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, phosphate oxide or pyridine N-oxide moieties, as replacements for the previously 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,1,2 it has been found that it can not achieve virus eradication.3 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.4 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.3

The compound 1, which we first reported as a small molecule CCR5 antagonist, exhibited highly potent anti-HIV 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, phosphate 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,
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 8e—m, followed by m-chloroperbenzoic acid (mCPBA) 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 13 gave the corresponding nitro compounds 10a—c 14. The key anilines 8b—d 15 were prepared by catalytic hydrogenation of the nitro compounds 10a—c.

The 4-[hydroxy(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-fluorobenzyl)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-fluorobenzyl)pyridines 16a—e with sodium azide and

![Chart 1](image1)

![Chart 2](image2)

![Chart 3](image3)

![Chart 4](image4)

![Chart 5](image5)
subsequent lithium aluminumhydride (LiAlH₄) 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 with the corresponding anilines 8a, b by the acid chloride method afforded the target phosphonates 5a and phosphine 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, 13b into acid chlorides and subsequent coupling with the anilines 8c—e gave the anilide derivatives 20a—d containing the pyridine moieties. The target pyridine N-oxide derivatives 5c—f were prepared by mCPBA 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, 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 mCPBA 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 (NaBH₄) and subsequent reductive amination of the resulting 26a—i with the appropriate aldehydes. The optically active compounds (S)-5s and (R)-5s were obtained by optical resolution of racemate 5s utilizing chiral HPLC.

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 [¹²⁵I]RANTES and various concentrations of the test compounds. The results are summarized in Tables 1 and 2 as IC₅₀ 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 IC₅₀ 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-
Table 1. Physical Properties and Inhibitory Effects of Compounds 5 on Chemokine Binding to CCR5-Expressing CHO Cells

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Y</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Recrystln solvent</th>
<th>Formula</th>
<th>Anal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td></td>
<td>0.40</td>
<td>87</td>
<td>268–269</td>
<td>EA–ET</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;28&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;P</td>
<td>CHN</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>0.41</td>
<td>59</td>
<td>283–286</td>
<td>ET</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;28&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>CHN</td>
</tr>
<tr>
<td>5e</td>
<td></td>
<td>0.43</td>
<td>51</td>
<td>208–210</td>
<td>ET</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CHN</td>
</tr>
</tbody>
</table>

a) The concentration required to inhibit the binding of [125I]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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>X</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Recrystln solvent</th>
<th>Formula</th>
<th>Anal.</th>
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<tr>
<td>5f</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>430</td>
<td>79</td>
<td>125–128</td>
<td>ET–EA</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CHN</td>
</tr>
<tr>
<td>5m</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>4-Me</td>
<td>32</td>
<td>73</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<tr>
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<td>SO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>180</td>
<td>72</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>H</td>
<td>H</td>
<td>32</td>
<td>91</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>H</td>
<td>H</td>
<td>22</td>
<td>92</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>H</td>
<td>H</td>
<td>24</td>
<td>88</td>
<td>105–107</td>
<td>EA–H</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>H</td>
<td>H</td>
<td>14</td>
<td>87</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>H</td>
<td>H</td>
<td>72</td>
<td>72</td>
<td>114–116</td>
<td>EA–IPE</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CHN</td>
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</table>

a) The concentration required to inhibit the binding of [125I]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.

derivatives. 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<sub>50</sub> values of 0.40 μM and 0.41 μM, respectively. However, the biaryl type pyridine N-oxide derivative 5e 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<sub>max</sub> and AUC<sub>0–24h</sub> 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 and 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 and benzene ring of the anilide moiety. We selected the isobutyl group at the same position was as active as compound (S)-5h. Optically active compound (S)-5h showed highly potent inhibitory activity, on the HIV-1 Env-mediated inhibitory activity. Capitalizing on this finding, we investigated introduction of substituents on the pyridine ring and benzene ring into the 1-propyl-1-benzazepine (S)-5g, the 1-propyl-1-benzazepine (S)-5g enhanced the activity about 11 times.

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 Cmax and AUC 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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R1</th>
<th>R2</th>
<th>IC50 (nM)</th>
<th>Fusion</th>
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<tr>
<td>5m</td>
<td>i-Bu</td>
<td>Me</td>
<td>32</td>
<td>170</td>
</tr>
<tr>
<td>5p</td>
<td>i-Bu</td>
<td>Me</td>
<td>32</td>
<td>610</td>
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<td>5q</td>
<td>i-Bu</td>
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</tr>
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<td>i-Bu</td>
<td>Cl</td>
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<tr>
<td>5s</td>
<td>i-Bu</td>
<td>CF3</td>
<td>7.2</td>
<td>5.4</td>
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Table 4. Pharmacokinetic Parameters of Compound (S)-5s in Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>10</td>
</tr>
<tr>
<td>Cmax (μg/ml)</td>
<td>2.33</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>4.00</td>
</tr>
<tr>
<td>AUC0–24h (μg·h/ml)</td>
<td>33.1</td>
</tr>
</tbody>
</table>

Conclusion

In order to develop orally active CCR5 antagonists, a search for polar substituents, such as phosphonate, phosphate 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...
**Experimental**

Melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. Proton nuclear magnetic resonance (1H-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). Spectra were recorded with a Varian DI-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 silica gel column (Kieselgel 60, 63—200 mesh, Merck). Yields were not optimized.

**1-(4-Aminobenzyl)imidazol-1-yl)aniline (8b)** This compound was prepared in 85% yield from 10c by a method similar to that described for 8a. Yellow oil. 1H-NMR (CDCl3): 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-monomesuccinimide (NMS) (31.8 g, 179 mmol) and 2,2'-azobis(isobutyronitrile) (ABN) (ca. 30 mol%) in EtOAc (400 ml) 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 solution of the oil in MeOH (300 ml) was added NaOAc (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 MgSO4, and concentrated in vacuo. The residue was purified by column chromatography (hexane:EtOAc=10:1) to give 1.38 g (5%) of 11b as colorless crystals. Compound 11b was used in the next reaction without further purification. 1H-NMR (CDCl3): 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 compound was prepared in 85% yield from 2-methoxy-4-nitroaniline by a method similar to that described for 11b; colorless crystals (EtOAc–hexane), mp 119—121 °C. 1H-NMR (CDCl3): δ: 4.06 (3H, s), 7.86—7.91 (2H, m), 8.00 (1H, d, J=8.8 Hz), 10.53 (1H, s). Anal. Calc. for C7H6NO3: C, 53.16; H, 3.81; N, 7.54. Found: C, 53.16; H, 3.81; N, 7.54.

2-Chloro-4-nitrobenzaldehyde (11d) To a suspension of NaBH4 (10.7 g, 283 mmol) in 1,2-dimethoxyethane (150 ml) was added 2-chloro-4-nitrobenzaldehyde (25.9 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 MgSO4, and concentrated in vacuo. A mixture of the residue (17.0 g and activated MnO2 (50.0 g) in acetone (200 ml) was stirred under stirring at night room temperature. MnO2 was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexane:EtOAc=1:1) to give 12.1 g (58% yield) of 11d as colorless crystals. Compound 11d was used in the next reaction without further purification. 1H-NMR (CDCl3): 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-bromo-4-nitrobenzaldehyde (11c) and sodium hydroxide (5 mol%) in methanol (100 ml) was added 2-(2-chloro-4-nitrophenyl)ethanol (15.9 g, 78.7 mmol) in 45% yield from 2-methoxy-4-nitroaniline by a method similar to that described for 11b; colorless crystals (EtOAc–hexane), mp 119—121 °C. 1H-NMR (CDCl3): δ: 4.06 (3H, s), 7.86—7.91 (2H, m), 8.00 (1H, d, J=8.8 Hz), 10.53 (1H, s). Anal. Calc. for C12H12N2O3: C, 56.92; H, 4.71; N, 13.08. Found: C, 56.92; H, 4.76; N, 13.04.

(2-Amino-4-nitrophenyl)phosphinic acid (2d) 2.45 g (4.0 mol) of 2d was added to a solution of 2-(2-chloro-4-nitrophenyl)ethanol (15.9 g, 78.7 mmol) in 45% yield from 2-methoxy-4-nitroaniline by a method similar to that described for 11b; colorless crystals (EtOAc–hexane), mp 119—121 °C. 1H-NMR (CDCl3): 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). Anal. Calc. for C13H14N2O3: C, 56.92; H, 4.76; N, 13.04. Found: C, 56.92; H, 4.76; N, 13.04.
pale yellow crystals (EtOAc–hexane), mp 126—129 °C (dec.). 1H-NMR (CDCl3): 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), 8.74 (1H, dd, J = 8.4, 1.8 Hz), 8.56 (1H, d, J = 5.2 Hz). Anal. Calcld for C12H12N2O: C, 71.98; H, 6.04; N, 13.99. Found: C, 70.98; H, 6.04; N, 13.98.

(2-Chloro-4-nitrophenyl)(pyridin-2-yl)methanol (12d) Yield 30%, yellow crystals (EtOAc–hexane), mp 124—127 °C. 1H-NMR (CDCl3): 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. Calcld for C13H11NO: C, 54.66; 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—e 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. 1H-NMR (CDCl3): δ 3.65 (3H, bs), 5.14 (1H, br), 5.65 (1H, s), 6.55 (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. Calcld for C10H11NO: C, 71.39; 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 85%, colorless crystals, mp 102—104 °C. 1H-NMR (CDCl3): 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 (2H, m), 7.60 (1H, d, J = 7.7, 1.4 Hz), 8.57 (1H, d, J = 5.2 Hz). Anal. Calcld for C14H14NO: C, 60.09; H, 4.58; N, 10.60. Found: C, 60.09; H, 4.58; N, 10.60.

(4-Amino-2-methoxyphenyl)(pyridin-2-yl)methanol (8k) Yield 95%, yellow crystals (EtOAc–hexane), mp 123—125 °C (dec.). 1H-NMR (CDCl3): 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, d, J = 7.7, 1.8 Hz), 8.54 (1H, d, J = 4.4 Hz). Anal. Calcld for C13H12NO: 0.1H2O: 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 (80) To a solution of 12d (1.00 g, 4.05 mmol) in THF (15 ml), EtOH (15 ml) and water (15 ml) was added Na2S2O3 (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, dried over MgSO4, and concentrated in vacuo. The residue was purified by column chromatography (hexane: EtOAc=3:1) to give 4.19 g 15a as a brown oil. 1H-NMR (CDCl3): δ 7.27—7.30 (2H, m), 7.39—7.46 (2H, m), 8.44 (1H, d, J = 5.0 Hz).

(4-Fluorophenyl)(4-methylpyridin-2-yl)acetanilide (15b) Yield 65%, brown oil. 1H-NMR (CDCl3): 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)acetanilide (15c) Yield 83%, yellow oil. 1H-NMR (CDCl3): 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).

(4-Fluorobenzo[y]3-methylpyridine (16a) A solution of 15a (5.14 g, 22.7 mmol) and K2CO3 (2.90 g, 21.0 mmol) in dimethylsulfoxide (DMSO) (250 ml) and water (50 ml) was stirred at room temperature for 6 h under an oxygen atmosphere. The reaction mixture was poured into water and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over MgSO4, and concentrated in vacuo.

(4-Fluorophenyl)(4-methylpyridin-2-yl)acetanilide (15b) Yield 65%, brown oil. 1H-NMR (CDCl3): δ 2.36 (3H, s), 5.26 (1H, s), 7.02—7.11 (3H, 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).
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 EtO. The organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. A solution of the residue (3.90 g) in THF (40 ml) was added dropwise to a suspension of LiAlH₄ (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 water (excessively water (1.24 ml), 15% aqueous NaOH (1.24 ml), and water (1.24 ml) under ice cooling. After being stirred at room temperature for 16 h, MgSO₄ was added to the mixture and the solid was removed by filtra.

The filtrate was concentrated in vacuo and the residue was purified by recrystallization from EtOAc to give 2.60 g (65%) of 5b.

[4-Amino(4)-methylpyridin-2-yl)methanol (8g) Yield 70%, pale yellow crystals, mp 153—154 °C. 1H-NMR (CDCl₃) 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, d, J = 7.8, 4.8 Hz), 7.41—7.45 (1H, m), 8.45—8.47 (1H, m). Anal. Calc. for C₁₃H₁₁F₃N₂O: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.17; H, 4.2; N, 10.33.

[4-Amino(6)-methylpyridin-2-yl)methanol (8b) Yield 72%, pale yellow crystals (EtOAc), mp 165—166 °C. 1H-NMR (CDCl₃) 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, d, J = 7.8, 6.6 Hz). Anal. Calc. for C₁₃H₁₄N₂O: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.64; H, 6.18; N, 12.87.

[4-Amino-2-(trifluoromethyl)phenyl]pyridin-2-yl)methanol (8m) Yield 86%, colorless crystals (EtOAc-hexane), mp 163—164 °C. 1H-NMR (CDCl₃) 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), 15.88 (1H, d, J = 5.2 Hz). Anal. Calc. for C₁₃H₁₄F₃N₂O: C, 78.21; H, 4.13; N, 10.44. Found: C, 78.17; H, 4.12; N, 10.33.

[7-(4-Methylphenyl)-2-(trifluoromethyl)phenyl]-(pyridin-2-yl)methanol (8n) Yield 72%, colorless crystals (EtOAc), mp 173—174 °C. 1H-NMR (CDCl₃) δ: 2.40 (3H, s), 3.06 (2H, t, J = 8.4 Hz), 3.09 (2H, t, J = 8.4 Hz). Anal. Calc. for C₁₃H₁₄F₃N₂O: C, 68.55; H, 5.75; N, 10.22. Found: C, 68.60; H, 5.89; N, 10.44.

[7-(4-Methylphenyl)-2-(trifluoromethyl)phenyl]-(pyridin-2-yl)methanol (8o) Yield 82%, colorless crystals (EtOAc), mp 177—178 °C. 1H-NMR (CDCl₃) δ: 2.39 (3H, s), 3.06 (2H, t, J = 8.4 Hz), 3.09 (2H, t, J = 8.4 Hz). Anal. Calc. for C₁₃H₁₄F₃N₂O: C, 68.53; H, 5.75; N, 10.22. Found: C, 68.60; H, 5.89; N, 10.44.

[7-(4-Methylphenyl)-2-(trifluoromethyl)phenyl]-(pyridin-2-yl)methanol (8p) Yield 84%, colorless crystals (EtOAc), mp 176—177 °C. 1H-NMR (CDCl₃) δ: 2.41 (3H, s), 3.06 (2H, t, J = 8.4 Hz). Anal. Calc. for C₁₃H₁₄F₃N₂O: C, 68.61; H, 5.89; N, 10.44. Found: C, 68.60; H, 5.89; N, 10.43.
hydro-1-benzazepine-4-carboxamide (5e) [H-NMR (CDCl3)] 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. Calc. for C_{23}H_{24}F_3N_3O_5: C, 67.74; H, 5.69; N, 6.24. Found: C, 67.69; H, 5.60; N, 6.32.

The following compounds (24a—i) were prepared from 23 and the corresponding dihydro derivatives 8a—h in a method similar to that described for 24a.

7-[4-(Butoxy)ethoxy]phenyl]-N-[4-(hydroxyl-1-oxaziridin-2-yl)methylphenyl]-1-trifuoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (24d) Yield 54%, colorless amorphous. [H-NMR (CDCl3)] δ: 0.93 (3H, t, J = 7.1 Hz), 1.29—1.48 (2H, m), 1.51—1.66 (2H, m), 2.86—3.27 (3H, m), 3.56 (2H, t, J = 6.6 Hz), 3.83 (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. Calc. for C_{23}H_{24}F_3N_3O_5: 0.25H_2O, C, 66.91; H, 5.54; N, 6.33. Found: C, 66.93; H, 5.60; N, 6.32.

7-[4-(Butoxy)ethoxy]phenyl]-N-[4-(hydroxyl-1-oxaziridin-2-yl)methylphenyl]-1-trifuoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (24e) Yield 72%, colorless crystals (EtOAc–hexane), mp 122—125 °C. [H-NMR (CDCl3)] δ: 0.93 (3H, t, J = 7.1 Hz), 1.29—1.48 (2H, m), 1.51—1.66 (2H, m), 2.86—3.26 (3H, m), 3.56 (2H, t, J = 6.6 Hz), 3.83 (2H, t, J = 4.9 Hz), 4.18 (2H, t, J = 4.9 Hz), 4.74—4.89 (1H, m), 5.34—5.46 (2H, m), 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), 9.07—9.14 (1H, m). Anal. Calc. for C_{23}H_{24}F_3N_3O_5: 0.25H_2O, C, 66.91; H, 5.54; N, 6.33. Found: C, 66.93; H, 5.60; N, 6.32.

7-[4-(Butoxy)ethoxy]phenyl]-N-[4-(hydroxyl-1-oxaziridin-2-yl)methylphenyl]-1-trifuoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (24f) Yield 78%, colorless amorphous (EtOAc–hexane), mp 123—125 °C. [H-NMR (CDCl3)] δ: 0.93 (3H, t, J = 7.2 Hz), 1.26—1.65 (4H, m), 2.93—3.31 (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 (7H, m), 8.58 (1H, d, J = 5.2 Hz). Anal. Calc. for C_{23}H_{24}F_3N_3O_5: C, 67.74; H, 5.69; N, 6.20. Found: C, 67.75; H, 5.55; N, 6.15.

7-[4-(Butoxy)ethoxy]phenyl]-N-[4-(hydroxyl-1-oxaziridin-2-yl)methylphenyl]-1-trifuoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (24g) Yield 78%, colorless amorphous (EtOAc–hexane), mp 123—125 °C. [H-NMR (CDCl3)] δ: 0.93 (3H, t, J = 7.2 Hz), 1.26—1.65 (4H, m), 2.93—3.31 (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 (7H, m), 8.58 (1H, d, J = 5.2 Hz). Anal. Calc. for C_{23}H_{24}F_3N_3O_5: C, 67.74; H, 5.69; N, 6.20. Found: C, 67.75; H, 5.55; N, 6.15.
3-(trifluoromethyl)phenyl)-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (24b) Yield 97%, colorless crystals. Anal. Calcd for C38H38F3N3O7 · 0.5H2O: C, 63.86; H, 5.50; N, 5.88. Found: C, 63.5; H, 5.6; N, 5.93. The following compounds (25a—i) were prepared from 24a—i by a method similar to that described for 25c.

(5)-7-[(2-Butoxyethoxy)phenyl]-4-(hydroxy-1-oxidopyridin-2-yl)methyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25a) Yield 52%, colorless crystals. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.7; H, 5.6; N, 5.75.

7-[(2-Butoxyethoxy)phenyl]-4-(hydroxy-1-oxidopyridin-2-yl)methyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25b) Yield 79%, colorless crystals. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.7; H, 5.6; N, 5.75.

7-[(2-Butoxyethoxy)phenyl]-4-(hydroxy-1-oxidopyridin-2-yl)methyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25c) Yield 84%, colorless crystals. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 64.0; H, 5.3; N, 5.79.

7-[(2-Butoxyethoxy)phenyl]-N-(7-{4-[2-(Butoxy)ethoxy]phenyl}methyl)phenyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25d) Yield 84%, colorless crystals (EtOAc). Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 64.0; H, 5.3; N, 5.79.

7-[(2-Butoxyethoxy)phenyl]-N-(7-{4-[2-(Butoxy)ethoxy]phenyl}methyl)phenyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25e) Yield 84%, colorless crystals (EtOAc). Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 64.0; H, 5.3; N, 5.79.

7-[(2-Butoxyethoxy)phenyl]-N-[4-(hydroxy-1-oxidopyridin-2-yl)methyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25f) Yield 94%, colorless crystals. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.6; H, 5.6; N, 5.75.

7-[(2-Butoxyethoxy)phenyl]-N-[4-(hydroxy-1-oxidopyridin-2-yl)methyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25g) Yield 79%, colorless amorphous. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 64.0; H, 5.3; N, 5.79.

7-[(2-Butoxyethoxy)phenyl]-N-[3-chloro-4-(hydroxy-1-oxidopyridin-2-yl)methyl]phenyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25h) Yield 56%, pale red oil. Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.6; H, 5.6; N, 5.75.

7-[(2-Butoxyethoxy)phenyl]-N-[4-(hydroxy-1-oxidopyridin-2-yl)methyl]-4-(3-trifluoromethyl)phenyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25i) Yield 79%, colorless crystals (EtOAc). Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.6; H, 5.6; N, 5.75.

7-[(2-Butoxyethoxy)phenyl]-N-[4-(hydroxy-1-oxidopyridin-2-yl)methyl]-4-(3-trifluoromethyl)phenyl]-1-trifluoroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (25j) Yield 79%, colorless crystals (EtOAc). Anal. Calcd for C38H38F3N3O6 · 0.25H2O: C, 65.74; H, 5.59; N, 6.05. Found: C, 65.6; H, 5.6; N, 5.75.
Yield 97%, yellow crystals (EtOAc·0.5PrO), mp 175—177°C. 1H-NMR (CDCl3): δ = 6.93 (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), 2.9 (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), 1.40—1.46 (2H, m), 3.80 (2H, t, J = 5.0 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.07 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 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 C37H37N3O6 · 0.5H2O: C, 71.72; H, 6.65; N, 6.97.

Found: C, 71.75; H, 6.65; N, 6.81.

7-(4-[Butyl]oxy)phenyl)-N-[4-(hydroxy-1-oxidopyridin-2-yl)-methyl]-3-methylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (26d) Yield 97%, yellow crystals (EtOAc), mp 178—182°C (dec.). 1H-
NMR (CDCl3): δ = 0.93 (3H, t, J = 7.1 Hz), 1.26—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, 2.72 (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), 8.50 (1H, d, J = 1.0, 5.8 Hz). Anal. Calcd for C37H37N3O6 · 0.5H2O: C, 71.74; H, 6.69; N, 6.97.

Found: C, 71.75; H, 6.65; N, 6.81.

7-(4-[Butyl]oxy)phenyl)-N-[3-chloro-4-(hydroxy-1-oxidopyridin-2-yl)-methyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (26b) Yield quant., yellow amorphous. 1H-NMR (CDCl3): 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, m), 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 (8H, m), 8.26 (1H, br, 7.61 (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 C37H37N3O6 · 0.5H2O: C, 71.74; H, 6.69; N, 6.65. Found: C, 71.64; H, 6.08; N, 6.10.

(S)-7-(4-[Butyl]oxy)phenyl)-N-[4-(hydroxy-1-oxidopyridin-2-yl) methyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (5a) Yield 71%, yellow crystals (EtOAc·1PrO). 1H-NMR (CDCl3): δ = 0.97 (3H, t, J = 7.3 Hz), 1.80—2.20 (3H, m), 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), 7.21—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 C37H37N3O6 · 0.5H2O: C, 72.36; H, 7.03; N, 6.66. Found: C, 72.07; H, 7.01; N, 6.51.

The following compounds (S)-5k—k, S—S were prepared from 26a—i and corresponding aldehydes by a method similar to that described for (S)-5g.
6.99 (3H, m), 7.16—7.30 (2H, m), 7.37—7.60 (7H, m), 7.72 (1H, s), 8.30 (1H, s). Anal. Calcd For C_{40}H_{44}O_{7}N_{3}: C, 72.96; H, 7.34; N, 5.81. Found: C, 71.20; H, 7.34; N, 5.85.

7-([2-(Butyloxy)ethyl]phenyl)-N-[4-(hydroxy-1-oxopyridin-2-yl)-methyl]-3-methoxyphenyl]-1-isobutyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (5q) 1H-NMR (CDCl3): 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 = 4.6 Hz), 6.33 (1H, d, J = 4.8 Hz), 6.69 (1H, d, J = 6.6 Hz), 7.00—7.30 (1H, m), 3.75—4.00 (5H, m), 7.16—7.26 (1H, m), 7.40—7.52 (6H, m), 7.63—7.68 (2H, m), 7.77 (1H, s). Anal. Calcd For C_{40}H_{44}F_{3}N_{3}O_{5} · 0.5H_{2}O: C, 67.40; H, 6.36; N, 5.89. Found: C, 67.58; H, 6.72; N, 6.27.

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Reference


7-([2-(Butyloxy)ethyl]phenyl)-N-[4-(hydroxy-1-oxopyridin-2-yl)-methyl]-3-(3-fluorophenyl)-1-isobutyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (5s) 1H-NMR (CDCl3): δ = 0.85—0.99 (9H, m), 1.26—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 = 4.6 Hz), 3.75—4.00 (5H, m), 7.16—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_{44}N_{3}O_{5} · 0.5H_{2}O: C, 71.67; H, 7.14; N, 6.27. Found: C, 71.51; H, 7.24; N, 6.17.

Receptor Binding Assays CHO-K1 and CCR5-expressing CHO cells 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 µl/10^6 IUNATES. 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 µM penicillin, and 100 µg/ml streptomycin. MOLT-4/CCR5/Luc cells were seeded in a 96-well plate at 10^4 cells 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 µM penicillin, and 100 µg/ml streptomycin was used as medium for membrane fusion. After an overnight incubation,Luc-Scan (Tripos) 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 ARVOx).