (150 ml) was added drop-

wise a solution of *n*-BuLi in hexane (1.6 M, 50.0 ml, 80.0 mmol) at −78 °C. After being stirred at −78 °C for 1 h, a solution of trimethyl borate (24.8 ml, 221 mmol) in THF (25 ml) at −78 °C. The mixture was stirred at room temperature for 2 h. To the reaction mixture was added 10% aqueous H_2SO_4 (50 ml) and the mixture was stirred for 30 min. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 1 : 1) gave 7.17 g (50%) of **10a** as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ 3.47 (3H, s), 3.79 (2H, t, J=4.7 Hz), 4.19 (2H, t, J=4.7 Hz), 7.00 (2H, d, J=8.7 Hz), 7.76 (2H, d, J=8.7 Hz).

{4-[2-(Ethoxy)ethoxy]phenyl}boronic Acid (10b) This compound was prepared in 27% yield from **27b** by a method similar to that described for **10a**. ^{1}H-NMR (DMSO-d_6) δ 1.13 (3H, t, J=7.0 Hz), 3.50 (2H, q, J=7.0 Hz), 3.66—3.71 (2H, m), 4.06—4.11 (2H, m), 6.89 (2H, d, J=8.4 Hz), 7.14 (2H, d, J=8.4 Hz).

{4-[2-(Propoxy)ethoxy]phenyl}boronic Acid (10c) To a mixture of Mg (2.17 g, 89.3 mmol) and THF (43 ml) was added 1,2-dibromoethane (cat. amount) at room temperature. Then a solution of **27c** (22.0 g, 86.2 mmol) in THF (176 ml) was added dropwise to the mixture under reflux. The mixture was refluxed for 15 min. The mixture was cooled to −78 °C and a solution of trimethyl borate (13.2 g, 118 mmol) in THF (13 ml) at −78 °C. The mixture was stirred at room temperature for 6 h and 5% aqueous H_2SO_4 (5.0 ml) was added to the mixture. The mixture was stirred at room temperature for 15 min and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 8.6 g (45%) of **10c** as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ 0.87 (3H, t, J=7.4 Hz), 1.44—1.62 (2H, m), 3.41 (2H, t, J=6.6 Hz), 3.67—3.72 (2H, m), 4.07—4.12 (2H, m), 6.89 (2H, d, J=8.8 Hz), 7.73 (2H, d, J=8.8 Hz).

The following compounds (**10d**—**f**) were prepared from the corresponding bromides (**27d**—**f**) by a method similar to that described for **10c**.

{4-[2-(Butoxy)ethoxy]phenyl}boronic Acid (10d) Yield 64%. ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, J=7.2 Hz), 1.29—1.47 (2H, m), 1.53—1.66 (2H, m), 3.56 (2H, t, J=6.6 Hz), 3.83 (2H, t, J=4.9 Hz), 4.21 (2H, t, J=4.9 Hz), 7.03 (2H, d, J=8.8 Hz), 8.15 (1H, d, J=8.8 Hz).

{4-[2-(Pentyloxy)ethoxy]phenyl}boronic Acid (10e) Yield 54%. ^{1}H-NMR (DMSO-d_6) δ 0.86 (3H, t, J=6.6 Hz), 1.22—1.59 (6H, m), 3.44 (2H, t, J=6.6 Hz), 3.66—3.71 (2H, m), 4.05—4.13 (2H, m), 6.88 (2H, d, J=8.6 Hz), 7.72 (2H, d, J=8.6 Hz).

{4-[3-(Ethoxy)propoxy]phenyl}boronic Acid (10f) Yield 65%. ^{1}H-NMR (DMSO-d_6) δ 1.11 (3H, t, J=7.0 Hz), 1.89—1.98 (2H, m), 3.42 (2H, q, J=7.0 Hz), 3.50 (2H, t, J=6.2 Hz), 4.02 (2H, t, J=6.2 Hz), 6.84—6.93 (2H, m), 7.69—7.81 (2H, m).

7-(4-Ethylphenyl)-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5a) To a solution of **7a** (180 mg, 0.53 mmol) in THF (10 ml) was added oxalyl chloride (0.090 ml, 1.03 mmol) and DMF (cat. amount) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. A solution of the residue in THF (15 ml) was added dropwise to a solution of **8** (128 mg, 0.58 mmol) and Et_3N (0.15 ml, 1.08 mmol) in THF (5.0 ml) under ice cooling. The reaction mixture was stirred at room temperature for 64 h under a nitrogen atmosphere. Water was added to the reaction mixture at room temperature and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give crystals. Recrystallization from EtOH gave 174 mg (60%) of **5a** as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, t, J=6.7 Hz), 1.56—1.83 (4H, m), 2.21 (3H, s), 2.54—2.71 (1H, m), 2.72 (2H, q, J=6.7 Hz), 3.17 (2H, t, J=6.7 Hz), 3.31—3.44 (2H, m), 3.58 (2H, s), 3.70—3.76 (2H, m), 3.98—4.11 (2H, m), 7.31—7.35 (5H, m), 7.54 (2H, d, J=8.0 Hz), 7.55 (2H, d, J=8.4 Hz), 7.66 (1H, s), 7.71 (1H, dd, J=8.4, 1.8 Hz), 7.92 (1H, br s), 8.21 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{32}H_{36}N_2O_4S$: C, 70.56; H, 6.66; N, 5.14. Found: C, 70.30; H, 6.73; N, 5.29.

The following compounds (**5b**—**c**) were prepared from the corresponding carboxylic acids (**7b**—**c**) by a method similar to that described for **5a**.

***N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-7-(4-propylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5b)** ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, t, J=7.3 Hz), 1.56—1.83 (6H, m), 2.21 (3H, s), 2.52—2.74 (3H, m), 3.18 (2H, t, J=6.6 Hz), 3.31—3.44 (2H, m), 3.58 (2H, s), 3.70—3.76 (2H, m), 3.97—4.10 (2H, m), 7.28—7.35 (5H, m), 7.52 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.66—7.73 (2H, m), 7.94 (1H, br s), 8.21 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{33}H_{38}N_2O_4S$: 70.94; H, 6.86; N, 5.01. Found: C, 70.99; H, 6.51; N, 5.05.

7-(4-Isopropylphenyl)-*N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)-amino]methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5c) ^{1}H-NMR ($CDCl_3$) δ 1.30 (6H, d, J=7.0 Hz), 1.52—1.83 (4H, m), 2.21 (3H, s), 2.55—2.77 (1H, m), 2.90—3.04 (1H, m), 3.17 (2H, t, J=6.6 Hz), 3.37 (2H, dt, J=2.8, 11.0 Hz), 3.58 (2H, s), 3.70—3.76 (2H, m), 3.98—4.09 (2H, m), 7.31—7.38 (5H, m), 7.52—7.58 (4H, m), 7.66—7.73 (2H, m), 7.98 (1H, br s), 8.21 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{33}H_{38}N_2O_4S$: C, 70.94; H, 6.86; N, 5.01. Found: C, 70.89; H, 6.61; N, 7.75.

***N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-7-(4-propoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5d)** To a suspension of **7d** (170 mg, 0.456 mmol) in THF (5.0 ml) was added $SOCl_2$ (0.070 ml, 0.96 mmol) and DMF (cat. amount) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. A solution of the residue in THF (10 ml) was added dropwise to a solution of **8** (111 mg, 0.50 mmol) and Et_3N (0.18 ml, 1.29 mmol) in THF (2.0 ml) at room temperature. The reaction mixture was stirred at room temperature for 21 h under a nitrogen atmosphere. Water was added to the reaction mixture at room temperature, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc : EtOH = 3 : 1) and recrystallization from EtOH gave 148 mg (56%) of **5d** as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 1.06 (3H, t, J=7.4 Hz), 1.57—1.90 (6H, m), 2.21 (3H, s), 2.54—2.75 (1H, m), 3.13—3.20 (2H, m), 3.31—3.44 (2H, m), 3.58 (2H, s), 3.69—3.76 (2H, m), 3.98 (2H, t, J=6.6 Hz), 3.99—4.11 (2H, m), 7.01 (2H, d, J=8.8 Hz), 7.31—7.35 (3H, m), 7.52—7.56 (4H, m), 7.62 (1H, d, J=1.8 Hz), 7.67 (1H, dd, J=8.0, 1.8 Hz), 7.92 (1H, br s), 8.19 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{33}H_{38}N_2O_5S$: C, 68.96; H, 6.66; N, 4.87. Found: C, 68.72; H, 6.70; N, 4.88.

The following compounds (**6e**, **6i**, **6k**, **6m**—**s**) were prepared from the corresponding carboxylic acids (**7f**—**g**, **7i**—**o**, **7p**) by a method similar to that described for **5d**.

1-Acetyl-7-(4-morpholinophenyl)-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6e) ^{1}H-NMR ($CDCl_3$) δ 1.65—1.87 (4H, m), 2.09 (3H, s), 2.23 (3H, s), 2.61—2.78 (1H, m), 2.81—3.05 (3H, m), 3.24 (4H, t, J=4.7 Hz), 3.37 (2H, td, J=11.4, 2.7 Hz), 3.60 (2H, s), 3.90 (4H, t, J=4.8 Hz), 4.02—4.07 (2H, m), 4.75—4.91 (1H, m), 7.01 (2H, d, J=8.8 Hz), 7.23—7.27 (1H, m), 7.34 (2H, d, J=8.4 Hz), 7.52—7.69 (8H, m). *Anal.* Calcd for $C_{36}H_{42}N_4O_4$: C, 72.70; H, 7.12; N, 9.42. Found: C, 72.79; H, 7.07; N, 9.38.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6i) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 0.97 (6H, d, J=6.6 Hz), 1.33—1.46 (2H, m), 1.54—1.77 (6H, m), 1.95—2.16 (1H, m), 2.20 (3H, s), 2.64 (1H, m), 2.88—2.95 (2H, m), 3.18 (2H, d, J=7.4 Hz), 3.30—3.43 (4H, m), 3.55 (2H, t, J=6.6 Hz), 3.56 (2H, s), 3.77—3.83 (2H, m), 3.98—4.07 (2H, m), 4.12—4.18 (2H, m), 6.91 (1H, d, J=8.8 Hz), 6.99 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.36—7.58 (8H, m). *Anal.* Calcd for $C_{40}H_{53}N_3O_4$: C, 75.08; H, 8.35; N, 6.57. Found: C, 74.99; H, 8.16; N, 6.69.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclopropylmethyl-*N*-(4-{[methyl-(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6k) ^{1}H-NMR ($CDCl_3$) δ 0.26—0.33 (2H, m), 0.60—0.69 (2H, m), 0.93 (3H, t, J=7.4 Hz), 1.05—1.18 (1H, m), 1.22—2.05 (8H, m), 2.21 (3H, s), 2.59—2.67 (1H, m), 2.95 (2H, t-like), 3.25 (2H, d, J=6.2 Hz), 3.32—3.58 (8H, m), 3.80 (2H, t, J=5.0 Hz), 3.93—4.18 (4H, m), 6.95—7.00 (3H, m), 7.29 (2H, d, J=8.8 Hz), 7.41—7.58 (8H, m). *Anal.* Calcd for $C_{40}H_{51}N_3O_4$: C, 75.32; H, 8.06; N, 6.59. Found: C, 75.21; H, 8.12; N, 6.49.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclohexylmethyl-*N*-(4-{[methyl-(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6m) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 0.93—1.84 (19H, m) 2.21 (3H, s), 2.58—2.66 (1H, m), 2.91 (2H, t-like), 3.22 (2H, d, J=6.6 Hz), 3.30—3.46 (4H, m), 3.50—3.58 (4H, m), 3.80 (2H, t, J=4.9 Hz), 4.01—4.06 (2H, m), 4.16 (2H, t, J=4.9 Hz), 6.91 (1H, d, J=8.8 Hz), 6.98 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.4 Hz), 7.37—7.56 (8H, m). *Anal.* Calcd for $C_{43}H_{57}N_3O_4$: C, 75.96; H, 8.45; N, 6.18. Found: C, 75.93; H, 8.58; N, 6.21.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-1-phenyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6n) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.27—1.49 (2H, m), 1.55—1.74 (6H, m), 2.19 (3H, s), 2.58—2.66 (1H, m), 2.93 (2H, t, J=4.8 Hz), 3.36 (2H, dt, J=3.2, 10.8 Hz), 3.52—3.59 (4H, m), 3.81 (2H, t, J=5.0 Hz), 3.89 (2H, t, J=4.8 Hz), 4.00—4.06 (2H, m), 4.17 (2H, t, J=5.0 Hz), 6.88—7.02 (5H, m), 7.21—7.30 (4H, m), 7.41 (1H, dd, J=8.6, 2.2 Hz), 7.48—7.53 (7H, m), 7.64 (1H, d, J=2.2 Hz). *Anal.* Calcd for $C_{42}H_{49}N_3O_4 \cdot 0.25H_2O$: C, 75.93; H, 7.51; N, 6.32. Found: C, 75.80; H, 7.40;

N, 6.30.

1-Benzyl-7-{4-[2-(butoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6o) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.1 Hz), 1.30—1.75 (8H, m), 2.21 (3H, s), 2.55—2.70 (1H, m), 2.85 (2H, t-like), 3.31—3.38 (4H, m), 3.52—3.58 (4H, m), 3.80 (2H, t, J=4.9 Hz), 4.01—4.05 (2H, m), 4.16 (2H, t, J=4.9 Hz), 4.61 (2H, s), 6.90 (1H, d, J=8.4 Hz), 6.98 (2H, d, J=8.8 Hz), 7.26—7.56 (15H, m). *Anal.* Calcd for $C_{43}H_{51}N_3O_4 \cdot 0.25H_2O$: C, 76.13; H, 7.65; N, 6.19. Found: C, 76.19; H, 7.55; N, 6.19.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(thiazol-2-yl)methyl]-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6p) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.33—1.45 (2H, m), 1.58—1.80 (6H, m), 2.21 (3H, s), 2.51—2.73 (1H, m), 2.88—2.99 (2H, m), 3.30—3.57 (8H, m), 3.80 (2H, t, J=4.8 Hz), 3.96—4.10 (2H, m), 4.16 (2H, t, J=4.8 Hz), 4.88 (2H, s), 6.96—7.03 (3H, m), 7.26—7.60 (11H, m), 7.80 (1H, d, J=3.2 Hz). *Anal.* Calcd for $C_{40}H_{48}N_4O_4S$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.38; H, 7.12; N, 8.18.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-imidazol-2-yl)-methyl]-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6q) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.30—1.45 (2H, m), 1.55—1.80 (6H, m), 2.20 (3H, s), 2.43—2.70 (3H, m), 3.30—3.45 (4H, m), 3.52—3.59 (7H, m), 3.81 (2H, t, J=5.0 Hz), 3.97—4.08 (2H, m), 4.17 (2H, t, J=5.0 Hz), 4.62 (2H, s), 6.90 (1H, d, J=1.2 Hz), 6.97—7.01 (3H, m), 7.07 (1H, d, J=8.0 Hz), 7.27—7.32 (2H, m), 7.46—7.57 (8H, m). *Anal.* Calcd for $C_{41}H_{51}N_5O_4 \cdot 0.5H_2O$: C, 71.69; H, 7.63; N, 10.30. Found: C, 71.80; H, 7.75; N, 10.38.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-[(1-methyl-1*H*-pyrazol-5-yl)-methyl]-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6r) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.34—1.45 (2H, m), 1.50—1.80 (6H, m), 2.21 (3H, s), 2.40—2.70 (3H, m), 3.30—3.45 (4H, m), 3.55 (2H, t, J=6.6 Hz), 3.57 (2H, s), 3.79—3.84 (5H, m), 3.97—4.09 (2H, m), 4.17 (2H, t, J=5.0 Hz), 4.55 (2H, s), 6.25 (1H, d, J=1.8 Hz), 6.95 (1H, d, J=8.4 Hz), 6.99 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.4 Hz), 7.42—7.57 (9H, m). *Anal.* Calcd for $C_{41}H_{51}N_5O_4 \cdot 0.25H_2O$: C, 72.17; H, 7.61; N, 10.26. Found: C, 72.02; H, 7.46; N, 10.03.

7-[4-[2-(Butoxy)ethoxy]phenyl]-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-*N*-[4-[[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6s) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.34—1.45 (2H, m), 1.50—1.80 (6H, m), 2.21 (3H, s), 2.51—2.72 (3H, m), 2.79—2.88 (2H, m), 3.28—3.45 (4H, m), 3.55 (2H, t, J=6.4 Hz), 3.57 (2H, s), 3.80 (2H, d, J=4.9 Hz), 3.90 (3H, s), 3.97—4.09 (2H, m), 4.16 (2H, t, J=4.9 Hz), 4.44 (2H, s), 6.96—7.01 (3H, m), 7.26—7.39 (3H, m), 7.45—7.55 (9H, m). *Anal.* Calcd for $C_{41}H_{51}N_5O_4$: C, 72.64; H, 758; N, 10.33. Found: C, 72.34; H, 7.59; N, 10.34.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclobutylmethyl-*N*-(4-{[methyl-(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide Dihydrochloride (6l) The free amine was prepared from **7h** by a method similar to that described for **5d**. To a solution of the free amine in EtOAc and EtOH was added 6 N HCl and the mixture was concentrated *in vacuo*. To the residue was added Et_2O and the pale yellow amorphous solid was collected by filtration to give **6l**. ^{1}H-NMR (DMSO-d_6) δ 0.89 (3H, t, J=7.1 Hz), 1.24—1.58 (4H, m), 1.73—2.15 (1H, m), 2.57 (2H, d, J=4.8 Hz), 2.60—2.85 (3H, m), 3.20—3.49 (10H, m), 3.96—4.13 (5H, m), 4.38—4.44 (1H, m), 6.97—7.02 (3H, m), 7.40—7.63 (7H, m), 7.80 (2H, d, J=8.8 Hz), 10.02 (1H, s), 10.41 (1H, s). *Anal.* Calcd for $C_{41}H_{53}N_3O_4 \cdot 2HCl \cdot 1.5H_2O$: C, 65.50; H, 7.78; N, 5.59. Found: C, 65.51; H, 7.77; N, 5.24.

***N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-7-(4-morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5e)** A mixture of **7e** (177 mg, 0.44 mmol) and HOBt (90 mg, 0.67 mmol) in DMF (5.0 ml) was added EDC (127 mg, 0.66 mmol) at room temperature. After being stirred for 1 h at room temperature, a solution of **8** (107 mg, 0.49 mmol) and Et_3N (0.12 ml, 0.86 mmol) in DMF (5.0 ml) and DMAP (cat. amount) was added to the reaction mixture at room temperature. The mixture was stirred at room temperature for 64 h. The mixture was evaporated *in vacuo*, and water was added to the residue. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc : EtOH = 1 : 1) gave 31.6 mg (12%) of **5e** as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ 1.38—1.84 (4H, m), 2.23 (3H, s), 2.58—2.80 (1H, m), 3.10—3.45 (8H, m), 3.61 (2H, s), 3.67—3.78 (2H, m), 3.83—3.94 (4H, m), 3.99—4.09 (2H, m), 7.00 (2H, d, J=8.8 Hz), 7.19—7.38 (3H, m), 7.49—7.60 (4H, m), 7.62—7.71 (2H, m), 7.89—7.95 (1H, m), 8.19 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{34}H_{39}N_3O_5S \cdot 1.5H_2O$: C, 64.95; H, 6.73; N, 6.68. Found: C, 64.74; H, 6.57; N, 6.43. The hydrochloride salts were prepared by mixing **5e** with an excess of conc. HCl in EtOH and MeOH, followed by evaporation of the solvent and crystallization. ^{1}H-NMR (DMSO-d_6) δ 1.65—2.18 (4H, m), 2.60 (3H, s), 3.01—3.12 (2H, m), 3.16—3.51 (7H, m), 3.62—3.87 (6H, m), 3.93—4.07 (2H, m), 4.10—4.22 (1H, m), 4.39—4.51 (1H, m), 7.08 (2H, d, J=8.8 Hz), 7.53—7.58 (3H, m), 7.72 (2H, d, J=8.8 Hz), 7.80—7.92 (3H, m), 8.02—8.10 (2H, m), 10.42 (1H, br s).

7-{4-[2-(Methoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5f) A mixture of **9a** (300 mg, 0.578 mmol), **10a** (124 mg, 0.633 mmol) and K_2CO_3 (160 mg, 1.16 mmol) in toluene (10 ml), EtOH (1.0 ml) and water (1.0 ml) was stirred at room temperature for 1 h under an argon atmosphere. $Pd(PP_3)_4$ (44.0 mg, 0.038 mmol) was added, and the mixture was refluxed for 6 h under an argon atmosphere. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization from EtOH to give 246 mg (72%) of **5f** as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ 1.64—1.84 (4H, m), 2.21 (3H, s), 2.55—2.74 (1H, m), 3.13—3.19 (2H, m), 3.32—3.44 (2H, m), 3.47 (3H, s), 3.58 (2H, s), 3.69—3.81 (4H, m), 3.99—4.09 (2H, m), 4.16—4.21 (2H, m), 7.04 (2H, d, J=8.8 Hz), 7.30—7.35 (3H, m), 7.52—7.56 (4H, m), 7.62—7.69 (2H, m), 7.92 (1H, s), 8.19 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{33}H_{38}N_2O_6S$: C, 67.10; H, 6.48; N, 4.74. Found: C, 66.85; H, 6.40; N, 4.62.

The following compounds (**5g**—**k**, **6a**—**d**, **6f**—**h**, **6j**) were prepared form the corresponding bromides (**9a**—**e**) by a method similar to that described for **5f**.

7-{4-[2-(Ethoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5g) ^{1}H-NMR ($CDCl_3$) δ 1.26 (3H, t, J=7.0 Hz), 1.60—1.81 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13—3.21 (2H, m), 3.31—3.44 (2H, m), 3.57 (2H, s), 3.63 (2H, q, J=7.0 Hz), 3.67—3.75 (2H, m), 3.83 (2H, t, J=5.0 Hz), 3.98—4.09 (2H, m), 4.19 (2H, t, J=5.0 Hz), 7.24 (2H, d, J=8.8 Hz), 7.30 (1H, s), 7.35 (1H, s), 7.51—7.69 (6H, m), 7.81 (1H, s), 8.19 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{34}H_{40}N_2O_6S$: C, 67.53; H, 6.67; N, 4.63. Found: C, 67.55; H, 6.58; N, 4.71.

***N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-7-{4-[2-(propoxy)ethoxy]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5h)** ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.2 Hz), 1.60—1.80 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13—3.20 (2H, m), 3.31—3.44 (2H, m), 3.52 (2H, t, J=6.8 Hz), 3.57 (2H, s), 3.68—3.75 (2H, m), 3.82 (2H, t, J=4.8 Hz), 4.10—4.20 (2H, m), 4.19 (2H, t, J=4.8 Hz), 7.04 (2H, d, J=8.8 Hz), 7.30—7.35 (3H, m), 7.51—7.68 (6H, m), 7.83 (1H, s), 8.19 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{35}H_{42}N_2O_6S$: C, 67.94; H, 6.84; N, 4.53. Found: C, 67.87; H, 6.98; N, 4.45.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5i) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.33—1.55 (2H, m), 1.57—1.77 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.16 (2H, t, J=6.4 Hz), 3.31—3.44 (2H, m), 3.52—3.59 (2H, m), 3.57 (2H, s), 3.67—3.74 (2H, m), 3.79—3.84 (2H, m), 3.98—4.08 (2H, m), 4.18 (2H, t, J=4.8 Hz), 7.03 (2H, d, J=8.8 Hz), 7.30—7.35 (3H, m), 7.50—7.66 (6H, m), 7.88 (1H, s), 8.18 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{36}H_{44}N_2O_6S$: C, 68.33; H, 7.01; N, 4.43. Found: C, 68.33; H, 6.85; N, 4.39.

***N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-7-{4-[2-(pentyloxy)ethoxy]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5j)** ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t, J=6.6 Hz), 1.38—1.40 (4H, m), 1.56—1.77 (6H, m), 2.20 (3H, s), 2.64 (1H, m), 3.10—3.19 (2H, m), 3.30—3.44 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.56 (2H, s), 3.65—3.73 (2H, m), 3.79—3.85 (2H, m), 3.98—4.10 (2H, m), 4.15—4.21 (2H, m), 7.00—7.06 (2H, m), 7.29—7.34 (2H, m), 7.47—7.66 (7H, m), 7.95 (1H, s), 8.17 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{37}H_{46}N_2O_6S$: C, 68.70; H, 7.17; N, 4.33. Found: C, 68.64; H, 7.03; N, 4.31.

7-{4-[3-(Ethoxy)propoxy]phenyl}-*N*-(4-{[Methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide (5k) ^{1}H-NMR ($CDCl_3$) δ 1.21 (3H, t, J=7.0 Hz), 1.69—1.77 (4H, m), 2.05—2.13 (2H, m), 2.21 (3H, s), 2.65 (1H, m), 3.16 (2H, t, J=6.6 Hz), 3.31—3.44 (2H, m), 3.51 (2H, q, J=7.0 Hz), 3.57 (2H, s), 3.62 (2H, t, J=6.2 Hz), 3.67—3.75 (2H, m), 3.98—4.16 (4H, m), 7.01 (2H, d, J=8.8 Hz), 7.29—7.35 (3H, m), 7.50—7.67 (6H, m), 7.86 (1H, s), 8.18 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{35}H_{42}N_2O_6S$: C, 67.94; H, 6.84; N, 4.53. Found: C, 67.67; H, 6.77; N, 4.54.

1-Methyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-

phenyl)-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6a) ^{1}H-NMR ($CDCl_3$) δ 1.64—1.77 (4H, m), 2.21 (3H, s), 2.57—2.75 (1H, m), 2.96 (2H, t, J=5.2 Hz), 3.09 (3H, s), 3.20 (2H, t, J=4.8 Hz), 3.18—3.22 (2H, m), 3.33—3.43 (4H, m), 3.58 (2H, s), 3.89 (4H, t, J=4.8 Hz), 4.01—4.06 (2H, m), 6.88 (1H, d, J=8.4 Hz), 6.97 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.8 Hz), 7.41—7.56 (8H, m). *Anal.* Calcd for $C_{35}H_{42}N_4O_3$: C, 74.18; H, 7.47; N, 9.89. Found: C, 73.92; H, 7.36; N, 9.95.

1-Methyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-7-{4-[2-(propoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6b) ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, J=7.3 Hz), 1.65 (2H, sextet, J=7.2 Hz), 1.69—1.76 (4H, m), 2.21 (3H, s), 2.57—2.72 (1H, m), 2.96 (2H, t, J=4.4 Hz), 3.09 (3H, s), 3.32—3.43 (4H, m), 3.51 (2H, t, J=6.8 Hz), 3.56 (2H, s), 3.81 (2H, t, J=5.0 Hz), 4.01—4.06 (2H, m), 4.16 (2H, t, J=5.0 Hz), 6.88 (1H, d, J=8.4 Hz), 6.98 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.6 Hz), 7.40—7.56 (8H, m). *Anal.* Calcd for $C_{36}H_{45}N_3O_4 \cdot 0.25H_2O$: C, 73.50; H, 7.80; N, 7.14. Found: C, 73.12; H, 7.67; N, 7.08.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-methyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6c) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 1.39 (2H, sextet, J=7.3 Hz), 1.55—1.79 (6H, m), 2.21 (3H, s), 2.57—2.75 (1H, m), 2.96 (2H, t, J=4.4 Hz), 3.09 (3H, s), 3.31—3.38 (2H, m), 3.37 (2H, td, J=11.6, 2.7 Hz), 3.55 (2H, t, J=6.6 Hz), 3.57 (2H, s), 3.81 (2H, t, J=5.0 Hz), 4.00—4.08 (2H, m), 4.16 (2H, t, J=5.0 Hz), 6.88 (1H, d, J=8.6 Hz), 6.96—7.01 (2H, m), 7.30 (2H, d, J=8.4 Hz), 7.40—7.56 (4H, m), 7.48 (2H, d, J=9.0 Hz), 7.54 (2H, d, J=8.6 Hz). *Anal.* Calcd for $C_{37}H_{47}N_3O_4 \cdot 0.1H_2O$: C, 74.12; H, 7.93; N, 7.01. Found: C, 73.90; H, 7.82; N, 7.12.

1-Ethyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6d) ^{1}H-NMR ($CDCl_3$) δ 1.32 (3H, t, J=7.1 Hz), 1.65—1.77 (4H, m), 2.21 (3H, s), 2.57—2.72 (1H, m), 2.92 (2H, t, J=4.2 Hz), 3.20 (4H, t, J=4.9 Hz), 3.31—3.38 (4H, m), 3.44 (2H, q, J=6.9 Hz), 3.57 (2H, s), 3.89 (4H, t, J=4.8 Hz), 4.01—4.07 (2H, m), 6.92 (1H, d, J=8.6 Hz), 6.97 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.4 Hz), 7.40—7.56 (8H, m). *Anal.* Calcd for $C_{36}H_{44}N_4O_3$: C, 74.45; H, 7.64; N, 9.65. Found: C, 74.34; H, 7.54; N, 9.61.

1-Ethyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-7-{4-[2-(propoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6f) ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, J=7.5 Hz), 1.32 (3H, t, J=6.9 Hz), 1.65 (2H, sextet, J=7.1 Hz), 1.70—1.76 (4H, m), 2.21 (3H, s), 2.56—2.69 (1H, m), 2.92 (2H, t, J=4.0 Hz), 3.31—3.46 (6H, m), 3.51 (2H, t, J=6.8 Hz), 3.56 (2H, s), 3.81 (2H, t, J=4.9 Hz), 4.01—4.06 (2H, m), 4.16 (2H, t, J=5.0 Hz), 6.92 (1H, d, J=8.4 Hz), 6.98 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.8 Hz), 7.40 (1H, s), 7.47 (2H, d, J=8.8 Hz), 7.54 (2H, d, J=8.8 Hz), 7.40—7.56 (3H, m). *Anal.* Calcd for $C_{37}H_{47}N_3O_4 \cdot 0.25H_2O$: C, 73.78; H, 7.95; N, 6.98. Found: C, 73.52; H, 7.76; N, 6.95.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-ethyl-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6g) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.0 Hz), 1.39 (2H, sextet, J=7.4 Hz), 1.54—1.76 (6H, m), 2.21 (3H, s), 2.54—2.72 (1H, m), 2.92 (2H, t, J=4.6 Hz), 3.31—3.50 (6H, m), 3.55 (2H, t, J=6.6 Hz), 3.57 (2H, s), 3.81 (2H, t, J=4.9 Hz), 4.01—4.07 (2H, m), 4.16 (2H, t, J=5.0 Hz), 6.92 (1H, d, J=8.6 Hz), 6.98 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.4 Hz), 7.40 (1H, s), 7.44—7.56 (3H, m), 7.47 (2H, d, J=9.0 Hz), 7.54 (2H, d, J=8.4 Hz). *Anal.* Calcd for $C_{38}H_{49}N_3O_4 \cdot 0.2H_2O$: C, 74.16; H, 8.09; N, 6.83. Found: C, 73.92; H, 8.19; N, 6.59.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6h) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.1 Hz), 0.99 (3H, t, J=7.3 Hz), 1.39 (2H, sextet, J=7.2 Hz), 1.54—1.80 (8H, m), 2.20 (3H, s), 2.53—2.71 (1H, m), 2.91 (2H, t, J=4.0 Hz), 3.27—3.43 (6H, m), 3.52—3.58 (4H, m), 3.80 (2H, t, J=4.8 Hz), 4.01—4.06 (2H, m), 4.15 (2H, t, J=4.8 Hz), 6.89 (1H, d, J=8.8 Hz), 6.97 (2H, d, J=8.8 Hz), 7.29 (2H, d, J=8.4 Hz), 7.37—7.59 (8H, m). *Anal.* Calcd for $C_{39}H_{51}N_3O_4$: C, 74.85; H, 8.21; N, 6.71. Found: C, 74.64; H, 8.36; N, 6.93.

7-{4-[2-(Butoxy)ethoxy]phenyl}-1-(3-methylbutyl)-*N*-(4-{[methyl-(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6j) ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=6.2 Hz), 1.30—1.46 (2H, m), 1.49—1.81 (9H, m), 2.21 (3H, s), 2.52—2.71 (1H, m), 2.86—2.98 (2H, m), 3.27—3.46 (6H, m), 3.55 (2H, t, J=6.6 Hz), 3.56 (2H, s), 3.80 (2H, t, J=5.0 Hz), 3.96—4.07 (2H, m), 4.16 (2H, t, J=5.0 Hz), 6.89 (1H, d, J=8.8 Hz), 6.98 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.8 Hz), 7.39—7.55 (8H, m). *Anal.* Calcd for $C_{41}H_{55}N_3O_4$: C, 75.31; H, 8.48; N, 6.43. Found: C, 74.94; H, 8.70; N, 6.50.

Receptor Binding Assays CHO-K1 and CCR5-expressing CHO cells[16] were incubated with various concentrations of test compound in the binding buffer (Ham's F-12 medium containing 20 mM HEPES and 0.5% bovine serum albumin, pH 7.2) containing 200 pM [^{125}I]RANTES. Binding reactions were performed at room temperature for 40 min. The binding reaction was terminated by washing out the free ligand with cold phosphate-buffered saline, and the cell-associated radioactivity was counted using a TopCount scintillation counter (Packard).

HIV-1 Envelope-Mediated Membrane Fusion Assay COS-7 cells were maintained in Dulbecco's modified Eagle medium (D-MEM) supplemented with 10% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin. MOLT-4/CCR5/Luc$^+$ cells, a lymphoblastoid cell line that expresses human CCR5 and that has an integrated copy of the HIV-1 long terminal repeat-driven luciferase reporter gene, were maintained in RPMI 1640 medium supplemented with 10% FBS, 100 U/ml penicillin, 100 μg/ml streptomycin, and 500 μg/ml geneticin. Tat, rev, and envelope cDNA were amplified from total RNA of R5 HIV-1 (JR-FL)-infected cells and cloned into an expression vector for mammalian cells. Those expression vectors were mixed at a ratio of 3 : 1 : 5 and co-transfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After 2 d incubation, transfected COS-7 cells and MOLT-4/CCR5/Luc$^+$ cells were seeded in a 96-well plate at 10^4 cells each per well, and various concentrations of the test compounds were added to the wells. The cell suspension was incubated at 37 °C. The mixture of D-MEM and RPMI 1640 medium supplemented with 10% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin was used as medium for membrane fusion. After an overnight incubation, Luc-Screen (Tropix) was added to each well, and the mixtures were incubated at room temperature for 10 min. The luciferase activity was measured with a luminometer (Wallac 1420 ARVOsx).

Preliminary pharmacokinetic Analysis Compounds (10 mg/kg) suspended in 0.5% methylcellulose were orally administered to SD (IGS) rats (male, 8 weeks old). Blood samples were collected at different time points (pre, 15, 30 min, 1, 2, 4, 8, 24 h) from the tail vein. Acetonitrile (200 μl) was added to each plasma sample (100 μl), and the precipitated plasma proteins were removed by centrifugation. The compound concentrations in the supernatant were measured by HPLC (column; Inertsil ODS-3, 4.6×150 mm, 5 mm particle size, GL Science: mobile phase; acetonitrile–0.01 mol/l ammonium acetate or acetonitrile–0.01 mol/l phosphate buffer (pH 7) at a flow rate of 1.0 ml/min at 40 °C: UV detection; 280 or 285 nm).

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