Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 363–386
Bioorganic & Medicinal Chemistry

Orally active CCR5 antagonists as anti-HIV-1 agents. Part 3: Synthesis and biological activities of 1-benzazepine derivatives containing a sulfoxide moiety

Masaki Seto,[a,*] Naoki Miyamoto,[a] Katsuji Aikawa,[a] Yoshio Aramaki,[a] Naoyuki Kanzaki,[a] Yuji Iizawa,[a] Masanori Baba[b] and Mitsuru Shiraishi[a]

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

Received 17 September 2004; revised 8 October 2004; accepted 8 October 2004

Abstract—In order to develop orally active CCR5 antagonists, 1-propyl- or 1-isobutyl-1-benzazepine derivatives containing a sulfoxide moiety have been designed, synthesized, and evaluated for their biological activities. Sulfoxide compounds containing a 2-pyridyl group were first investigated, which led to discovering that the presence of a methylene group between the sulfoxide moiety and 2-pyridyl group was necessary for increased inhibitory activity in a binding assay. After further chemical modification, it was found that replacement of the pyridyl group with an imidazolyl or 1,2,4-triazolyl group enhanced activity in the binding assay and that *S*-sulfoxide compounds were more active than *R*-isomers. Particularly, compounds (***S***)-**4r**, (***S***)-**4s**, and (***S***)-**4w** exhibited highly potent CCR5 antagonistic activities (IC_{50} = 1.9, 1.7, 1.6 nM, respectively) and inhibitory effects (IC_{50} = 1.0, 2.8, 7.7 nM, respectively) in the HIV-1 envelope mediated membrane fusion assay, together with good pharmacokinetic properties in rats. In addition, we established the synthesis of (***S***)-**4r** and (***S***)-**4w** by asymmetric oxidation with titanium-(*S*)-(−)-1,1′-bi-2-naphthol complex.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the causative agent of AIDS, and it is well documented that suppression of HIV-1 replication leads to delay of disease progression. Establishment of the highly active anti-retroviral therapy (HAART) using HIV-1 reverse transcriptase inhibitors and protease inhibitors has been successful in suppressing viral replication, which led to reduction of mortality in HIV-1 infected individuals.[1] However, development of novel anti-HIV-1 agents with new mechanisms of action is thought to be essential because of several problems associated with combination chemotherapy, such as the unfeasibility of viral eradication,[2] emergence of drug resistance[3] and long-term toxicities.[4] Therefore, HIV-1 entry inhibitors are considered to be attractive candidates in HAART to circumvent the above problems.[5] Since the CC chemokine receptor 5 (CCR5) was identified as a co-receptor for entry of macrophage-tropic (CCR5-using or R5) HIV-1 into host cells in 1996,[6–10] CCR5 antagonists have attracted a great deal of attention as anti-HIV-1 agents. CCR5 is a member of the seven-transmembrane G-protein coupled receptors, and its natural ligands are regulated on activation normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α and MIP-1β. Natural ligands for CCR5 and their modifications are reported to inhibit R5 HIV-1 infection.[11] Therefore, CCR5 antagonists are thought to be new and promising agents against HIV-1 infection, and many pharmaceutical companies have searched for CCR5 antagonists as anti-HIV-1 agents.[12] The first non-peptide, small molecule CCR5 antagonist was compound **1**, which we reported in 1999.[13,14] Compound **1** exhibited poor oral absorption because of its polar quaternary ammonium moiety, but it was selected as a

Keywords: CCR5 antagonist; HIV-1; Sulfoxide; S-isomer; 1-Benzazepine.
* Corresponding author. Tel.: +81 663006651; fax: +81 663006306; e-mail: seto_masaki@takeda.co.jp

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.10.021

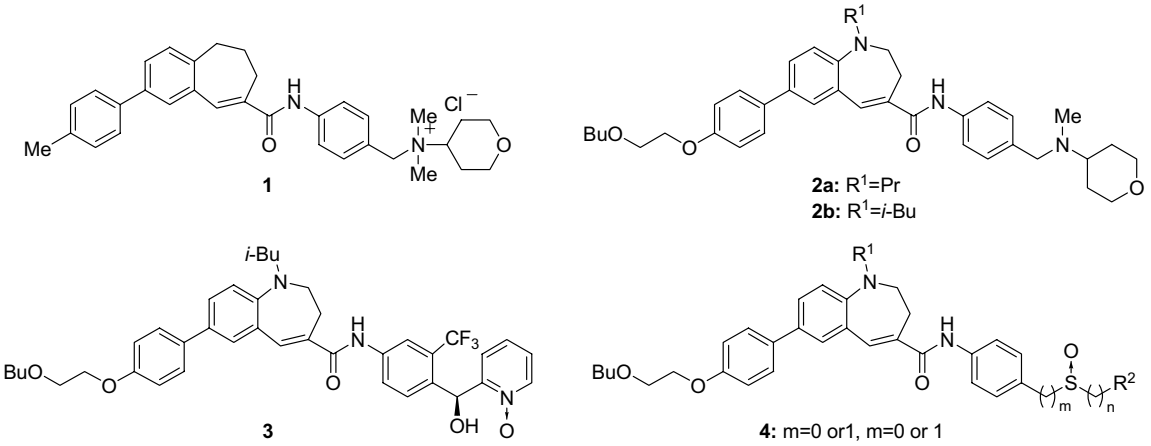


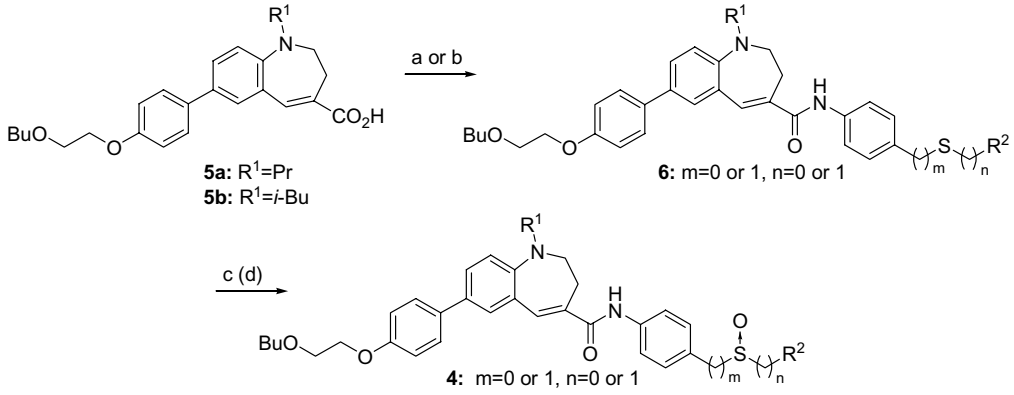
Figure 1.

clinical candidate for a subcutaneous injectable agent. For orally active CCR5 antagonists, it was reported that Schering–Plough's clinical candidate, SCH-C has started clinical trials.[15,16]

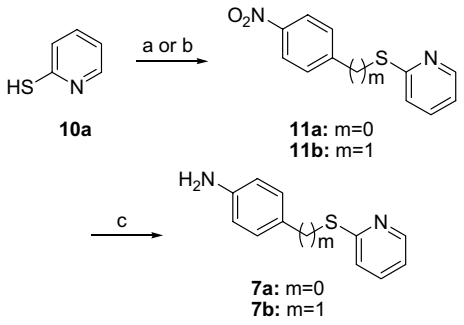
In order to develop an orally active CCR5 antagonist, we had investigated the replacement of the quaternary ammonium moiety of **1** with other polar substituents. First, the chemical modification of the tertiary amine derivatives was performed. Consequently, we discovered the potent, orally active 1-propyl-1-benzazepine **2a** and 1-isobutyl-1-benzazepine **2b**. For the tertiary amine derivatives, it was found that introduction of the 2-(butoxy)ethoxy group at the 4-position on the 7-phenyl group of the [6,7]-fused nucleus led to both enhanced binding affinity and improvement of the pharmacokinetic profiles, and that substitution of the 1-(bulky)alkyl groups on the 1-benzazepine ring further enhanced the activity in both the binding assay and HIV-1 envelope (Env)-mediated membrane fusion assay.[17,18] We next investigated the pyridine *N*-oxide derivatives, which resulted in the finding of the potent, orally active 2-(α-hydroxybenzyl)pyridine *N*-oxide **3** containing the 1-isobutyl-1-benzazepine moiety.[19] We continued a search for new polar substituents in place of the quaternary ammonium moiety. On the basis of our experiences, we designed the 1-benzazepine derivatives **4**, which had a sulfoxide moiety containing a heteroaryl group, and performed chemical modifications of the sulfoxide derivatives. In this paper, we describe the design, synthesis, and structure–activity relationships (SAR) of the 1-benzazepine derivatives containing a sulfoxide moiety (Fig. 1).

2. Chemistry

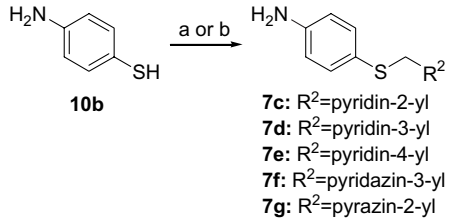
The synthetic method to the target compounds is outlined in Scheme 1. The target sulfoxide derivatives **4** were prepared by *m*-chloroperbenzoic acid (*m*CPBA) oxidation of the corresponding sulfide compounds **6**. The sulfide compounds were prepared by two methods. Condensation of the two key intermediates, the 1-benzazepine-4-carboxylic acids **5**[18] and the aniline derivatives **7** containing the sulfide moieties, gave the sulfide compounds **6** (method A). The alternative synthetic route to the sulfide derivatives **6** used the other two key intermediates, *S*-Cbz protected 4-aminothiophenol **8** and heteroarylmethylchlorides **9** (method B). The synthetic methods for the key aniline derivatives **7**, **8**, and heteroarylmethylchlorides **9** are illustrated in Schemes 2–9.



Scheme 1. Reagents: (a) (1) $SOCl_2$ or $(COCl)_2$, cat. DMF, THF, (2) **7**, Et_3N, THF; (b) (1) $SOCl_2$, cat. DMF, THF, (2) **8**, Et_3N, THF, then 1 N NaOH, **9**, MeOH; (c) *m*CPBA, CH_2Cl_2; (d) optical resolution by HPLC.



Scheme 2. Reagents: (a) 1-fluoro-4-nitrobenzene, NaH, DMF; (b) 4-nitrobenzylbromide, Et_3N, THF; (c) Fe, AcOH.

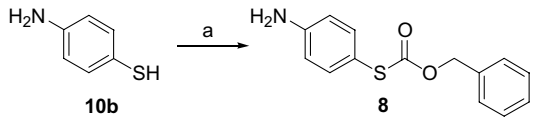


Scheme 3. Reagents: (a) heteroarylmethylchloride, 1 N NaOH, EtOH; (b) (1) pyrazin-2-ylmethanol, MsCl, Et_3N, THF, (2) 1 N NaOH.

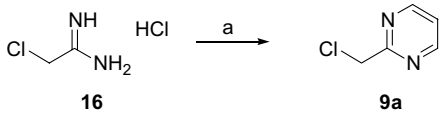
The key aniline derivatives **7a**,**b** were prepared according to Scheme 2. Alkylation of the 2-mercaptopyridine **10a** with the alkyl or aryl halides gave the nitro compounds **11a**,**b**. The aniline derivatives **7a**,**b** were prepared by Fe reduction of the nitro compounds **11a**,**b**.

The synthetic route to the anilines **7c**–**g** is shown in Scheme 3. Alkylation of the 4-aminothiophenol (**10b**) with the corresponding heteroarylmethylchlorides gave the aniline derivatives **7c**–**f**. The aniline derivative **7g** was prepared by methanesulfonylation of pyrazin-2-ylmethanol and subsequent reaction of the resulting methanesulfonate with **10b**.

The aniline derivatives **7h**–**m** containing azole moieties were prepared according to Scheme 4. Alkylation of the 2-formylimidazole **12** and lithium aluminum hydride ($LiAlH_4$) reduction afforded the 2-(hydroxymethyl)imidazoles **14a**–**d**. The aniline derivatives **7h**–**m** were prepared by chlorination of the alcohols **14a**–**d**, **15a**[20], **b**[21] and subsequent coupling with the 4-aminothiophenol (**10b**).



Scheme 5. Reagents: (a) benzyl chlorocarbonate, Et_3N, THF.



Scheme 6. Reagents: (a) 1,1,3,3-tetramethoxypropane.

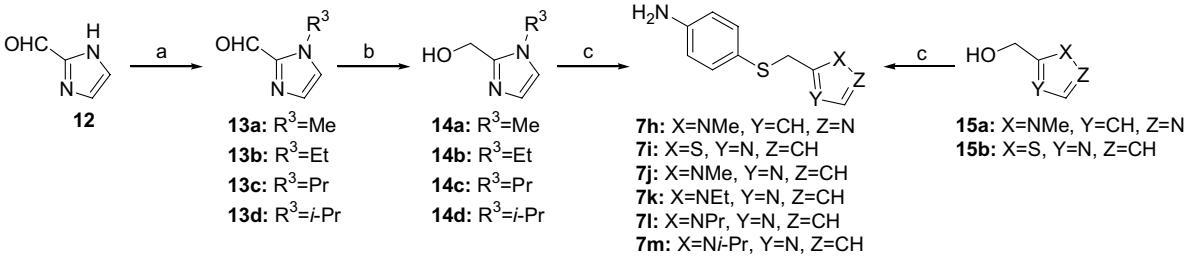
The key *O*-benzyl-*S*-(4-aminophenyl)thiocarbonate (**8**) was synthesized by reaction of 4-aminothiophenol (**10b**) with benzyl chlorocarbonate (Scheme 5).

2-(Chloromethyl)pyrimidine (**9a**) was prepared by reaction of 2-chloroacetamidine (**16**) with 1,1,3,3-tetramethoxypropane (Scheme 6).

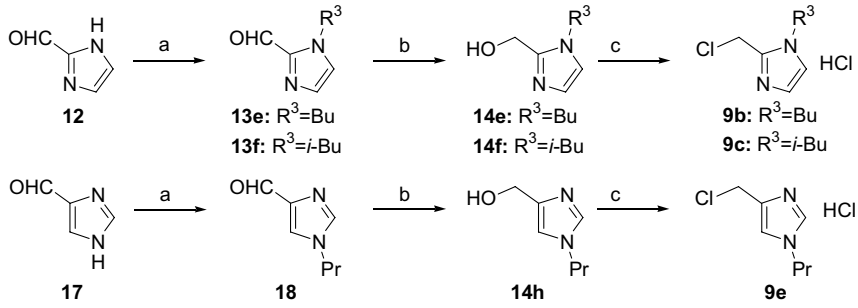
The synthetic route to the imidazole derivatives **9b**,**c**,**e** is illustrated in Scheme 7. Alkylation of formylimidazoles **12**, **17** and $LiAlH_4$ reduction gave the alcohols **14e**,**f**,**h**. The key intermediates **9b**,**c**,**e** were prepared by chlorination of the corresponding alcohols **14e**,**f**,**h** using thionyl chloride.

The 5-(chloromethyl)-1-propyl-1*H*-imidazole hydrochloride (**9d**) and 4-alkyl-3-(chloromethyl)-4*H*-1,2,4-triazole derivatives **9f**,**g** were prepared according to Scheme 8. Reaction of dihydroxyacetone (**19**) with potassium thiocyanate and propylamine hydrochloride gave 2-mercaptoimidazole **21a**.[22] The 3-mercaptotriazoles **21b**,**c** were synthesized by reaction of ethyl glycolate (**20**) with hydrazine hydrate, followed by reaction with methyl- or propylisothiocyanate and cyclization reaction under basic condition using aqueous NaOH.[23] The key chloromethylazoles **9d**,**f**,[23]**g** were prepared by desulfurization of the compounds **21a**–**c** and chlorination of the resulting alcohols **14g**,**i**,**j**.

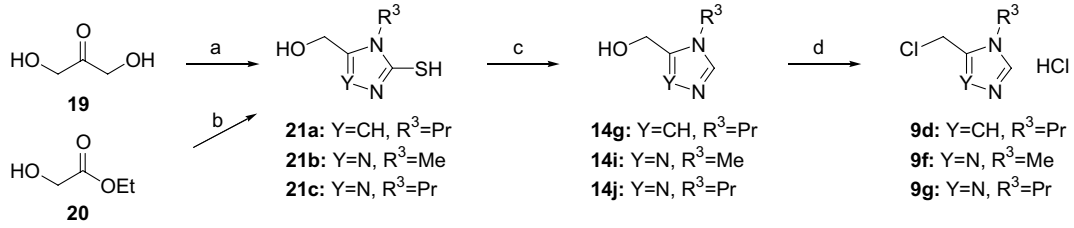
The 1-methyl-1*H*-1,2,4-triazole compound **9h** was synthesized by the literature procedure[24] illustrated in Scheme 9.



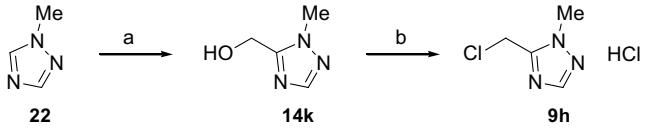
Scheme 4. Reagents: (a) R^3I, K_2CO_3, DMF; (b) $LiAlH_4$, THF; (c) (1) $SOCl_2$, cat. DMF, $CHCl_3$, (2) **10b**, 1 N NaOH, EtOH or MeOH.



Scheme 7. Reagents: (a) R^3I, K_2CO_3, DMF or PrI, NaH, THF; (b) $LiAlH_4$, THF; (c) $SOCl_2$.



Scheme 8. Reagents: (a) KSCN, propylamine hydrochloride, BuOH; (b) (1) hydrazine monohydrate, MeOH, (2) R^3NCS, MeOH, (3) aq NaOH; (c) $NaNO_2$, HNO_3; (d) $SOCl_2$.



Scheme 9. Reagents: (a) formalin; (b) $SOCl_2$.

The 1,2,3-triazole derivative **9i** was synthesized according to Scheme 10. Alkylation of methyl 1,2,3-trizole-4-carboxylate **23** gave a mixture of propyl-substituted 1,2,3-triazoles, which was separated by column chromatography to afford the desired **24**. The key intermediate **9i** was synthesized by a procedure similar to that used for the above (chloro) methylazoles.

The target sulfoxide derivatives **4a**–**y** were prepared according to Scheme 1. Conversion of the key 1-benzazepine-4-carboxylic acids **5a**,**b** into acid chlorides and coupling with the key aniline derivatives **7a**–**m** afforded the sulfide derivatives **6a**–**g**, **6i**–**o**. The other sulfide derivatives **6h**, **6p**–**y** were synthesized by condensation of the carboxylic acids **5a**,**b** with *S*-Cbz-protected 4-aminothiophenol **8** by an acid chloride method, followed by removal of the *S*-Cbz group and subsequent reaction with the heteroarylmethyl chlorides **9**. The target sulfoxide derivatives **4a**–**y** were prepared by *m*CPBA oxidation of the sulfide derivatives **6a**–**y**. The racemates **4r**,**s**,**v**,**w** were optically resolved with chiral high performance liquid chromatography (HPLC) to afford optically pure compounds (***S***)- and (***R***)-**4r**,**s**,**v**,**w**. The absolute configuration was determined by X-ray crystallographic analysis of the compound (***S***)-**4r** (Fig. 2). The sulfone compound **25** was obtained by *m*CPBA oxidation of **6r** (Scheme 11).

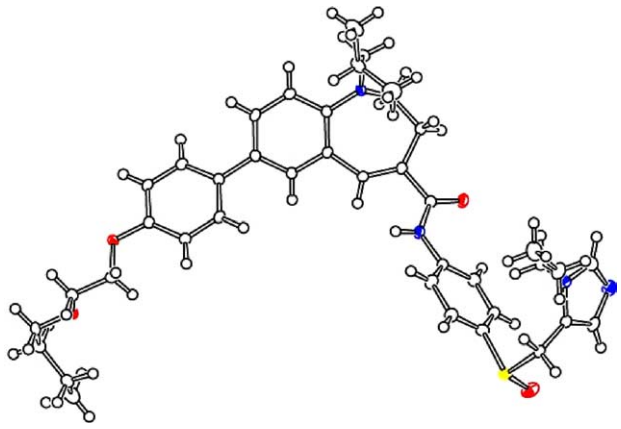
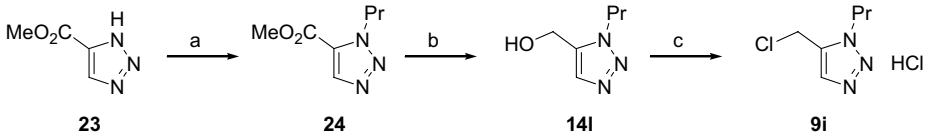
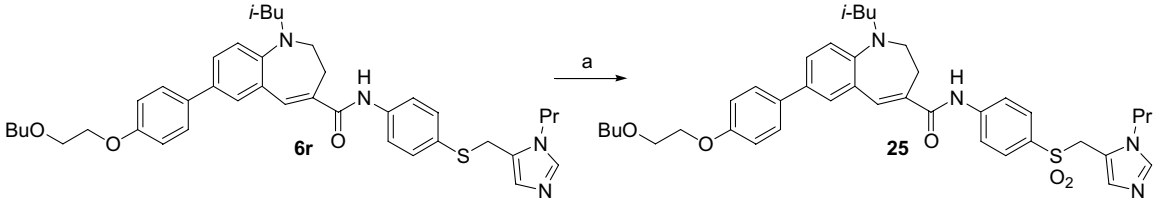


Figure 2. Molecular structure of (***S***)-**4r** as determined by X-ray crystallographic analysis.



Scheme 10. Reagents: (a) 1-iodopropane, K_2CO_3, DMF; (b) $LiAlH_4$, THF; (c) $SOCl_2$.



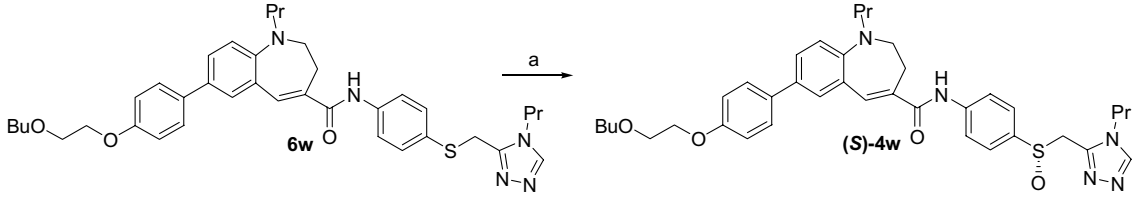
Scheme 11. Reagents: (a) *m*CPBA, CH_2Cl_2.

From the results of the biological evaluation, it was found that the absolute configuration of the sulfoxide moiety significantly influenced the inhibitory effect on a HIV-1 Env-mediated membrane fusion. Therefore, we investigated the asymmetric synthesis of the imidazole compound (***S***)-**4r** and triazole compound (***S***)-**4w** by asymmetric oxidation of the sulfide compounds **6r**,**w**.

First, we examined the asymmetric oxidation of the sulfide compound **6w** containing the 1,2,4-triazole moiety. The results are illustrated in Table 1. Cumene hydroperoxide (CHP) was used as the oxidant in all reactions. Oxidation of the compound **6w** by Kagan's method[25] [Ti(O*i*-Pr)$_4$:(*D*)-(−)-diethyl tartarate (DET)/H_2O/**6w** = 1:2:1:1] in dichloromethane (CH_2Cl_2) at −23 °C gave (***S***)-**4w** in a low optical yield (26% ee) and low chemical yield (42%) (entry 1). We next examined the catalytic asymmetric oxidation of **6w** using (*R*,*R*)-1,2-diphenylethan-1,2-diol (DPED) as a ligand[26] [Ti(O*i*-Pr)$_4$:(*R*,*R*)-DPED/H_2O/**6w** = 0.1:0.2:1.0:1.0] and found it also resulted in a low optical yield (23% ee) (entry 2). Interestingly, reduction of the amount of water (0.2 equiv) led to great increases in both the optical (87% ee) and chemical (71%) yields (entry 3) and performing the reaction at room temperature was also found to give a high enantioselectivity and good chemical yield (91% ee, 71%, entry 4). Next, we examined Uemura's method[27] using (*S*)-(−)-1,1′-bi-2-naphthol (BINOL) as a ligand and found improved enantioselectivity and chemical yields could be achieved (entries 5 and 6). Reactions performed at room temperature gave the same results as those performed at 0 °C. Thus, oxidation of **6w** using titanium complex [Ti(O*i*-Pr)$_4$/(*S*)-BINOL/H_2O/**6w** = 0.1:0.2:2.0:1.0] in toluene at room temperature gave the target (***S***)-**4w** in a high optical yield (96% ee) and good chemical yield (84%) (entry 6).

Next, asymmetric synthesis of (***S***)-**4r** was investigated. The results are summarized in Table 2. Oxidation by Kagan's method at 0 °C afforded target (***S***)-**4r** in a low optical yield (42% ee) and low chemical yield (42%) (entry 1). The combination of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DPED/H_2O/**6r** = 0.1:0.2:0.1:1.0, using the method that gave a good result for oxidation of **6w**, resulted in a decreased enantioselectivity and chemical yield (entry 2). Next, we examined Uemura's method, using the optimized condition for the 1,2,4-triazole compound **6w**. However, this reaction condition gave (***S***)-**4r** in a low optical yield (30% ee) and low chemical yield (28%) (entry 3). In this case, the reaction rate was very slow and the starting material **6r** was recovered. Therefore, excess oxidant (3.0 equiv) was used and the reaction was performed for a long time (six days). As a result, the target sulfoxide compound (***S***)-**4r** was obtained in a fair optical yield (84% ee) but low chemical yield (45%) (entry 4),

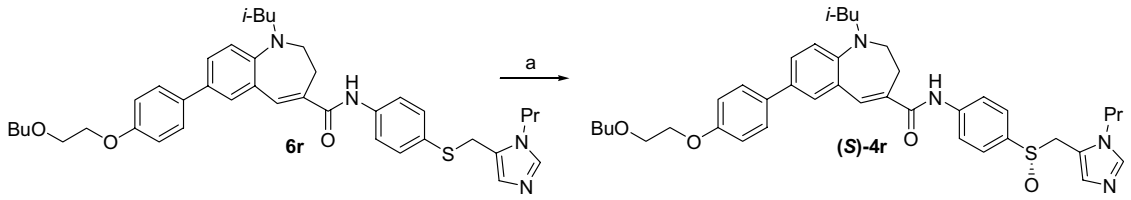
Table 1.



Entry	Ti(O*i*-Pr)$_4$ (equiv)	Diol (equiv)[b]	H_2O (equiv)	Conditions	Solvent	Yield (%)	ee (%)[c]
1	1.0	(*D*)-DET (2.0)	1.0	−20 °C, 7 d	CH_2Cl_2	42	26
2	0.1	(*R*,*R*)-DPED (0.2)	1.0	0 °C, 4 d	Toluene	54	23
3	0.1	(*R*,*R*)-DPED (0.2)	0.1	0 °C, 5 d	Toluene	71	87
4	0.1	(*R*,*R*)-DPED (0.2)	0.1	rt, 3 d	Toluene	71	91
5[d]	0.1	(*S*)-BINOL (0.2)	2.0	0 °C, 7 d	Toluene	83	95
6[e]	0.1	(*S*)-BINOL (0.2)	2.0	rt, 30 h	Toluene	84	96

[a] Ti(O*i*-Pr)$_4$, diol, H_2O, 80% cumene hydroperoxide (CHP, 2.0 equiv), solvent.
[b] (*D*)-DET = (*D*)-(−)-diethyl tartarate, (*R*,*R*)-(+)-DPED = (*R*,*R*)-1,2-diphenylethan-1,2-diol, (*S*)-BINOL = (*S*)-(−)-1,1′-bi-2-naphthol.
[c] Determined by HPLC on a CHIRAL PAK AD (DAICEL).
[d] 80% CHP (3.0 equiv).
[e] 80% CHP (1.5 equiv).

Table 2.



Entry	Ti(O*i*-Pr)$_4$ (equiv)	Diol (equiv)[b]	H_2O (equiv)	Conditions	Solvent	Yield (%)	ee (%)[c]
1	1.0	(*D*)-DET (2.0)	1.0	0 °C, 20 h	CH_2Cl_2	42	42
2	0.1	(*R*,*R*)-DPED (0.2)	0.1	0 °C, 11 d	Toluene	32[d]	18
3	0.1	(*S*)-BINOL (0.2)	2.0	rt, 16 h	Toluene	28[d]	30
4[e]	0.1	(*S*)-BINOL (0.2)	2.0	rt, 6 d	Toluene	45[f]	84

[a] Ti(O*i*-Pr)$_4$, diol, H_2O, 80% cumene hydroperoxide (CHP, 2.0 equiv).
[b] (*D*)-DET = (*D*)-(−)-diethyl tartarate, (*R*,*R*)-DPED = (*R*,*R*)-(+)-1,2-diphenylethan-1,2-diol, (*S*)-BINOL = (*S*)-(−)-1,1′-bi-2-naphthol.
[c] Determined by HPLC on a CHIRAL PAK AD (DAICEL).
[d] **6r** was recovered.
[e] 80% CHP (3.0 equiv).
[f] Sulfone compound **25** was obtained.

whereas the sulfone compound **25** was obtained as a byproduct.

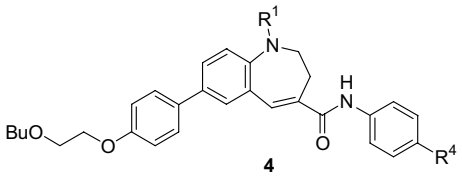
3. Results and discussion

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 3 and 4 as IC_{50} values.

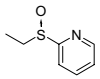
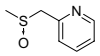
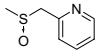
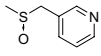
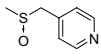
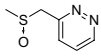
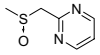
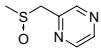
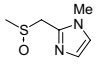
First of all, the 1-propyl-1-benzazepine derivatives containing the 2-pyridyl groups were investigated. Among the 2-pyridyl compounds **4a**–**c**, compound **4c** with a methylene group between the sulfoxide and pyridine moieties exhibited the most potent activity. Therefore, we targeted the compounds with a [(*N*-containing heteroaryl)methyl]sulfinyl moiety and performed further chemical modification. Replacing the propyl group of **4c** with the isobutyl group (**4d**) enhanced activity and this result was similar to that of the pyridine *N*-oxide derivative previously reported. Moving the nitrogen atom of the pyridine ring from the 2-position (**4d**) to the 3-position (**4e**) led to increased activity, but replacement of the 2-pyridyl group with the 4-pyridyl group (**4f**) decreased activity. Next, we investigated the aromatic azine or azole compounds **4g**–**l** containing two hetero atoms, keeping the 1-isobutyl-1-benzazepine ring. Replacement of the 3-pyridyl group of **4e** with the pyridazin-3-yl group (**4g**) retained activity, but the pyrimidin-2-yl (**4h**) or pyrazin-2-yl (**4i**) compounds showed reduced activity, compared with the compound **4e**. Among the azole compounds (**4j**–**l**), the 1-methylimidazol-2-yl compound **4l** was the most active and equivalent to the 3-pyridyl compound **4e**. We selected the imidazole compound **4l** as a new lead compound and investigated the effects of the *N*-substituent and the connecting position of the imidazolyl group. The results are summarized in Table 4. As the size of the 1-alkyl group on the imidazole ring was enlarged from the methyl (**4l**) to the ethyl (**4m**) or propyl (**4n**) group, the activities were found to become more potent. However, substitution of the more bulky isopropyl (**4o**), butyl (**4p**), or isobutyl (**4q**) group led to a slight decrease of activity compared with the 1-propylimidazol-2-yl compound **4n**. Shifting the bond position of the 1-propylimidazole ring from the 2-position (**4n**) to the 5-position (**4r**) retained potent activity, and the corresponding 1-propyl-1-benzazepine **4s** was as highly active as the 1-isobutyl-1-benzazepine **4r**. However, the 1-propylimidazol-4-yl compound **4t** resulted in a ca. 10-fold reduction of activity, when compared with the imidazol-2-yl compound **4n**. From the above results, it was considered that the position of the nitrogen atom of the heteroaryl group played an important part in the appearance of potent inhibitory activity. In addition, the results of the imidazole compounds indicated that introduction of an alkyl group, with suitable bulkiness, on the *N*-atom neighboring the connecting bond contributed to further increase of activity.

Secondly, we examined the effects of the triazole groups with an *N*-alkyl group at the α-position of the connecting bond, keeping the 1-isobutyl-1-benzazepine ring (Table 4). 4-Methyl-1,2,4-triazol-3-yl compound **4u** was more active than the 2-methyl-1,2,4-triazol-3-yl compound **4x**. Thus, compound **4u** inhibited the chemokine binding with an IC_{50} value of 4.4 nM, and was as highly active as the imidazole compound **4r**. Considering the results of the imidazole compounds, replacement of the methyl group of **4u** with the propyl group (**4v**) led to a slight increase of activity, and the corresponding 1-propyl-1-benzazepine compound **4w** also exhibited highly potent activity, comparable to the compound **4v**. The propyl-substituted 1,2,3-triazole compound **4y** exhibited relatively potent activity, but its activity was less potent than that of the 1,2,4-triazole compound **4v**. In order to investigate the effect of the configuration of the sulfoxide group, we next prepared the optically active compounds ((***R***)- and (***S***)-**4r**,**s**,**v**,**w**) and

Table 3. Physical properties and inhibitory effects of compounds **4** on Chemokine binding to CCR5-expressing CHO cells



4

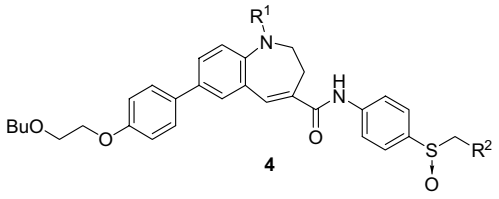
Compd.	R^1	R^4	IC_{50}[a] (nM)	Yield (%)	Formula	Anal[b]
4a	Pr		450	20	$C_{37}H_{41}N_3O_4S{\cdot}0.25H_2O$	CHN
4b	Pr		250	32	$C_{38}H_{43}N_3O_4S{\cdot}0.5H_2O$	CHN
4c	Pr		67	45	$C_{38}H_{43}N_3O_4S$	CHN
4d	*i*-Bu		38	34	$C_{39}H_{45}N_3O_4S{\cdot}0.25H_2O$	CHN
4e	*i*-Bu		15	30	$C_{39}H_{45}N_3O_4S{\cdot}0.7H_2O$	CHN
4f	*i*-Bu		160	41	$C_{39}H_{45}N_3O_4S$	CHN
4g	*i*-Bu		22	40	$C_{39}H_{44}N_4O_4S$	CHN
4h	*i*-Bu		100	61	$C_{39}H_{44}N_4O_4S{\cdot}0.5H_2O$	CHN
4i	*i*-Bu		46	51	$C_{39}H_{44}N_4O_4S$	CHN
4j	*i*-Bu		35	68	$C_{38}H_{46}N_4O_4S{\cdot}0.3H_2O$	CHN
4k	*i*-Bu		43	66	$C_{37}H_{43}N_3O_4S_2$	CHN
4l	*i*-Bu		14	58	$C_{38}H_{46}N_4O_4S{\cdot}0.8H_2O$	CHN

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

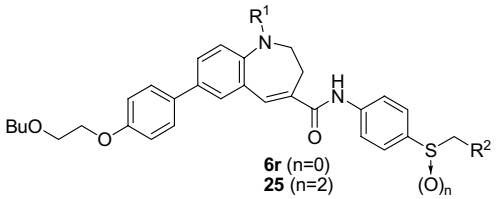
examined their inhibitory effects. As shown in Table 4, it was found that *S*-configuration sulfoxide compounds (***S***)-**4r**,**s**,**v**,**w** were slightly more active than the corresponding *R*-isomers. Interestingly, the less active *R*-isomers (***R***)-**4r**,**s**,**v**,**w** also showed potent inhibitory activities with IC_{50} values of 4.4–8.3 nM in the binding assay. Furthermore, we investigated the imidazole compounds containing a sulfide or sulfone moiety in place of the sulfoxide moiety. As expected, it was found that sulfoxide compounds **4r**, (***S***)-**4r**, (***R***)-**4r** were more active than the sulfide (**6r**) and sulfone (**25**) compounds (Table 4).

Next, we examined the inhibitory effects of the compounds with potent RANTES binding inhibition on the HIV-1 Env-mediated membrane fusion. The membrane fusion assay was carried out using R5 HIV-1 (JR-FL strain) Env-expressing COS-7 cells and CCR5-expressing MOLT-4 cells. The results are summarized in Table 5 as IC_{50} values. The 1-propylimidazol-2-yl compound **4n** exhibited relatively potent inhibitory activity (IC_{50} = 11 nM). The 1-propylimidazol-5-yl compound **4r** showed potent activity in comparison with the imidazol-2-yl compound **4n**, and its activity (IC_{50} = 3.0 nM) in the fusion assay was equivalent to that in the binding assay. Among the 1,2,4-triazole compounds, the 4-propyl-1,2,4-triazole **4v** showed potent activity with an IC_{50} value of 8.7 nM, whereas the 1-methyl-1,2,4-triazole **4u** had remarkably reduced activity in the fusion assay. The optically active 1-isobutyl-1-benzazepine compounds (***S***)-**4r** and (***S***)-**4v** exhibited remarkably potent activities (IC_{50} = 1.0, 2.2 nM, respectively), comparable to compound **1**. The 1-propyl-1-benzazepine compounds (***S***)-**4s** and (***S***)-**4w** also showed highly potent activities (IC_{50} = 2.8, 7.7 nM, respectively). Compared to the 1-isobutyl-1-benzazepines and

Table 4. Physical properties and inhibitory effects of compounds **6r**, **4**, **25** on Chemokine binding to CCR5-expressing CHO cells



4



6r (n=0)
25 (n=2)

Compd.	R^1	R^2	IC_{50}[a] (nM)	Yield (%)	Formula	Anal.[b]
4l	*i*-Bu		14	58	$C_{38}H_{46}N_4O_4S{\cdot}0.8H_2O$	CHN
4m	*i*-Bu		6.6	55	$C_{39}H_{48}N_4O_4S{\cdot}0.2H_2O$	CHN
4n	*i*-Bu		4.3	36	$C_{40}H_{50}N_4O_4S{\cdot}0.3H_2O$	CHN
4o	*i*-Bu		8.4	43	$C_{40}H_{50}N_4O_4S{\cdot}0.3H_2O$	CHN
4p	*i*-Bu		14	68	$C_{41}H_{52}N_4O_4S{\cdot}0.5H_2O$	CHN
4q	*i*-Bu		8.7	68	$C_{41}H_{52}N_4O_4S{\cdot}0.4H_2O$	CHN
4r	*i*-Bu		3.6	83	$C_{40}H_{50}N_4O_4S$	CHN
(***R***)-**4r**	*i*-Bu		6.8		$C_{40}H_{50}N_4O_4S{\cdot}0.5H_2O$	CHN
(***S***)-**4r**	*i*-Bu		1.9		$C_{40}H_{50}N_4O_4S{\cdot}0.5H_2O$	CHN
4s	Pr		4.3	57	$C_{39}H_{48}N_4O_4S{\cdot}0.25H_2O$	CHN
(***R***)-**4s**	Pr		8.3		$C_{39}H_{48}N_4O_4S{\cdot}0.5H_2O$	CHN
(***S***)-**4s**	Pr		1.7		$C_{39}H_{48}N_4O_4S{\cdot}0.5H_2O$	CHN
4t	*i*-Bu		44	72	$C_{40}H_{50}N_4O_4S$	CHN
4u	*i*-Bu		4.4	66	$C_{37}H_{45}N_5O_4S{\cdot}2H_2O$	CHN
4v	*i*-Bu		2.6	75	$C_{39}H_{49}N_5O_4S{\cdot}0.5H_2O$	CHN
(***R***)-**4v**	*i*-Bu		4.4		$C_{39}H_{49}N_5O_4S{\cdot}0.5H_2O$	CHN
(***S***)-**4v**	*i*-Bu		1.5		$C_{39}H_{49}N_5O_4S$	CHN
4w	Pr		4.3	57	$C_{38}H_{47}N_5O_4S$	CHN
(***R***)-**4w**	Pr		5.8		$C_{38}H_{47}N_5O_4S$	CHN

Table 4 (*continued*)

Compd.	R^1	R^2	IC_{50}[a] (nM)	Yield (%)	Formula	Anal.[b]
(***S***)-**4w**	Pr		1.6		$C_{38}H_{47}N_5O_4S$	CHN
4x	*i*-Bu		35	89	$C_{37}H_{45}N_5O_4S$	CHN
4y	*i*-Bu		12	64	$C_{39}H_{49}N_5O_4S{\cdot}0.2H_2O$	CHN
6r	*i*-Bu		19	91	$C_{40}H_{50}N_4O_3S$	CHN
25	*i*-Bu		33	39	$C_{40}H_{50}N_4O_5S{\cdot}EtOAc$	CHN

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

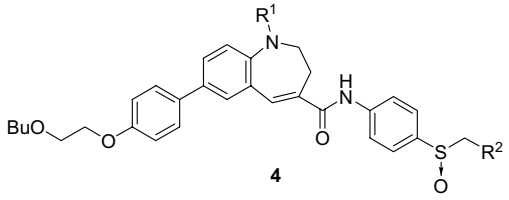
1-propyl-1-benzazepines retaining the [(*N*-propylazol-yl)methyl]sulfinyl group, the 1-isobutyl compound (***S***)-**4r** with an imidazole moiety was about three times more active than the 1-propyl compound (***S***)-**4s**, and the 1-isobutyl compound (***S***)-**4v** with a triazole moiety was also more active than the 1-propyl compound (***S***)-**4w**. Surprisingly, the *R*-isomers (***R***)-**4r** and (***R***)-**4v**, which inhibited the chemokine binding with IC_{50} values of 4.4–6.8 nM, showed significantly reduced activity in the fusion assay. The above-mentioned results suggested that an *S*-configuration sulfoxide moiety was necessary to exhibit the potent activity in the fusion assay. It has been reported that the binding site of β-chemokines on CCR5 does not completely overlap with that of either recombinant gp120 or virions,[28] thus, it is considered possible that the difference in the inhibitory effects of *S*- and *R*-isomers in the binding and fusion assays may have a similar origin. Namely, the above-mentioned results suggest that the binding site of the *S*-isomers on CCR5 is more closely related to that of the HIV-1 envelope gp120 than is that of the *R*-isomers. Alternatively, it may be that *S*-isomers give more steric interference to binding between CCR5 and the HIV-1 envelope glycoprotein, through direct or allosteric interactions, than do the *R*-isomers. In addition, the results in the binding and fusion assays suggested that the position of the sp^2 nitrogen atom of the azole and the presence of an *N*-alkyl group with suitable bulkiness on the azolyl group were essential for the appearance of highly potent activity.

Finally, preliminary pharmacokinetic studies of compounds with potent activity were investigated. Compounds ((***S***)-**4r**,**s**,**v**,**w**) were orally administered at 10 mg/kg to SD (IGS) rats and the results are indicated in Table 6. Consequently, the compounds (***S***)-**4r**, (***S***)-**4s**, and (***S***)-**4w** exhibited high plasma levels after oral administration. Thus, the AUC_{0-24h} values of compounds (***S***)-**4r**, (***S***)-**4s**, and (***S***)-**4w** were 14.1, 75.1, 22.4 μg·h/mL, respectively. These results indicated that the plasma concentration levels of the 1-propyl-1-benzazepine derivatives (***S***)-**4s** and (***S***)-**4w** were higher than those of the corresponding 1-isobutyl-1-benzazepine derivatives (***S***)-**4r** and (***S***)-**4v**, which was opposite to the results in the fusion assay.

4. Conclusion

In order to develop orally active CCR5 antagonists, we investigated whether sulfoxide moieties containing a heteroaryl group can be used as new polar substituents to replace the quaternary ammonium moiety of the anilide derivative **1**. Based on our experience, the 1-propyl- or 1-isobutyl-1-benzazepine ring with a 7-[4-(2-butoxy)ethoxy]phenyl group was selected as a [6,7]-fused nucleus. Investigation of the sulfoxide compounds containing a 2-pyridyl group led to the discovery that insertion of a methylene group between the sulfoxide moiety and the 2-pyridyl group resulted in an increase of activity in the binding assay. From further investigation of the [(*N*-containing heteroaryl)methyl]sulfinyl group, it was found that the compounds with 1-propylimidazol-5-yl or 4-propyl-1,2,4-triazol-3-yl groups exhibited highly potent binding inhibitory activities and that *S*-configuration sulfoxide compounds were more active than the corresponding *R*-isomers. Especially, the *S*-isomers showed greatly potent activities compared with the *R*-isomers in the HIV-1 Env-mediated membrane fusion assay. Among the *S*-sulfoxide compounds, 1-isobutyl-1-benzazepine (***S***)-**4r** and 1-propyl-1-benzazepines (***S***)-**4s** and (***S***)-**4w** exhibited highly potent CCR5 antagonistic activities (IC_{50} = 1.9, 1.7, 1.6 nM, respectively) in the binding assay and inhibitory effects (IC_{50} = 1.0, 2.8, 7.7 nM, respectively) in the fusion assay, comparable to compound **1**, together with good pharmacokinetic properties in rats. Additionally, we established a synthetic method to the chiral compounds (***S***)-**4r** and (***S***)-**4w**, by asymmetric oxidation of the corresponding sulfide compounds using titanium-(*S*)-(−)-1,1′-bi-2-naphthol complex. The above results suggested that the *S*-sulfoxide moieties containing the 1-propylimidazol-5-yl or 4-propyl-1,2,4-triazol-3-yl groups might replace the previous tertiary amine and 2-(α-hydroxybenzyl)pyridine *N*-oxide moieties as polar substituents for orally active CCR5 antagonists.

Table 5. Inhibitory effects of compounds **4** on HIV-1 Env-mediated membrane fusion



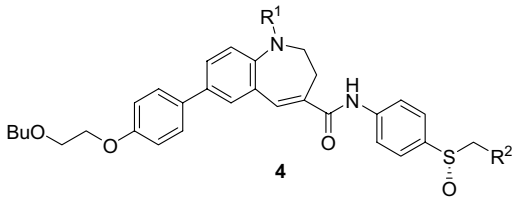
4

Compd.	R^1	R^2	RANTES	Fusion
			IC_{50}[a] (nM)	IC_{50}[b] (nM)
1	—	—	1.4	1.4
4n	*i*-Bu		4.3	11
4r	*i*-Bu		3.6	3.0
(***R***)-**4r**	*i*-Bu		6.8	410
(***S***)-**4r**	*i*-Bu		1.9	1.0
(***S***)-**4s**	Pr		1.7	2.8
4u	*i*-Bu		4.4	210
4v	*i*-Bu		2.6	8.7
(***R***)-**4v**	*i*-Bu		4.4	280
(***S***)-**4v**	*i*-Bu		1.5	2.2
(***S***)-**4w**	Pr		1.6	7.7

[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%.

Table 6. Pharmacokinetic parameters of compounds **4** in rats



4

Compd.	R^1	R^2	Oral administration[a]		
			C_{max} (μg/mL)[b]	T_{max} (h)[c]	AUC_{0-24h} (μg h/mL)[d]
(***S***)-**4r**	*i*-Bu		2.00	2.0	14.1
(***S***)-**4s**	Pr		8.56	2.0	75.1
(***S***)-**4v**	*i*-Bu		0.16	3.3	1.39
(***S***)-**4w**	Pr		2.13	3.3	22.4

[a] Compounds (10 mg/kg) suspended in 0.5% aqueous methylcellulose solution were orally administered to SD (IGS) rats (male, eight weeks old, $n = 3$).

[b] Maximum plasma concentration after 10 mg/kg oral dosing.

[c] Time to reach C_{max}.

[d] Area under the plasma concentration–time curve for 0–24 h after 10 mg/kg oral dosing.

5. 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). Optical resolutions were recorded with a Jasco DIP-370 or P-1030 digital polarimeter. Elemental analyses were carried out by Takeda Analytical Research Laboratories, Ltd., and results obtained were within ±0.4% of the theoretical values. Column chromatography was carried out on a silica gel column (Kieselgel 60, 63–200 mesh, Merck or Chromatorex® NH-DM1020, 100–200 mesh, Fuji Silysia chemical). Yields were not optimized.

5.1. 2-[(4-Nitrophenyl)sulfanyl]pyridine (11a)

To a solution of **10a** (10.0 g, 90.0 mmol) in *N*,*N*-dimethylformamide (DMF) (100 mL) was added NaH (60% dispersion in mineral oil, 3.60 g, 90.0 mmol) at room temperature. After being stirred at room temperature for 15 min, 1-fluoro-4-nitrobenzene (9.75 g, 69.1 mmol) was added dropwise to the reaction mixture at room temperature. The mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration, washed with diisopropyl ether (*i*-Pr_2O) to give 12.6 g (79%) of **11a** as pale brown crystals, mp 84–85 °C. ^{1}H NMR ($CDCl_3$) δ 7.15–7.23 (2H, m), 7.58–7.69 (3H, m), 8.15–8.22 (2H, m), 8.50–8.55 (1H, m). Anal. Calcd for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.06. Found: C, 57.28; H, 3.61; N, 11.85.

5.2. 2-[(4-Nitrobenzyl)sulfanyl]pyridine (11b)

To a solution of **10a** (2.60 g, 23.4 mmol) and triethylamine (Et_3N) (3.90 mL, 28.0 mmol) in tetrahydrofuran (THF) (52 mL) was added dropwise a solution of 4-nitrobenzyl bromide (4.80 g, 22.2 mmol) at room tem-

perature, and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to the water, 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 = 5:1 → 4:1) to give 4.20 g (77%) of **11b** as pale brown crystals. ^{1}H NMR ($CDCl_3$) δ 4.51 (2H, s), 6.98–7.05 (1H, m), 7.16 (1H, d, J = 8.4 Hz), 7.44–7.53 (1H, m), 7.58 (2H, d, J = 8.8 Hz), 8.13 (2H, d, J = 8.8 Hz), 8.42–8.47 (1H, m). Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.52; H, 4.20; N, 11.39.

5.3. 4-[(2-Pyridinyl)sulfanyl]aniline (7a)

A mixture of **11a** (8.00 g, 34.4 mmol) and reduced iron (24.0 g, 430 mmol) in AcOH (64 mL) was stirred at room temperature for 16 h. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 1:2) to give 6.3 g (91%) of **7a** as a pale yellow solid, mp 89–91 °C. ^{1}H NMR ($CDCl_3$) δ 4.05 (2H, br s), 6.72 (2H, d, J = 8.8 Hz), 6.76 (1H, d, J = 8.8 Hz), 6.89–6.96 (1H, m), 7.38 (2H, d, J = 8.8 Hz), 7.39–7.45 (1H, m), 8.37–8.41 (1H, m). Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.26; H, 4.86; N, 13.91.

5.4. 4-{[(2-Pyridyl)sulfanyl]methyl}aniline (7b)

This compound was prepared in 53% yield from **11b** by a method similar to that described for **7a**. ^{1}H NMR ($CDCl_3$) δ 3.68 (2H, br s), 4.34 (2H, s), 6.61 (2H, d, J = 8.4 Hz), 6.93–7.01 (1H, m), 7.11–7.26 (3H, m), 7.45 (1H, td, J = 7.4, 1.8 Hz), 8.43–8.48 (1H, m). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.68; H, 5.65; N, 12.90.

5.5. 4-{[(2-Pyridyl)methyl]sulfanyl}aniline (7c)

To a solution of **10b** (1.00 g, 7.99 mmol) and 2-(chloromethyl)pyridine hydrochloride (1.44 g, 8.78 mmol) in MeOH (50 mL) was added 1 N NaOH (24 mL, 24.0 mmol) at room temperature, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo. Water was added to the residue and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 1:1 → 1:3 → 1:9) to give 1.58 g (91%) of **7c** as colorless crystals, mp 64–65 °C. ^{1}H NMR ($CDCl_3$) δ 3.70 (2H, br s), 4.08 (2H, s), 6.52–6.57 (2H, m), 7.08–7.17 (2H, m), 7.51–7.60 (1H, m), 8.49–8.53 (1H, m). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.46; N, 13.01.

5.6. 4-{[(3-Pyridyl)methyl]sulfanyl}aniline (7d)

This compound was prepared in 76% yield from **10b** and 3-(chloromethyl)pyridine hydrochloride by a method similar to that described for **7c**, colorless crystals, mp 93–94 °C. ^{1}H NMR ($CDCl_3$) δ 3.83 (2H, br s), 3.88 (2H, s), 6.51–6.58 (2H, m), 7.05–7.11 (2H, m), 7.13–7.20 (1H, m), 7.43–7.49 (1H, m), 8.29–8.31 (1H, m), 8.44 (1H, dd, J = 4.8, 1.8 Hz). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.46; N, 13.01.

5.7. 4-{[(4-Pyridyl)methyl]sulfanyl}aniline (7e)

This compound was prepared in 89% yield from **10b** and 4-(chloromethyl)pyridine hydrochloride by a method similar to that described for **7c**, colorless crystals, mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ 3.62 (2H, br s), 3.84 (2H, s), 6.56 (2H, d, J = 8.4Hz), 7.02–7.10 (4H, m), 8.46 (2H, d, J = 6.4 Hz). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.60; H, 5.63; N, 13.00.

5.8. 4-{[(3-Pyridazinyl)methyl]sulfanyl}aniline (7f)

This compound was prepared in 55% yield from **10b** and 3-(chloromethyl)pyridazine[29] by a method similar to that described for **7c**. Compound **7f** was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 3.78 (2H, br s), 4.26 (2H, s), 6.51–6.56 (2H, m), 7.08–7.13 (2H, m), 7.36–7.41 (2H, m), 9.02 (1H, dd, J = 4.6, 2.0 Hz).

5.9. 4-{[(2-Pyrazinyl)methyl]sulfanyl}aniline (7g)

To a solution of pyrazin-2-ylmethanol (1.00 g, 9.08 mmol) and Et_3N (2.00 mL, 14.3 mmol) in THF (100 mL) was added methanesulfonyl chloride (MsCl) (1.00 mL, 12.9 mmol) under ice cooling. After being stirred at room temperature for 1 h, the reaction mixture was added to water, 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 **10b** (1.02 g, 8.15 mmol) in MeOH (20 mL) was added 3 N NaOH (9.1 mL) at room temperature. The mixture was stirred at room temperature for 16 h and concentrated in vacuo. Water was added to the residue 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 = 1:2) to give 0.71 g (40%) of **7g** as colorless crystals. Compound **7g** was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 3.75 (2H, br s), 4.05 (2H, s), 6.52–6.57 (2H, m), 7.09–7.13 (2H, m), 8.32 (1H, d, J = 1.6 Hz), 8.39 (1H, d, J = 2.4 Hz), 8.46–8.48 (1H, m).

5.10. 1-Ethyl-1*H*-imidazole-2-carbaldehyde (13b)

To a mixture of **12** (2.50 g, 26.0 mmol) and K_2CO_3 (4.31 g, 31.2 mmol) in DMF (25 mL) was added iodoethane (4.87 g, 31.2 mmol) at room temperature. After being stirred at 50 °C for 5 h, the solid was removed by filtration. Water was added to the filtrate 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 2.90 g (90%) of **13b** as a

brown oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 7.2 Hz), 4.45 (2H, q, J = 7.2 Hz), 7.17–7.19 (1H, m), 7.28–7.29 (1H, m), 9.82 (1H, s).

The following compounds (**13c–f**) were prepared from 2-formylimidazole (**12**) by a method similar to that described for **13b**.

5.11. 1-Propyl-1*H*-imidazole-2-carbaldehyde (13c)

Yield quant., brown oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.73–1.91 (2H, m), 4.37 (2H, t, J = 7.4 Hz), 7.16 (1H, s), 7.29 (1H, s), 9.82 (1H, s).

5.12. 1-Isopropyl-1*H*-imidazole-2-carbaldehyde (13d)

Yield 93%, brown oil. ^{1}H NMR ($CDCl_3$) δ 1.47 (6H, d, J = 7.0 Hz), 5.41–5.55 (1H, m), 7.31–7.33 (2H, m), 9.83 (1H, s).

5.13. 1-Butyl-1*H*-imidazole-2-carbaldehyde (13e)

Yield quant., brown oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz), 1.20–1.50 (2H, m), 1.60–1.90 (2H, m), 4.40 (2H, t, J = 7.2 Hz), 7.15–7.17 (1H, m), 7.26–7.29 (1H, m), 9.82 (1H, s).

5.14. 1-Isobutyl-1*H*-imidazole-2-carbaldehyde (13f)

Yield 75%, brown oil. ^{1}H NMR ($CDCl_3$) δ 0.92 (6H, d, J = 7.0 Hz), 2.01–2.15 (1H, m), 4.22 (2H, d, J = 7.4 Hz), 7.13 (1H, s), 7.29 (1H, s), 9.82 (1H, s).

5.15. (1-Methyl-1*H*-imidazol-2-yl)methanol (14a)

To a suspension of $LiAlH_4$ (758 mg, 20.0 mmol) in THF (10 mL) was added dropwise a solution of **13a** (2.00 g, 18.2 mmol) in THF (20 mL) under ice cooling. After being stirred under ice cooling for 5 min, water (0.80 mL), 15% aqueous NaOH (0.80 mL) and water (2.40 mL) were added dropwise to the reaction mixture under ice cooling. The mixture was stirred at room temperature for 2.5 h. $MgSO_4$ was added to the mixture and the solid was removed by filtration. The filtrate was concentrated in vacuo. The residue was purified by recrystallization from EtOAc–hexane to give 1.82 g (81%) of **14a** as colorless crystals, mp 114–116 °C. ^{1}H NMR ($CDCl_3$) δ 3.73 (3H, s), 4.63 (2H, s), 6.81 (1H, d, J = 1.2 Hz), 6.86 (1H, d, J = 1.2 Hz). Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.42; H, 7.45; N, 24.57.

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

5.16. (1-Ethyl-1*H*-imidazol-2-yl)methanol (14b)

Yield 72%, colorless crystals (EtOAc–hexane), mp 93–94 °C. ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 7.4 Hz), 4.06 (2H, q, J = 7.4 Hz), 4.65 (2H, s), 6.87–6.89 (2H, m). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.06; H, 7.98; N, 22.20.

5.17. (1-Propyl-1*H*-imidazol-2-yl)methanol (14c)

Yield 75%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.4 Hz), 1.74–1.92 (2H, m), 3.96 (2H, t, J = 7.4 Hz), 4.65 (2H, s), 6.86 (1H, d, J = 1.4 Hz), 6.90 (1H, d, J = 1.4 Hz).

5.18. (1-Isopropyl-1*H*-imidazol-2-yl)methanol (14d)

Yield 87%, brown crystals (EtOAc–hexane), mp 87–89 °C. ^{1}H NMR ($CDCl_3$) δ 1.45 (6H, d, J = 6.8 Hz), 4.53–4.67 (1H, m), 4.68 (2H, s), 6.91 (1H, d, J = 1.2 Hz), 6.94 (1H, d, J = 1.2 Hz). Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.90; H, 8.53; N, 20.07.

5.19. (1-Butyl-1*H*-imidazol-2-yl)methanol (14e)

Yield 88%, yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.4 Hz), 1.26–1.42 (2H, m), 1.69–1.85 (2H, m), 4.00 (2H, t, J = 7.4 Hz), 4.64 (2H, s), 6.85 (1H, d, J = 1.0 Hz), 6.88 (1H, d, J = 1.0 Hz).

5.20. (1-Isobutyl-1*H*-imidazol-2-yl)methanol (14f)

Yield 91%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (6H, d, J = 6.6 Hz), 2.00–2.20 (1H, m), 3.79 (2H, d, J = 7.6 Hz), 4.66 (2H, s), 6.84 (1H, d, J = 1.4 Hz), 6.92 (1H, d, J = 1.4 Hz).

5.21. 4-[[(1-Methyl-1*H*-pyrazol-5-yl)methyl]sulfanyl]aniline (7h)

5.21.1. Step 1: (1-Methyl-1*H*-pyrazol-5-yl)methanol (15a). This compound was prepared in quantitative yield from 1-methyl-1*H*-pyrazole-5-carbaldehyde[20] by a method similar to that described for **14a**, colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 4.68 (2H, s), 6.19 (1H, d, J = 2.0 Hz), 6.39 (1H, d, J = 1.8 Hz).

5.21.2. Step 2: 4-{[(1-Methyl-1*H*-pyrazol-5-yl)methyl]sulfanyl}aniline (7h). To a solution of **15a** (645 mg, 5.75 mmol) and DMF (cat. amount) in $CHCl_3$ (10 mL) was added $SOCl_2$ (0.55 mL, 7.54 mmol) under ice cooling. After being stirred at room temperature for 4 h under a nitrogen atmosphere, the mixture was concentrated in vacuo. To a solution of the residue in MeOH (10 mL) was added a solution of **10b** (600 mg, 4.79 mmol) and NaOH (460 mg, 11.5 mmol) in MeOH (10 mL) and water (6.0 mL) under ice cooling. The mixture was stirred at room temperature for 0.5 h, and concentrated in vacuo. Water was added to the residue and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization from EtOAc–hexane to give 972 mg (93%) of **7h** as brown crystals, mp 115–116 °C. ^{1}H NMR ($CDCl_3$) δ 3.75 (3H, s), 3.89 (2H, s), 5.92 (1H, d, J = 1.8 Hz), 6.57 (2H, d, J = 8.8 Hz), 7.10 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 1.8 Hz). Anal. Calcd for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.97; N, 19.16. Found: C, 60.09; H, 6.08; N, 19.11.

The following compounds (**7i**–**m**) were prepared from **15b**, **14a**–**d** and **10b** by a method similar to that described for **7h**.

5.22. 4-[(1,3-Thiazol-2-ylmethyl)sulfanyl]aniline (7i)

Yield 25%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.72 (2H, br s), 4.28 (2H, s), 6.58 (2H, d, J = 8.6 Hz), 7.18–7.25 (3H, m), 7.65 (1H, d, J = 3.2 Hz).

5.23. 4-{[(1-Methyl-1*H*-imidazol-2-yl)methyl]sulfanyl}-aniline (7j)

Yield quant., colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.53 (3H, s), 4.03 (2H, s), 6.57 (2H, d, J = 8.6 Hz), 6.78 (1H, d, J = 1.2 Hz), 6.90 (1H, d, J = 1.2 Hz), 7.14 (2H, d, J = 8.6 Hz).

5.24. 4-{[(1-Ethyl-1*H*-imidazol-2-yl)methyl]sulfanyl}-aniline (7k)

Yield quant., colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.2 Hz), 3.91 (2H, q, J = 7.2 Hz), 4.04 (2H, s), 6.58 (2H, d, J = 8.8 Hz), 6.85 (1H, d, J = 1.0 Hz), 6.92 (1H, d, J = 1.0 Hz), 7.15 (2H, d, J = 8.8 Hz).

5.25. 4-{[(1-Propyl-1*H*-imidazol-2-yl)methyl]sulfanyl}-aniline (7l)

Yield 99%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.68–1.86 (2H, m), 3.80 (2H, t, J = 7.4 Hz), 4.04 (2H, s), 6.57 (2H, d, J = 8.8 Hz), 6.83 (1H, d, J = 1.2 Hz), 6.91 (1H, d, J = 1.2 Hz), 7.15 (2H, d, J = 8.8 Hz).

5.26. 4-{[(1-Isopropyl-1*H*-imidazol-2-yl)methyl]sulfanyl}-aniline (7m)

Yield 97%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.41 (6H, d, J = 6.6 Hz), 3.71 (2H, br s), 4.06 (2H, s), 4.38–4.60 (1H, m), 6.58 (2H, d, J = 8.8 Hz), 6.92–6.93 (2H, m), 7.16 (2H, d, J = 8.8 Hz).

5.27. *S*-(4-Aminophenyl)-*O*-benzylthiocarbonate (8)

To a mixture of **10b** (9.60 g, 76.7 mmol) and Et_3N (54.0 mL, 387 mmol) was added dropwise benzyl chloroformate (13.1 g, 76.8 mmol) at −78 °C. After being stirred at −78 °C for 0.5 h, the mixture was warmed to room temperature. 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 to give colorless crystals. The crystals were purified by recrystallization from EtOAc–hexane to give 19.3 g (97%) of **8** as colorless crystals, mp 92–93 °C. ^{1}H NMR ($CDCl_3$) δ 3.85 (2H, br s), 5.23 (2H, s), 6.63–6.70 (2H, m), 7.26–7.35 (7H, m). Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.83; H, 5.00; N, 5.39.

5.28. 2-(Chloromethyl)pyrimidine (9a)

A mixture of **16** (19.7 g, 153 mmol) and 1,1,3,3-tetramethoxypropane (50 mL) was stirred at 100 °C for 16 h. The mixture was added to the water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgOS_4$, and concentrated in vacuo to give 2.00 g (10%) of **9a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.76 (2H, s), 7.27–7.30 (1H, m), 8.78 (2H, d, J = 5.2 Hz).

5.29. 1-Propyl-1*H*-imidazole-4-carbaldehyde (18)

To a suspension of NaH (60% dispersion in mineral oil, 3.12 g, 78.0 mmol) in THF (400 mL) was added **17** (5.00 g, 52.0 mmol) under ice cooling. The mixture was refluxed for 2 h under a nitrogen atmosphere. The mixture was cooled to room temperature and 1-iodopropane (88.4 g, 520 mmol) was added to the mixture. The mixture was refluxed for 2 h. The solid was removed by filtration and water was added to the filtrate. 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 (EtOAc/MeOH = 8:1) to give 4.45 g (62%) of **18** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.2 Hz), 1.77–1.95 (2H, m), 3.97 (2H, t, J = 7.2 Hz), 7.56 (1H, s), 7.63 (1H, s), 9.88 (1H, s).

5.30. (1-Propyl-1*H*-imidazol-4-yl)methanol (14h)

This compound was prepared in 87% yield from **18** by a method similar to that described for **14a**, yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.71–1.89 (2H, m), 3.80 (2H, t, J = 7.0 Hz), 4.60 (2H, s), 6.87 (1H, d, J = 1.4 Hz), 7.42 (1H, d, J = 1.4 Hz).

5.31. 1-Butyl-2-(chloromethyl)-1*H*-imidazole hydrochloride (9b)

$SOCl_2$ (30 mL, 411 mmol) was added to **14e** (3.00 g, 19.5 mmol) under ice cooling. The mixture was stirred at 90 °C for 0.5 h. The mixture was concentrated in vacuo. The crystals were collected by filtration, washed with EtOAc to give 3.50 g (86%) of **9b** as brown crystals, mp 161–162 °C. ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, t, J = 7.8 Hz), 1.23–1.41 (2H, m), 1.71–1.87 (2H, m), 4.21 (2H, t, J = 7.6 Hz), 5.17 (2H, s), 7.73 (1H, d, J = 2.0 Hz), 7.84 (1H, d, J = 2.0 Hz). Anal. Calcd for $C_8H_{14}N_2Cl_2$: C, 45.95; H, 6.75; N, 13.40. Found: C, 46.25; H, 6.93; N, 13.53.

The following compounds (**9c**,**e**) were prepared from **14f**,**h** by a method similar to that described for **9b**.

5.32. 2-(Chloromethyl)-1-isobutyl-1*H*-imidazole hydrochloride (9c)

Yield 67%, brown crystals (MeOH–EtOAc), mp 164–166 °C. ^{1}H NMR (DMSO-d_6) δ 0.90 (6H, d, J = 6.6 Hz), 2.05–2.25 (1H, m), 4.05 (2H, d, J = 7.8 Hz), 5.18 (2H, s), 7.75 (1H, d, J = 2.2 Hz), 7.81 (1H, d, J = 2.2 Hz). Anal. Calcd for $C_8H_{14}N_2Cl_2$: C, 45.95; H, 6.75; N, 13.40. Found: C, 45.79; H, 7.08; N, 13.37.

5.33. 4-(Chloromethyl)-1-propyl-1*H*-imidazole hydrochloride (9e)

Yield quant., brown oil. ^{1}H NMR (DMSO-d_6) δ 0.85 (3H, t, J = 7.4 Hz), 1.60–2.00 (2H, m), 4.13 (2H, t, J = 6.6 Hz), 4.88 (2H, s), 7.84 (1H, s), 9.16 (1H, s).

5.34. (1-Propyl-2-sulfanyl-1*H*-imidazol-5-yl)methanol (21a)

A mixture of KSCN (119.2 g, 1.23 mol), **19** (73.9 g, 410 mmol) and propylamine hydrochloride (100 g, 1.05 mmol) was added to a mixture of AcOH (89 mL) and 1-BuOH (590 mL) at room temperature. After being stirred at room temperature for 24 h, water (118 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 30 min, and the precipitated crystals were collected by filtration. The crystals were washed with water and hexane to give 71.2 g (50%) of **21a** as colorless crystals, mp 173–175 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.4 Hz), 1.61–1.79 (2H, m), 3.91 (2H, t, J = 7.4 Hz), 4.32 (2H, s), 5.26 (1H, br), 6.79 (1H, s), 11.95 (1H, s). Anal. Calcd for $C_7H_{12}N_2OS{\cdot}0.25H_2O$: C, 47.57; H, 7.13; N, 15.85. Found: C, 47.22; H, 6.94; N, 15.99.

5.35. (4-Propyl-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methanol (21c)

To a solution of hydrazine monohydrate (9.66 g, 193 mmol) in EtOH was added dropwise **20** (20.09 g, 200 mmol) under ice cooling. The mixture was stirred at room temperature for 4 h. To the reaction mixture was added dropwise propyl isothiocyanate (20.0 mL, 193 mmol) under ice cooling, and the mixture was stirred at 40 °C for 64 h. To the reaction mixture was added ice water (50 mL) at room temperature and the mixture was stirred at room temperature for 15 min. 5 N NaOH (40 mL) was added to the mixture and the mixture was stirred at 60 °C for 4 h. The mixture was neutralized using conc. HCl under ice cooling. The precipitated solid was removed by filtration and the filtrate was concentrated in vacuo. The precipitated solid was collected by filtration, washed with water to give 23.45 g (70%) of **21c** as a colorless solid. Compound **21c** was used in the next reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 0.88 (3H, t, J = 7.4 Hz), 1.62–1.84 (2H, m), 3,92 (2H, t, J = 7.7 Hz), 4.49 (2H, s), 5.32–5.90 (1H, m).

5.36. (1-Propyl-1*H*-imidazol-5-yl)methanol (14g)

$NaNO_2$ (1.14 g, 16.5 mmol) was added to 5 N HNO_3 (370 mL) at room temperature, and then **21a** (71.0 g, 412 mmol) was added to the mixture under ice cooling. After being stirred at room temperature for 2 h, water (200 mL) was added to the mixture. The mixture was neutralized using K_2CO_3 under ice cooling and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (EtOAc/MeOH = 8:1) to give 33.6 g (58%) of **14g** as brown crystals. Compound **14g** was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.4 Hz), 1.76–1.94 (2H, m), 3.97 (2H, t, J = 7.2 Hz), 4.63 (2H, s), 6.97 (1H, s), 7.48 (1H, s).

5.37. (4-Propyl-4*H*-1,2,4-triazol-3-yl)methanol (14j)

This compound was prepared in 73% yield from **21c** by a method described similar to that for **14g**. Compound **14j** was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.76–1.98 (2H, m), 4.05 (2H, t, J = 7.3 Hz), 4.80 (2H, s), 5.11–5.49 (1H, m), 8.07 (1H, s).

The following compounds (**9d**,**g**) were prepared from **14g**,**j** by a method similar to that described for **9b**.

5.38. 5-(Chloromethyl)-1-propyl-1*H*-imidazole hydrochloride (9d)

Yield 96%, colorless crystals (EtOAc), 167–169 °C. ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, t, J = 7.4 Hz), 1.84–1.95 (2H, m), 4.18 (2H, t, J = 7.2 Hz), 5.04 (2H, s), 7.82 (1H, s), 9.24 (1H, s). Anal. Calcd for $C_7H_{12}N_2Cl_2{\cdot}0.25H_2O$: C, 42.12; H, 6.31; N, 14.04. Found: C, 42.16; H, 6.30; N, 14.14.

5.39. 3-(Chloromethyl)-4-propyl-4*H*-1,2,4-triazole hydrochloride (9g)

Yield 34%, pale yellow crystals (EtOAc), mp 91–94 °C. ^{1}H NMR (DMSO-d_6) δ 0.80 (3H, t, J = 7.3 Hz), 1.73–1.94 (2H, m), 4.11 (2H, t, J = 7.4 Hz), 5.10 (2H, s), 9.26 (1H, s). Anal. Calcd for $C_6H_{11}N_3Cl_2{\cdot}0.25H_2O$: C, 35.93; H, 5.78; N, 20.95. Found: C, 36.13; H, 5.77; N, 21.23.

5.40. Methyl 1-propyl-1*H*-1,2,3-triazole-5-carboxylate (24)

A mixture of **23** (17.6 g, 138 mmol), 1-iodopropane (14.9 mL, 153 mmol) and K_2CO_3 (11.5 g, 83.2 mmol) in DMF (210 mL) was stirred at room temperature for 16 h. The solid was removed by filtration, and the filtrate was concentrated in vacuo. Water was added to the residue, and the aqueous layer 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 (hexane/EtOAc = 3:1 → 2:1 → 1:1 → 1:2) to give 3.20 g (14%) of **24**, 10.3 g (44%) of methyl 2-propyl-2*H*-1,2,3-triazole-4-carboxylate, and 2.6 g (11%) of methyl 1-propyl-1*H*-1,2,3-triazole-4-carboxylate. **24**: ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.4 Hz), 1.86–2.02 (2H, m), 3.94 (3H, s), 4.71 (2H, t, J = 7.4 Hz), 8.13 (1H, s).

5.41. (1-Propyl-1*H*-1,2,3-triazol-5-yl)methanol (14l)

This compound was prepared in quantitative yield from **24** by a method similar to that described for **14a**. ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz), 1.86–2.03 (2H, m), 4.31 (2H, t, J = 7.2 Hz), 4.71 (2H, s), 7.41 (1H, s).

5.42. 5-(Chloromethyl)-1-propyl-1*H*-1,2,3-triazole hydrochloride (9i)

This compound was prepared in 57% yield from **14l** by a method similar to that described for **9b**. ^{1}H NMR (DMSO-d_6) δ 0.90 (3H, t, J = 7.2 Hz), 1.79–1.95 (2H, m), 4.34 (2H, t, J = 7.0 Hz), 5.03 (2H, s), 9.53 (1H, br s).

5.43. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-{4-[(2-pyridyl)sulfanyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6a)

5.43.1. Step 1: 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (5a). To a solution of methyl 7-{4-[2-(butoxy)ethoxy]phenyl}-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate[18] (1.00 g, 2.53 mmol) and propionaldehyde (1.00 mL, 13.9 mmol) in 1,2-dichloroethane (30 mL) sodium triacetoxyborohydride (1.9 g, 8.96 mmol) at room temperature. After being stirred at room temperature for 24 h, 1 N NaOH 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. To a solution of the residue in THF (50 mL) and MeOH (50 mL) was added 1 N NaOH (25 mL, 25 mmol). The mixture was refluxed for 1 h and the mixture was concentrated in vacuo. The residue was acidified using 1 N HCl 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 0.895 g (84%) of **5a** as yellow crystals, mp 145–146 °C. ^{1}H NMR ($CDCl_3$) δ 0.96–1.02 (6H, m), 1.34–1.45 (2H, m), 1.54–1.80 (4H, m), 2.84 (2H, m), 3.28–3.35 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.98 (2H, t, J = 8.8 Hz), 7.39–7.52 (4H, m), 7.88 (1H, s). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.68; H, 8.11; N, 3.23.

5.43.2. Step 2: 7-{4-[2-(butoxy)ethoxy]phenyl}-1-propyl-*N*-{4-[(2-pyridyl)sulfanyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6a). To a solution of **5a** (1.00 g, 2.36 mmol) and DMF (cat. amount) in THF (20 mL) was added $SOCl_2$ (0.34 mL, 4.66 mmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was added dropwise to a solution of **7a** (0.53 g, 2.62 mmol) under ice cooling. The mixture was stirred at room temperature for 2 h. 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 = 2:1) to give 0.57 g (38%) of **6a** as a yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.0 Hz), 1.00 (3H, t, J = 7.2 Hz), 1.33–1.45 (2H, m), 1.57–1.77 (4H, m), 2.87–2.95 (2H, m), 3.28–3.36 (4H, m), 3.55 (2H, t, J = 7.0 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.85 (1H, d, J = 8.0 Hz), 6.90 (1H, t, J = 8.8 Hz), 6.95–7.00 (3H, m), 7.40–7.50 (6H, m), 7.58 (2H, d, J = 8.8 Hz), 7.66–7.71 (3H, m), 8.40–8.43 (1H, m).

The following compounds (**6b**,**g**, **6i**–**o**) were prepared from the carboxylic acids **5a**,**b**[18] and anilines **7b**,**f**,**g**–**m** by a method similar to that described for **6a**.

5.44. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-({4-[(2-pyridyl)sulfanyl]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6b)

Yield 58%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 6.8 Hz), 0.98 (3H, t, J = 7.4 Hz), 1.33–1.45 (2H, m), 1.54–1.80 (4H, m), 2.89 (2H, m), 3.26–3.34 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.77–3.83 (2H, m), 4.12–4.18 (2H, m), 4.41 (2H, s), 6.88 (1H, d, J = 8.4 Hz), 6.94–7.02 (2H, m), 6.97 (2H, d, J = 8.8 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.35–7.56 (10H, m), 8.45 (1H, d, J = 5.2 Hz).

5.45. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-({4-[(3-pyridazinyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6g)

Yield 42%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.96 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.55–1.65 (2H, m), 1.96–2.07 (1H, m), 2.84–2.93 (2H, m), 3.18 (2H, d, J = 6.8 Hz), 3.28–3.38 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78–3.83 (2H, m), 4.13–4.18 (2H, m), 4.38 (2H, s), 6.91 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.31–7.54 (11H, m), 7.70 (1H, s), 9.01–9.05 (1H, m).

5.46. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-({4-[(2-pyrazinyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6i)

Yield 49%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.96 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.54–1.68 (2H, m), 1.98–2.14 (1H, m), 2.83–2.94 (2H, m), 3.18 (2H, d, J = 7.2 Hz), 3.32–3.37 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.2 Hz), 4.15 (2H, t, J = 5.2 Hz), 4.19 (2H, s), 6.91 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.28–7.61 (11H, m), 8.41–8.50 (2H, m).

5.47. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-pyrazol-5-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6j)

Yield 81%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89–0.99 (9H, m), 1.34–1.45 (2H, m), 1.54–1.64 (2H, m), 2.00–2.20 (1H, m), 2.90 (2H, t, J = 4.2 Hz), 3.19 (2H, d, J = 7.0 Hz), 3.36 (2H, t, J = 4.4 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.78–3.83 (5H, m), 4.01 (2H, s), 4.16 (2H, t, J = 5.0 Hz), 5.97 (1H, d, J = 1.8 Hz), 6.90–7.00 (3H, m), 7.27–7.33 (3H, m), 7.37–7.58 (8H, m). Anal. Calcd for $C_{38}H_{46}N_4O_3S{\cdot}0.25H_2O$: C, 70.94; H, 7.28; N, 8.71. Found: C, 70.95; H, 7.22; N, 8.74.

5.48. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1,3-thiazol-2-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6k)

Yield 66%, yellow crystals (EtOAc–hexane), mp 97–98 °C. ^{1}H NMR ($CDCl_3$) δ 0.90–0.98 (9H, m),

1.34–1.70 (4H, m), 1.95–2.20 (1H, m), 2.90 (2H, t, J = 4.4 Hz), 3.18 (2H, d, J = 7.2 Hz), 3.36 (2H, t, J = 4.4 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 4.40 (2H, s), 6.92 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.24 (1H, d, J = 3.2 Hz), 7.35–7.55 (10H, m), 7.67 (1H, d, J = 3.2 Hz). Anal. Calcd for $C_{37}H_{43}N_3O_3S_2$: C, 69.23; H, 6.75; N, 6.55. Found: C, 69.34; H, 6.79; N, 6.60.

5.49. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6l)

Yield 56%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (9H, m), 1.34–1.45 (2H, m), 1.54–1.80 (2H, m), 2.00–2.15 (1H, m), 2.91 (2H, t, J = 5.6 Hz), 3.18 (2H, d, J = 7.0 Hz), 3.36 (2H, t, J = 5.6 Hz), 3.52–3.59 (5H, m), 3.80 (2H, t, J = 4.8 Hz), 4.11 (2H, s), 4.16 (2H, t, J = 4.8 Hz), 6.78 (1H, d, J = 1.0 Hz), 6.89 (1H, d, J = 1.4 Hz), 6.93–7.00 (3H, m), 7.31–7.55 (9H, m), 7.80 (1H, s). Anal. Calcd for $C_{38}H_{46}N_4O_3S$: C, 71.44; H, 7.26; N, 8.77. Found: C, 71.28; H, 7.29; N, 8.38.

5.50. 7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[(1-ethyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6m)

Yield 45%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–0.98 (9H, m), 1.34–1.50 (5H, m), 1.55–1.70 (2H, m), 1.95–2.15 (1H, m), 2.85–2.95 (2H, m), 3.18 (2H, d, J = 7.4 Hz), 3.30–3.40 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 4.8 Hz), 3.94 (2H, q, J = 7.2 Hz), 4.10–4.18 (4H, m), 6.86 (1H, d, J = 1.4 Hz), 6.89–7.00 (4H, m), 7.31–7.55 (9H, m), 7.81 (1H, s).

5.51. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6n)

Yield 45%, yellow crystals (EtOH–hexane), mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (12H, m), 1.34–1.45 (2H, m), 1.50–1.65 (2H, m), 1.75–1.85 (2H, m), 1.95–2.15 (1H, m), 2.85–2.95 (2H, m), 3.19 (2H, d, J = 7.2 Hz), 3.30–3.40 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.78–3.89 (4H, m), 4.14–4.19 (4H, m), 6.85–7.00 (5H, m), 7.33–7.56 (9H, m), 7.64 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_3S{\cdot}0.1H_2O$: C, 71.84; H, 7.57; N, 8.38. Found: C, 71.59; H, 7.59; N, 8.18.

5.52. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-isopropyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6o)

Yield 39%, yellow crystals (EtOH–hexane), mp 122–124 °C. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (9H, m), 1.30–1.45 (8H, m), 1.55–1.70 (2H, m), 1.95–2.10 (1H, m), 2.90 (2H, t, J = 4.8 Hz), 3.18 (2H, d, J = 7.0 Hz), 3.35 (2H, t, J = 4.8 Hz), 3.56 (2H, t, J = 7.0 Hz), 3.80 (2H, t, J = 4.4 Hz), 4.13–4.18 (4H, m), 4.40–4.60 (1H, m), 6.89–7.00 (5H, m), 7.32–7.55 (9H, m), 7.75 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_3S{\cdot}0.25H_2O$: C, 71.55; H, 7.58; N, 8.34. Found: C, 71.32; H, 7.52; N, 8.17.

5.53. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-({4-[(2-pyridyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6c)

To a solution of **5a** (0.80 g, 1.89 mmol) and DMF (cat. amount) in THF (16 mL) was added oxalyl chloride (0.25 mL, 1.87 mmol) 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 (16 mL) was added dropwise to a solution of **7c** (0.45 g, 2.08 mmol) and Et_3N (2.1 mL, 15.1 mmol) in THF (13.5 mL) under ice cooling. The mixture was stirred at room temperature for 1 h. 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 to give 0.68 g (58%) of **6c** as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 0.98 (3H, t, J = 6.8 Hz), 1.33–1.45 (2H, m), 1.57–1.76 (4H, m), 2.88 (2H, m), 3.26–3.35 (4H, m), 3.51–3.58 (2H, m), 3.77–3.83 (2H, m), 4.12–4.18 (2H, m), 4.21 (2H, s), 6.89 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.14–7.60 (13H, m), 8.51–8.55 (1H, m).

The following compounds (**6d–f**) were prepared from the carboxylic acids **5b**[18] and anilines **7c–e** by a method similar to that described for **6c**.

5.54. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-({4-[(2-pyridyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6d)

Yield 56%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.96 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.57–1.68 (2H, m), 1.95–2.04 (1H, m), 2.84–2.92 (2H, m), 3.17 (2H, d, J = 7.4 Hz), 3.31–3.36 (2H, m), 3.55 (2H, t, J = 6.2 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.15 (2H, t, J = 4.8 Hz), 4.21 (2H, s), 6.91 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.10–7.17 (1H, m), 7.22–7.63 (12H, m), 8.51–8.54 (1H, m). Anal. Calcd for $C_{39}H_{45}N_3O_3S$: C, 73.67; H, 7.13; N, 6.61. Found: C, 73.78; H, 7.37; N, 6.62.

5.55. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-({4-[(3-pyridyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6e)

Yield 32%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.97 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.54–1.68 (2H, m), 1.97–2.16 (1H, m), 2.83–2.94 (2H, m), 3.18 (2H, d, J = 7.8 Hz), 3.32–3.38 (2H, m), 3.55 (2H, t, J = 6.2 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.01 (2H, s), 4.15 (2H, t, J = 4.8 Hz), 6.91 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.15–7.29 (3H, m), 7.37–7.60 (9H, m), 8.38 (1H, d, J = 2.2 Hz), 8.46 (1H, dd, J = 4.6, 1.8 Hz).

5.56. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-({4-[(4-pyridyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6f)

Yield 27%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.97 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.54–1.65 (2H, m), 1.97–2.14 (1H, m), 2.84–

2.95 (2H, m), 3.18 (2H, d, $J = 7.4$ Hz), 3.35 (2H, t, $J = 4.8$ Hz), 3.55 (2H, t, $J = 6.6$ Hz), 3.78–3.82 (2H, m), 3.98 (2H, s), 4.12–4.18 (2H, m), 6.91 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.12 (2H, d, $J = 6.2$ Hz), 7.27 (2H, d, $J = 8.8$ Hz), 7.38–7.58 (8H, m), 8.47–8.51 (2H, m).

5.57. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(2-pyrimidinyl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6h)

To a solution of **5b** (1.00 g, 2.29 mmol) and DMF (cat. amount) in THF (20 mL) was added $SOCl_2$ (0.25 mL, 3.43 mmol) 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 (20 mL) was added dropwise to a solution of **8** (0.59 g, 2.28 mmol) and Et_3N (1.91 mL, 13.7 mmol) in THF (17.7 mL) under ice cooling. The mixture was stirred at room temperature for 2 h. MeOH (40 mL) and 1 N NaOH (15 mL) were added to the mixture, and the mixture was stirred at room temperature for 0.5 h. To the mixture was added **9a** (0.35 g, 2.72 mmol) at room temperature, and the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated in vacuo, and water was added to the residue. 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 (EtOAc/EtOH = 15:1) to give 0.94 g (64%) of **6h** as a yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.4$ Hz), 0.96 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.55–1.68 (2H, m), 2.00–2.17 (1H, m), 2.84–2.97 (2H, m), 3.17 (2H, d, $J = 7.4$ Hz), 3.30–3.36 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.77–3.83 (2H, m), 4.15 (2H, t, $J = 4.8$ Hz), 4.34 (2H, s), 6.91 (1H, d, $J = 8.4$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.15 (1H, t, $J = 4.8$ Hz), 7.34–7.60 (10H, m), 8.68 (2H, d, $J = 4.6$ Hz).

The following compounds (**6p**–**y**) were prepared from the carboxylic acids **5a**,**b**,[18] the aniline **8** and heteroarylmethylchlorides **9b**–**i** by a method similar to that described for **6h**.

5.58. 7{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[(1-butyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6p)

Yield 24%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (12H, m), 1.33–1.78 (8H, m), 2.00–2.10 (1H, m), 2.85–2.95 (2H, m), 3.19 (2H, d, $J = 6.8$ Hz), 3.30–3.40 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.78–3.92 (4H, m), 4.07–4.18 (4H, m), 6.84 (1H, d, $J = 1.2$ Hz), 6.89–7.00 (4H, m), 7.32–7.55 (9H, m), 7.65 (1H, s). Anal. Calcd for $C_{41}H_{52}N_4O_3S \cdot 0.25H_2O$: C, 71.84; H, 7.72; N, 8.17. Found: C, 71.61; H, 7.85; N, 8.21.

5.59. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-isobuthyl-1*H*-imidazol-2-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6q)

Yield 60%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (15H, m), 1.34–1.45 (2H, m), 1.54–1.70 (2H, m), 1.95–2.10 (2H, m), 2.85–2.95 (2H, m), 3.18 (2H, d, $J = 7.6$ Hz), 3.30–3.42 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.70 (2H, d, $J = 7.8$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 4.14–4.18 (4H, m), 6.81 (1H, d, $J = 1.6$ Hz), 6.89–7.00 (4H, m), 7.32–7.55 (9H, m), 7.71 (1H, s). Anal. Calcd for $C_{41}H_{52}N_4O_3S$: C, 72.32; H, 7.70; N, 8.23. Found: C, 71.99; H, 7.64; N, 8.24.

5.60. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6r)

Yield 91%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–1.00 (12H, m), 1.30–1.48 (2H, m), 1.54–1.68 (2H, m), 1.75–1.89 (2H, m), 2.00–2.20 (1H, m), 2.88–2.98 (2H, m), 3.19 (2H, d, $J = 7.4$ Hz), 3.35–3.45 (2H, m), 3.55 (2H, t, $J = 7.4$ Hz), 3.81 (2H, t, $J = 4.8$ Hz), 3.92 (2H, t, $J = 7.6$ Hz), 3.99 (2H, s), 4.16 (2H, t, $J = 4.8$ Hz), 6.70 (1H, s), 6.92 (1H, d, $J = 8.8$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.25–7.29 (2H, m), 7.38–7.56 (8H, m), 7.66 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_3S$: C, 72.04; H, 7.56; N, 8.40. Found: C, 71.76; H, 7.63; N, 8.16.

5.61. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6s)

Yield 64%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89–1.03 (9H, m), 1.27–1.50 (2H, m), 1.55–1.95 (6H, m), 2.85–2.95 (2H, m), 3.25–3.40 (4H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 3.92 (2H, t, $J = 7.4$ Hz), 3.99 (2H, s), 4.16 (2H, t, $J = 4.8$ Hz), 6.70 (1H, s), 6.90 (1H, d, $J = 7.8$ Hz), 6.98 (2H, d, $J = 8.4$ Hz), 7.25–7.30 (2H, m), 7.39–7.55 (8H, m), 7.62 (1H, s). Anal. Calcd for $C_{39}H_{48}N_4O_3S$: C, 71.75; H, 7.41; N, 8.58. Found: C, 71.54; H, 7.37; N, 8.53.

5.62. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-4-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6t)

Yield 20%, yellow crystals (hexane–*i*-Pr_2O–EtOAc), mp 142–144 °C. ^{1}H NMR ($CDCl_3$) δ 0.85–0.99 (12H, m), 1.30–1.48 (2H, m), 1.54–1.80 (4H, m), 1.95–2.15 (1H, m), 2.85–2.95 (2H, m), 3.19 (2H, d, $J = 7.2$ Hz), 3.30–3.40 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.76–3.83 (4H, m), 4.07 (2H, s), 4.16 (2H, t, $J = 5.2$ Hz), 6.69 (1H, s), 6.92 (1H, d, $J = 9.2$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.32–7.55 (11H, m). Anal. Calcd for $C_{40}H_{50}N_4O_3S$: C, 72.04; H, 7.56; N, 8.40. Found: C, 71.78; H, 7.41; N, 8.48.

5.63. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-methyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6u)

Yield 49%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.4$ Hz), 0.98 (6H, d, $J = 6.6$ Hz), 1.29–1.48 (2H, m), 1.51–1.68 (2H, m), 1.97–2.18 (1H, m), 2.86–2.96 (2H, m), 3.19 (2H, d, $J = 6.6$ Hz), 3.28–3.39 (2H, m), 3.56 (2H, t, $J = 6.6$ Hz), 3.60 (3H, s), 3.81 (2H, t, $J = 5.0$ Hz), 4.11 (2H, s), 4.16 (2H, t, $J = 5.0$ Hz),

6.89–7.00 (3H, m), 7.29–7.43 (5H, m), 7.46 (2H, d, $J = 8.4$ Hz), 7.57 (2H, d, $J = 8.4$ Hz), 7.97 (1H, s), 806 (1H, br s).

5.64. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6v)

Yield 63%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89–2.99 (12H, m), 1.29–1.49 (2H, m), 1.53–1.85 (4H, m), 1.96–2.17 (1H, m), 2.86–2.96 (2H, m), 3.18 (2H, d, $J = 7.0$ Hz), 3.28–3.38 (2H, m), 3.56 (2H, t, $J = 6.6$ Hz), 3.79–3.86 (4H, m), 4.06 (2H, s), 4.16 (2H, t, $J = 4.9$ Hz), 6.90 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.31–7.46 (7H, m), 7.60 (2H, d, $J = 8.8$ Hz), 7.97 (1H, s), 8.42 (1H, br s). Anal. Calcd for $C_{39}H_{49}N_5O_3S{\cdot}0.5H_2O$: C, 69.20; H, 7.45; N, 10.35. Found. C, 69.12; H, 7.58; N, 10.41.

5.65. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6w)

Yield 67%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89–1.03 (9H, m), 1.28–1.47 (2H, m), 1.51–1.88 (6H, m), 2.85–2.96 (2H, m), 3.23–3.36 (4H, m), 3.56 (2H, t, $J = 6.6$ Hz), 3.77–3.84 (4H, m), 4.04 (2H, s), 4.16 (2H, t, $J = 4.8$ Hz), 6.87 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.26–7.45 (7H, m), 7.60 (2H, d, $J = 8.8$ Hz), 7.96 (1H, s), 8.52 (1H, s). Anal. Calcd for $C_{38}H_{47}N_5O_3S{\cdot}0.5H_2O$: C, 68.85; H, 7.30; N, 10.56. Found: C, 68.54; H, 7.41; N, 10.70.

5.66. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-1,2,4-triazol-5-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6x)

Yield 30%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.1$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.30–1.48 (2H, m), 1.51–1.68 (2H, m), 1.98–2.16 (1H, m), 2.85–2.95 (2H, m), 3.19 (2H, d, $J = 7.2$ Hz), 3.33–3.78 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.74 (3H, s), 3.80 (2H, t, $J = 5.0$ Hz), 4.12 (2H, s), 4.16 (2H, t, $J = 5.0$ Hz), 6.92 (1H, d, $J = 8.4$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.31–7.49 (7H, m), 7.55 (2H, d, $J = 8.8$ Hz), 7.62 (1H, s), 7.76 (1H, s). Anal. Calcd for $C_{37}H_{45}N_5O_3S{\cdot}0.5H_2O$: C, 68.49; H, 7.15; N, 10.79. Found: C, 68.62; H, 7.14; N, 11.00.

5.67. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-1,2,3-triazol-5-yl)methyl]sulfanyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (6y)

Yield 50%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.97 (3H, t, $J = 7.4$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.57–1.66 (2H, m), 1.89–2.05 (3H, m), 2.91 (2H, m), 3.18 (2H, d, $J = 7.4$ Hz), 3.33–3.38 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.77–3.83 (2H, m), 3.89 (2H, s), 4.15 (2H, t, $J = 4.8$ Hz), 4.24 (2H, t, $J = 7.2$ Hz), 6.91 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.24–7.29 (2H, m), 7.38–7.58 (8H, m), 7.72 (1H, s).

5.68. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-[4-[(2-pyridyl)sulfinyl]phenyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4a)

To a solution of **6a** (150 mg, 0.25 mmol) in CH_2Cl_2 (7.5 mL) was added *m*CPBA (70%, 95 mg, 0.39 mmol) under ice cooling. After being stirred under ice cooling for 15 min, *m*CPBA (70%, 95 mg, 0.39 mmol) was added to the mixture under ice cooling for 15 min. The mixture was stirred under ice cooling for 15 min, and the mixture was added to aqueous $Na_2S_2O_3$. The mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 1:3) to give 30 mg (20%) of **4a** as a yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.4$ Hz), 0.98 (3H, t, $J = 7.5$ Hz), 1.33–1.44 (2H, m), 1.45–1.82 (4H, m), 2.82–2.92 (2H, m), 3.25–3.36 (4H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 5.0$ Hz), 4.15 (2H, t, $J = 5.0$ Hz), 6.89 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.26–7.50 (6H, m), 7.60–7.80 (5H, m), 7.82–7.93 (1H, m), 8.01–8.09 (1H, m), 8.50–8.57 (1H, m). Anal. Calcd for $C_{37}H_{41}N_3O_4S{\cdot}0.25H_2O$: C, 70.73; H, 6.66; N, 6.69. Found: C, 70.50; H, 6.65; N, 6.54.

5.69. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(2-pyridyl)sulfinyl]methyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4b)

To a solution of **6b** (300 mg, 0.48 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (70%, 83 mg, 0.34 mmol) at -30 °C. After being stirred under ice cooling for 1 h, the mixture was added to aqueous $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 1:3) to give 97 mg (32%) of **4b** as a yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.98 (3H, t, $J = 7.4$ Hz), 1.33–1.45 (2H, m), 1.55–1.76 (4H, m), 2.89 (2H, m), 3.26–3.34 (4H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.78 (2H, t, $J = 4.8$ Hz), 4.05 (1H, d, $J = 13.2$ Hz), 4.12–4.18 (2H, m), 4.34 (1H, d, $J = 13.2$ Hz), 6.86–6.89 (5H, m), 7.32–7.59 (9H, m), 7.70–7.76 (2H, m), 8.64–8.68 (1H, m). Anal. Calcd for $C_{38}H_{43}N_3O_4S{\cdot}0.5H_2O$: C, 70.56; H, 6.86; N, 6.50. Found: C, 70.59; H, 6.73; N, 6.61.

5.70. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(2-pyridyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4c)

This compound was prepared in 45% yield from **6c** by a method similar to that described for **4b**, yellow crystals (EtOAc–*i*-Pr_2O), 118–120 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.0$ Hz), 0.99 (3H, t, $J = 7.0$ Hz), 1.33–1.45 (2H, m), 1.57–1.76 (4H, m), 2.83–2.93 (2H, m), 3.27–3.35 (4H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 4.13 (1H, d, $J = 12.2$ Hz), 4.15 (2H, m), 4.25 (1H, d, $J = 12.2$ Hz), 6.89 (1H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 7.12–

7.25 (2H, m), 7.38–7.49 (7H, m), 7.61 (1H, td, $J = 7.6$, 1.8 Hz), 7.71 (2H, d, $J = 8.8$ Hz), 7.90 (1H, s), 8.53–8.57 (1H, m). Anal. Calcd for $C_{38}H_{43}N_3O_4S$: C, 71.56; H, 6.80; N, 6.59. Found: C, 71.38; H, 7.06; N, 6.44.

5.71. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(2-pyridyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4d)

This compound was prepared in 34% yield from **6d** by a method similar to that described for **4a**, yellow crystals (EtOAc–hexane), mp 114–117 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.97 (6H, d, $J = 6.2$ Hz), 1.33–1.45 (2H, m), 1.54–1.62 (2H, m), 2.00–2.17 (1H, m), 2.84–2.95 (2H, m), 3.19 (2H, d, $J = 7.0$ Hz), 3.36 (2H, m), 3.55 (2H, t, $J = 6.2$ Hz), 3.78–3.83 (2H, m), 4.13–4.19 (2H, m), 4.15 (1H, d, $J = 12.3$ Hz), 4.26 (1H, d, $J = 12.3$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.14–7.26 (2H, m), 7.38–7.51 (7H, m), 7.63 (1H, td, $J = 7.6$, 1.8 Hz), 7.69–7.78 (3H, m), 8.54–8.57 (1H, m). Anal. Calcd for $C_{39}H_{45}N_3O_4S{\cdot}0.25H_2O$: C, 71.37; H, 6.98; N, 6.40. Found: C, 71.14; H, 7.05; N, 6.37.

The following compounds (**4e**,**f**) were prepared from **6e**,**f** by a method similar to that described for **4b**.

5.72. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(3-pyridyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4e)

Yield 30%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.54–1.68 (2H, m), 2.00–2.17 (1H, m), 2.84–2.96 (2H, m), 3.19 (2H, d, $J = 7.2$ Hz), 3.36 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 3.91 (1H, d, $J = 12.8$ Hz), 4.05–4.12 (1H, m), 4.16 (2H, t, $J = 4.8$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.19–7.31 (3H, m), 7.39–7.51 (6H, m), 7.70 (2H, d, $J = 8.8$ Hz), 7.76–7.85 (1H, m), 8.01–8.05 (1H, m), 8.52 (1H, dd, $J = 4.8$, 1.6 Hz). Anal. Calcd for $C_{39}H_{45}N_3O_4S{\cdot}0.7H_2O$: C, 70.49; H, 7.04; N, 6.32. Found: C, 70.38; H, 6.82; N, 6.15.

5.73. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-pyridyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4f)

Yield 41%, yellow crystals (EtOAc–hexane), mp 155–157 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.54–1.68 (2H, m), 1.99–2.16 (1H, m), 2.84–2.97 (2H, m), 3.19 (2H, d, $J = 7.2$ Hz), 3.44–3.50 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 3.92 (1H, d, $J = 12.6$ Hz), 4.05 (1H, d, $J = 12.6$ Hz), 4.13–4.18 (2H, m), 6.88–6.92 (3H, m), 6.98 (2H, d, $J = 8.8$ Hz), 7.31–7.49 (7H, m), 7.69–7.82 (3H, m), 8.50 (2H, d, $J = 5.8$ Hz). Anal. Calcd for $C_{39}H_{45}N_3O_4S$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.65; H, 7.04; N, 6.56.

5.74. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(3-pyridazinyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4g)

To a solution of **6g** (150 mg, 0.24 mmol) in CH_2Cl_2 (6.0 mL) was added dropwise a solution of *m*CPBA (70%, 61 mg, 0.25 mmol) in CH_2Cl_2 (4.5 mL) at −78 °C. After being stirred at −78 °C for 15 min, the mixture was added to aqueous $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (EtOH/EtOAc = 1:20) to give 62 mg (40%) of **4g** as yellow crystals, mp 138–141 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 0.98 (6H, d, $J = 6.6$ Hz), 1.33–1.43 (2H, m), 1.54–1.62 (2H, m), 1.97–2.17 (1H, m), 2.84–2.97 (2H, m), 3.20 (2H, d, $J = 7.6$ Hz), 3.31–3.41 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.78–3.83 (2H, m), 4.13–4.19 (2H, m), 4.27 (1H, d, $J = 13.2$ Hz), 4.38 (1H, d, $J = 13.2$ Hz), 6.89–7.00 (3H, m), 7.36–7.46 (9H, m), 7.72 (2H, d, $J = 8.4$ Hz), 7.96–8.04 (1H, m), 9.08 (1H, dd, $J = 4.4$, 1.8 Hz). Anal. Calcd for $C_{38}H_{44}N_4O_4S$: C, 69.91; H, 6.79; N, 8.58. Found: C, 69.51; H, 6.80; N, 8.37.

The following compounds (**4h**–**y**) were prepared from **6h**–**y** by a method similar to that described for **4g**.

5.75. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyll-*N*-(4-{[(2-pyrimidinyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4h)

Yield 61%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.0$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.57–1.67 (2H, m), 2.08 (1H, m), 2.92 (2H, m), 3.19 (2H, d, $J = 7.4$ Hz), 3.33–3.39 (2H, m), 3.55 (2H, t, $J = 6.2$ Hz), 3.78–3.83 (2H, m), 4.13–4.18 (2H, m), 4.35 (1H, d, $J = 12.4$ Hz), 4.52 (1H, d, $J = 12.4$ Hz), 6.92 (1H, d, $J = 8.4$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.22 (1H, t, $J = 4.8$ Hz), 7.38–7.51 (5H, m), 7.58 (2H, d, $J = 8.8$ Hz), 7.74 (2H, d, $J = 8.8$ Hz), 7.83 (1H, m), 8.71 (2H, d, $J = 5.2$ Hz). Anal. Calcd for $C_{38}H_{44}N_4O_4S{\cdot}0.5H_2O$: C, 68.96; H, 6.85; N, 8.46. Found: C, 68.78; H, 6.71; N, 8.65.

5.76. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(2-pyrazinyl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4i)

Yield 51%, yellow crystals (EtOAc–hexane), mp 146–149 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.0$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 1.33–1.45 (2H, m), 1.54–1.64 (2H, m), 2.08 (1H, m), 2.92 (2H, m), 3.19 (2H, d, $J = 7.4$ Hz), 3.37 (2H, m), 3.55 (2H, t, $J = 6.6$ Hz), 3.80 (2H, t, $J = 4.8$ Hz), 4.16 (2H, t, $J = 4.8$ Hz), 4.32 (2H, s), 6.92 (1H, d, $J = 8.8$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.38–7.59 (7H, m), 7.72–7.80 (3H, m), 8.36 (1H, s), 8.49 (1H, s), 8.51 (1H, s). Anal. Calcd for $C_{38}H_{44}N_4O_4S$: C, 69.91; H, 6.79; N, 8.58. Found: C, 69.78; H, 6.98; N, 8.67.

5.77. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-pyrazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4j)

Yield 68%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.88–0.99 (9H, m), 1.34–1.70 (4H, m), 2.00–2.20 (1H, m), 2.90–2.97 (2H, m), 3.20 (2H, d, J = 7.2 Hz), 3.30–3.45 (2H, m), 3.52–3.58 (5H, m), 3.81 (2H, t, J = 4.6 Hz), 4.12–4.18 (4H, m), 5.98 (1H, d, J = 2.2 Hz), 6.91–7.02 (3H, m), 7.34–7.52 (8H, m), 7.72–7.76 (3H, m). Anal. Calcd for $C_{38}H_{46}N_4O_4S{\cdot}0.3H_2O$: C, 69.12; H, 7.11; N, 8.49. Found: C, 68.94; H, 6.96; N, 8.15.

5.78. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1,3-thiazol-2-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4k)

Yield 66%, yellow crystals (EtOAc–hexane), mp 142–144 °C. ^{1}H NMR ($CDCl_3$) δ 0.89–0.99 (9H, m), 1.30–1.70 (4H, m), 2.00–2.20 (1H, m), 2.92 (2H, t, J = 5.2 Hz), 3.19 (2H, d, J = 7.2 Hz), 3.37 (2H, t, J = 5.2 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 4.40 (1H, d, J = 13.2 Hz), 4.48 (1H, d, J = 13.2 Hz), 6.93 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 3.4 Hz), 7.39–7.49 (7H, m), 7.71–7.78 (4H, m). Anal. Calcd for $C_{37}H_{43}N_3O_4S_2$: C, 67.55; H, 6.59; N, 6.39. Found: C, 67.46; H, 6.39; N, 6.39.

5.79. 7-{4-[2-(Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4l)

Yield 58%, yellow crystals (EtOAc–hexane), mp 134–136 °C. ^{1}H NMR ($CDCl_3$) δ 0.90–1.00 (9H, m), 1.34–1.50 (2H, m), 1.55–1.65 (2H, m), 2.00–2.20 (1H, m), 2.90–3.00 (2H, m), 3.20 (2H, d, J = 7.4 Hz), 3.33–3.43 (2H, m), 3.46 (3H, s), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 4.8 Hz), 4.05–4.28 (4H, m), 6.81 (1H, d, J = 1.2 Hz), 6.90–7.00 (4H, m), 7.40–7.48 (7H, m), 7.74 (2H, d, J = 8.8 Hz), 7.91 (1H, s). Anal. Calcd for $C_{38}H_{46}N_4O_4S{\cdot}0.8H_2O$: C, 68.19; H, 7.17; N, 8.37. Found: C, 68.13; H, 6.92; N, 7.97.

5.80. 7-{[4-(2-Butoxy)ethoxy]phenyl}-*N*-(4-{[(1-ethyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4m)

Yield 55%, yellow crystals (EtOAc–hexane), mp 139–141 °C. ^{1}H NMR ($CDCl_3$) δ 0.90–1.00 (9H, m), 1.29–1.68 (7H, m), 2.00–2.15 (1H, m), 2.90–2.98 (2H, m), 3.20 (2H, d, J = 7.6 Hz), 3.30–3.42 (2H, m), 3.55 (2H, t, J = 6.4 Hz), 3.78–3.91 (4H, m), 4.07–4.30 (4H, m), 6.90–7.02 (5H, m), 7.39–7.48 (7H, m), 7.72–7.81 (3H, m). Anal. Calcd for $C_{39}H_{48}N_4O_4S{\cdot}0.2H_2O$: C, 69.65; H, 7.25; N, 8.33. Found: C, 69.51; H, 7.11; N, 8.23.

5.81. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4n)

Yield 36%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.84–1.00 (12H, m), 1.22–1.80 (6H, m), 2.00–2.20 (1H, m), 2.85–3.00 (2H, m), 3.20 (2H, d, J = 7.2 Hz), 3.30–3.45 (2H, m), 3.55 (2H, t, J = 7.0 Hz), 3.58–3.83 (4H, m), 4.06–4.30 (4H, m), 6.87 (1H, d, J = 1.4 Hz), 6.90–7.00 (4H, m), 7.39–7.48 (7H, m), 7.73 (2H, d, J = 8.4 Hz), 7.89 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_4S{\cdot}0.3H_2O$; C, 69.80; H, 7.41; N, 8.14. Found: C, 69.56; H, 7.19; N, 7.92.

5.82. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-isopropyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4o)

Yield 43%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (9H, m), 1.22–1.49 (8H, m), 1.54–1.75 (2H, m), 2.00–2.20 (1H, m), 2.90–3.00 (2H, m), 3.20 (2H, d, J = 7.6 Hz), 3.30–3.40 (2H, m), 3.55 (2H, t, J = 7.6 Hz), 3.80 (2H, t, J = 4.4 Hz), 4.10–4.30 (4H, m), 4.40–4.50 (1H, m), 6.90–7.02 (5H, m), 7.38–7.48 (7H, m), 7.73 (2H, d, J = 8.8 Hz), 7.88 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_4S{\cdot}0.3H_2O$: C, 69.80; H, 7.41; N, 8.14. Found: C, 69.56; H, 7.18; N, 7.91.

5.83. 7-{[4-(2-Butoxy)ethoxy]phenyl}-*N*-(4-{[(1-butyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4p)

Yield 68%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.86–1.00 (12H, m), 1.17–1.70 (8H, m), 1.95–2.20 (1H, m), 2.90–3.00 (2H, m), 3.17 (2H, d, J = 7.2 Hz), 3.30–3.43 (2H, m), 3.55 (2H, t, J = 7.0 Hz), 3.70–3.95 (4H, m), 4.03–4.25 (4H, m), 6.85 (1H, d, J = 1.2 Hz), 6.89–6.99 (4H, m), 7.38–7.46 (7H, m), 7.73 (2H, d, J = 8.8 Hz), 8.18 (1H, s). Anal. Calcd for $C_{41}H_{52}N_4O_4S{\cdot}0.5H_2O$: C, 69.76; H, 7.57; N, 7.94. Found: C, 69.98; H, 7.84; N, 7.58.

5.84. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-isobuthyl-1*H*-imidazol-2-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4q)

Yield 68%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d, J = 6.6 Hz), 0.89–0.99 (9H, m), 1.34–1.45 (2H, m), 1.54–1.65 (2H, m), 1.80–2.20 (2H, m), 2.90–2.98 (2H, m), 3.20 (2H, d, J = 7.2 Hz), 3.35–3.40 (2H, m), 3.45–3.70 (4H, m), 3.80 (2H, t, J = 4.4 Hz), 4.07–4.18 (3H, m), 4.29 (1H, d, J = 13.4 Hz), 6.81 (1H, d, J = 1.6 Hz), 6.90–7.00 (4H, m), 7.38–7.48 (7H, m), 7.73 (2H, d, J = 8.6 Hz), 7.88 (1H, s). Anal. Calcd for $C_{41}H_{52}N_4O_4S{\cdot}0.4H_2O$: C, 69.93; H, 7.56; N, 7.96. Found: C, 69.79; H, 7.31; N, 7.66.

5.85. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4r)

Yield 83%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.86–0.99 (12H, m), 1.29–1.50 (2H, m), 1.55–1.77 (4H, m), 1.95–2.20 (1H, m), 2.90–3.00 (2H, m), 3.20 (2H, d, J = 7.4 Hz), 3.30–3.45 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.74–3.83 (4H, m), 4.02 (1H, d, J = 14.4 Hz), 4.07–4.18 (3H, m), 6.56 (1H, s), 6.92 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.32–7.50 (8H, m), 7.75 (2H, d, J = 8.8 Hz), 7.97 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_4S$:

C, 70.35; H, 7.38; N, 8.20. Found: C, 70.03; H, 7.40; N, 8.06.

5.86. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4s)

Yield 81%, yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–1.025 (9H, m), 1.33–1.46 (2H, m), 1.56–1.79 (6H, m), 2.90–2.95 (2H, m), 3.31–3.37 (4H, m), 3.55 (2H, t, J = 6.3 Hz), 3.76–3.82 (4H, m), 4.02 (1H, d, J = 14.1 Hz), 4.09 (1H, d, J = 14.1 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.57 (1H, s), 6.91 (1H, d, J = 9.0 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.33–7.51 (8H, m), 7.74 (2H, d, J = 9.0 Hz), 7.84 (1H, s). Anal. Calcd for $C_{39}H_{48}N_4O_4S\cdot0.25H_2O$: C, 69.56; H, 7.26; N, 8.32. Found: C, 69.49; H, 7.23; N, 8.18.

5.87. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-4-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4t)

Yield 72%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.88–0.99 (12H, m), 1.30–1.50 (2H, m), 1.55–1.85 (4H, m), 1.95–2.20 (1H, m), 2.85–2.95 (2H, m), 3.20 (2H, d, J = 7.6 Hz), 3.30–3.45 (2H, m), 3.55 (2H, t, J = 7.2 Hz), 3.78–3.87 (4H, m), 3.98 (1H, d, J = 12.8 Hz), 4.09 (1H, d, J = 12.8 Hz), 4.16 (2H, t, J = 4.8 Hz), 6.80 (1H, s), 6.93 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.39–7.53 (8H, m), 7.70–7.75 (3H, m). Anal. Calcd for $C_{40}H_{50}N_4O_4S$: C, 70.35; H, 7.38; N, 8.20. Found: C, 70.10; H, 7.34; N, 8.12.

5.88. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-methyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4u)

Yield 66%, yellow crystals (EtOH–EtOAc), mp 103–105 °C. ^{1}H NMR ($CDCl_3$)δ 0.93 (3H, t, J = 7.2 Hz), 1.01 (6H, d, J = 6.2 Hz), 1.29–1.47 (2H, m), 1.53–1.72 (2H, m), 1.96–2.17 (1H, m), 2.89–3.01 (2H, m), 3.22 (2H, d, J = 7.8 Hz), 3.30–3.40 (2H, m), 3.53–3.61 (5H, m), 3.81 (2H, t, J = 4.9 Hz), 3.96 (1H, d, J = 14.0 Hz), 4.11 (1H, d, J = 14.0 Hz), 4.16 (2H, t, J = 4.9 Hz), 6.89–6.99 (3H, m), 7.16–7.22 (2H, m), 7.34–7.48 (5H, m), 7.85 (2H, d, J = 8.4 Hz), 8.00 (1H, s), 8.64 (1H, br s). Anal. Calcd for $C_{37}H_{45}N_5O_4S\cdot2.0H_2O$: C, 64.23; H, 7.14; N, 10.12. Found: C, 64.44; H, 7.20; N, 10.01.

5.89. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4v)

Yield 75%, yellow amorphous. ^{1}H NMR ($CDCl_3$)δ 0.88 (3H, t, J = 7.3 Hz), 0.93 (3H, t, J = 7.1 Hz), 1.01 (6H, d, J = 6.6 Hz), 1.28–1.47 (2H, m), 1.51–1.78 (4H, m), 1.95–2.18 (1H, m), 2.90–3.01 (2H, m), 3.21 (2H, d, J = 7.2 Hz), 3.31–3.41 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.76–3.86 (4H, m), 3.97 (1H, d, J = 14.2 Hz), 4.11 (1H, d, J = 14.2 Hz), 4.15 (2H, t, J = 4.9 Hz), 6.91 (1H, d, J = 8.8 Hz), 6.96 (2H, d, J = 8.4 Hz), 7.27–7.43 (7H, m), 7.85 (2H, d, J = 8.8 Hz), 8.04 (1H, s), 8.70 (1H, br s). Anal. Calcd for $C_{39}H_{49}N_5O_4S\cdot0.5H_2O$: C, 67.60; H, 7.27; N, 10.11. Found: C, 67.25; H, 7.28; N, 9.82.

5.90. 7-{[4-(2-Butoxy)ethoxy]phenyl}1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4w)

Yield 57%, yellow crystals (EtOAc), mp 179–181 °C. ^{1}H NMR ($CDCl_3$)δ 0.89 (3H, t, J = 7.2 Hz), 0.93 (3H, t, J = 7.4 Hz), 1.02 (3H, d, J = 7.3 Hz), 1.27–1.48 (2H, m), 1.51–1.86 (6H, m), 2.89–3.00 (2H, m), 3.28–3.41 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78–3.89 (4H, m), 4.00 (1H, d, J = 14.4 Hz), 4.12–4.19 (3H, m), 6.90 (1H, d, J = 8.4 Hz), 6.96 (2H, d, J = 9.2 Hz), 7.27–7.44 (7H, m), 7.84 (2H, d, J = 8.4 Hz), 8.06 (1H, s), 8.54 (1H, br s). Anal. Calcd for $C_{38}H_{47}N_5O_4S$: C, 68.13; H, 7.07; N, 10.45. Found: C, 67.79; H, 7.10; N, 10.46.

5.91. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-methyl-1*H*-1,2,4-triazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4x)

Yield 89%, yellow crystals (EtOAc–hexane), mp 135–138 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2 Hz), 0.98 (6H, d, J = 6.6 Hz), 1.35–1.47 (2H, m), 1.52–1.68 (2H, m), 1.96–2.17 (1H, m), 2.87–2.97 (2H, m), 3.20 (2H, d, J = 7.4 Hz), 3.32–3.41 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.76 (3H, s), 3.81 (2H, t, J = 4.9 Hz), 4.16 (2H, t, J = 4.9 Hz), 4.19 (1H, d, J = 13.6 Hz), 4.28 (1H, d, J = 13.6 Hz), 6.91–7.01 (3H, m), 7.36–7.52 (7H, m), 7.74 (1H, br s), 7.78 (2H, d, J = 8.8 Hz), 7.83 (1H, s). Anal. Calcd for $C_{37}H_{45}N_5O_4S$: C, 67.76; H, 6.92; N, 10.68. Found: C, 67.52; H, 6.76; N, 10.43.

5.92. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-1,2,3-triazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (4y)

Yield 64%, yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz), 0.93 (3H, t, J = 7.0 Hz), 0.97 (6H, d, J = 6.6 Hz), 1.33–1.45 (2H, m), 1.54–1.65 (2H, m), 1.77–1.91 (2H, m), 2.07 (1H, m), 2.93 (2H, m), 3.19 (2H, d, J = 7.4 Hz), 3.36 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 4.8 Hz), 3.97 (1H, d, J = 14.0 Hz), 4.08–4.16 (4H, m), 4.21 (1H, d, J = 14.0 Hz), 6.92 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.8 Hz), 7.32–7.50 (6H, m), 7.78 (2H, d, J = 8.8 Hz), 8.07 (1H, s). Anal. Calcd for $C_{39}H_{49}N_5O_4S\cdot0.2H_2O$: C, 68.13; H, 7.24; N, 10.19. Found: C, 68.04; H, 7.08; N, 10.19.

5.93. 7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfonyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25)

To a solution of **6r** (300 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) was added a solution of *m*CPBA (70%, 221 mg, 0.90 mmol) at −78 °C. The mixture was stirred at room temperature for 1 h at −15 °C. To the mixture was added dimethyl sulfide (0.1 mL) and stirred at room temperature for 0.5 h. The mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and

concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (hexane/EtOAc = 1:1) and recrystallization from EtOAc to give 122 mg (39%) of **25** as yellow crystals, mp 101–103 °C. ^{1}H NMR ($CDCl_3$) δ 0.85–0.99 (12H, m), 1.30–1.50 (2H, m), 1.55–1.85 (4H, m), 1.95–2.15 (1H, m), 2.90–3.00 (2H, m), 3.20 (2H, d, J = 7.0 Hz), 3.35–3.45 (2H, m), 3.56 (2H, t, J = 7.0 Hz), 3.81 (2H, t, J = 4.4 Hz), 3.95 (2H, t, J = 7.8 Hz), 4.16 (2H, t, J = 4.4 Hz), 4.32 (2H, s), 6.53 (1H, d, J = 0.8 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.39–7.50 (6H, m), 7.60 (2H, d, J = 8.8 Hz), 7.77 (2H, d, J = 8.8 Hz), 8.05 (1H, s). Anal. Calcd for $C_{40}H_{50}N_4O_5S\cdot C_4H_8O_2$ (EtOAc): C, 67.15; H, 7.43; N, 7.12. Found: C,67.24; H,7.21; N,7.21.

5.94. (*R*)-(+)-7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*R*)-4r) and (*S*)-(−)-7-{[4-(2-butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-4r)

The racemate **4r** (1.33 g) was resolved with HPLC to afford optically pure (*R*)-**4r** (0.58 g) and (*S*)-**4r** (0.60 g) [column, CHIRAL PAK AD (50 mm × 500 mm), column temperature, room temperature; mobile phase, EtOH → 2-propanol; flow rate 70 mL/min (EtOH) → 80 mL/min (2-propanol); UV detection, 254 nm, amount injected 400 mg]. Compound (*R*)-**4r**; yellow amorphous, $[\alpha]_D$ +131.8 (*C* 0.498%, EtOH). Anal. Calcd for $C_{40}H_{50}N_4O_4S\cdot 0.5H_2O$: C, 69.43; H, 7.43; N, 8.10. Found: C, 69.50; H, 7.54; N, 8.02. Compound (*S*)-**4r**; yellow amorphous, $[\alpha]_D$ −126.9 (*C* 0.497%, EtOH). Anal. Calcd for $C_{40}H_{50}N_4O_4S\cdot 0.5H_2O$: C, 69.43; H, 7.43; N, 8.10. Found: C, 69.53; H, 7.62; N, 8.04. Crystallization from EtOAc gave (*S*)-**4r** as yellow crystals. Anal. Calcd for $C_{40}H_{50}N_4O_4S\cdot C_4H_8O_2$ (EtOAc): C, 68.54; H, 7.58; N, 7.27. Found: C, 68.35; H, 7.63; N, 7.35. ^{1}H NMR data of the chiral compounds were identical with those of **4r**.

5.95. (*R*)-(+)-7-{[4-(2-Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*R*)-4s) and (*S*)-(−)-7-{[4-(2-butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-4s)

The racemate **4s** (1.30 g) was resolved with HPLC to afford optically pure (*R*)-**4s** (0.60 g) and (*S*)-**4s** (0.63 g) [column, CHIRAL PAK AD (50 mm × 500 mm), column temperature, room temperature; mobile phase, EtOH → 2-propanol; flow rate 70 mL/min; UV detection, 254 nm, amount injected 490 mg]. Compound (*R*)-**4s**; yellow amorphous, $[\alpha]_D$ +136.0 (*C* 0.495%, EtOH). Anal. Calcd for $C_{39}H_{48}N_4O_4S\cdot 0.5H_2O$: C, 69.10; H, 7.29; N, 8.26. Found: C, 69.28; H, 7.51; N, 8.24. Compound (*S*)-**4s**; yellow amorphous, $[\alpha]_D$ −138.2 (*C* 0.499%, EtOH). Anal. Calcd for $C_{39}H_{48}N_4O_4S\cdot 0.5H_2O$: C, 69.10; H, 7.29; N, 8.26. Found: C, 69.16; H, 7.49; N, 8.28. ^{1}H NMR data of the chiral compounds were identical with those of **4s**.

5.96. (*R*)-(+)-7-{[4-(2-Butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*R*)-4v) and (*S*)-(−)-7-{[4-(2-butoxy)ethoxy]phenyl}-1-isobutyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]-sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-4v)

The racemate **4v** (387 mg) was resolved with HPLC to afford optically pure (*R*)-**4v** (170 mg) and (*S*)-**4v** (171 mg) [column, CHIRAL PAK AD (50 mm × 500 mm), column temperature, 40 °C; mobile phase, EtOH; flow rate 60 mL/min; UV detection, 254 nm, amount injected 387 mg]. Compound (*R*)-**4v**; yellow amorphous, $[\alpha]_D$ +146.6 (*C* 0.498%, EtOH). Anal. Calcd for $C_{39}H_{49}N_5O_4S$: C, 68.49; H, 7.22; N, 10.24. Found: C, 68.68; H, 7.36; N, 10.10. Compound (*S*)-**4v**; yellow amorphous, $[\alpha]_D$ −147.0 (*C* 0.506%, EtOH). Anal. Calcd for $C_{39}H_{49}N_5O_4S\cdot 0.5H_2O$: C, 67.60; H, 7.27; N, 10.11. Found: C, 67.42; H, 7.34; N, 10.14. ^{1}H NMR data of the chiral compounds were identical with those of **4v**.

5.97. (*R*)-(+)-7-{[4-(2-Butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*R*)-4w) and (*S*)-(−)-7-{[4-(2-butoxy)ethoxy]phenyl}-1-propyl-*N*-(4-{[(4-propyl-4*H*-1,2,4-triazol-3-yl)methyl]sulfinyl}phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-4w)

The racemate **4w** (376 mg) was resolved with HPLC to afford optically pure (*R*)-**4w** (148 mg) and (*S*)-**4w** (164 m) [column, CHIRAL PAK AD (50 mm × 500 mm), column temperature, 25 °C; mobile phase, hexane/EtOH = 20:80; flow rate 80 mL/min → 100 mL/min; UV detection, 254 nm, amount injected 188 mg]. Compound (*R*)-**4w**; yellow crystals (EtOAc), mp 133–135 °C, $[\alpha]_D$ +141.8 (*C* 0.495%, EtOH). Anal. Calcd for $C_{38}H_{47}N_5O_4S$: C, 68.13; H, 7.07; N, 10.45. Found: C, 67.96; H, 6.92; N, 10.44. Compound (*S*)-**4w**; yellow crystals (EtOAc), mp 133–135 °C, $[\alpha]_D$ −140.8 (*C* 0.504%, EtOH). Anal. Calcd for $C_{38}H_{47}N_5O_4S$: C, 68.13; H, 7.07; N, 10.45. Found: C, 67.89; H, 7.16; N, 10.41. ^{1}H NMR data of the chiral compounds were identical with those of **4w**.

5.98. Asymmetric oxidation of 6w

To a (*S*)-(−)-1,1′-bi-2-naphthol (0.88 g, 3.07 mmol) in toluene (70 mL) was added Ti(O*i*-Pr)$_4$ (0.454 mL, 1.54 mmol) and water (0.5 mL, 30.5 mmol) at room temperature. After being stirred at room temperature for 1 h, **6w** (10.0 g, 15.3 mmol) and 80% cumenehydroperoxide (4.2 mL, 22.7 mmol) were added to the mixture. The mixture was stirred at room temperature for 30 h. To the reaction mixture was added aq $Na_2S_2O_3$ and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was

purified by column chromatography on NH silica gel (EtOAc → EtOAc/EtOH = 19:1) to give 8.69 g (85%) of (***S***)-**4w** as yellow crystals. Recrystallization from EtOAc gave (***S***)-**4w** as yellow crystals, $[\alpha]_D$ −189.2 (*C* 0.472%, $CHCl_3$), mp 133–135 °C. Anal. Calcd for $C_{38}H_{47}N_5O_4S$: C, 68.13; H, 7.07; N, 10.45. Found: C, 67.87; H, 7.10; N, 10.44. The enantiomeric excess of (***S***)-**4w** was determined by HPLC as 96.0% ee [column, CHIRALPAK AD (4 mm × 25 mm), column temperature, room temperature; mobile phase, hexane/2-propanol = 6:4; flow rate, 0.5 mL/min; UV detection, 254 nm].

5.99. Asymmetric oxidation of 6r

To a (*S*)-(−)-1,1′-bi-2-naphthol (60 mg, 1.05 mmol) in toluene (5.0 mL) was added $Ti(O\textit{i}\text{-}Pr)_4$ (31 μL, 0.105 mmol) and water (38 μL, 2.1 mmol) at room temperature. After being stirred at room temperature for 1 h, **6r** (0.70 g, 1.05 mmol) and 80% cumenehydroperoxide (0.39 mL, 2.1 mmol) were added to the mixture. After being stirred at room temperature for 30 h, 80% cumenehydroperoxide (0.20 mL, 1.08 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 5 days. To the reaction mixture was added aq $Na_2S_2O_3$ and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (EtOAc → EtOAc/EtOH = 19:1) to give 320 mg (45%) of (***S***)-**4r** as yellow amorphous, $[\alpha]_D$ −115.0 (*C* 0.492%, EtOH). Anal. Calcd for $C_{40}H_{50}N_4O_4S{\cdot}0.5H_2O$: C, 69.43; H, 7.43; N, 8.10. Found: C, 69.58; H, 7.40; N, 8.14. The enantiomeric excess of (***S***)-**4r** was determined by HPLC as 85.0% ee [column, CHIRALPAK AD (4 mm × 25 mm), column temperature, room temperature; mobile phase, hexane/2-propanol = 1:1; flow rate, 0.7 mL/min; UV detection, 254 nm].

5.100. X-ray crystallographic analysis

Yellow prismatic crystals of (***S***)-**4r** as a solvate of ethyl acetate were obtained from ethyl acetate solution. A diffractometer, Rigaku RAXIS-RAPID Imaging Plate, was used with graphite monochromated Mo-Kα radiation at −173.0 °C to obtain the following crystal data: $a = 40.699(9)$, $b = 11.154(2)$, $c = 19.379(3)$ Å, $\beta = 106.08(2)°$, $V = 8453(11)$ Å^3, monoclinic, C2(#5), $D_{calcd} = 1.212$ g/cm^3, $Z = 8$. Of the 18133 collected reflections, 15377 were unique ($R_{int} = 0.135$). Final *R*-values were $R1 = 0.070$ and $wR2(F^2; \text{all data}) = 0.176$. The absolute configuration was determinated using the Flack parameter[30] of −0.02(6). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 246694).

5.101. Receptor binding assays

CHO-K1 and CCR5-expressing CHO cells[13] 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).

5.102. HIV-1 envelope-mediated membrane fusion assay

COS-7 cells were maintained in Dulbecco's modified Eagle medium (D-MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin G, and 100 μg/mL streptomycin. MOLT-4/CCR5/Luc$^+$ cells, a lymphoblastoid cell line that expresses human CCR5 and that has an integrated copy of the HIV-1 long terminal repeat-driven luciferase reporter gene, were maintained in RPMI 1640 medium supplemented with 10% FBS, 100 U/mL penicillin G, 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. Expression vectors encoding Tat, Rev, and envelope were mixed at a ratio of 5:1:3 and co-transfected into COS-7 cells using Lipofectamine 2000 (Invitrogen). After a 2-day incubation, transfected COS-7 cells and MOLT-4/CCR5/Luc$^+$ cells were seeded in a 96-well plate at 10^4 cells in each well, and various concentrations of the test compounds were added to the wells. The cell suspension was incubated at 37 °C. The mixture of D-MEM and RPMI 1640 medium supplemented with 10% FBS, 100 U/mL penicillin G, 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).

5.103. Preliminary pharmacokinetic analysis

Compounds (10 mg/kg) suspended in 0.5% aqueous methylcellulose solution were orally administered to SD (IGS) rats (male, eight weeks old). Blood samples were collected at different time points (pre-dose, 15, 30 min, 1, 2, 4, 8, 24 h) from the tail vein. The blood was centrifuged to obtain the plasma fraction. Acetonitrile (200 μl) was added to each plasma sample (100 L), and the precipitated plasma proteins were removed by centrifugation. The compound concentrations in the supernatant were measured by HPLC but the column used could not separate optically active compounds (column, Inertsil ODS-3, 4.6 × 150 mm, 5 μm particle size, GL Sciences; column temperature, 40 °C; mobile phase, acetonitrile–0.01 mol/L ammonium acetate ((***S***)-**4r**: 70:30, (***S***)-**4s**: 68:32, (***S***)-**4v**: 65:35, (***S***)-**4w**: 67:33, v/v); flow rate, 1.0 mL/min; UV detection, 280 nm).

Acknowledgements

We thank Mr. Kenichi Kuroshima for the CCR5 binding assay; Mr. Katsunori Takashima, Dr. Hiroshi Miyake, and Ms. Shikiko Shiki for the membrane fusion assay; Mr. Mitsutaka Tanaka for optical resolution by HPLC; Mr. Akira Fujishima and Ms. Keiko

Higashikawa for X-ray crystallographic analysis; Mr. Atsutoshi Furuta for pharmacokinetic analysis.

References and notes

1. Carpenter, C. C.; Fischl, M. A.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J. S.; Richman, D. D.; Saag, M. S.; Schooley, R. T.; Thompson, M. A.; Vella, S.; Yeni, P. G.; Volberding, P. A. *J. Am. Med. Assoc.* **1998**, *280*, 78.
2. Finzi, D.; Blankson, J.; Siliciano, J. D.; Margolick, J. B.; Chadwick, K.; Pierson, T.; Smith, K.; Lisziewicz, J.; Lori, F.; Flexner, C.; Quinn, T. C.; Chaisson, R. E.; Rosenberg, E.; Walker, B.; Gange, S.; Gallant, J.; Siliciano, R. F. *Nat. Med.* **1999**, *5*, 512.
3. Pomerantz, R. J. *J. Am. Med. Assoc.* **1999**, *282*, 1177.
4. Deeks, S. G.; Smith, M.; Holodniy, M.; Kahn, J. O. *J. Am. Med. Assoc.* **1997**, *277*, 145.
5. Blair, W. S.; Lin, P.-F.; Meanwell, N. A.; Wallace, O. B. *Drug Discovery. Today* **2000**, *5*, 183.
6. Deng, H.; Liu, R.; Ellmeier, W.; Choe, S.; Unutmaz, D.; Burkhart, M.; DiMarzio, P.; Marmon, S.; Sutton, R. E.; Hill, C. M.; Davis, C. B.; Peiper, S. C.; Schall, T. J.; Littman, D. R.; Landau, N. R. *Nature* **1996**, *381*, 661.
7. Dragic, T.; Litwin, V.; Allaway, G. P.; Martin, S. R.; Huang, Y.; Nagashima, K. A.; Cayanan, C.; Maddon, P. J.; Koup, R. A.; Moore, J. P.; Paxton, W. A. *Nature* **1996**, *381*, 667.
8. Alkhatib, G.; Combadiere, C.; Broder, C. C.; Feng, Y.; Kennedy, P. E.; Murphy, P. M.; Berger, E. A. *Science* **1996**, *272*, 1955.
9. Choe, H.; Farzan, M.; Sun, Y.; Sullivan, N.; Rollins, B.; Ponath, P. D.; Wu, L.; Mackay, C. R.; LaRosa, G.; Newman, W.; Gerard, N.; Gerard, C.; Sodroski, J. *Cell* **1996**, *85*, 1135.
10. Doranz, B. J.; Rucker, J.; Yi, Y.; Smyth, R. J.; Samson, M.; Peiper, S. C.; Parmentier, M.; Collman, R. G.; Doms, R. W. *Cell* **1996**, *85*, 1149.
11. Cocchi, F.; DeVico, A. L.; Garzino-Demo, A.; Arya, S. K.; Gallo, R. C.; Lusso, P. *Science* **1995**, *270*, 1811.
12. Kazmierski, W.; Bifulco, N.; Yang, H.; Boone, L.; DeAnda, F.; Watson, C.; Kenakin, T. *Bioorg. Med. Chem.* **2003**, *11*, 2663.
13. Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5698.
14. Shiraishi, M.; Aramaki, Y.; Seto, M.; Imoto, H.; Nishikawa, Y.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Nishimura, O.; Baba, M.; Fujino, M. *J. Med. Chem.* **2000**, *43*, 2049.
15. Strizki, J. M.; Xu, S.; Wagner, N. E.; Wojcik, L.; Liu, J.; Hou, Y.; Endres, M.; Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Tagat, J. R.; McCombie, S.; Cox, K.; Fawzi, A. B.; Chou, C. C.; Pugliese-Sivo, C.; Davies, L.; Moreno, M. E.; Ho, D. D.; Trkola, A.; Stoddart, C. A.; Moore, J. P.; Reyes, G. R.; Baroudy, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 12718.
16. Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S. I.; Neustadt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. *J. Med. Chem.* **2002**, *45*, 3143.
17. Aramaki, Y.; Seto, M.; Okawa, T.; Oda, T.; Kanzaki, N.; Shiraishi, M. *Chem. Pharm. Bull.* **2004**, *52*, 254.
18. Seto, M.; Aramaki, Y.; Okawa, T.; Miyamoto, N.; Aikawa, K.; Kanzaki, N.; Niwa, S.; Iizawa, Y.; Baba, M.; Shiraishi, M. *Chem. Pharm. Bull.* **2004**, *52*, 577.
19. Seto, M.; Aramaki, Y.; Imoto, H.; Aikawa, K.; Oda, T.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Shiraishi, M. *Chem. Pharm. Bull.* **2004**, *52*, 818.
20. Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Sakurai, M.; Matsumoto, Y.; Tawara, S.; Chiba, T.; Sakane, K. *Bioorg. Med. Chem.* **1997**, *7*, 1409.
21. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Fedrini, P. *Tetrahedron* **1998**, *44*, 2021.
22. Dener, J. M.; Zhang, L.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159.
23. Tomori, M.; Sakuma, O.; Ohto, H.; Nagaoka, K.; Tsuji, M. PCT Int. Appl. WO9534542, 1995.
24. Christensen, B. G.; Johnston, D. B. R.; Schmitt, S. M. Eur. Pat. Appl. EP 170073, 1986.
25. Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049–1052.
26. Donnoli, M. I.; Superchi, S.; Rosini, C. J. *J. Org. Chem.* **1998**, *63*, 9392.
27. Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391.
28. Wu, L.; LaRosa, G.; Kassam, N.; Gordon, C. J.; Heath, H.; Ruffing, N.; Chen, H.; Humblias, J.; Samson, M.; Parmentier, M.; Moore, J. P.; Mackay, C. R. *J. Exp. Med.* **1997**, *186*, 1373.
29. Carling, W. R.; Ladduwahetty, T.; MacLeod, A. M.; Merchant, K. J.; Moore, K. W.; Sternfeld, F.; Street, L. J. PCT Int. Appl. WO98050385, 1998.
30. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.