

# Diamine Derivatives Containing Imidazolidinylidene Propanedinitrile as a New Class of Histamine H<sub>3</sub> Receptor Antagonists: Conformationally Restricted Derivatives

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**Novel conformationally restricted diamine derivatives containing imidazolidinylidene propanedinitrile were synthesized and evaluated for human and rat histamine H<sub>3</sub> receptor (H<sub>3</sub>R) binding affinities. Among them, compounds 2b, 2c, 2j, 2k and 2m were found to be potent ligands for both H<sub>3</sub>R with K<sub>i</sub> values in the sub-nanomolar range, and showed potent H<sub>3</sub> receptor antagonism.**

**Key words** histamine H<sub>3</sub> receptor; antagonist; imidazolidinylidene propanedinitrile; diamine

In the central nerve system, the histamine H<sub>3</sub> receptor (H<sub>3</sub>R) is thought to control the release of a various neurotransmitters such as histamine, serotonin, dopamine and acetylcholine. H<sub>3</sub>R antagonists induce release of these neurotransmitters, and in animal models they have been shown to enhance attention and cognition, and influence feeding. Therefore, they may be useful in treatment of, for example, attention-deficit disorder, Alzheimer's disease, schizophrenia and obesity.<sup>2–8)</sup>

Recently, we reported novel diamine derivatives containing an imidazolidinylidene propanedinitrile moiety as potent H<sub>3</sub>R antagonists.<sup>9)</sup> For example, compound **1** showed good affinities both for human and rat H<sub>3</sub>R (K<sub>i</sub>=2.4 nM and 2.6 nM, respectively) with excellent selectivity for human H<sub>1</sub>, H<sub>2</sub> and H<sub>4</sub> receptors. Furthermore, a functional assay established that compound **1** was a rat neuronal H<sub>3</sub>R antagonist. In 2005, researchers from Johnson & Johnson identified a series of conformationally restricted JNJ-5207852 derivatives as potent H<sub>3</sub>R antagonists. For example, JNJ-7737782 represented pK<sub>i</sub> of 9.32 (0.48 nM) and 8.67 (2.14 nM) for human and rat H<sub>3</sub>R, respectively, and showed wake-promoting activity.<sup>10)</sup> These observations motivated us to design a novel diamine series **2** in which a 1-alkylated-4-piperidinyl moiety was introduced as a conformationally restricted linker in the imidazolidinylidene propanedinitrile core in place of the aminopropyl chain of compound **1**. Analogs were prepared with various alkyl substituents (R), linker lengths (*m*=2, 3; *n*=0, 1) and amines (Fig. 1).

Syntheses of compounds **2a—m** are shown in Charts 1—5. First, in order to examine the effect of substituent R of the 4-piperidinyl part on human and rat H<sub>3</sub>R affinities, com-

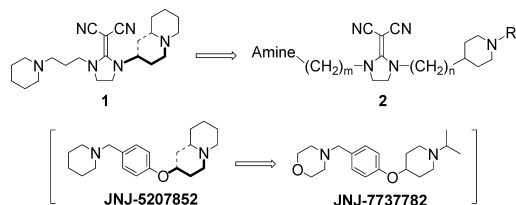
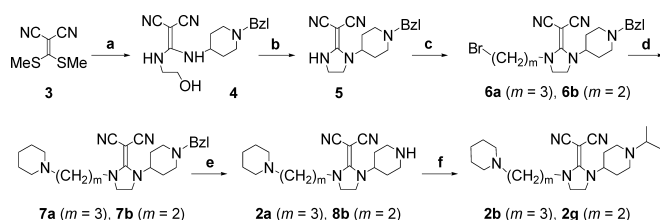


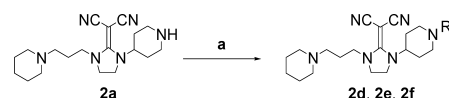
Fig. 1. Design of Conformationally Restricted Diamine-Based Novel Histamine H<sub>3</sub> Receptor Antagonists **2** with Imidazolidinylidene Propanedinitrile Moiety

pounds **2a—f** having a piperidinopropyl moiety were prepared (*i.e.* Amine=piperidino, *m*=3, *n*=0). As shown in Chart 1, commercially available [bis(methylthio)methyl]malononitrile **3** and 4-amino-1-benzylpiperidine were re-



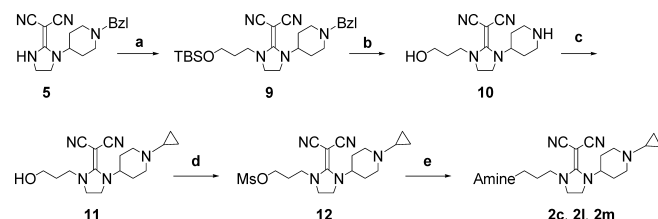
Reagents and conditions: (a) 4-amino-1-benzylpiperidine, THF, room temperature, 19 h, then 2-aminoethanol, reflux, 10 h, 58% (2 steps); (b) MsCl, TEA, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 69 h, 40%; (c) 1,3-dibromopropane, 71% (**6a**) or 1,2-dibromoethane, 59% (**6b**), K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature; (d) piperidine, KI, 1,4-dioxane, 51% (**7a**) or 72% (**7b**); (e) 1-chloroethyl chloroformate, 1,2-dichloroethane, reflux, then MeOH, reflux, 85% (**2a**); (f) acetone, Na(OAc)<sub>2</sub>BH, THF, room temperature, 44 h, 37% (**2b**), 2-iodopropane, K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature, 111 h, 14% (**2g** from **7b**, 2 steps).

Chart 1



Reagents and conditions: (a) 1-bromo-2-fluoroethane, K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature, 64 h, 19% (**2d**), 2,2,2-trifluoroethyl trifluoromethanesulfonate,<sup>11)</sup> K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature, 6 h, 50% (**2e**), 1-iodoacetonitrile, K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature, 64 h, 17% (**2f**).

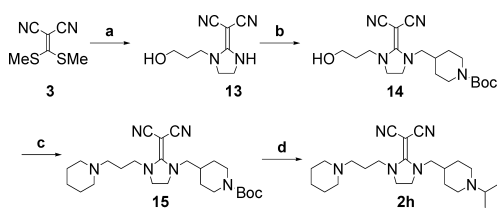
Chart 2



Reagents and conditions: (a) (3-bromopropoxy)-*tert*-butylidimethylsilyl, K<sub>2</sub>CO<sub>3</sub>, DMF, 50 °C, 20 h, 90%; (b) 1-chloroethyl chloroformate, 1,2-dichloroethane, reflux, 1 h, then MeOH, reflux, 1 h, 93%; (c) (1-ethoxycyclopropoxy)trimethylsilyl, NaBH<sub>3</sub>CN, TEA, AcOH, THF, 60 °C, 3 h, 70%; (d) MsCl, TEA, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 2 h, 83%; (e) corresponding amine, K<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane, 80 °C, 12–24 h, 83% (**2c**), 59% (**2l**), 29% (**2m**).

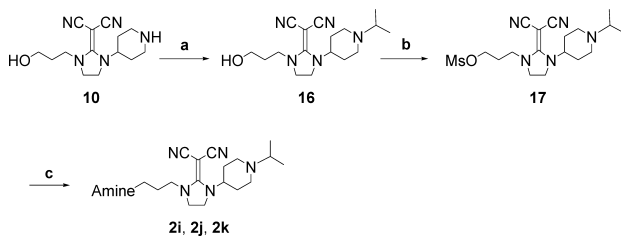
Chart 3

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Reagents and conditions: (a) *N*-(3-hydroxypropyl)ethylenediamine, THF, room temperature, 3 h, 82%; (b) 1-*tert*-butoxycarbonyl-4-methanesulfonyloxymethylpiperidine,<sup>12</sup> K<sub>2</sub>CO<sub>3</sub>, DMF, 80–100 °C, 46 h, 50%; (c) MsCl, TEA, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 5 h, 97%, then piperidine, KI, 1,4-dioxane, 80 °C, 2.5 h, 64%; (d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 0.5 h, then 2-iodopropane, K<sub>2</sub>CO<sub>3</sub>, DMF, 50 °C, 5 h, 20% (2 steps).

Chart 4



Reagents and conditions: (a) 2-iodopropane, K<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 23 h, 30%; (b) MsCl, TEA, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 1.5 h, 55%; (c) corresponding amine, K<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane, 80 °C, 12–24 h, 77% (2i), 58% (2j), 49% (2k).

Chart 5

acted in THF at room temperature and the resulting mixture refluxed with 2-aminoethanol to yield alcohol 4. Mesylation of primary hydroxyl group of compound 4 and the resulting mesylate was stirred at ambient temperature to give imidazolidinylidene propanedinitrile 5 by spontaneous intramolecular cyclization. Compound 5 was then treated with 1,3-dibromopropane and introduction of piperidine to the bromide 6a yielded compound 7a. The benzyl group of compound 7a was removed to yield compound 2a (R=H) in 85% yield. Reductive alkylation of compound 2a with acetone in presence of Na(OAc)<sub>3</sub>BH gave compound 2b (R=*iso*-Pr). Furthermore, as illustrated in Chart 2, compound 2a was treated with corresponding electrophiles and K<sub>2</sub>CO<sub>3</sub> in DMF to provide compounds 2d, 2e<sup>11</sup>) and 2f. The cyclopropyl containing compound 2c was synthesized as depicted in Chart 3. Compound 5 was reacted with (3-bromopropoxy)-*tert*-butyldimethylsilane to give compound 9 in 90% yield. Simultaneous debenylation and desilylation of compound 9 afforded amino alcohol 10 in 93% yield. Then, cyclopropylation of compound 10 by use of (1-ethoxycyclopropoxyl)trimethylsilane under reductive alkylation condition gave compound 11 in 70% yield. Finally, alcohol 11 was mesylated and the resulting mesylate 12 heated with excess piperidine in 1,4-dioxane to give target molecule 2c with a yield of 83%.

In order to examine the effect of the distance between two basic nitrogen atoms on human and rat H<sub>3</sub>R affinities, compounds 2g (Chart 1: *m*=2, *n*=0) and 2h (Chart 4: *m*=3, *n*=1) were synthesized. As shown in Chart 1, compound 2g was obtained by a method similar to that of preparation of compound 2b. Namely, 1,2-dibromoethane was used instead of 1,3-dibromopropane in step c to give compound 6b in 59% yield. Then, compound 6b was transformed to target compound 2g by addition of piperidine, debenylation and *iso*-propylation. On the other hand, compound 2h was synthesized as follows. Compound 13,<sup>9</sup>) obtained from malono-

nitrile 5 and *N*-(3-hydroxypropyl)ethylenediamine, was reacted with 1-*tert*-butoxycarbonyl-4-methanesulfonyloxymethylpiperidine<sup>12</sup>) to give compound 14 with a yield of 50%. Mesylation of compound 14, and then introduction of piperidine to the mesylate afforded compound 15. Finally, the Boc protecting group was removed by TFA and the resulting amine treated with 2-iodopropane to yield compound 2h (Chart 4).

Modification of the piperidino moiety of compound 2b or 2c was performed as illustrated in Charts 3 and 5. By virtue of the use of an intermediate 12 or 17, three kinds of amines were effectively introduced in the last step to yield compounds 2i–m.

The binding assay results for compounds 2a–m in human and rat H<sub>3</sub>Rs are shown in Table 1. The effects of the alkyl group R modification were analyzed first. Although compound 2a (R=H) exhibited negligible affinities, introduction of *iso*-propyl (2b) and *cyclo*-propyl (2c) substituents at the *N*-1 position of a 4-piperidinyl moiety in compound 2a caused an increase in affinities for both H<sub>3</sub>Rs. For example, compound 2b showed six-fold and nine-fold affinity to human and rat H<sub>3</sub>Rs (*K*<sub>i</sub>=0.37 nM and 0.28 nM, respectively) than those of parent compound 1. Furthermore, compound 2b showed excellent selectivity over human H<sub>1</sub>, H<sub>2</sub> and H<sub>4</sub> receptors (percent inhibition of hH<sub>1</sub>R, hH<sub>2</sub>R, hH<sub>4</sub>R at 10 μM; 20%, –12%, –4%). Compound 2c also showed high affinities to both H<sub>3</sub>Rs (*K*<sub>i</sub>=0.20 nM for human and 0.23 nM for rat, respectively). In contrast to 2b and 2c, compounds 2d–f, having alkyl substituents with electron withdrawing characteristics, exhibited low affinities for human and rat H<sub>3</sub>Rs.

Modification of linker length (*i.e.* compounds 2g, 2h) caused decrease in affinity for both human and rat H<sub>3</sub>Rs. These results indicate that the distance between two basic nitrogen atoms is important for high affinities to both H<sub>3</sub>Rs.

With regard to modification of the variable amine moiety (Table 1), compounds 2j, 2k and 2m, in which the piperidine moiety was replaced with thiomorpholine or 4-oxopiperidine, retained good affinities for human and rat H<sub>3</sub>Rs with *K*<sub>i</sub> values roughly equal to those of their parent compounds 2b and 2c. Conversely, compounds 2i and 2l possessing morpholine had less affinity for both H<sub>3</sub>Rs than 2b or 2c.

Compounds 2b, 2c, 2d, 2i, 2j, 2k, 2l and 2m were selected for a functional assay.<sup>13</sup>) Among them, compounds 2b and 2c reversed NAMH-mediated inhibition of [<sup>3</sup>H]-histamine release from rat forebrain synaptosomes with IC<sub>50</sub> values of 10.2 nM and 11.6 nM, respectively (Table 1). Therefore, these compounds were found to be twice as potent as antagonists of rat neuronal H<sub>3</sub>R than compound 1. Somehow, there is a poor correlation between *K*<sub>i</sub> values and IC<sub>50</sub> values. Although the reason is not clear, remarkable differences between thioperamide (known as an inverse agonist) and proxyfan (known as a neutral antagonist) in these assays were found as shown in Table 1. In the functional assay, thioperamide and proxyfan showed IC<sub>50</sub> values of 54.1 nM and 3397 nM, respectively, in spite of their similar affinities for rat H<sub>3</sub>Rs (*K*<sub>i</sub>; 5.14 nM, 3.95 nM, respectively). These results have led to speculation that the potency of inverse agonistic activity might affect the reverse activity toward NAMH-mediated inhibition of [<sup>3</sup>H]-histamine release. Further study of characterization of compounds 2 and this speculation are necessary.

In conclusion, we have developed a new series of imidazo-

Table 1. Human and Rat H<sub>3</sub>R Binding Affinities and H<sub>3</sub>R Antagonistic Activities of Compounds 2a—m

Compound	Amine	R	Linker <i>m, n</i>	<i>K<sub>i</sub></i> (nM)		Synaptosome <sup>b)</sup>
				hH <sub>3</sub> <sup>a)</sup>	rH <sub>3</sub> <sup>a)</sup>	IC <sub>50</sub> (nM)
JNJ-7737782				0.48 <sup>c)</sup>	2.14 <sup>c)</sup>	<sup>d)</sup>
Thioperamide				43.1	5.14	54.1 ± 13.1 <sup>f)</sup>
Proxofan				9.14	3.95	3397 ± 713 <sup>f)</sup>
<b>1</b>				2.4 (78/98) <sup>e)</sup>	2.6 (88/96) <sup>e)</sup>	27.9 ± 4.2 <sup>f)</sup>
<b>2a</b>	Piperidino	H	3, 0	(-8/50) <sup>e)</sup>	(32/50) <sup>e)</sup>	<sup>d)</sup>
<b>2b</b>	Piperidino	<i>iso</i> -Pr	3, 0	0.37	0.28	10.2 ± 2.9 <sup>f)</sup>
<b>2c</b>	Piperidino	<i>cyclo</i> -Pr	3, 0	0.20	0.23	11.6 ± 1.8 <sup>f)</sup>
<b>2d</b>	Piperidino	CH <sub>2</sub> CH <sub>2</sub> F	3, 0	1.48	1.55	63.8 ± 28.3 <sup>f)</sup>
<b>2e</b>	Piperidino	CH <sub>2</sub> CF <sub>3</sub>	3, 0	(42/66) <sup>e)</sup>	(40/76) <sup>e)</sup>	<sup>d)</sup>
<b>2f</b>	Piperidino	CH <sub>2</sub> CN	3, 0	(18/67) <sup>e)</sup>	(40/86) <sup>e)</sup>	<sup>d)</sup>
<b>2g</b>	Piperidino	<i>iso</i> -Pr	2, 0	(72/96) <sup>e)</sup>	(54/88) <sup>e)</sup>	<sup>d)</sup>
<b>2h</b>	Piperidino	<i>iso</i> -Pr	3, 1	(60/87) <sup>e)</sup>	(70/96) <sup>e)</sup>	<sup>d)</sup>
<b>2i</b>	Morpholino	<i>iso</i> -Pr	3, 0	2.58	2.81	23.8 ± 8.4 <sup>f)</sup>
<b>2j</b>	Thiomorpholino	<i>iso</i> -Pr	3, 0	0.33	0.22	16.9 ± 1.2 <sup>f)</sup>
<b>2k</b>	4-Oxopiperidino	<i>iso</i> -Pr	3, 0	0.51	0.48	18.5 ± 1.1 <sup>f)</sup>
<b>2l</b>	Morpholino	<i>cyclo</i> -Pr	3, 0	1.6	2.3	80.8 ± 14.2 <sup>f)</sup>
<b>2m</b>	Thiomorpholino	<i>cyclo</i> -Pr	3, 0	0.38	0.37	26.7 <sup>g)</sup>

a) Binding potencies were assessed by displacement of [<sup>3</sup>H]-N<sup>α</sup>-methylhistamine (NAMH). The human H<sub>3</sub> values were from cloned human H<sub>3</sub>R expressed in COS-7 cells, while rat H<sub>3</sub>R values were from rat striatal membranes. b) H<sub>3</sub>R antagonism was assessed by reverse effect on NAMH-mediated inhibition of [<sup>3</sup>H]-histamine release from rat fore-brain synaptosomes. c) Data from ref. 10. d) Not tested. e) Percent inhibition at 0.1 μM/1 μM. f) Values with standard error of the mean (SEM): *n* = 3 or 4. g) *n* = 1.

lidinylidene propanedinitrile based novel H<sub>3</sub>R ligands possessing a 1-alkylated-4-piperidinyl moiety as a conformationally restricted linker. This shows potent affinity to both human and rat H<sub>3</sub>Rs, some of which are proven potent antagonists at H<sub>3</sub>Rs in rat cortical synaptosomes. Further structural modification and pharmacological evaluation of these compounds are in progress.

### Experimental

<sup>1</sup>H-NMR spectra were obtained on a JEOL JNM-EX270 (270 MHz) instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Mass spectra were recorded using a MICROMASS Quattro. Elemental analyses were performed by Perkin-Elmer Series II CHNS/O Analyzer 2400 or Thermo Quest Flash EA1112. Column chromatography was carried out on YMC GEL SIL-60-S150. Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator.

**Synthesis of Compound 2a (Chart 1). Step a** To a solution of [bis(methylthio)methylene]malononitrile **3** (3.00 g, 17.6 mmol) in THF (30 ml) was added 4-amino-1-benzylpiperidine (3.59 ml, 17.6 mmol). After the mixture was stirred at room temperature for 19 h, 2-aminoethanol (0.70 ml, 11.6 mmol) was added to the solution and refluxed for a further 10 h. The resulting mixture was concentrated under reduced pressure and the residue was triturated with ethyl acetate and diisopropyl ether to give **4** (3.18 g, 58%) as a brown solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.52—1.68 (2H, m, piperidine 3-CH and 5-CH), 1.92—2.04 (2H, m, piperidine 3-CH and 5-CH), 2.10—2.22 (2H, m, piperidine 2-CH and 6-CH), 2.82—2.93 (2H, m, piperidine 2-CH and 6-CH), 3.31 (2H, t, *J* = 4.5 Hz, -NH-CH<sub>2</sub>-CH<sub>2</sub>-OH), 3.52 (2H, s, Ph-CH<sub>2</sub>-), 3.62—3.80 (3H, m, -NH-CH<sub>2</sub>-CH<sub>2</sub>-OH and piperidine 4-CH), 7.20—7.35 (5H, m, Ph).

**Step b** To a solution of compound **4** (1.88 g, 5.78 mmol) and triethylamine (3.38 ml, 24.3 mmol) in dichloromethane (20 ml) was added methanesulfonyl chloride (0.805 ml, 10.4 mmol). The mixture was stirred at room temperature for 69 h and diluted with brine. The mixture was extracted with chloroform. The combined organic extracts were washed with brine and dried (MgSO<sub>4</sub>), filtered, and concentrated under vacuum to give compound **5** (0.705 g, 40%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.68—1.90 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.08—2.22 (2H, m, piperidine 2-CH and 6-CH), 2.92—3.05 (2H, m, piperidine 2-CH and 6-CH), 3.50 (2H, s, Ph-CH<sub>2</sub>-), 3.55—3.76 (4H, m, imidazolidine ring CH<sub>2</sub> × 2), 4.26 (1H, m,

piperidine 4-CH), 7.22—7.36 (5H, m, Ph).

**Step c** To a solution of compound **5** (0.705 g, 2.29 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.475 g, 3.44 mmol) in DMF (7 ml) was added 1,3-dibromopropane (1.39 ml, 13.7 mmol) and the mixture was stirred at room temperature for 26 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was triturated with *n*-hexane to afford **6a** (0.694 g, 71%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.72—1.88 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.08—2.32 (4H, m, piperidine 2-CH and 6-CH and Br-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.93—3.03 (2H, m, piperidine 2-CH and 6-CH), 3.45—3.75 (10H, m, Ph-CH<sub>2</sub>-, Br-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub> × 2), 4.21 (1H, m, piperidine 4-CH), 7.23—7.36 (5H, m, Ph).

**Step d** Compound **6a** (0.694 g, 1.62 mmol) was dissolved in 1,4-dioxane (7 ml), and K<sub>2</sub>CO<sub>3</sub> (0.448 g, 3.24 mmol), KI (0.269 g, 1.62 mmol) and piperidine (0.481 ml, 4.86 mmol) were added. After the solution was stirred at 80 °C for 7 h, the mixture was allowed to cool to room temperature and diluted with ethyl acetate. The organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under vacuum. The residue was recrystallized from acetone and diisopropyl ether to give **7a** (360 mg, 51%) as a white solid. mp 156—158 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.37—1.93 (12H, m, 3-CH<sub>2</sub>, 4-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.08—2.22 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 2.29—2.43 (6H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.9—3.02 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.47—3.65 (8H, m, Ph-CH<sub>2</sub>-, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub> × 2), 4.21 (1H, m, piperidine 4-CH), 7.23—7.36 (5H, m, Ph).

**Step e** To a solution of **7a** (200 mg, 0.463 mmol) in 1,2-dichloroethane (3 ml) was added 1-chloroethyl chloroformate (0.18 ml, 1.7 mmol). The mixture was refluxed for 4.5 h and concentrated *in vacuo*. The residue was dissolved in methanol (3 ml) and resulting solution refluxed for further 1.5 h. The resulting mixture was concentrated under reduced pressure and the residue dissolved in 1 mol/l NaOH aq. The alkaline solution was extracted with ethyl acetate twice and the combined organic layer was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give compound **2a** (0.134 g, 85%) as brown oil. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.46—1.54 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.58—1.96 (10H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.08—2.20 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 2.64—2.78 (6H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 3.11—3.22 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.60—3.70 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub> × 2), 4.22 (1H, m,

piperidine 4-CH).

**Synthesis of Compound 2b (Chart 1). Step f** To a solution of **2a** (196 mg, 0.572 mmol) and acetone (0.418 ml, 5.73 mmol) in THF (10 ml) was added sodium triacetoxyborohydride (604 mg, 2.85 mmol) and the mixture was stirred at room temperature for 44 h. After the reaction was completed, the solution was diluted with Na<sub>2</sub>CO<sub>3</sub> aq. and extracted with ethyl acetate. The organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was recrystallized from diisopropyl ether to give compound **2b** (81 mg, 37%) as a white solid. mp 199–201 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (6H, d, *J*=6.4 Hz, CH<sub>3</sub> of *iso*-Pr), 1.37–1.50 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.51–1.93 (10H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.22–2.42 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.75 (1H, m, CH of *iso*-Pr), 2.89–3.01 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.50–3.65 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.17 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 385 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>36</sub>N<sub>6</sub>: C, 68.71; H, 9.44; N, 21.85. Found: C, 68.95; H, 9.51; N, 22.01.

**Synthesis of Compound 2d (Chart 2). Step a** Compound **2a** (78 mg, 0.23 mmol) was dissolved in DMF (2 ml), and K<sub>2</sub>CO<sub>3</sub> (190 mg, 1.38 mmol) and 1-bromo-2-fluoroethane (0.051 ml, 0.69 mmol) were added. After the solution was stirred at room temperature for 64 h, the mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with 10% 2 mol/l NH<sub>3</sub>-CH<sub>3</sub>OH/CHCl<sub>3</sub> to provide crude **2d**, which was recrystallized from diisopropyl ether to afford pure **2d** (17 mg, 19%) as a white solid. mp 56–57 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.38–1.50 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.50–1.93 (10H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20–2.45 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.70 (2H, dt, *J*=28.4, 5.0 Hz, N-CH<sub>2</sub>CH<sub>2</sub>F), 3.00–3.10 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.50–3.67 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.21 (1H, m, piperidine 4-CH), 4.54 (2H, dt, *J*=47.5, 5.0 Hz, N-CH<sub>2</sub>CH<sub>2</sub>F). APCI-MS *m/z*: 389 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>31</sub>F<sub>3</sub>N<sub>6</sub>·0.5H<sub>2</sub>O: C, 63.45; H, 8.62; N, 21.14. Found: C, 63.47; H, 8.81; N, 21.30.

**Synthesis of Compounds 2e and 2f (Chart 2)** Compounds **2e** and **2f** were synthesized using a method similar to that for preparation of compound **2d**.

Compound **2e** (White Solid): mp 103–105 °C (*n*-hexane/ethyl acetate). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.36–1.62 (6H, m, 3-CH<sub>2</sub>, 4-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group), 1.73–1.92 (6H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.34–2.57 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.88–3.07 (4H, m, 2-CH and 6-CH of 4-piperidinyl group, N-CH<sub>2</sub>CF<sub>3</sub>), 3.52–3.66 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.21 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 425 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>31</sub>F<sub>3</sub>N<sub>6</sub>: C, 59.42; H, 7.36; N, 19.80. Found: C, 59.68; H, 7.61; N, 20.13.

Compound **2f** (White Solid): mp 135–136 °C (2-propanol). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40–1.50 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.50–2.00 (10H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.32–2.56 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.90–3.00 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.46 (2H, s, N-CH<sub>2</sub>CN), 3.50–3.70 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.24 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 382 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>31</sub>N<sub>7</sub>: C, 66.11; H, 8.19; N, 25.70. Found: C, 66.40; H, 8.22; N, 25.87.

**Synthesis of Compound 2g (Chart 1)** Compound **2g** was synthesized using a method similar to that for compound **2b** and **2d** by use of 1,2-dibromoethane and 2-iodopropane instead of 1,3-dibromopropane and 1-bromo-2-fluoroethane, respectively.

Compound **2g** (White Solid): mp 93–95 °C (diisopropyl ether). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.38–1.95 (10H, m, 3-CH<sub>2</sub>, 4-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of 4-piperidinyl group), 2.24–2.50 (6H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group), 2.53–2.65 (2H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-), 2.76 (1H, m, CH of *iso*-Pr), 2.90–3.00 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.50–3.72 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.16 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 371 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>34</sub>N<sub>6</sub>: C, 68.07; H, 9.25; N,

22.68. Found: C, 68.11; H, 9.34; N, 22.95.

**Synthesis of Compound 2c (Chart 3). Step a** To a solution of compound **5** (9.00 g, 29.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.1 g, 58.6 mmol) in DMF (30 ml) was added (3-bromopropoxy)-*tert*-butyldimethylsilane (8.15 ml, 35.2 mmol) and the mixture was stirred at 50 °C for 20 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was triturated with diisopropyl ether to afford **9** (12.3 g, 90%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.05 (6H, s, 2×CH<sub>3</sub> of TBS), 0.89 (9H, s, *tert*-butyl of TBS), 1.70–1.93 (6H, m, TBSO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.10–2.23 (2H, m, piperidine 2-CH and 6-CH), 2.92–3.02 (2H, m, piperidine 2-CH and 6-CH), 3.56 (2H, s, Ph-CH<sub>2</sub>-), 3.53–3.72 (8H, m, TBSO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.21 (1H, m, piperidine 4-CH), 7.22–7.36 (5H, m, Ph).

**Step b** To a solution of **9** (500 mg, 1.02 mmol) in 1,2-dichloroethane (5 ml) was added 1-chloroethyl chloroformate (0.275 ml, 2.55 mmol). The mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was dissolved in methanol (5 ml) and the solution was refluxed for further 1 h. The resulting mixture was concentrated under reduced pressure and the residue was triturated with ethyl acetate to give compound **10** (HCl salt; 0.295 g, 93%) as a white solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.84–2.15 (6H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 3.04–3.15 (2H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 3.45–3.58 (2H, m, piperidine 2-CH and 6-CH), 3.61–3.80 (8H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), piperidine 2-CH and 6-CH-, imidazolidine ring CH<sub>2</sub>×2), 4.39 (1H, m, piperidine 4-CH).

**Step c** To a solution of **10** (720 mg, 2.31 mmol), triethylamine (0.32 ml, 2.3 mmol), acetic acid (3.96 ml) and (1-ethoxycyclopropoxy)trimethylsilane (0.93 ml, 4.6 mmol) in THF (35 ml) and methanol (0.36 ml) was added sodium cyanoborohydride (310 mg, 4.62 mmol) and the mixture was stirred at 60 °C for 3 h. After the reaction was completed, the solution was diluted with H<sub>2</sub>O (110 ml) and 2 mol/l HCl aq. and washed with ethyl acetate. The aqueous layer was neutralized with K<sub>2</sub>CO<sub>3</sub>, and then extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue triturated with *n*-hexane and ethyl acetate (20:1) to give compound **11** (510 mg, 70%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.34–0.39 and 0.42–0.51 (each 2H, each m, *cyclo*-Pr CH<sub>2</sub>×2), 1.63–1.68 (3H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), *cyclo*-Pr CH), 1.71–1.99 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.36 (2H, m, piperidine 2-CH and 6-CH), 3.11 (2H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 3.54–3.76 (8H, m, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), piperidine 2-CH and 6-CH-, imidazolidine ring CH<sub>2</sub>×2), 4.21 (1H, m, piperidine 4-CH).

**Step d** To a solution of compound **11** (500 mg, 1.60 mmol) and triethylamine (0.89 ml, 6.41 mmol) in dichloromethane (6 ml) was added methanesulfonyl chloride (0.19 ml, 2.4 mmol). The mixture was stirred at room temperature for 2 h and diluted with brine. The mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to afford the mesylate **12** (520 mg, 83%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.41–0.50 (4H, m, *cyclo*-Pr CH<sub>2</sub>×2), 1.64–1.86 (5H, m, piperidine 3-CH and 5-CH, HO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), *cyclo*-Pr CH), 2.12–2.22 (2H, m, piperidine 3-CH and 5-CH), 2.38 (2H, m, piperidine 2-CH and 6-CH), 3.05 (3H, s, CH<sub>3</sub>SO<sub>2</sub>-), 3.06–3.15 (2H, m, piperidine 2-CH and 6-CH), 3.57–3.72 (6H, m, MsO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.22 (1H, m, piperidine 4-CH), 4.34 (2H, t, *J*=5.8 Hz, MsO-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-).

**Step e** The mesylate **12** (0.21 g, 0.52 mmol) was dissolved in 1,4-dioxane (12 ml), and K<sub>2</sub>CO<sub>3</sub> (145 mg, 1.04 mmol) and piperidine (0.104 ml, 1.04 mmol) were added. After the solution was stirred at 80 °C for 15 h, the mixture was allowed to cool to room temperature and diluted with brine. The mixture was extracted with ethyl acetate and the combined organic extracts washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was recrystallized from *n*-hexane and ethyl acetate to give compound **2c** (166 mg, 83%). mp 104–105 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.34–0.51 (4H, m, *cyclo*-Pr CH<sub>2</sub>×2), 1.42–1.44 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.53–1.73 (8H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH and 5-CH of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 1.81–1.91 (2H, m, 3-CH and 5-CH of 4-piperidinyl group), 2.31–2.36 (9H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, 2-CH and 6-CH of 4-piperidinyl group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), *cyclo*-Pr CH), 3.08–3.12 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.53–3.60 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), imidazolidine ring CH<sub>2</sub>×2), 4.27 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 383 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>34</sub>N<sub>6</sub>: C, 69.07; H, 8.96; N, 21.97. Found: C, 69.15; H, 9.21; N, 22.35.

**Synthesis of Compounds 2l and 2m (Chart 3)** The following compounds were prepared using a method similar to that of synthesis of com-

ound **2c**.

Compound **2l** (White Solid): mp 104–106 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.34–0.41 and 0.43–0.51 (each 2H, each m, *cyclo*-Pr CH<sub>2</sub>×2), 1.65–1.75 (3H, m, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, *cyclo*-Pr CH), 1.81–1.91 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.30–2.45 (8H, m, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, morpholine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, piperidine 2-CH and 6-CH), 3.11 (2H, m, piperidine 2-CH and 6-CH), 3.52–3.63 (6H, m, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.23 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 385 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>6</sub>O: C, 65.59; H, 8.39; N, 21.86. Found: C, 68.97; H, 8.44; N, 22.23.

Compound **2m** (White Solid): mp 129–130 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.36–0.41 and 0.43–0.51 (each 2H, each m, *cyclo*-Pr CH<sub>2</sub>×2), 1.62–1.75 (5H, m, thiomorpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, piperidine 3-CH and 5-CH, *cyclo*-Pr CH), 1.81–1.90 (4H, m, thiomorpholino 2-CH and 6-CH, piperidine 3-CH and 5-CH), 2.31–2.44 (4H, m, thiomorpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, thiomorpholine 2-CH and 6-CH), 2.65–2.72 (6H, m, thiomorpholine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, piperidine 2-CH and 6-CH), 3.11 (2H, m, piperidine 2-CH and 6-CH), 3.51–3.60 (6H, m, thiomorpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.22 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 401 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>6</sub>S: C, 62.96; H, 8.05; N, 20.98. Found: C, 63.07; H, 8.14; N, 21.21.

**Synthesis of Compound 2h (Chart 4).** **Step a** To an ice-cooled solution of **3** (10.2 g, 59.9 mmol) in THF (68 ml) was added THF solution (10 ml) of *N*-(3-hydroxypropyl)ethylenediamine (7.24 g, 61.3 mmol). The mixture was stirred at room temperature for 3 h and diluted with ethyl acetate/diisopropyl ether (each 35 ml). This solution was stirred in an ice bath for 1 h and the resulting white precipitate filtered and dried to give compound **13** (9.48 g, 82%). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.65–1.79 (2H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 3.38–3.55 (6H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>), 3.63–3.75 (2H, m, imidazolidine ring CH<sub>2</sub>), 4.54 (1H, t, *J*=4.6 Hz, OH), 7.87 (1H, br, s, NH).

**Step b** To a solution of compound **13** (1.19 g, 6.19 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.71 g, 12.4 mmol) in DMF (12 ml) was added 1-*tert*-butoxycarbonyl-4-methanesulfonyloxymethylpiperidine<sup>(2)</sup> (2.94 g, 9.29 mmol) and the mixture was stirred at 80 °C for 21 h and 100 °C for 25 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with CH<sub>3</sub>OH/CHCl<sub>3</sub> (from 3 to 8%) to provide compound **14** (1.21 g, 50%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.20–1.40 (2H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.46 (9H, s, *tert*-butyl), 1.65–1.75 (2H, m, 3-CH and 5-CH of piperidine), 1.88–2.04 (3H, m, 3-CH, 4-CH and 5-CH of piperidine), 2.62–2.80 (2H, m, 2-CH and 6-CH of piperidine), 3.30–3.50 (2H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 3.60–3.78 (8H, m, 4-piperidinyl-CH<sub>2</sub>-, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.05–4.24 (2H, m, 2-CH and 6-CH of piperidine).

**Step c** To a solution of compound **14** (600 mg, 1.60 mmol) and triethylamine (0.445 ml, 3.20 mmol) in dichloromethane (6 ml) was added methanesulfonyl chloride (0.186 ml, 2.40 mmol). The mixture was stirred at room temperature for 5 h and diluted with brine. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (MgSO<sub>4</sub>), filtered, and concentrated under vacuum to give {1-[[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methyl]-3-(3-methanesulfonyloxypropyl)imidazolidine-2-ylidene}malononitrile (700 mg, 97%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.12–1.28 (2H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.46 (9H, s, *tert*-butyl), 1.65–1.75 (2H, m, 3-CH and 5-CH of piperidine), 1.90–2.05 (1H, m, 4-CH of piperidine), 2.12–2.45 (2H, m, 3-CH and 5-CH of piperidine), 2.63–2.78 (2H, m, 2-CH and 6-CH of piperidine), 3.06 (3H, s, CH<sub>3</sub>SO<sub>2</sub>-), 3.30–3.78 (8H, m, 4-piperidinyl-CH<sub>2</sub>-, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.05–4.24 (2H, m, 2-CH and 6-CH of piperidine), 4.35 (2H, t, *J*=6.0 Hz, MsO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-).

The mesylate (780 mg, 1.67 mmol) was dissolved in 1,4-dioxane (8 ml), and KI (415 mg, 2.50 mmol) and piperidine (0.496 ml, 5.01 mmol) were added. After the solution was stirred at 80 °C for 2.5 h, the mixture was allowed to cool to room temperature and diluted with brine. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (from 1 to 15% CH<sub>3</sub>OH/CHCl<sub>3</sub>) to give compound **15** (490 mg, 64%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.12–1.29 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.43–1.52 (11H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, *tert*-butyl), 1.58–1.75 (6H, m, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group, 3-CH and 5-CH of 4-piperidinylmethyl group), 1.87–2.05 (3H, m, 3-CH, 4-CH and 5-CH of 4-piperidinylmethyl group), 2.40–2.55 (6H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.62–2.79 (2H, m, 2-CH and 6-CH of 4-piperidinylmethyl group),

3.28–3.50 (2H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 3.55–3.70 (6H, m, 4-piperidinyl-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.08–4.24 (2H, m, 2-CH and 6-CH of piperidine).

**Step d** To a solution of compound **15** (72 mg, 0.16 mmol) in methylene chloride (2 ml) was added trifluoroacetic acid (1 ml) and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in DMF (2 ml). K<sub>2</sub>CO<sub>3</sub> (110 mg, 0.800 mmol) and 2-iodopropane (0.031 ml, 0.32 mmol) were added to the solution and stirred at 50 °C for 5 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with 20% 2 mol/l NH<sub>3</sub>-CH<sub>3</sub>OH/CHCl<sub>3</sub> to yield compound **2h** (13 mg, 20%) as a white solid. mp 115–117 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.23–1.50 (2H, m, 4-CH<sub>2</sub> of piperidino group), 1.51–1.63 (6H, m, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 3-CH<sub>2</sub> and 5-CH<sub>2</sub> of piperidino group), 1.68–1.94 (5H, m, 3-CH<sub>2</sub>, 4-CH and 5-CH<sub>2</sub> of 4-piperidinylmethyl group), 2.10–2.23 (2H, m, 2-CH and 6-CH of 4-piperidinylmethyl group), 2.25–2.47 (6H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub> of piperidino group, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.67–2.79 (1H, m, CH of *iso*-Pr), 2.84–2.95 (2H, m, 2-CH and 6-CH of 4-piperidinylmethyl group), 3.38 (2H, d, *J*=7.3 Hz, piperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 3.53–3.67 (6H, m, 4-piperidinyl-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2). APCI-MS *m/z*: 399 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>23</sub>H<sub>38</sub>N<sub>6</sub>: C, 69.31; H, 9.61; N, 21.08. Found: C, 69.47; H, 9.92; N, 21.45.

**Synthesis of Compound 2i (Chart 5).** **Step a** To a solution of compound **10** (HCl salt; 6.36 g, 20.4 mmol) in DMF (50 ml) were added K<sub>2</sub>CO<sub>3</sub> (14.1 g, 102 mmol) and 2-iodopropane (6.1 ml, 61.2 mmol). After the mixture was stirred at 60 °C for 23 h, the reaction mixture was diluted with ethyl acetate and washed with brine. The organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with 10% CH<sub>3</sub>OH/CHCl<sub>3</sub> to yield compound **16** (1.96 g, 30%) as a pale yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.05 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.72–1.98 (6H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.28–2.35 (2H, m, piperidine 2-CH and 5-CH), 2.73–2.81 (1H, m, CH of *iso*-Pr), 2.97 (2H, m, piperidine 2-CH and 5-CH), 3.61 (4H, s, imidazolidine ring CH<sub>2</sub>×2), 3.66–3.71 (2H, m, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 3.74 (2H, t, *J*=6.8 Hz, HO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 4.18 (1H, m, piperidine 4-CH).

**Step b** To a solution of compound **16** (1.96 g, 6.19 mmol) and triethylamine (3.45 ml, 24.8 mmol) in dichloromethane (20 ml) was added methanesulfonyl chloride (0.72 ml, 9.3 mmol). The mixture was stirred at room temperature for 1.5 h and diluted with brine. The mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to afford the mesylate **17** (1.34 g, 55%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.06 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.75–1.80 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.13–2.21 (2H, m, MsO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 2.30–2.37 (2H, m, piperidine 2-CH and 6-CH), 2.80 (1H, m, CH of *iso*-Pr), 2.99 (2H, m, piperidine 2-CH and 6-CH), 3.05 (3H, s, CH<sub>3</sub>SO<sub>2</sub>-), 3.62 (4H, s, imidazolidine ring CH<sub>2</sub>×2), 3.72 (2H, t, *J*=7.2 Hz, MsO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 4.20 (1H, m, piperidine 4-CH), 4.35 (2H, t, *J*=5.9 Hz, MsO-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-).

**Step c** The mesylate **17** (1.77 g, 4.47 mmol) was dissolved in 1,4-dioxane (20 ml), and K<sub>2</sub>CO<sub>3</sub> (1.23 g, 8.94 mmol) and morpholine (0.78 ml, 8.9 mmol) were added. After the solution was stirred at 80 °C for 13 h, the mixture was allowed to cool to room temperature and diluted with brine. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was recrystallized from *n*-hexane and ethyl acetate to give compound **2i** (1.32 g, 77%) as a white solid. mp 109–110 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.70–1.93 (6H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.24–2.50 (8H, m, piperidine 2-CH and 6-CH, morpholine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.76 (1H, m, CH of *iso*-Pr), 2.90–3.01 (2H, m, piperidine 2-CH and 6-CH), 3.55–3.77 (10H, m, morpholine 2-CH<sub>2</sub> and 6-CH<sub>2</sub>, morpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.18 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 387 (M+H<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>34</sub>N<sub>6</sub>O: C, 65.25; H, 8.87; N, 21.74. Found: C, 65.60; H, 9.10; N, 22.09.

**Synthesis of Compounds 2j and 2k (Chart 5)** The following compounds were prepared using a method similar to that of synthesis of compound **2i**.

Compound **2j** (White Solid): mp 124–125 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.67–1.88 (6H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, thiomorpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.27–2.37 (2H, m, thiomorpholine 2-CH and 6-CH), 2.41 (2H, t, *J*=7.0 Hz, thiomorpholino-CH<sub>2</sub>-CH-

CH<sub>2</sub>-), 2.65–2.79 (9H, m, piperidine 2-CH and 6-CH, thiomorpholine 2-CH, 6-CH, 3-CH<sub>2</sub> and 5-CH<sub>2</sub>, CH of *iso*-Pr), 2.94–2.98 (2H, m, piperidine 2-CH and 6-CH), 3.54–3.60 (6H, m, thiomorpholino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.19 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 403 (M+H<sup>+</sup>). Anal. Calcd for C<sub>21</sub>H<sub>34</sub>N<sub>6</sub>S: C, 62.65; H, 8.51; N, 20.87. Found: C, 62.81; H, 8.60; N, 20.92.

Compound **2k** (White Solid): mp 103–105 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (6H, d, *J*=6.6 Hz, CH<sub>3</sub> of *iso*-Pr), 1.75 (2H, m, 4-oxopiperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 1.87–1.99 (4H, m, piperidine 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.27–2.34 (2H, m, 3-CH and 5-CH of 4-oxopiperidine), 2.46 (4H, t, *J*=6.0 Hz, 4-oxopiperidine 2-CH, 3-CH, 4-CH and 5-CH), 2.53 (2H, t, *J*=6.8 Hz, 4-oxopiperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-), 2.75 (5H, m, 4-oxopiperidine 3-CH and 5-CH, piperidine 2-CH and 6-CH, CH of *iso*-Pr), 2.96 (2H, m, piperidine 2-CH and 6-CH), 3.60–3.67 (6H, m, 4-oxopiperidino-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, imidazolidine ring CH<sub>2</sub>×2), 4.19 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 399 (M+H<sup>+</sup>). Anal. Calcd for C<sub>22</sub>H<sub>34</sub>N<sub>6</sub>O: C, 66.30; H, 8.60; N, 21.09. Found: C, 66.51; H, 8.56; N, 21.18.

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#### References and Notes

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