Orally Active CCR5 Antagonists as Anti-HIV-1 Agents 2: Synthesis and Biological Activities of Anilide Derivatives Containing a Pyridine *N*-Oxide Moiety

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In order to develop orally active CCR5 antagonists, we investigated 1-benzoxepine derivatives containing new polar substituents, such as phosphonate, phosphine oxide or pyridine *N*-oxide moieties, as replacements for the previoiusly reported quaternary ammonium moiety. Among these compounds, the 2-(α-hydroxybenzyl)pyridine *N*-oxide 5e exhibited moderate CCR5 antagonistic activity and had an acceptable pharmacokinetic profile in rats. Subsequent chemical modification was performed and compound (*S*)-5f possessing the (*S*)-configuration hydroxy group was found to be more active than the (*R*)-isomer. Replacement of the 1-benzoxepine ring with a 4-methylphenyl group by a 1-benzazepine ring with a 4-[2-(butoxy)ethoxy]phenyl group enhanced the activity in the binding assay. In addition, introduction of a 3-trifluoromethyl group on the phenyl group of the anilide moiety led to greatly increased activity in the HIV-1 envelope-mediated membrane fusion assay. In particular, compound (*S*)-5s showed the most potent CCR5 antagonistic activity (IC_{50}=7.2 nM) and inhibitory effect (IC_{50}=5.4 nM) in the fusion assay, together with good pharmacokinetic properties in rats.

Key words CCR5 antagonist; HIV-1; 2-(α-hydroxybenzyl)pyridine *N*-oxide; (*S*)-configuration; 1-benzazepine

Currently, human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors and protease inhibitors are used for the treatment of HIV-1 infection. Although combination chemotherapy, which uses these two types of anti-HIV-1 agents, has been successful for suppression of viral load in HIV-1 infected individuals and reduction of mortality,[1)] it has been found that it can not achieve virus eradication.[2)] Therefore, new anti-HIV-1 agents that target other events in the HIV-1 replication cycle are necessary and recently, inhibition against HIV-1 cell entry or fusion, the first stage of the HIV-1 life cycle, is considered to be an attractive target for viral coreceptor antagonists, gp120-mediated CD4 binding inhibitors and gp41-mediated HIV-1 fusion inhibitors.[3)] Among these targets, the CC chemokine receptor 5 (CCR5), a coreceptor for macrophage-tropic (R5) HIV-1 cell entry,[4—8)] attracts many research groups to develop its antagonists.[9)]

The compound **1**, which we first reported as a small molecule CCR5 antagonist, exhibited highly potent anti-HIV-1 activity.[10,11)] However, its oral absorption was very poor because of its polar quaternary ammonium moiety. In order to develop an orally active CCR5 antagonist, chemical modification of the tertiary amine derivative was performed, which led to the discovery of the orally active 1-benzothiepine 1,1-dioxide (**3**) and 1-benzazepine (**4**) derivatives.[12,13)] In our previous paper, we described that incorporation of a 2-(butoxy)-ethoxy group at the 4-position on the 7-phenyl group of the [6,7]fused nucleus resulted in both enhanced activity and improved pharmacokinetic profiles, and introduction of an isobutyl or 1-methylpyrazol-4-ylmethyl group as the 1-substituent on the 1-benzazepine ring further increased the activity.[13)] We also searched for other polar substituents to replace the quaternary ammonium moiety, and in our first paper, we reported a phosphonium salt **2** as a lead compound of small-molecule CCR5 antagonists.[11)] We have now designed and synthesized the anilide derivatives **5**, containing phosphonate, phosphine oxide or pyridine *N*-oxide moieties as new polar substituents to replace the phosphonium salt and quaternary ammonium salt moieties, and have examined their inhibitory effects on chemokine binding (Fig. 1). In this paper,

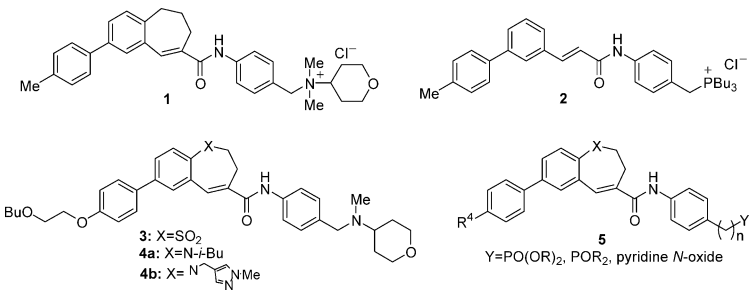

Fig. 1

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we describe the search for the new polar substituents, especially the 2-(α-hydroxybenzyl)pyridine *N*-oxides.

Chemistry

General synthetic methods to the target compounds are outlined in Charts 6—8. The phosphonate **5a** and phosphine oxide **5b** were prepared by condensation of the carboxylic acid **19a** with the aniline derivatives **8a**, **b** (Chart 6). The target compounds **5c**—**s** with the pyridine *N*-oxide moieties were synthesized by condensation of the carboxylic acids **19a**, **b**, **23** with aniline derivatives **8c**—**m**, followed by *m*-chloroperbenzoic acid (*m*CPBA) oxidation (Charts 7, 8).

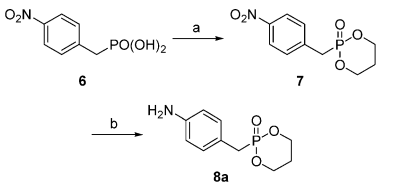
The aniline derivative **8a** was prepared according to Chart 1. The nitro compound **7** with a cyclic phosphonate moiety was synthesized by the reaction of 1,3-propanediol with the acid chloride, which was generated from the phosphonic acid **6**. Catalytic hydrogenation of the nitro compound **7** gave the key aniline **8a**.

The aniline derivatives **8b**—**d**, containing a cyclic phosphine oxide or pyridyl moiety, were synthesized according to Chart 2. Nitration of **9a**—**c**[14] gave the corresponding nitro compounds **10a**—**c**.[15] The key anilines **8b**—**d**[15] were prepared by catalytic hydrogenation of the nitro compounds **10a**—**c**.

The 4-[hydroxyl(pyridin-2-yl)methyl]anilines **8e**, **8j**—**l** were synthesized by coupling reaction of 2-lithiopyridine with the corresponding benzaldehydes **11a**—**d** and subsequent catalytic hydrogenation of the resulting nitro compounds **12a**—**d** (Chart 3).

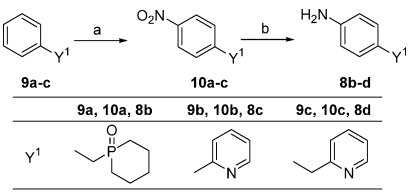
The optically active aniline derivatives (*S*)-**8e** and (*R*)-**8e** were obtained by optical resolution of **8e** utilizing a chiral high-performance liquid chromatography (HPLC) (Chart 3). The absolute configuration was determined by X-ray crystallographic analysis (Fig. 2) of the *m*-bromobenzanilide (*R*)-**13**, which was prepared from the aniline (*R*)-**8e** (Chart 4).

The synthetic method for the anilines **8f**—**i**, **m** is illustrated in Chart 5. Coupling reaction of the 4-fluorobenzylcyanide with the 2-bromopyridines **14a**—**d** and subsequent oxidative decyanation of the resulting 2-(α-cyanobenzyl)pyridines **15a**—**d** gave 2-(4-fluorobenzoyl)pyridine derivatives **16a**—**d**.[16] The 2-benzoylpyridine **16e** was synthesized by coupling reaction of 2-lithiopyridine with the Weinreb amide **18**, which was prepared from the benzoic acid **17**. The aniline derivatives **8f**—**i**, **m** were prepared by reaction of the 2-(4-fluorobenzoyl)pyridines **16a**—**e** with sodium azide and



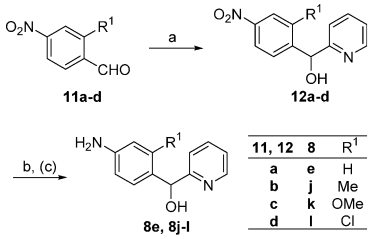
Reagents: (a) (1) $(COCl)_2$, pyridine, THF, (2) 1,3-propanediol, pyridine; (b) 10% Pd-C, H_2, EtOH, EtOAc.

Chart 1



Reagents: (a) conc. H_2SO_4, conc. HNO_3 ; (b) 10% Pd-C, H_2, EtOH.

Chart 2



Reagents: (a) *n*-BuLi, 2-bromopyridine, THF; (b) 10% Pd-C, H_2, EtOH; (c) optical resolution by HPLC.

Chart 3

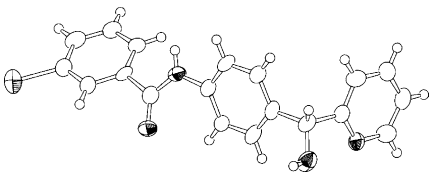
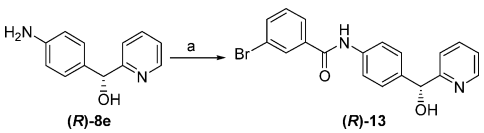
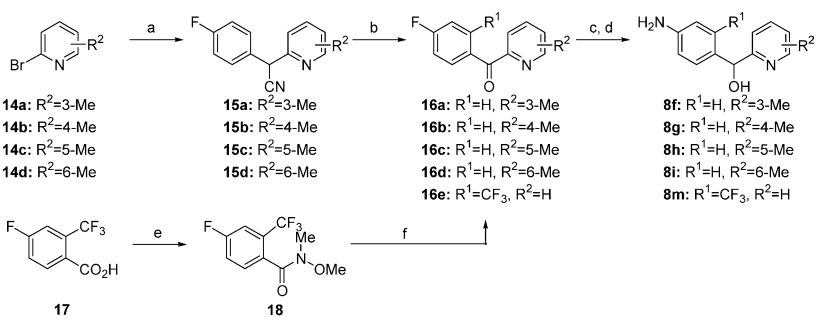


Fig. 2. Molecular Structure of (*R*)-**13** as Determined by X-Ray Crystallographic Analysis



Reagents: (a) *m*-bromobenzoylchloride, Et_3N, THF.

Chart 4



Reagents: (a) 4-fluorobenzylcyanide, NaH, 4-$MePhSO_2Na$, THF; (b) K_2CO_3, O_2, DMSO, water; (c) NaN_3, DMSO; (d) $LiAlH_4$, THF; (e) (1) $(COCl)_2$, cat. DMF, THF, (2) $MeOMeNH_2Cl$, Et_3N; (f) *n*-BuLi, 2-bromopyridine, Et_2O.

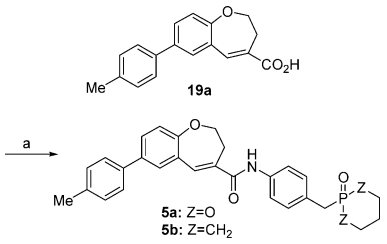
Chart 5

subsequent lithium aluminumhydride ($LiAlH_4$) reduction of both the azide and carbonyl moieties.

The target compounds **5a**, **b** were prepared according to Chart 6. Coupling reaction of the 1-benzoxepine-4-carboxylic acid **19a**[11] with the corresponding anilines **8a**, **b** by the acid chloride method afforded the target phosphonate **5a** and phospine oxide **5b**.

Synthesis of the target pyridine *N*-oxide compounds **5c**—**f** containing the 1-benzoxepine or 1,1-dioxo-1-benzothiepine ring moieties is illustrated in Chart 7. Conversion of the carboxylic acids **19a**,[11] **b**[13] into acid chlorides and subsequent coupling with the aniline derivatives **8c**—**e** gave the anilide derivatives **20a**—**d** containing the pyridine moieties. The target pyridine *N*-oxide derivatives **5c**—**f** were prepared by *m*CPBA oxidation of the pyridine derivatives **20a**—**d**.

The target 1-benzazepine derivatives **5g**—**s** were prepared according to Chart 8. Alkaline hydrolysis of the ester **21**,[13] followed by trifluoroacetylation of the resulting carboxylic acid **22** gave 1-trifluoroacetyl-1-benzazepine-4-carboxylic acid **23**. Coupling reaction of the carboxylic acid **23** with the aniline derivatives **8e**—**m** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt), followed by *m*CPBA oxidation gave the pyridine *N*-oxide derivatives **25a**—**i** containing the *N*-trifluoroacetyl protected 1-benzazepine moiety. The target pyridine *N*-oxide derivatives **5g**—**s** were prepared by removal of the *N*-trifluoroacetyl group of **25a**—**i** using sodium borohydride ($NaBH_4$)[17] and subsequent reductive amination of the resulting **26a**—**i** with the appropriate aldehydes.[18] The optically active compounds (*S*)-**5s** and (*R*)-**5s** were obtained by optical resolution of racemate **5s** utilizing chiral HPLC.



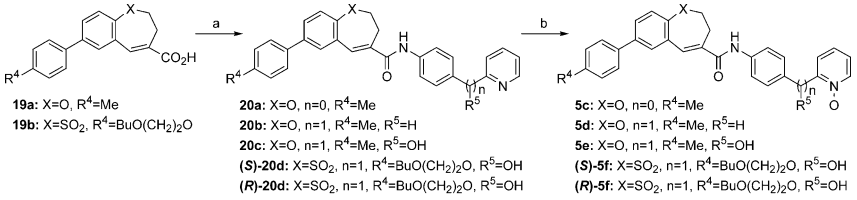
Reagents: (a) (1) $(COCl)_2$, cat. DMF, CH_2Cl_2 or THF, (2) **8a** or **8b**, Et_3N, THF.

Chart 6

Biological Results and Discussion

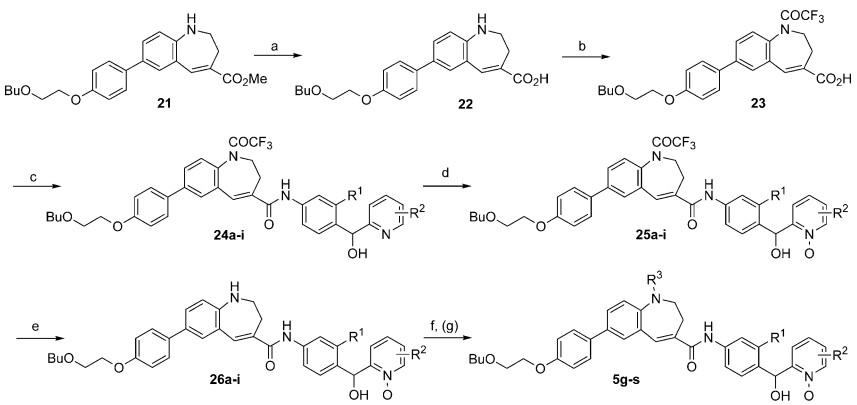
The compounds prepared were evaluated for their inhibitory effects on chemokine binding to CCR5-expressing CHO cells. Binding reactions were performed in the presence of [^{125}I]RANTES and various concentrations of the test compounds. The results are summarized in Tables 1 and 2 as IC_{50} values. The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

First of all, the search for new polar substituents to replace the quaternary ammonium moiety was performed while keeping the 7-(4-methylphenyl)-1-benzoxepine moiety, which contributed to the appearance of potent activity, as well as the benzocycloheptane moiety of the quaternary ammonium de-



Reagents: (a)(1) $(COCl)_2$ or $SOCl_2$, cat. DMF, THF, (2) **8**, Et_3N, THF; (b) *m*CPBA, CH_2Cl_2 (for **5c**) or THF (for **5d**-**f**).

Chart 7

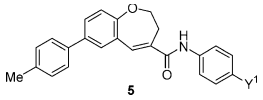


24-26	a	b	c	d	e	f	g	h	i
R^1	H	H	H	H	H	Me	MeO	Cl	CF_3
R^2	H	3-Me	4-Me	5-Me	6-Me	H	H	H	H

Reagents: (a) 1N NaOH, THF, EtOH; (b) $(CF_3CO)_2O$, Et_3N, THF; (c) EDC, HOBt, Et_3N, **8**, DMF; (d) *m*CPBA, THF; (e) $NaBH_4$, EtOH; (f) appropriate aldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; (g) optical resolution by HPLC.

Chart 8

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

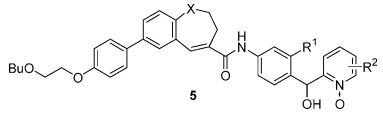


5

Compd.	Y^1	IC_{50}[a] (μM)	Yield (%)	mp (°C)	Recrystln solvent[c]	Formula	*Anal.*[d]
5a		0.40	87	268—269	EA–ET	$C_{28}H_{28}NO_5P$	CHN
5b		0.41	59	283—286	ET	$C_{30}H_{32}NO_3P$	CHN
5c		27%[b]	14	255—256 (dec.)	ET–C	$C_{29}H_{24}N_2O_3 \cdot 0.5H_2O$	CHN
5d		1.1	60	188—190	ET	$C_{30}H_{26}N_2O_3 \cdot 0.3H_2O$	CHN
5e		0.43	51	208—210	ET	$C_{30}H_{26}N_2O_4 \cdot 0.1H_2O$	CHN

a) The concentration required to inhibit the binding of [^{125}I]RANTES to CCR5-expressing CHO cells by 50%. *b*) Percent inhibition at 10 μM. *c*) EA=ethyl acetate, ET=ethanol, C=chloroform. *d*) All compounds gave satisfactory elemental analysis (±0.4%) for C, H and N.

Table 2. Physical Properties and Inhibitory Effects of Compounds **5** on Chemokine Binding to CCR5-expressing CHO Cells



5

Compd.	X	R^1	R^2	IC_{50}[a] (nM)	Yield (%)	mp (°C)	Recrystln solvent[b]	Formula	*Anal.*[c]
(*S*)-**5f**	SO_2	H	H	430	79	125—128	ET–EA	$C_{35}H_{36}N_2O_7S \cdot 1.0H_2O$	CHN
(*R*)-**5f**	SO_2	H	H	3600	41	104—107	ET–EA	$C_{35}H_{36}N_2O_7S \cdot 1.0H_2O$	CHN
(*S*)-**5g**	NPr	H	H	38	82	87—89	ET–EA	$C_{38}H_{43}N_3O_5 \cdot 0.5H_2O$	CHN
(*S*)-**5h**	N-*i*-Bu	H	H	15	71	amorphous	—	$C_{39}H_{45}N_3O_5 \cdot 0.75H_2O$	CHN
(*S*)-**5i**		H	H	34	77	85—88	EA–IPE	$C_{39}H_{43}N_3O_5 \cdot 1.0H_2O$	CHN
(*S*)-**5j**	N-Bn	H	H	20	73	89—93	EA–IPE	$C_{42}H_{43}N_3O_5 \cdot 1.0H_2O$	CHN
(*S*)-**5k**		H	H	17	41	94—97	EA–IPE	$C_{40}H_{43}N_5O_5 \cdot 0.75H_2O$	CHN
5l	N-*i*-Bu	H	3-Me	130	43	amorphous	—	$C_{40}H_{47}N_3O_5 \cdot 1.25H_2O$	CHN
5m	N-*i*-Bu	H	4-Me	32	73	amorphous	—	$C_{40}H_{47}N_3O_5 \cdot 0.5H_2O$	CHN
5n	N-*i*-Bu	H	5-Me	210	67	amorphous	—	$C_{40}H_{47}N_3O_5 \cdot 0.5H_2O$	CHN
5o	N-*i*-Bu	H	6-Me	180	72	114—116	EA–IPE	$C_{40}H_{47}N_3O_5$	CHN
5p	N-*i*-Bu	Me	H	32	91	amorphous	—	$C_{40}H_{47}N_3O_5 \cdot 0.5H_2O$	CHN
5q	N-*i*-Bu	MeO	H	22	92	amorphous	—	$C_{40}H_{47}N_3O_6 \cdot 0.25H_2O$	CHN
5r	N-*i*-Bu	Cl	H	24	88	105—107	EA–H	$C_{39}H_{44}ClN_3O_5 \cdot 0.25H_2O$	CHN
5s	N-*i*-Bu	CF_3	H	14	87	amorphous	—	$C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$	CHN
(*S*)-**5s**	N-*i*-Bu	CF_3	H	7.2	—	amorphous	—	$C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$	CHN
(*R*)-**5s**	N-*i*-Bu	CF_3	H	43	—	amorphous	—	$C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$	CHN

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

rivatives. Based on our experience, we designed derivatives with 6-membered phosphonate, phosphine oxide or pyridine *N*-oxide moieties as the polar substituents and examined their inhibitory effects on chemokine binding (Table 1). The compounds with the polar phosphonate (**5a**) and phosphine oxide (**5b**) moieties inhibited the binding with IC_{50} values of 0.40 μM and 0.41 μM, respectively. However, the biaryl type pyridine *N*-oxide derivative **5c** exhibited weak inhibitory activity. Insertion of the methylene group (**5d**) between the pyridine and benzene moieties of **5c** resulted in a moderate increase of activity. Interestingly, introduction of a hydroxy group onto the methylene of **5d** led to further enhancement of activity, and the compound **5e** was as active as the phosphonate **5a** and phosphine oxide **5b**. It was considered that a further increase of polarity by introduction of a hydroxy group in the neighborhood of the pyridine *N*-oxide moiety might contribute to improving the binding capability of the active site. From the results of preliminary pharmacokinetic studies in SD (IGS) rats, it was found that the pyridine *N*-oxide derivative **5e** exhibited the best oral absorption among the compounds (**5a**, **b**, **e**) (details not shown). Thus, its C_{max} and $AUC_{0—24\,h}$ values were 0.09 μg/ml and 1.14 μg·h/ml (10 mg/kg, *p.o.*), respectively. Therefore, we selected the 2-(α-hydroxybenzyl)pyridine *N*-oxide moiety as a new polar substituent to replace the quaternary ammonium moiety. For the previous tertiary amine derivatives, we described that both replacement of the 1-benzoxepine ring with the 1,1-dioxo-1-benzothiepine or a 1-(bulky)alkyl-1-benzazepine ring and substitution with the 2-(butoxy)ethoxy group at the 4-position on the phenyl group of the [6,7]fused nucleus, increased the activity. Therefore, we investigated the 1,1-dioxo-1-benzothiepine or 1-alkyl-1-benzazepine with the 4-[2-(butoxy)ethoxy]phenyl group in place of the 1-benzoxepine with the 4-methylphenyl group. The effect of the configuration of the hydroxy group was first examined, keeping the 1,1-dioxo-1-benzothiepine moiety. As shown in Table 2, compound (*S*)-

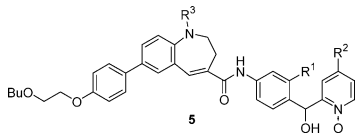
5f possessing the (*S*)-configuration hydroxy group was about 8 times more active than the (*R*)-isomer (*R*)-**5f**, which indicated that not only the pyridine *N*-oxide moiety but also the (*S*)-configuration hydroxy group was necessary for inhibitory activity. Although the optically active 1-benzothiepine 1,1-dioxide (*S*)-**5f** was as active as the racemic 1-benzoxepine **5e**, the 1-propyl-1-benzazepine (*S*)-**5g** enhanced the activity about 11 times.

Secondly, we also examined the effects of the 1-substituent on the 1-benzazepine ring (Table 2). Consequently, the 1-cyclopropylmethyl compound (*S*)-**5i** was found to be as active as the propyl compound (*S*)-**5g**. Replacement of the propyl group with the isobutyl ((*S*)-**5h**), benzyl ((*S*)-**5j**) or 1-methylpyrazol-4-ylmethyl ((*S*)-**5k**) group led to slight increase of activity. These results were generally similar to those of the tertiary amine derivatives. Next, the inhibitory effects of the compounds (*S*)-**5h** and (*S*)-**5k** on the HIV-1 Env-mediated membrane fusion were tested. As shown in Table 3, the inhibitory effects in the fusion assay were significantly weaker than those in the binding assay.

In an attempt to alter the activity in the fusion assay, we tried to sterically cover some parts of the 2-(α-hydroxybenzyl)pyridine *N*-oxide moiety. Namely, assuming that activity might be related to protein binding in the fusion assay, we investigated introduction of substituents on the pyridine ring and benzene ring of the anilide moiety. We selected the isobutyl group as the 1-substituent on the 1-benzazepine ring considering activity, ease of synthesis and molecular weight, and the racemic compounds **5l**—**s** were prepared and tested (Table 2). Introduction of a methyl group at the 4-position on the pyridine ring (**5m**) retained the activity in the binding assay, whereas substitution of a methyl group at the 3-, 5- or 6-position (**5l**, **n**, **o**) decreased the activity. Introduction of a methyl (**5p**), methoxy (**5q**) or chloro (**5r**) group at the 3-position on the benzene ring, neighboring the hydroxy group, retained the activity. Compound **5s** with a trifluoromethyl group at the same position was as active as compound (*S*)-**5h**. Optically active compound (*S*)-**5s** showed highly potent inhibitory activity (IC_{50}=7.2 nM), and was about 6 times more active then the (*R*)-isomer. Additionally, the inhibitory effects of the compounds [**5m**, **5p**—**r**, (*S*)-**5s**], with potent binding inhibitory activity, on the HIV-1 Env-mediated membrane fusion were examined (Table 3). Introduction of substituents onto the 2-(α-hydroxybenzyl)pyridine *N*-oxide moiety was generally effective in the fusion assay, when compared with compound (*S*)-**5h**, which showed activity about 270 times lower than that of the binding assay. The 4-methylpyridine *N*-oxide **5m** inhibited the membrane fusion with an IC_{50} value of 170 nM. Compound **5p**, with 3-methyl group on the phenyl group, exhibited moderate activity. Surprisingly, introduction of a 3-trifluoromethyl group on the phenyl group, led to a great enhancement of activity. Thus, optically active compound (*S*)-**5s** strongly inhibited the membrane fusion with an IC_{50} value of 5.4 nM, and the effect was equivalent to that in the binding assay. Compound (*S*)-**5s** showed highly potent effects both in the binding and fusion assays, comparable to the quaternary ammonium compound **1**.

Finally, preliminary pharmacokinetic studies of compound (*S*)-**5s** were investigated. Compound (*S*)-**5s** was orally administered at 10 mg/kg to SD (IGS) rats and the results are indicated in Table 4. The C_{max} and $AUC_{0—24\,h}$ values of compound (*S*)-**5s** were 2.33 μg/ml and 33.1 μg·h/ml, respectively, and compound (*S*)-**5s** exhibited high plasma level in rats.

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



5

Compd.	R^3	R^1	R^2	RANTES	Fusion
				IC_{50} [a] (nM)	IC_{50} [b] (nM)
1	—	—	—	1.4	1.4
(*S*)-**5h**	*i*-Bu	H	H	15	4000
(*S*)-**5k**		H	H	17	7100
5m	*i*-Bu	H	Me	32	170
5p	*i*-Bu	Me	H	32	610
5q	*i*-Bu	MeO	H	22	1500
5r	*i*-Bu	Cl	H	24	2300
(*S*)-**5s**	*i*-Bu	CF_3	H	7.2	5.4

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 4. Pharmacokinetic Parameters of Compound (*S*)-**5s** in Rats

	p.o.
Dose (mg/kg)[a]	10
C_{max} (μg/ml)[b]	2.33
T_{max} (h)[c]	4.00
$AUC_{0—24\,h}$ (μg·h/ml)[d]	33.1

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

Conclusion

In order to develop orally active CCR5 antagonists, a search for polar substituents, such as phosphonate, phosphine oxide and pyridine *N*-oxide moieties, to replace the quaternary ammonium moiety of the anilide derivative **1** was performed. Among the 1-benzoxepine and 1-benzothiepine 1,1-dioxide derivatives containing the polar substituents, it was found that the 2-(α-hydroxybenzyl)pyridine *N*-oxide showed CCR5 antagonistic activity and oral absorption in rats, and that the compound possessing the (*S*)-configuration hydroxy group was more active than the (*R*)-isomer. Further investigation of the 2-(α-hydroxybenzyl)pyridine *N*-oxide derivatives containing the 1-benzazepine moiety led to discovering that introduction of a trifluoromethyl group at the 3-position on the phenyl group significantly enhanced activity in the HIV-1 Env-mediated membrane fusion assay. In particular, the optically active compound (*S*)-**5s** exhibited highly potent CCR5 antagonistic activity and inhibitory effect on the membrane fusion, comparable to compound **1**, together with good pharmacokinetic properties in rats. These results showed the possibility that the (*S*)-2-(α-hydroxybenzyl)pyridine *N*-oxide moiety might replace the tertiary amine moiety as a polar

substituent for orally active CCR5 antagonists.

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). Yields were not optimized.

2-(4-Nitrobenzyl)-1,3,2-dioxaphosphorinane 2-oxide (7) To a mixture of **6** (22.7 g, 105 mmol) and pyridine (17.8 ml, 220 mmol) in THF (500 ml) was added oxalyl chloride (19.2 ml, 220 mmol) at −78 °C. The mixture was stirred at −78 °C for 0.5 h and at room temperature for 1.5 h. The precipitated solid was removed by filtration, and the filtrate was concentrated *in vacuo*. To a solution of the residue in THF (500 ml) was added dropwise a solution of 1,3-propanediol (8.00 g, 105 mmol) in acetonitrile (30 ml) at −78 °C. Then pyridine (17.8 ml, 220 mmol) was added to the mixture at −78 °C, and the mixture was stirred at room temperature for 15 h. The precipitate was filtered off on a plug of $MgSO_4$, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc→EtOAc : MeOH : Et_3N=100 : 10 : 1) to give 7.00 g (26%) of **7** as colorless crystals, mp 144—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.85—1.97 (2H, m), 3.36 (2H, d, *J*=22.0 Hz), 4.10—4.28 (2H, m), 4.46—4.62 (2H, m), 7.49 (2H, dd, *J*=9.0, 2.0 Hz), 8.20 (2H, d, *J*=8.0 Hz). *Anal.* Calcd for $C_{10}H_{12}NO_5P$: C, 46.70; H, 4.70; N, 5.45. Found: C, 46.56; H, 4.75; N, 5.38.

4-[(2-Oxido-1,3,2-dioxaphosphorinan-2-yl)methyl]aniline (8a) A mixture of **7** (7.00 g, 27.2 mmol) and 10% Pd–C (50% wet, 0.50 g) in EtOH (100 ml) and EtOAc (50 ml) was stirred at room temperature for 19 h under a hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by recrystallization from EtOAc–hexane to give 5.68 g (92%) of **8a** as colorless crystals, mp 172—173 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.94 (2H, m), 3.16 (2H, d, *J*=21.0 Hz), 3.66 (1H, br s), 3.99—4.16 (2H, m), 4.35—4.51 (2H, m), 6.65 (2H, dd, *J*=9.0, 1.0 Hz), 7.07 (1H, d, *J*=9.0, 3.0 Hz). *Anal.* Calcd for $C_{10}H_{14}NO_3P$: C, 52.87; H, 6.21; N, 6.16. Found: C, 52.83; H, 6.26; N, 5.91.

1-(4-Nitrobenzyl)phosphorinane 1-Oxide (10a) To a mixture of nitric acid (1.94 ml) and sulfuric acid (15 ml) was added **9a**[14] (5.39 g, 25.9 mmol) under ice cooling. It was stirred at 50 °C for 2 d. The reaction mixture was poured into ice. The mixture was neutralized using aqueous ammonia, 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 (EtOAc : EtOH=9 : 1→2 : 1) to give 2.47 g (38%) of **10a** as colorless crystals, mp 173—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46—2.18 (10H, m), 3.28 (2H, d, *J*=13.6 Hz), 7.48 (2H, dd, *J*=8.8, 2.2 Hz), 8.21 (2H, d, *J*=8.8 Hz). *Anal.* Calcd for $C_{12}H_{16}NO_3P$: C, 56.92; H, 6.37; N, 5.53. Found: C, 57.02; H, 6.42; N, 5.25.

4-[(1-Oxidophosphorinan-1-yl)methyl]aniline (8b) This compound was prepared in 76% yield from **10a** by a method similar to that described for **8a**, pale yellow crystals (EtOAc–hexane), mp 163—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27—2.16 (10H, m), 3.06 (2H, d, *J*=13.8 Hz), 3.53—3.80 (2H, m), 6.65 (2H, d, *J*=8.3 Hz), 7.05 (2H, dd, *J*=8.3, 2.0 Hz). *Anal.* Calcd for $C_{12}H_{18}NOP$: C, 64.56; H, 8.13; N, 6.27. Found: C, 64.19; H, 8.16; N, 6.15.

2-(4-Aminophenyl)pyridine (8c)[15] This compound was prepared in 26% yield from **9b** according to literature procedure, pale yellow crystals (diethyl ether (Et_2O)), mp 75—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.63—4.02 (2H, m), 6.73—6.83 (2H, m), 7.06—7.17 (1H, m), 7.58—7.74 (2H, m), 7.79—7.89 (2H, m), 8.58—8.66 (1H, m). *Anal.* Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.63; H, 5.90; N, 16.46.

2-(4-Nitrobenzyl)pyridine (10c) To a mixture of nitric acid (2.1 ml) and sulfuric acid (15 ml) was added **9c** (4.5 ml, 28.0 mmol) under ice cooling. The mixture was stirred at 50 °C for 5 min. The mixture was poured into ice, and the mixture was basified using aqueous ammonia. The mixture was extracted with Et_2O. 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) and recrystallization form EtOAc–hexane to give 3.40 g (57%) of **10c** as pale yellow crystals, mp 95—96 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (2H, s), 7.11—7.23 (2H, m), 7.43 (2H, d, *J*=8.8 Hz), 7.64 (1H, dt, *J*=7.6, 1.8 Hz), 8.16 (2H, d, *J*=8.8 Hz), 8.54—8.60 (1H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.33; H, 4.69; N, 13.34.

2-(4-Aminobenzyl)pyridine (8d) This compound was prepared in 85% yield from **10c** by a method similar to that described for **8a**, yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.41—3.75 (2H, m), 4.05 (2H, s), 6.50—6.69 (2H, m), 6.97—7.16 (4H, m), 7.51—7.60 (1H, m), 8.48—8.57 (1H, m).

2-Methyl-4-nitrobenzaldehyde (11b) A mixture of 1,2-dimethyl-4-nitrobenzene (25.68 g, 170 mmol), N-bromosuccinimide (NBS) (31.8 g, 179 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN) (cat. amount) in EtOAc (400 ml) was refluxed for 7.5 h. NBS (10.5 g, 59.0 mmol) and AIBN (cat. amount) were added to the reaction mixture and the mixture was refluxed for 20 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (hexane : EtOAc=20 : 1) to give a pale yellow oil. A mixture of the oil and NaOAc (61.6 g, 751 mmol) in AcOH (200 ml) was stirred at 120 °C for 7 h. The mixture was concentrated *in vacuo*. To the residue was added aqueous $NaHCO_3$ 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=10 : 1) to give a pale yellow oil. To a solution of the oil in MeOH (300 ml) was added NaOH (7.4 g, 185 mmol) at room temperature, and the mixture was refluxed for 2 h. The mixture was concentrated *in vacuo* and the residue was neutralized using 1 N HCl. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=2 : 1) to give yellow crystals. A mixture of the crystals and activated MnO_2 (8.90 g) in acetone (100 ml) was stirred at room temperature for 20 h. MnO_2 was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=20 : 1) to give 1.38 g (5%) of **11b** as colorless crystals. Compound **11b** was used in the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (3H, s), 8.00 (1H, d, *J*=8.0 Hz), 8.16—8.22 (2H, m), 10.40 (1H, s).

2-Methoxy-4-nitrobenzaldehyde (11c) This compounds was prepared in 45% yield from 2-methoxy-4-nitrotoluene by a method similar to that described for **11b**; colorless crystals (EtOAc–hexane), mp 119—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (3H, s), 7.86—7.91 (2H, m), 8.00 (1H, d, *J*=8.8 Hz), 10.53 (1H, s). *Anal.* Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.16; H, 3.81; N, 7.54.

2-Chloro-4-nitrobenzaldehyde (11d) To a suspension of $NaBH_4$ (10.7 g, 283 mmol) in 1,2-dimethoxyethane (150 ml) was added 2-chloro-4-nitrobenzoyl chloride (25 g, 114 mmol) under ice cooling, and the mixture was stirred at room temperature for 1 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 1 N HCl, 1 N NaOH, water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. A mixture of the residue (17.0 g) and activated MnO_2 (50.0 g) in acetone (200 ml) was stirred over night at room temperature. MnO_2 was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=9 : 1) to give 12.1 g (58%) of **11d** as yellow crystals. Compound **11d** was used in the next reaction without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 8.11 (1H, d, *J*=9.2 Hz), 8.21—8.27 (1H, m), 8.36 (1H, d, *J*=2.2 Hz), 10.55 (1H, s).

(4-Nitrophenyl)(pyridin-2-yl)methanol (12a) To a solution of 2-bromopyridine (9.09 g, 57.5 mmol) in Et_2O (200 ml) was added dropwise a solution of *n*-BuLi in hexane (1.6 M, 39.6 ml, 63.3 mmol) at −78 °C. After being stirred at −78 °C for 1 h under an argon atmosphere, a solution of **8a** (8.70 g, 57.5 mmol) in tetrahydrofuran (THF) (50 ml) was added to the reaction mixture at −78 °C. The mixture was stirred at −78 °C for 3 h under an argon atmosphere. Water was added to the reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (toluene : EtOAc=10 : 1→4 : 1→2 : 1) and recrystallization from diisopropyl ether (*i*-Pr_2O) to give 4.5 g (34%) of **9a** as orange crystals, mp 114—115 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.44 (1H, br s), 5.86 (1H, s), 7.14—7.29 (2H, m), 7.55—7.73 (3H, m), 8.20 (2H, d, *J*=8.8 Hz), 8.59 (1H, d, *J*=5.0 Hz). *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.61; H, 4.27; N, 12.16.

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

(2-Methyl-4-nitrophenyl)(pyridin-2-yl)methanol (12b) Yield 44%, pale brown crystals (EtOAc–hexane), mp 119—121 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 5.22 (1H, s), 6.02 (1H, s), 7.00 (1H, d, *J*=7.8 Hz), 7.23—7.30 (1H, m), 7.48 (1H, d, *J*=8.8 Hz), 7.66 (1H, dt, *J*=1.8, 7.7 Hz), 8.00—8.05 (2H, m), 8.62 (1H, d, *J*=3.6 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.12; H, 4.86; N, 11.34.

(2-Methoxy-4-nitrophenyl)(pyridin-2-yl)methanol (12c) Yield 55%,

pale yellow crystals (EtOAc–hexane), mp 126—129 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 5.40 (1H, d, J=4.2 Hz), 6.24 (1H, d, J=4.2 Hz), 7.19—7.31 (2H, m), 7.57 (1H, d, J=8.4 Hz), 7.64 (1H, dt, J=7.7, 1.8 Hz), 7.76 (1H, d, J=2.2 Hz), 7.84 (1H, dd, J=8.4, 1.8 Hz), 8.56 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.09; H, 4.58; N, 10.60.

(2-Chloro-4-nitrophenyl)(pyridin-2-yl)methanol (12d) Yield 30%, yellow crystals (EtOAc–hexane), mp 124—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.61 (1H, d, J=2.2 Hz), 6.32 (1H, d, J=2.2 Hz), 7.24—7.30 (2H, m), 7.63—7.72 (2H, m), 8.10 (1H, dd, J=8.2, 2.6 Hz), 8.28 (1H, d, J=2.6 Hz), 8.58—8.62 (1H, m). *Anal.* Calcd for $C_{12}H_9ClN_2O_3$: C, 54.46; H, 3.43; N, 10.58. Found: C, 54.61; H, 3.38; N, 10.38.

The following compounds (**8e**, **j**, **k**) were prepared from **12a**—**c** by a method similar to that described for **8a**.

(4-Aminophenyl)(pyridin-2-yl)methanol (8e) Yield 95%, pale yellow crystals (EtOAc–hexane), mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (2H, br s), 5.14 (1H, br s), 5.65 (1H, s), 6.65 (2H, d, J=8.8 Hz), 7.10—7.22 (4H, m), 7.61 (1H, dt, J=1.8, 7.6 Hz), 8.55 (1H, d, J=4.8 Hz). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.76; H, 6.01; N, 13.82.

(4-Amino-2-methylphenyl)(pyridin-2-yl)methanol (8j) Yield 58%, colorless crystals, mp 102—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 3.60 (2H, br), 5.00 (1H, d, J=3.2 Hz), 5.86 (1H, d, J=3.2 Hz), 6.45—6.50 (2H, m), 6.95 (1H, d, J=8.0 Hz), 7.05 (1H, d, J=7.8 Hz), 7.15—7.22 (1H, m), 7.60 (1H, dt, J=7.7, 1.4 Hz), 8.57 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.68; H, 6.23; N, 13.00.

(4-Amino-2-methoxyphenyl)(pyridin-2-yl)methanol (8k) Yield 95%, colorless crystals (EtOAc–hexane), mp 123—125 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, br), 3.80 (3H, s), 5.00 (1H, br), 6.08 (1H, s), 6.21—6.27 (2H, m), 6.98 (1H, d, J=8.8 Hz), 7.12—7.26 (2H, m), 7.60 (1H, dt, J=7.7, 1.8 Hz), 8.54 (1H, d, J=4.4 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O_2\cdot 0.1H_2O$: C, 67.28; H, 6.17; N, 12.07. Found: C, 67.36; H, 6.26; N, 11.79.

(4-Amino-2-chlorophenyl)(pyridin-2-yl)methanol (8l) To a solution of **12d** (1.00 g, 4.05 mmol) in THF (15 ml), EtOH (15 ml) and water (15 ml) was added $Na_2S_2O_4$ (3.30 g, 19.0 mmol) at room temperature, and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* 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 0.21 g (24%) of **8l** as colorless crystals, mp 142—146 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.71 (2H, br), 5.32 (1H, d, J=4.2 Hz), 6.15 (1H, d, J=4.2 Hz), 6.53 (1H, dd, J=8.4, 2.4 Hz), 6.70 (1H, d, J=2.4 Hz), 7.08 (1H, d, J=8.4 Hz), 7.17—7.23 (2H, m), 7.62 (1H, dt, J=1.8, 7.7 Hz), 8.56 (1H, d, J=4.4 Hz). *Anal.* Calcd for $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.72; N, 11.94. Found: C, 61.11; H, 4.82; N, 11.61.

(*S*)-(4-Aminophenyl)(pyridin-2-yl)methanol ((*S*)-8e) and (*R*)-(4-Aminophenyl)(pyridin-2-yl)methanol ((*R*)-8e) The racemate **8e** was resolved with HPLC to afford optically pure (*S*)-**8e** and (*R*)-**8e** [column, CHIRAL CEL OD (50 mm×500 mm); column temperature, 25 °C; mobile phase, hexane : EtOH=80 : 20; flow rate 60 ml/min; UV detection, 254 nm; amount injected, 260 mg]. Compound (*S*)-**8e**: pale yellow crystals (EtOAc–hexane), mp 149—150 °C. $[\alpha]_D$=+43.4° (c=1.00, MeOH). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.77; H, 6.02; N, 13.97. Compound (*R*)-**8e**: pale yellow crystals (EtOAc–hexane), mp 149—150 °C. $[\alpha]_D$=−43.6° (c=1.00, MeOH). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.80; H, 6.04; N, 13.96. ^{1}H-NMR data of the chiral compounds were identical with those of **8e**.

(*R*)-3-Bromo-*N*-{4-[hydroxy(pyridin-2-yl)methyl]phenyl}benzamide ((*R*)-13) To a solution of (*R*)-**8e** (0.50 g, 2.50 mmol) and Et_3N (1.1 ml, 7.90 mmol) in THF (10 ml) was added 3-bromobenzoyl chloride (0.54 g, 2.46 mmol) under ice cooling. After being stirred at room temperature for 20 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=1 : 1→2 : 1) to and recrystallization from EtOAc–*i*-Pr_2O to give 349.9 mg (37%) of (*R*)-**13** as pale yellow crystals, mp 153—154 °C. $[\alpha]_D$=+5.87° (c=0.296, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 5.34 (1H, d, J=4.2 Hz), 5.75 (1H, d, J=4.2 Hz), 7.09—7.25 (2H, m), 7.32—7.43 (3H, m), 7.54—7.81 (6H, m), 7.96—8.02 (1H, m), 8.56—8.61 (1H, m). *Anal.* Calcd for $C_{19}H_{15}BrN_2O_2$: C, 59.55; H, 3.95; N, 7.31. Found: C, 59.49; H, 4.09; N, 7.21.

(4-Fluorophenyl)(3-methylpyridin-2-yl)acetonitrile (15a) To a mixture of 4-fluorobenzylcyanide (3.97 g, 29.2 mmol), **11a** (5.0 g, 29.1 mmol) and sodium *p*-toluenesulfinate (10.48 g, 58.8 mmol) in THF (125 ml) was added NaH (60% dispersion in mineral oil, 2.35 g, 58.8 mmol) under ice cooling. The mixture was refluxed for 3.5 h under an argon atmosphere. The reaction mixture was poured into 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=3 : 1) to give 5.14 g (77%) of **15a** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 5.45 (1H, s), 7.00—7.10 (2H, m), 7.19—7.26 (1H, m), 7.32—7.39 (2H, m), 7.48—7.57 (1H, m), 8.51—8.54 (1H, m).

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

(4-Fluorophenyl)(4-methylpyridin-2-yl)acetonitrile (15b) Yield 46%, brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 5.26 (1H, s), 7.02—7.11 (3H, m), 7.21 (1H, s), 7.39—7.46 (2H, m), 8.44 (1H, d, J=5.0 Hz).

(4-Fluorophenyl)(5-methylpyridin-2-yl)acetonitrile (15c) Yield 69%, yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 5.26 (1H, s), 7.02—7.10 (2H, m), 7.28 (1H, d, J=8.0 Hz), 7.37—7.44 (2H, m), 7.52 (1H, dd, J=8.0, 2.0 Hz), 8.42 (1H, d, J=2.2 Hz).

(4-Fluorophenyl)(6-methylpyridin-2-yl)acetonitrile (15d) Yield 83%, yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s), 5.26 (1H, s), 7.02—7.18 (4H, m), 7.39—7.46 (2H, m), 7.59 (1H, t, J=7.7 Hz).

2-(4-Fluorobenzoyl)-3-methylpyridine (16a) A solution of **15a** (5.14 g, 22.7 mmol) and K_2CO_3 (2.90 g, 21.0 mmol) in dimethylsulfoxide (DMSO) (250 ml) and water (50 ml) was stirred at room temperature for 6 d under an oxygen atmosphere. The reaction mixture was poured into 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=4 : 1) to give 5.17 g (quant.) of **16a** as an orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.10—7.20 (2H, m), 7.35 (1H, dd, J=7.6, 4.8 Hz), 7.68 (1H, d, J=7.6 Hz), 7.89—7.96 (2H, m), 8.33 (1H, d, J=4.4 Hz).

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

2-(4-Fluorobenzoyl)-4-methylpyridine (16b) Yield 55%, brown crystals (EtOAc–hexane), mp 98—100 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 7.11—7.20 (2H, m), 7.30—7.33 (1H, m), 7.88 (1H, s), 8.12—8.19 (2H, m), 8.57 (1H, d, J=5.0 Hz). *Anal.* Calcd for $C_{13}H_{10}FNO$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.61; H, 4.63; N, 6.48.

2-(4-Fluorobenzoyl)-5-methylpyridine (16c) Yield 57%, colorless crystals (EtOAc–hexane), mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 7.11—7.22 (2H, m), 7.68—7.74 (1H, m), 7.99 (1H, d, J=8.0 Hz), 8.12—8.19 (2H, m), 8.54—8.55 (1H, m). *Anal.* Calcd for $C_{13}H_{10}FNO$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.68; H, 4.64; N, 6.59.

2-(4-Fluorobenzoyl)-6-methylpyridine (16d) Yield 96%, pale yellow crystals (EtOAc–hexane), mp 53—54 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 7.09—7.21 (2H, m), 7.33—7.37 (1H, m), 7.73—7.85 (2H, m), 8.15—8.25 (2H, m). *Anal.* Calcd for $C_{13}H_{10}FNO$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.52; H, 4.74; N, 6.39.

4-Fluoro-*N*-methoxy-*N*-methyl-2-(trifluoromethyl)benzamide (18) To a solution of **17** (6.70 g, 32.2 mmol) of THF (50 ml) was added $SOCl_2$ (3.40 ml, 46.6 mmol) and DMF (cat. amount) under ice cooling. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. A solution of the residue in $CHCl_2$ (30 ml) was added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (3.80 g, 39.0 mmol) and triethylamine (Et_3N) (6.7 ml, 48.1 mmol) in $CHCl_2$ (50 ml) under ice cooling. The reaction mixture was stirred at room temperature for 24 h. Water was added to the reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtAOc=2 : 1) to give 9.7 g (quant) of **18** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.36 (3H, s), 3.42 (3H, s), 7.26—7.47 (3H, m).

2-[4-Fluoro-2-(trifluoromethyl)benzoyl]pyridine (16e) To a solution of 2-bromopyridine (4.10 g, 25.9 mmol) in Et_2O (50 ml) was added dropwise a solution of *n*-BuLi in hexane (1.6 M, 19.4 ml, 31.0 mmol) at −78 °C. The reaction mixture was stirred at −78 °C under an argon atmosphere for 1 h. A solution of **18** (5.00 g, 19.9 mmol) in Et_2O (50 ml) was added dropwise to the reaction mixture at −78 °C. After being stirred at room temperature for 1.5 h, water was added to the reaction mixture, and the mixture was neutralized using 1 N HCl under ice cooling. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=1 : 1) and recrystallization from hexane to give 3.40 g (63%) of **16e** as brown crystals, mp 85—86 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.33 (1H, td, J=8.2, 2.2 Hz), 7.45—7.54 (3H, m), 7.93 (1H, td, J=8.0, 1.8 Hz), 8.23 (1H, dd, J=8.0, 1.0 Hz), 8.65 (1H, d, J=4.0 Hz). *Anal.* Calcd for $C_{13}H_7F_4NO$: C, 58.00; H, 2.62; N, 5.20. Found: C, 58.02; H, 2.87; N, 5.03.

(4-Aminophenyl)(3-methylpyridin-2-yl)methanol (8f) A solution of

16a (4.00 g, 18.6 mmol) and sodium azide (6.70 g, 103 mmol) in DMSO (80 ml) was stirred at 90 °C for 21 h. Water was added to the reaction mixture and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. A solution of the residue (3.90 g) in THF (40 ml) was added dropwise to a suspension of $LiAlH_4$ (1.24 g, 32.7 mmol) in THF (40 ml) under ice cooling. The reaction mixture was stirred at room temperature for 3 h. To the reaction mixture was added dropwise successively water (1.24 ml), 15% aqueous NaOH (1.24 ml), and water (3.72 ml) under ice cooling. After being stirred at room temperature for 16 h, $MgSO_4$ was added to the mixture and the solid was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by recrystallization from EtOAc to give 2.60 g (65%) of **8f** as pale yellow crystals, mp 153—154 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 3.56—3.66 (2H, m), 5.64 (1H, d, J=6.2 Hz), 5.93 (1H, d, J=6.2 Hz), 6.60 (2H, d, J=8.4 Hz), 7.01 (2H, d, J=8.4 Hz), 7.17 (1H, dd, J=7.8, 4.8 Hz), 7.41—7.45 (1H, m), 8.45—8.47 (1H, m). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.77; H, 6.81; N, 12.93.

The following compounds (**8g**—**i**, **m**) were prepared from **16b**—**e** by a method similar to that described for **8f**.

(4-Aminophenyl)(4-methylpyridin-2-yl)methanol (8g) Yield quant., pale yellow crystals (EtOAc), mp 156—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.65 (2H, br), 5.18 (1H, br), 5.60 (1H, s), 6.65 (2H, d, J=8.4 Hz), 6.93 (1H, s), 6.99 (1H, d, J=5.0 Hz), 7.14 (2H, d, J=8.4 Hz), 8.40 (1H, d, J=5.0 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O \cdot 0.1H_2O$: C, 72.26; H, 6.62; N, 12.97. Found: C, 72.34; H, 6.62; N, 12.69.

(4-Aminophenyl)(5-methylpyridin-2-yl)methanol (8h) Yield 70%, pale yellow crystals (EtOAc), mp 114—115 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.53—3.72 (2H, m), 5.09 (1H, d, J=4.0 Hz), 5.62 (1H, d, J=4.0 Hz), 6.64 (2H, d, J=8.4 Hz), 7.02 (1H, d, J=8.0 Hz), 7.12 (2H, d, J=8.4 Hz), 7.42 (1H, dd, J=8.0, 2.2 Hz), 8.37 (1H, d, J=2.2 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.68; H, 6.88; N, 12.81.

(4-Aminophenyl)(6-methylpyridin-2-yl)methanol (8i) Yield 72%, pale yellow crystals (EtOAc), mp 165—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.58 (3H, s), 3.51—3.73 (2H, m), 5.55—5.61 (2H, m), 6.65 (2H, d, J=8.4 Hz), 6.88 (1H, d, J=7.8 Hz), 7.03 (1H, d, J=7.6 Hz), 7.13 (2H, d, J=8.4 Hz), 7.49 (1H, dd, J=7.8, 7.6 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.64; H, 6.68; N, 12.87.

[4-Amino-2-(trifluoromethyl)phenyl](pyridin-2-yl)methanol (8m) Yield 86%, colorless crystals (EtOAc–hexane), mp 163—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (2H, br), 5.57 (1H, d, J=4.0 Hz), 6.05 (1H, d, J=4.0 Hz), 6.74 (1H, dd, J=8.4, 2.6 Hz), 6.94 (1H, d, J=2.4 Hz), 7.01—7.10 (2H, m), 7.18—7.24 (1H, m), 7.61 (1H, td, J=7.6, 1.8 Hz), 7.58 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.17; H, 4.12; N, 10.33.

7-(4-Methylphenyl)-*N*-{4-[(2-oxido-1,3,2-dioxaphosphorinan-2-yl)-methyl]phenyl}-2,3-dihydro-1-benzoxepine-4-carboxamide (5a) To a solution of **19a**[11] (0.15 g, 0.54 mmol) in CH_2Cl_2 (7.0 ml) was added oxalyl chloride (0.14 ml, 1.60 mmol) and DMF (cat. amount) under ice cooling. After being stirred at room temperature for 3 h, the mixture was concentrated *in vacuo*. A solution of the residue in THF (10 ml) was added dropwise a solution of **8a** (0.13 g, 0.57 mmol) and Et_3N (0.23 ml, 1.65 mmol) in THF (10 ml) under ice cooling. The mixture was stirred at room temperature for 14 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 water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization from EtOAc to give 0.227 g (87%) of **5a** as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.97 (2H, m), 2.40 (2H, s), 3.09 (2H, t, J=4.5 Hz), 3.24 (2H, d, J=21.6 Hz), 4.00—4.20 (2H, m), 4.32—4.52 (4H, m), 7.06 (1H, d, J=8.4 Hz), 7.20—7.33 (4H, m), 7.44—7.60 (6H, m), 7.81 (1H, br s). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.17; H, 4.12; N, 10.33.

7-(4-Methylphenyl)-*N*-{4-[(1-oxidophosphorinan-1-yl)methyl]phenyl}-2,3-dihydro-1-benzoxepine-4-carboxamide (5b) To a solution of **19a** (0.25 g, 0.89 mmol) in THF (10 ml) was added oxalyl chloride (0.12 ml, 1.38 mmol) and DMF (cat. amount) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. A solution of the residue in THF (15 ml) was added to a solution of **8b** (0.22 g, 0.98 mmol) and Et_3N (0.25 ml, 1.79 mmol) in THF (5.0 ml) under ice cooling. After being stirred at room temperature for 4 h, water was added to the mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization from EtOH to give 253 mg (59%) of **5b** as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.32—2.09 (10H, m), 2.39 (3H, s), 3.04—3.18 (4H, m), 4.36 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.4 Hz), 7.19—7.29 (5H, m), 7.44—7.48 (3H, m), 7.53 (1H, d, J=2.6 Hz), 7.59 (2H, d, J=8.4 Hz), 8.09 (1H, br s). *Anal.* Calcd for $C_{30}H_{32}NO_3P$: C, 74.21; H, 6.64; N, 2.88. Found: C, 73.96; H, 6.53; N, 3.11.

The following compounds (**20a**—**c**) were prepared from **19a** and the corresponding anilines **8c**—**e** by a method similar to that described for **5b**.

7-(4-Methylphenyl)-*N*-[4-(pyridin-2-yl)phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (20a) Yield 76%, pale yellow crystals (EtOAc–THF), mp 228—229 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.09 (2H, t, J=4.4 Hz), 4.36 (2H, t, J=4.4 Hz), 7.06 (1H, d, J=8,2 Hz), 7.16—7.32 (4H, m), 7.42—7.56 (4H, m), 7.68—7.82 (5H, m), 8.02 (2H, dd, J=8.8, 2.0 Hz), 8.65—8.73 (1H, dt, J=4.8, 1.4 Hz). *Anal.* Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.46; H, 5.62; N, 6.46.

7-(4-Methylphenyl)-*N*-{4-[(pyridin-2-yl)methyl]phenyl}-2,3-dihydro-1-benzoxepine-4-carboxamide (20b) Yield 47%, colorless crystals (EtOAc), mp 189—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.06 (2H, t, J=4.6 Hz), 4.14 (2H, s), 4.35 (2H, t, J=4.6 Hz), 7.03—7.16 (3H, m), 7.18—7.31 (5H, m), 7.40—7.64 (8H, m), 8.52—8.58 (1H, m). *Anal.* Calcd for $C_{30}H_{26}N_2O_2$: C, 80.69; H, 5.87; N, 6.27. Found. C, 80.63; H, 5.80; N, 6.37.

***N*-{4-[Hydroxy(pyridin-2-yl)methyl]phenyl}-7-(4-Methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (20c)** Yield 47%, pale yellow crystals (EtOH–EtOAc), mp 215—217 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.06 (2H, t, J=4.4 Hz), 4.34 (2H, t, J=4.4 Hz), 5.26—5.38 (1H, m), 5.70—5.78 (1H, m), 7.03—7.27 (6H, m), 7.33—7.79 (10H, m), 8.57 (1H, d, J=4.8 Hz). *Anal.* Calcd for $C_{30}H_{26}N_2O_3 \cdot 0.2H_2O$: Calcd. C, 77.30; H, 5.71; N, 6.01. Found. C, 77.21; H, 5.75; N, 5.86.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(pyridin-2-yl)-methyl]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide ((*S*)-20d) To a solution of **19b** (0.30 g, 0.70 mmol) in THF (10 ml) was added $SOCl_2$ (0.10 ml, 1.37 mmol) and DMF (cat. amount) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. A solution of the residue in THF (20 ml) was added to a solution of (*S*)-**8e** (0.15 g, 0.75 mmol) and Et_3N (0.58 ml, 4.2 mmol) in THF (5.0 ml) under ice cooling. After being stirred at room temperature for 40 h, water was added to the mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) and recrystallization from EtOAc–*i*-Pr_2O to give 273 mg (64%) of (*S*)-**20d** as colorless crystals, mp 173—174 °C. $[\alpha]_D$=−3.26° (c=0.302, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.30—1.46 (2H, m), 1.52—1.66 (2H, m), 3.11—3.18 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.68—3.75 (2H, m), 3.79—3.84 (2H, m), 4.16—4.20 (2H, m), 5.32 (1H, d, J=4.4 Hz), 5.75 (1H, d, J=4.4 Hz), 7.04 (2H, d, J=8.8 Hz), 7.12—7.28 (2H, m), 7.34 (1H, s), 7.39 (2H, d, J=8.6 Hz), 7.52—7.69 (7H, m), 7.96 (1H, s), 8.19 (1H, d, J=8.4 Hz), 8.56—8.59 (1H, m). *Anal.* Calcd for $C_{35}H_{36}N_2O_6S$: C, 68.61; H, 5.92; N, 4.57. Found: C, 68.60; H, 5.98; N, 4.53.

(*R*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(pyridin-2-yl)-methyl]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide ((*R*)-20d) This compound was prepared in 85% yield from **19b** and (*R*)-**8e** by a method similar to that describe for (*S*)-**20d**, colorless crystals (EtOAc), mp 171—173 °C. $[\alpha]_D$=+5.30° (c=0.313, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.30—1.46 (2H, m), 1.52—1.72 (2H, m), 3.11—3.17 (2H, m), 3.56 (2H, t, J=6.8 Hz), 3.68—3.75 (2H, m), 3.79—3.84 (2H, m), 4.16—4.20 (2H, m), 5.34 (1H, br s), 5.75 (1H, br s), 7.03 (2H, d, J=8.8 Hz), 7.12—7.28 (2H, m), 7.33 (1H, s), 7.38 (2H, d, J=8.4 Hz), 7.52—7.69 (7H, m), 8.02 (1H, s), 8.18 (1H, d, J=8.2 Hz), 8.56—8.58 (1H, m). *Anal.* Calcd for $C_{35}H_{36}N_2O_6S \cdot 0.25H_2O$: C, 68.11; H, 5.96; N, 4.54. Found. C, 68.09; H, 5.84; N, 4.50.

7-(4-Methylphenyl)-*N*-[4-(1-oxidopyridin-2-yl)phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (5c) To a solution of **20a** (0.40 g, 0.92 mmol) in CH_2Cl_2 (10 ml) was added *m*CPBA (70%, 0.25 g, 1.10 mmol) under ice cooling. After being stirred at room temperature for 70 h, aqueous $Na_2S_2O_3$ was added to the mixture, and 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 purifed by column chromatography (EtOAc : EtOH=1 : 1) and recrystallization from $CHCl_3$–EtOH to give 59.5 mg (14%) of **5c** as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.06 (2H, t, J=4.4 Hz), 4.36 (2H, t, J=4.4 Hz), 7.00—7.14 (2H, m), 7.16—7.30 (4H, m), 7.38—7.51 (5H, m), 7.67 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.8 Hz), 8.19 (1H, d, J=7.0 Hz), 8.38—8.48 (1H, m). *Anal.* Calcd for $C_{29}H_{24}N_2O_3 \cdot 0.5H_2O$: C, 76.13; H, 5.51; N, 6.12. Found: C, 75.82; H, 5.27; N, 6.18.

The following compounds (**5d**—**f**) were prepared from **20b**—**d** by a method similar to that described for **5c**.

7-(4-Methylphenyl)-*N*-{4-[(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-di-

hydro-1-benzoxepine-4-carboxamide (5d) ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.09 (2H, t, J=4.6 Hz), 4.24 (2H, s), 4.36 (2H, t, J=4.6 Hz), 6.90—7.01 (1H, m), 7.06 (1H, d, J=8.4 Hz), 7.11—7.16 (2H, m), 7.22—7.29 (5H, m), 7.43—7.51 (4H, m), 7.54—7.76 (3H, m), 8.24—8.31 (1H, m). *Anal.* Calcd for $C_{30}H_{26}N_2O_3 \cdot 0.3H_2O$: C, 77.00; H, 5.73; N, 5.99. Found: C, 76.98; H, 5.59; N, 6.10.

***N*-{4-[Hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (5e)** ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.09 (2H, t, J=4.4 Hz), 4.37 (2H, t, J=4.5 Hz), 6.07 (1H, d, J=4.5 Hz), 6.41 (1H, d, J=4.6 Hz), 6.93—6.98 (1H, m), 7.06 (1H, d, J=8.4 Hz), 7.20—7.31 (5H, m), 7.41—7.55 (6H, m), 7.65 (2H, d, J=8.8 Hz), 7.73 (1H, br s), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{30}H_{26}N_2O_4 \cdot 0.1H_2O$: C, 75.01; H, 5.50; N, 5.83. Found. C, 74.96; H, 5.36; N, 5.73.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide ((*S*)-5f) $[\alpha]_D$=−21.6° (c=0.326, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.30—1.46 (2H, m), 1.54—1.68 (2H, m), 3.14—3.20 (2H, m), 3.56 (2H, t, J=6.6 Hz), 3.68—3.75 (2H, m), 3.79—3.84 (2H, m), 4.16—4.21 (2H, m), 6.07 (1H, d, J=4.6 Hz), 6.38 (1H, d, J=4.6 Hz), 6.94—7.01 (1H, m), 7.04 (2H, d, J=9.2 Hz), 7.24—7.28 (1H, m), 7.37 (1H, s), 7.44—7.56 (5H, m), 7.62—7.69 (4H, m), 8.06 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{35}H_{36}N_2O_7S \cdot 1.0H_2O$: C, 65.00; H, 5.92; N, 4.33. Found: C, 65.02; H, 5.90; N, 4.16.

(*R*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1-benzothiepine-4-carboxamide 1,1-Dioxide ((*R*)-5f) $[\alpha]_D$=+22.8° (c=0.318, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.30—1.46 (2H, m), 1.54—1.68 (2H, m), 3.14—3.20 (2H, m), 3.56 (2H, t, J=6.6 Hz), 3.68—3.75 (2H, m), 3.79—3.84 (2H, m), 4.16—4.21 (2H, m), 6.06 (1H, s), 6.94—7.01 (1H, m), 7.04 (2H, d, J=8.8 Hz), 7.24—7.28 (1H, m), 7.37 (1H, s), 7.44—7.56 (5H, m), 7.62—7.69 (4H, m), 8.13 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{35}H_{36}N_2O_7S \cdot 1.0H_2O$: C, 65.00; H, 5.92; N, 4.33. Found: C, 65.06; H, 5.81; N, 4.28.

7-{4-[2-(Butoxy)ethoxy]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (22) To a solution of **21**[13] (500 mg, 1.26 mmol) in THF (5 ml) and MeOH (5 ml) was added 1 N NaOH (2.50 ml, 2.50 mmol) at room temperature. After being stirred at room temperature for 20 h, the mixture was concentrated *in vacuo*. 1 N HCl (2.5 ml) 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 give 405 mg (84%) of **22** as yellow crystals, mp 205—207 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.29—1.49 (2H, m), 1.55—1.68 (2H, m), 2.86—2.95 (2H, m), 3.41—3.45 (2H, m), 3.56 (2H, t, J=6.6 Hz), 3.81 (2H, t, J=5.0 Hz), 4.16 (2H, t, J=5.0 Hz), 6.68 (1H, d, J=8.6 Hz), 6.98 (2H, d, J=8.8 Hz), 7.34 (1H, dd, J=8.6, 2.0 Hz), 7.43—7.48 (3H, m), 7.85 (1H, s). *Anal.* Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.32; H, 7.01; N, 3.84.

7-[4-(2-Butoxyethoxy)phenyl]-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic Acid (23) To a solution of **22** (12.5 g, 32.7 mmol) and Et_3N (18.4 ml, 13.2 mmol) in THF (150 ml) was added trifluoroacetic anhydride (18.4 ml, 13.0 mmol) under ice cooling. After being stirred at room temperature for 1 h, aqueous $NaHCO_3$ was added to the reaction mixture, and the mixture was stirred over night at room temperature. The mixture was neutralized using 1 N HCl under ice cooling, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 11.19 g (72%) of **23** as colorless crystals, mp 134—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.31—1.49 (2H, m), 1.56—1.69 (2H, m), 2.79—3.28 (3H, m), 3.57 (2H, t, J=6.6 Hz), 3.83 (2H, t, J=4.7 Hz), 4.19 (2H, t, J=4.7 Hz), 4.72—4.89 (1H, m), 7.03 (2H, d, J=8.8 Hz), 7.33 (1H, d, J=8.4 Hz), 7.52—7.60 (3H, m), 7.69 (1H, d, J=1.8 Hz), 7.87 (1H, s). *Anal.* Calcd for $C_{25}H_{26}F_3NO_5$: C, 62.89; H, 5.49; N, 2.93. Found: C, 62.74; H, 5.51; N, 2.68.

(*S*)-7-[4-(2-Butoxyethoxy)phenyl]-*N*-[4-[hydroxy(pyridin-2-yl)-methyl]phenyl]-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24a) To a solution of **23** (3.36 g, 7.04 mmol) and HOBt (2.47 g, 18.3 mmol) in DMF (60 ml) was added EDC (3.43 g, 17.9 mmol) at room temperature. After being stirred at room temperature for 1.5 h, a solution of (*S*)-**8e** (1.83 g, 9.74 mmol) and Et_3N (1.96 ml, 14.1 mmol) in DMF (10 ml) was added to the reaction mixture at room temperature. After being stirred at room temperature for 19 h, water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc=2 : 1→1 : 1) to give 3.59 g (71%) of **24a** as pale yellow crystals, mp 100—102 °C. $[\alpha]_D$=−2.48° (c=0.315, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 1.32—1.48 (2H, m), 1.51—1.66 (2H, m), 2.86—3.27 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.74—4.89 (1H, m), 5.34 (1H, d, J=3.0 Hz), 5.75 (1H, d, J=3.0 Hz), 7.03 (2H, d, J=8.8 Hz), 7.13—7.27 (3H, m), 7.30—7.42 (4H, m), 7.51—7.69 (7H, m), 8.5—8.62 (1H, m). *Anal.* Calcd for $C_{37}H_{36}F_3N_3O_5 \cdot 0.25H_2O$: C, 66.91; H, 5.54; N, 6.33. Found: C, 66.93; H, 5.60; N, 6.32.

The following compounds (**24b**—**i**) were prepared from **23** and the corresponding anilins **8f**—**m** by a method similar to that described for **24a**.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-[4-[hydroxy(3-methylpyridin-2-yl)-methyl]phenyl]-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24b) Yield 45%, colorless amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 1.30—1.48 (2H, m), 1.51—1.68 (2H, m), 2.09 (3H, s), 2.87—3.34 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.75—4.88 (1H, m), 5.73 (1H, d, J=5.9 Hz), 6.06 (1H, d, J=5.9 Hz), 7.02 (2H, d, J=8.8 Hz), 7.17—7.35 (5H, m), 7.42—7.43 (1H, m), 7.47—7.54 (6H, m), 7.62—7.66 (1H, m), 8.45—8.50 (1H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_5 \cdot 0.25H_2O$: C, 67.29; H, 5.72; N, 6.20. Found: C, 67.13; H, 5.56; N, 6.05.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(4-methylpyridin-2-yl)-methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24c) Yield 95%, colorless crystals (Et_2O–hexane), mp 101—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.30—1.49 (2H, m), 1.58—1.69 (2H, m), 2.30 (3H, s), 2.93—3.15 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=5.0 Hz), 4.18 (2H, t, J=5.0 Hz), 4.79—4.90 (1H, m), 5.39 (1H, br), 5.69 (1H, s), 6.93 (1H, s), 7.00—7.04 (3H, m), 7.31—7.65 (11H, m), 8.41 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_5$: C, 67.74; H, 5.69; N, 6.24. Found: C, 67.47; H, 5.81; N, 6.42.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(5-methylpyridin-2-yl)-methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24d) Yield 75%, pale yellow crystals (EtOAc–hexane), mp 110—113 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.28—1.48 (2H, m), 1.53—1.68 (2H, m), 2.33 (3H, s), 2.85—3.31 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.8 Hz), 4.18 (2H, t, J=4.8 Hz), 4.74—4.89 (1H, m), 5.31 (1H, d, J=4.2 Hz), 5.71 (1H, d, J=4.2 Hz), 7.01—7.05 (3H, m), 7.31—7.57 (11H, m), 7.62—7.67 (1H, m), 8.36—8.42 (1H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_5$: C, 67.74; H, 5.69; N, 6.24. Found: C, 67.43; H, 5.76; N, 6.01.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(6-methylpyridin-2-yl)-methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24e) Yield 54%, colorless amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.29—1.48 (2H, m), 1.52—1.70 (2H, m), 2.60 (3H, s), 2.88—3.26 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.74—4.89 (1H, m), 5.64—5.76 (2H, m), 6.89 (1H, d, J=7.6 Hz), 7.00—7.07 (3H, m), 7.30—7.65 (12H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_5 \cdot 0.25H_2O$: C, 67.29; H, 5.72; N, 6.20. Found: C, 67.25; H, 5.58; N, 6.35.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(pyridin-2-yl)methyl]-3-methylphenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24f) Yield 72%, colorless crystals (EtOAc–hexane), mp 122—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.30—1.68 (4H, m), 2.33 (3H, s), 2.91—3.19 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.81 (2H, t, J=4.9 Hz), 4.17 (2H, t, J=4.9 Hz), 4.80—4.84 (1H, m), 5.19 (1H, s), 5.93 (1H, s), 6.99—7.04 (3H, m), 7.19—7.41 (6H, m), 7.50—7.66 (6H, m), 8.58 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_5$: C, 67.74; H, 5.69; N, 6.24. Found: C, 67.47; H, 5.65; N, 6.22.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(pyridin-2-yl)methyl]-3-methoxyphenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24g) Yield 78%, colorless crystals (EtOAc–hexane), mp 123—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.26—1.65 (4H, m), 2.90—3.25 (3H, m), 3.56 (2H, t, J=6.8 Hz), 3.82 (2H, t, J=4.9 Hz), 3.91 (3H, s), 4.18 (2H, t, J=4.9 Hz), 4.80—4.90 (1H, m), 5.23 (1H, d, J=5.0 Hz), 6.18 (1H, d, J=5.0 Hz), 6.84—6.88 (1H, m), 7.03 (2H, d, J=8.4 Hz), 7.19—7.65 (11H, m), 8.55 (1H, d, J=4.8 Hz). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_6$: C, 66.17; H, 5.55; N, 6.09. Found: C, 65.99; H, 5.69; N, 5.74.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{3-chloro-4-[hydroxy(pyridin-2-yl)-methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24h) Yield 31%, yellow amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.29—1.49 (2H, m), 1.54—1.72 (2H, m), 2.90—3.19 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.81 (2H, t, J=4.8 Hz), 4.17 (2H, t, J=4.8 Hz), 4.80—4.86 (1H, m), 5.51 (1H, s), 6.23 (1H, s), 7.01 (2H, d, J=8.8 Hz), 7.19—7.68 (11H, m), 7.78—7.82 (2H, m), 8.56 (1H, d, J=4.4 Hz).

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(pyridin-2-yl)methyl]-

3-(trifluoromethyl)phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (24i) Yield 40%, colorless amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 1.30—1.50 (2H, m), 1.55—1.70 (2H, m), 2.90—3.30 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.8 Hz), 4.17 (2H, t, J=4.8 Hz), 4.75—4.90 (1H, m), 5.75 (1H, br), 6.14 (1H, s), 7.00—7.04 (3H, m), 7.21—7.80 (11H, m), 7.94 (1H, d, J=5.0 Hz), 8.60 (1H, d, J=3.6 Hz). *Anal.* Calcd for $C_{38}H_{35}F_6N_3O_5$: C, 62.72; H, 4.85; N, 5.77. Found: C, 62.44; H, 4.87; N, 5.85.

The following compounds (**25a**—**i**) were prepared from **24a**—**i** by a method similar to that described for **5c**.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25a) Yield 76%, colorless crystals (EtOH–*i*-Pr_2O), mp 107—110 °C. $[\alpha]_D$=−24.0° (c=0.295, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.29—1.48 (2H, m), 1.51—1.67 (2H, m), 2.86—3.34 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.76—4.91 (1H, m), 6.07 (1H, d, J=3.8 Hz), 6.41 (1H, d, J=3.8 Hz), 6.91—7.05 (3H, m), 7.20—7.38 (4H, m), 7.45—7.67 (9H, m), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{37}H_{36}F_3N_3O_6\cdot0.5H_2O$: C, 64.90; H, 5.45; N, 6.14. Found: C, 64.97; H, 5.37; N, 6.10.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(3-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25b) Yield 71%, pale yellow crystals (EtOAc–*i*-Pr_2O), mp 109—112 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.29—1.48 (2H, m), 1.55—1.68 (2H, m), 2.46 (3H, s), 2.88—3.30 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.81 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.72—4.88 (1H, m), 6.03 (1H, d, J=10.2 Hz), 7.02 (2H, d, J=8.8 Hz), 7.15—7.64 (13H, m), 7.90—8.02 (1H, m), 8.08—8.11 (1H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_6\cdot1.0H_2O$: C, 64.49; H, 5.70; N, 5.94. Found: C, 64.75; H, 5.42; N, 5.75.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(4-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25c) Yield 52%, colorless crystals (EtOAc), mp 121—123 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.26—1.45 (2H, m), 1.55—1.65 (2H, m), 2.29 (3H, s), 2.94—3.17 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=5.0 Hz), 4.18 (2H, t, J=5.0 Hz), 4.78—4.88 (1H, m), 6.00—6.03 (1H, m), 6.70—6.75 (2H, m), 7.00—7.06 (3H, m), 7.33 (1H, d, J=8.4 Hz), 7.45—7.22 (9H, m), 8.13 (1H, d, J=6.2 Hz). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_6\cdot0.25H_2O$: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.72; H, 5.64; N, 5.93.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(5-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25d) Yield 79%, colorless crystals (EtOAc–*i*-Pr_2O), mp 201—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz), 1.30—1.49 (2H, m), 1.54—1.70 (2H, m), 2.32 (3H, s), 2.89—3.35 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.78—4.97 (1H, m), 6.03 (1H, d, J=4.2 Hz), 6.52 (1H, d, J=4.2 Hz), 6.81 (1H, d, J=8.2 Hz), 7.01—7.10 (3H, m), 7.26—7.36 (1H, m), 7.44—7.66 (10H, m), 8.11 (1H, s). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_6$: C, 66.17; H, 5.55; N, 6.09. Found: C, 66.11; H, 5.40; N, 6.21.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(6-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25e) Yield 75%, colorless crystals (EtOAc–*i*-Pr_2O), mp 170—173 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz), 1.29—1.48 (2H, m), 1.54—1.68 (2H, m), 2.57 (3H, s), 2.93—3.27 (3H, m), 3.56 (2H, t, J=6.8 Hz), 3.82 (2H, t, J=4.9 Hz), 4.18 (2H, t, J=4.9 Hz), 4.76—4.91 (1H, m), 6.06 (1H, d, J=4.6 Hz), 6.68 (1H, d, J=4.6 Hz), 6.78—6.84 (1H, m), 7.03 (2H, d, J=8.8 Hz), 7.13—7.36 (3H, m), 7.46—7.66 (10H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_6$: C, 66.17; H, 5.55; N, 6.09. Found: C, 65.97; H, 5.48; N, 6.10.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]-3-methylphenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25f) Yield 84%, colorless crystals (EtOAc), mp 142—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 1.31—1.65 (4H, m), 2.23 (3H, s), 2.95—3.25 (3H, m), 3.56 (2H, t, J=6.8 Hz), 3.82 (2H, t, J=5.0 Hz), 4.18 (2H, t, J=5.0 Hz), 4.79—4.93 (1H, m), 6.28 (2H, s), 6.74 (1H, dd, J=7.7, 2.5 Hz), 7.03 (2H, d, J=8.6 Hz), 7.18—7.66 (11H, m), 8.31 (1H, dd, J=6.6, 1.0 Hz). *Anal.* Calcd. for $C_{38}H_{38}F_3N_3O_6\cdot0.5H_2O$: C, 65.32; H, 5.63; N, 6.01. Found: C, 65.56; H, 5.37; N, 5.98.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]-3-methoxyphenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25g) Yield 79%, colorless amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.26—1.49 (2H, m), 1.57—1.69 (2H, m), 2.90—3.30 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.74—3.84 (5H, m), 4.18 (2H, t, J=4.7 Hz), 4.78—4.90 (1H, m), 6.33 (1H, s), 6.65—6.75 (1H, m), 6.90—7.05 (4H, m), 7.20—7.36 (2H, m), 7.46—7.69 (9H, m), 8.22—8.26 (1H, m). *Anal.* Calcd for $C_{38}H_{38}F_3N_3O_7\cdot0.5H_2O$: C, 63.86; H, 5.50; N, 5.88. Found: C, 64.07; H, 5.36; N, 5.79.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{3-chloro-4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25h) Yield 63%, pale red oil. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.26—1.48 (2H, m), 1.54—1.68 (2H, m), 2.92—3.22 (3H, m), 3.55 (2H, t, J=6.7 Hz), 3.81 (2H, t, J=4.7 Hz), 4.17 (2H, t, J=4.7 Hz), 4.78—4.88 (1H, m), 6.38 (1H, s), 6.60 (1H, s), 6.89—7.02 (3H, m), 7.23—7.34 (2H, m), 7.46—7.56 (6H, m), 7.63—7.71 (2H, m), 7.87 (1H, d, J=6.2 Hz), 8.21—8.35 (2H, m).

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]-3-(trifluoromethyl)phenyl}-1-trifluoroacetyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (25i) Yield 78%, colorless amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.0 Hz), 1.30—1.65 (4H, m), 2.80—3.35 (3H, m), 3.56 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.8 Hz), 4.18 (2H, t, J=5.6 Hz), 4.80—4.95 (1H, m), 6.48—6.64 (2H, m), 6.71 (1H, d, J=3.0 Hz), 7.03 (2H, d, J=8.8 Hz), 7.22—7.37 (3H, m), 7.49—7.67 (5H, m), 7.79 (1H, s), 7.90—8.05 (3H, m), 8.29—8.32 (1H, m). *Anal.* Calcd. for $C_{38}H_{35}F_6N_3O_6\cdot0.5H_2O$: C, 60.63; H, 4.82; N, 5.58. Found: C, 60.61; H, 4.69; N, 5.52.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26a) To a solution of **25a** (180 mg, 0.27 mmol) in EtOH (30 ml) was added $NaBH_4$ (10 mg, 0.26 mmol) at room temperature, and it was stirred at room temperature for 2 h. $NaBH_4$ (10 mg, 0.26 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 2 h. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc : EtOH=2 : 1) to give 141.4 mg (90%) of **26a** as yellow amorphous. $[\alpha]_D$=−22.0° (c=0.300, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.28—1.48 (2H, m), 1.51—1.68 (2H, m), 2.89—3.01 (2H, m), 3.41—3.51 (2H, 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), 6.07 (1H, br s), 6.31—6.45 (1H, m), 6.71 (1H, d, J=8.0 Hz), 6.92—6.99 (3H, m), 7.20—7.36 (5H, m), 7.39—7.52 (4H, m), 7.62—7.66 (3H, m), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{35}H_{37}N_3O_5\cdot1.5H_2O$: C, 69.27; H, 6.65; N, 6.93. Found: C, 69.05; H, 6.31; N, 6.67.

The following compounds (**26b**—**i**) were prepared from **25b**—**i** by a method similar to that described for **26a**.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(3-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26b) Yield 56%, yellow crystals (EtOAc–*i*-Pr_2O), mp 101—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.28—1.47 (2H, m), 1.52—1.89 (2H, m), 2.46 (3H, s), 2.90—2.97 (2H, m), 3.39—3.49 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.15 (2H, t, J=4.9 Hz), 4.52—4.64 (1H, m), 6.03 (1H, d, J=11.2 Hz), 6.69 (1H, d, J=8.4 Hz), 6.97 (2H, d, J=8.8 Hz), 7.15—7.58 (12H, m), 8.00 (1H, d, J=11.2 Hz), 8.08—8.11 (1H, m). *Anal.* Calcd for $C_{36}H_{39}N_3O_5\cdot1.0H_2O$: C, 70.68; H, 6.76; N, 6.87. Found: C, 70.72; H, 6.43; N, 6.86.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(4-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26c) Yield quant., yellow crystals (EtOAc), mp 198—201 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.34—1.45 (2H, m), 1.57—1.65 (2H, m), 2.28 (3H, s), 2.97 (2H, t-like), 3.47 (2H, t-like), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.16 (2H, t, J=4.9 Hz), 4.61 (1H, br), 6.03—6.04 (1H, m), 6.69—6.73 (3H, m), 6.95—7.17 (3H, m), 7.26—7.34 (2H, m), 7.43—7.48 (5H, m), 7.63—7.67 (3H, m), 8.14 (1H, d, J=6.6 Hz). *Anal.* Calcd for $C_{36}H_{39}N_3O_5\cdot0.25H_2O$: C, 72.28; H, 6.66; N, 7.02. Found: C, 71.99; H, 6.57; N, 6.91.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(5-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26d) Yield 94%, yellow crystals (EtOAc–*i*-Pr_2O), mp 119—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.29—1.46 (2H, m), 1.53—1.70 (2H, m), 2.30 (3H, s), 2.90—3.01 (2H, m), 3.21—3.50 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.15 (2H, t, J=4.9 Hz), 4.56—4.65 (1H, m), 6.03 (1H, br s), 6.45—6.54 (1H, m), 6.70 (1H, d, J=8.0 Hz), 6.79 (1H, d, J=8.0 Hz), 6.97 (2H, d, J=8.8 Hz), 6.99—7.07 (1H, m), 7.29—7.33 (2H, m), 7.41—7.47 (5H, m), 7.64 (2H, d, J=8.4 Hz), 7.74 (1H, s), 8.10 (1H, s). *Anal.* Calcd for $C_{36}H_{39}N_3O_5\cdot0.5H_2O$: C, 71.74; H, 6.69; N, 6.97. Found: C, 71.76; H, 6.98; N, 6.91.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(6-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxam-

ide (26e) Yield 94%, yellow crystals (EtOAc–*i*-Pr_2O), mp 175—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.28—1.44 (2H, m), 1.48—1.68 (2H, m), 2.56 (3H, s), 2.92—3.01 (2H, m), 3.41—3.49 (2H, m), 3.55 (2H, t, J=6.8 Hz), 3.80 (2H, t, J=5.0 Hz), 4.16 (2H, t, J=5.0 Hz), 4.46—4.72 (1H, m), 6.06 (1H, s), 6.70 (1H, d, J=8.4 Hz), 6.78—6.84 (1H, m), 6.97 (2H, d, J=8.8 Hz), 7.11—7.18 (1H, m), 7.20—7.34 (3H, m), 7.43—7.47 (5H, m), 7.61—7.65 (3H, m). *Anal.* Cacld for $C_{36}H_{39}N_3O_5\cdot 1.0H_2O$: C, 70.68; H, 6.76; N, 6.87. Found. C, 70.53; H, 6.15; N, 6.93.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-methylphenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26f) Yield 97%, yellow crystals (EtOAc), mp 179—182 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.22—1.64 (4H, m), 2.21 (3H, s), 2.96 (2H, t, J=4.4 Hz), 3.46 (2H, t, J=4.4 Hz), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.15 (2H, t, J=4.9 Hz), 4.63 (1H, br), 6.27 (2H, s), 6.68—6.76 (2H, m), 6.97 (2H, d, J=8.8 Hz), 7.16—7.33 (3H, m), 7.43—7.47 (4H, m), 7.56—7.60 (2H, m), 7.70 (1H, s), 8.30 (1H, dd, J=1.0, 5.8 Hz). *Anal.* Calcd for $C_{36}H_{39}N_3O_5\cdot 0.5H_2O$: C, 71.74; H, 6.69; N, 6.97. Found: C, 71.75; H, 6.65; N, 6.81.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-methoxyphenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26g) Yield quant., yellow crystals (EtOAc), mp 116—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.26—1.57 (4H, m), 2.96 (2H, t-like), 3.48 (2H, t-like), 3.55 (2H, t, J=6.6 Hz), 3.73—3.90 (5H, m), 4.16 (2H, t, J=5.0 Hz), 4.61 (1H, br), 6.33 (1H, d, J=4.8 Hz), 6.67—6.73 (2H, m), 6.87—7.00 (4H, m), 7.21—7.48 (7H, m), 7.63—7.75 (3H, m), 8.22—8.26 (1H, m). *Anal.* Calcd for $C_{36}H_{39}N_3O_6\cdot 0.75H_2O$: C, 69.38; H, 6.55; N, 6.74. Found: C, 69.55; H, 6.66; N, 6.38.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{3-chloro-4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26h) Yield quant., yellow amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.29—1.48 (2H, m), 1.54—1.72 (2H, m), 2.92 (2H, br), 3.43 (2H, br), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.8 Hz), 4.12 (2H, t, J=4.8 Hz), 4.60 (1H, br), 6.39 (1H, s), 6.69 (1H, d, J=8.4 Hz), 6.85—6.98 (3H, m), 7.23—7.55 (9H, m), 7.60—8.00 (3H, m), 8.26 (1H, br).

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-(trifluoromethyl)phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (26i) Yield 94%, yellow crystals (EtOAc–*i*-Pr_2O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.33—1.45 (2H, m), 1.54—1.64 (2H, m), 2.97 (2H, t, J=4.8 Hz), 3.48 (2H, t, J=4.8 Hz), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.8 Hz), 4.15 (2H, t, J=4.8 Hz), 6.47 (1H, s), 6.61 (1H, dd, J=7.8, 2.2 Hz), 6.71 (1H, d, J=8.4 Hz), 6.97 (2H, d, J=8.8 Hz), 7.18—7.37 (4H, m), 7.43—7.47 (4H, m), 7.85—7.91 (3H, m), 8.03 (1H, s), 8.28—8.32 (1H, m). *Anal.* Calcd for $C_{36}H_{36}F_3N_3O_5\cdot 1.0H_2O$: C, 64.95; H, 5.75; N, 6.31. Found: C, 65.14; H, 5.84; N, 6.10.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5g) To a solution of **26a** (120 mg, 0.207 mmol) and propionaldehyde (0.15 ml, 2.08 mmol) in 1,2-dichloroethane (10 ml) was added $NaBH(OAc)_3$ (0.13 g, 0.613 mmol) at room temperature. After being stirred at room temperature for 20 h, water was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc : EtOH=2 : 1) to give 105 mg (82%) of (*S*)-**5g** as yellow crystals. $[\alpha]_D$=−26.5° (c=0.303, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.00 (3H, t, J=7.0 Hz), 1.29—1.48 (2H, m), 1.53—1.82 (4H, m), 2.86—2.96 (2H, m), 3.25—3.40 (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), 6.06 (1H, br s), 6.35—6.45 (1H, m), 6.88—7.00 (4H, m), 7.23—7.28 (2H, m), 7.38—7.51 (7H, m), 7.62—7.67 (3H, m), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{38}H_{43}N_3O_5\cdot 0.5H_2O$: C, 72.36; H, 7.03; N, 6.66. Found. C, 72.07; H, 7.01; N, 6.51.

The following compounds ((*S*)-**5h**—**k**, **5l**—**s**) were prepared from **26a**—**i** and corresponding aldehydes by a method similar to that described for (*S*)-**5g**.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5h) $[\alpha]_D$=−22.2° (c=0.319, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 0.98 (6H, d, J=6.6 Hz), 1.27—1.47 (2H, m), 1.53—1.68 (2H, m), 1.98—2.18 (1H, m), 2.89—2.98 (2H, m), 3.19 (2H, d, J=7.4 Hz), 3.32—3.42 (2H, 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), 6.07 (1H, d, J=4.1 Hz), 6.42 (1H, d, J=4.1 Hz), 6.90—7.00 (4H, m), 7.23—7.28 (2H, m), 7.38—7.52 (7H, m), 7.63—7.68 (3H, m), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{39}H_{45}N_3O_5\cdot 0.75H_2O$: C, 72.14; H, 7.22; N, 6.47. Found: C, 72.22; H, 7.29; N, 6.57.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-1-cyclopropylmethyl-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5i) $[\alpha]_D$=−25.2° (c=0.303, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.24—0.35 (2H, m), 0.60—0.70 (2H, m), 0.93 (3H, t, J=7.1 Hz), 1.02—1.22 (1H, m), 1.30—1.46 (2H, m), 1.53—1.66 (2H, m), 2.91—3.02 (2H, m), 3.26 (2H, d, J=6.2 Hz), 3.43—3.50 (2H, 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), 6.04—6.09 (1H, m), 6.36—6.46 (1H, m), 6.91—7.00 (4H, m), 7.24—7.28 (2H, m), 7.39—7.52 (7H, m), 7.63—7.67 (3H, m), 8.25—8.29 (1H, m). *Anal.* Calcd for $C_{39}H_{43}N_3O_5\cdot 1.0H_2O$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.10; H, 6.93; N, 6.50.

(*S*)-1-Benzyl-7-{4-[2-(butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5j) $[\alpha]_D$=−23.5° (c=0.314, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.28—1.48 (2H, m), 1.51—1.67 (2H, m), 2.81—2.89 (2H, m), 3.32—3.42 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.16 (2H, t, J=4.9 Hz), 4.62 (2H, s), 6.07 (1H, d, J=4.3 Hz), 6.41 (1H, d, J=4.9 Hz), 6.88—7.06 (4H, m), 7.24—7.67 (17H, m), 8.25—8.28 (1H, m). *Anal.* Calcd for $C_{42}H_{43}N_3O_5\cdot 1.0H_2O$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.70; H, 6.66; N, 5.99.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5k) $[\alpha]_D$=−24.7° (c=0.317, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.32—1.46 (2H, m), 1.51—1.68 (2H, m), 2.80—2.89 (2H, m), 3.29—3.39 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.81 (2H, t, J=5.0 Hz), 3.90 (3H, s), 4.16 (2H, t, J=5.0 Hz), 4.44 (2H, s), 6.07 (1H, d, J=4.4 Hz), 6.43 (1H, d, J=4.4 Hz), 6.91—7.00 (4H, m), 7.24—7.28 (2H, m), 7.32 (1H, s), 7.38—7.63 (8H, m), 7.62—7.67 (3H, m), 8.24—8.28 (1H, m). *Anal.* Calcd for $C_{40}H_{43}N_5O_5\cdot 0.75H_2O$: C, 69.90; H, 6.53; N, 10.19. Found: C, 69.98; H, 6.77; N, 9.90.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(3-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5l) ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 0.97 (6H, d, J=6.6 Hz), 1.30—1.48 (2H, m), 1.50—1.70 (2H, m), 1.96—2.17 (1H, m), 2.46 (3H, s), 2.84—2.95 (2H, m), 3.18 (2H, d, J=7.4 Hz), 3.29—3.40 (2H, 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), 6.03 (1H, d, J=10.8 Hz), 6.91 (1H, d, J=8.8 Hz), 6.98 (2H, d, J=9.2 Hz), 7.15—7.24 (2H, m), 7.38—7.58 (10H, m), 8.01 (1H, d, J=10.8 Hz), 8.08—8.11 (1H, m). *Anal.* Calcd for $C_{40}H_{47}N_3O_5\cdot 1.25H_2O$: C, 71.46; H, 7.42; N, 6.25. Found: C, 71.50; H, 7.32; N, 6.00.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(4-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5m) ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.99 (9H, m), 1.22—1.45 (2H, m), 1.54—1.65 (2H, m), 2.08 (1H, br), 2.28 (3H, s), 2.93 (2H, t-like), 3.19 (2H, d, J=7.4 Hz), 3.37 (2H, t-like), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=5.0 Hz), 4.16 (2H, t, J=5.0 Hz), 6.05 (1H, s), 6.65 (1H, br), 6.72—6.73 (1H, m), 6.90—7.06 (5H, m), 7.38—7.68 (10H, m), 8.16 (1H, d, J=6.6 Hz). *Anal.* Calcd for $C_{40}H_{47}N_3O_5\cdot 0.5H_2O$: C, 72.92; H, 7.34; N, 6.38. Found: C, 72.81; H, 7.43; N, 6.38.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(5-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5n) ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 0.98 (6H, d, J=6.6 Hz), 1.30—1.46 (2H, m), 1.52—1.68 (2H, m), 1.98—2.16 (1H, m), 2.31 (3H, s), 2.89—2.97 (2H, m), 3.19 (2H, d, J=7.0 Hz), 3.31—3.42 (2H, 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), 6.03 (1H, s), 6.79 (1H, d, J=8.0 Hz), 6.90—7.08 (4H, m), 7.38—7.52 (7H, m), 7.64 (2H, d, J=8.4 Hz), 7.65 (1H, s), 8.11 (1H, s). *Anal.* Calcd for $C_{40}H_{47}N_3O_5\cdot 0.5H_2O$: C, 71.94; H, 7.40; N, 6.29. Found: C, 71.90; H, 7.53; N, 6.13.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(6-methyl-1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5o) ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 0.98 (6H, d, J=6.6 Hz), 1.30—1.46 (2H, m), 1.50—1.71 (2H, m), 1.98—2.16 (1H, m), 2.57 (3H, s), 2.88—2.97 (2H, m), 3.19 (2H, d, J=6.6 Hz), 3.33—3.43 (2H, 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), 6.07 (1H, s), 6.77—6.84 (1H, m), 6.91—7.00 (3H, m), 7.15 (1H, t, J=7.7 Hz), 7.37—7.51 (8H, m), 7.63—7.70 (3H, m). *Anal.* Calcd for $C_{40}H_{47}N_3O_5$: C, 73.93; H, 7.29; N, 6.47. Found: C, 73.83; H, 7.21; N, 6.45.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-methylphenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5p) ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.99 (9H, m), 1.26—1.68 (4H, m), 2.04—2.14 (1H, m), 2.21 (3H, s), 2.93 (2H, t-like), 3.19 (2H, d, J=7.0 Hz), 3.36 (2H, t-like), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=5.0 Hz), 4.15 (2H, t, J=5.0 Hz), 6.27 (2H, br), 6.73 (1H, dd, J=7.8, 2.4 Hz), 6.90—

6.99 (3H, m), 7.16—7.30 (2H, m), 7.37—7.60 (7H, m), 7.72 (1H, s), 8.30 (1H, d, J=4.8 Hz). *Anal.* Calcd for $C_{40}H_{47}N_3O_5 \cdot 0.5H_2O$: C, 72.92; H, 7.34; N, 6.38. Found C, 72.74; H, 7.47; N, 6.18.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-methoxyphenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5q) ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.00 (9H, m), 1.26—1.65 (4H, m), 2.00—2.15 (1H, m), 2.93 (2H, t-like), 3.20 (2H, d, J=7.2 Hz), 3.38 (2H, t-like), 3.55 (2H, t, J=6.5 Hz), 3.74—3.83 (5H, m), 4.16 (2H, t, J=4.8 Hz), 6.33 (1H, d, J=4.8 Hz), 6.69 (1H, d, J=4.8 Hz), 6.88—7.00 (5H, m), 7.21—7.26 (1H, m), 7.40—7.52 (6H, m), 7.63—7.68 (2H, m), 7.77 (1H, s), 8.22—8.24 (1H, m). *Anal.* Calcd for $C_{40}H_{47}N_3O_6 \cdot 0.25H_2O$: C, 71.67; H, 7.14; N, 6.27. Found: C, 71.51; H, 7.24; N, 6.17.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{3-chloro-4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5r) ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.99 (9H, m), 1.22—1.68 (4H, m), 2.00—2.11 (1H, m), 2.92 (2H, t, J=4.6 Hz), 3.19 (2H, d, J=7.6 Hz), 3.37 (2H, t, J=4.6 Hz), 3.55 (2H, t, J=6.6 Hz), 3.80 (2H, t, J=4.9 Hz), 4.16 (2H, t, J=4.9 Hz), 6.39 (1H, d, J=3.7 Hz), 6.68 (1H, d, J=3.7 Hz), 6.82—7.00 (4H, m), 7.20—7.30 (1H, m), 7.38—7.51 (6H, m), 7.72 (1H, s), 7.78 (1H, d, J=8.8 Hz), 7.94 (1H, d, J=2.2 Hz), 8.26—8.30 (1H, m). *Anal.* Calcd. for $C_{39}H_{44}ClN_3O_5 \cdot 0.25H_2O$: C, 69.42; H, 6.65; N, 6.23. Found: C, 69.45; H, 6.52; N, 6.23.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)-methyl]-3-(trifluoromethyl)phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (5s) ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.00 (9H, m), 1.26—1.70 (4H, m), 2.00—2.20 (1H, m), 2.90—3.00 (2H, m), 3.21 (1H, d, J=7.4 Hz), 3.35—3.45 (2H, m), 3.56 (2H, t, J=7.0 Hz), 3.81 (2H, t, J=5.2 Hz), 4.16 (2H, t, J=5.2 Hz), 6.45—6.49 (1H, m), 6.57—6.63 (1H, m), 6.71 (1H, d, J=2.6 Hz), 6.92—7.01 (3H, m), 7.17—7.53 (7H, m), 7.77 (1H, s), 7.93 (2H, s), 8.04 (1H, s), 8.31 (1H, d, J=5.8 Hz). *Anal.* Calcd for $C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$: C, 67.40; H, 6.36; N, 5.89. Found: C, 67.58; H, 6.28; N, 5.85.

(*S*)-7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]-3-(trifluoromethyl)phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*S*)-5s) and (*R*)-7-{4-[2-(Butoxy)ethoxy]-phenyl}-*N*-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]-3-(trifluoromethyl)-phenyl}-1-isobutyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide ((*R*)-5s) The racemate **5s** was resolved with HPLC to afford optically pure (*S*)-**5s** and (*R*)-**5s** [column, CHIRAL PAK AD (50 mm×500 mm), column temperature, 25 °C; mobile phase, hexane : EtOH=50 : 50; flow rate 70 ml/min; UV detection, 254 nm, amount injected 210 mg]. Compound (*S*)-**5s**: $[\alpha]_D$=+13.7° (c=0.30, EtOH). *Anal.* Calcd for $C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$: C, 67.40; H, 6.36; N, 5.90. Found: C, 67.31; H, 6.26; N, 5.96. Compound (*R*)-**5s**; $[\alpha]_D$=−13.8° (c=0.26, EtOH). *Anal.* Calcd for $C_{40}H_{44}F_3N_3O_5 \cdot 0.5H_2O$: C, 67.40; H, 6.36; N, 5.90. Found: C, 67.01; H, 6.30; N, 5.87. ^{1}H-NMR data of the chiral compounds were identical with those of **5s**.

X-Ray Crystallographic Analysis Colorless platelet crystals of (*R*)-**13** were obtained from methanol solution. A diffractometer, Rigaku AFC5R, was used with graphite monochromated Cu-Kα radiation to obtain the following crystal data: a=19.293(2), b=20.023(2), c=8.419(3) Å, V=3252(1) Å^3, orthorhombic, $P2_12_12_1$, Z=8. Of the 5612 collected reflections, 2987 were unique (Rint=0.053). Final R-values were $R1$=0.051 and w$R2$(F^2; all data)=0.140. The absolute configuation was determinated using the Flack parameter[19] of −0.06(4). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 230601).

Receptor Binding Assays CHO-K1 and CCR5-expressing CHO cells[10] were incubated with various concentrations of test compound in the binding buffer (Ham's F-12 medium containing 20 mM HEPES and 0.5% bovine serum albumin, pH 7.2) containing 200 pM [^{125}I]RANTES. Binding reactions were performed at room temperature for 40 min. The binding reaction was terminated by washing out the free ligand with cold phosphate-buffered saline, and the cell-associated radioactivity was counted using a TopCount scintillation counter (Packard).

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

Preliminary Pharmacokinetic Analysis Compound (*S*)-**5s** (10 mg/kg) suspended in 0.5% methylcellulose was orally administered to SD (IGS) rats (male, 8 weeks old). Blood samples were collected at different time points (pre, 15, 30 min, 1, 2, 4, 8, 24 h) from the tail vein. Acetonitrile (250 μl) was added to each plasma sample (100 μl), and the precipitated plasma proteins were removed by centrifugation. The compound concentrations in the supernatant were measured by HPLC (column, Inertsil ODS-3, 4.6×150 mm, 5 mm particle size, GL Science; column temperature, 35 °C; mobile phase, acetonitrile–0.01 mol/l ammonium acetate; flow rate, 1.0 ml/min; UV detection, 280 nm).

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