Diamine Derivatives Containing Imidazolidinylidene Propanedinitrile as a New Class of Histamine H_3 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_3 receptor (H_3R) binding affinities. Among them, compounds 2b, 2c, 2j, 2k and 2m were found to be potent ligands for both H_3Rs with K_i values in the sub-nanomolar range, and showed potent H_3 receptor antagonism.

Key words histamine H_3 receptor; antagonist; imidazolidinylidene propanedinitrile; diamine

In the central nerve system, the histamine H_3 receptor (H_3R) is thought to control the release of a various neurotransmitters such as histamine, serotonin, dopamine and acetylcholine. H_3R 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.[2—8)]

Recently, we reported novel diamine derivatives containing an imidazolidinylidene propanedinitrile moiety as potent H_3R antagonists.[9)] For example, compound **1** showed good affinities both for human and rat H_3Rs (K_i=2.4 nM and 2.6 nM, respectively) with excellent selectivity for human H_1, H_2 and H_4 receptors. Furthermore, a functional assay established that compound **1** was a rat neuronal H_3R antagonist. In 2005, researchers from Johnson & Johnson identified a series of conformationally restricted JNJ-5207852 derivatives as potent H_3R antagonists. For example, JNJ-7737782 represented pK_i of 9.32 (0.48 nM) and 8.67 (2.14 nM) for human and rat H_3Rs, respectively, and showed wake-promoting activity.[10)] 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_3R affinities, compounds **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)methylene]malononitrile **3** and 4-amino-1-benzylpiperidine were re-

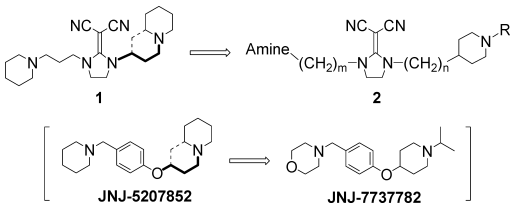
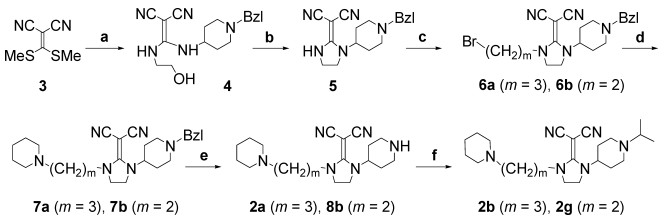
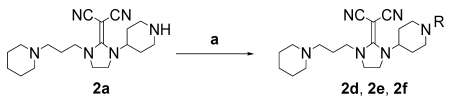


Fig. 1. Design of Conformationally Restricted Diamine-Based Novel Histamine H_3 Receptor Antagonists **2** with Imidazolidinylidene Propanedinitrile Moiety



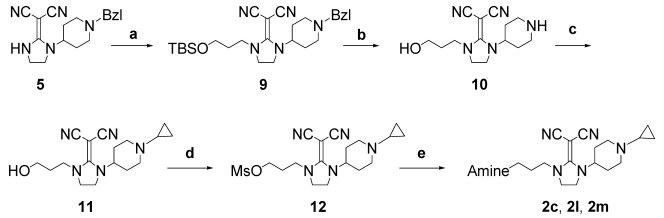
Reagents and conditions: (a) 4-amino-1-benzylpiperidine, THF, room temperature, 19 h, then 2-aminoethanol, reflux, 10 h, 58% (2 steps); (b) MsCl, TEA, CH_2Cl_2, room temperature, 69 h, 40%; (c) 1,3-dibromopropane, 71% (**6a**) or 1,2-dibromoethane, 59% (**6b**), K_2CO_3, DMF, room temperature; (d) piperidine, KI, 1,4-dioxane, 51% (**7a**) or 72% (**7b**); (e) 1-chloroethyl chloroformate, 1,2-dichloroethane, reflux, then MeOH, reflux, 85% (**2a**); (f) acetone, $Na(OAc)_3BH$, THF, room temperature, 44 h, 37% (**2b**), 2-iodopropane, K_2CO_3, DMF, room temperature, 111 h, 14% (**2g** from **7b**, 2 steps).

Chart 1



Reagents and conditions: (a) 1-bromo-2-fluoroethane, K_2CO_3, DMF, room temperature, 64 h, 19% (**2d**), 2,2,2-trifluoroethyl trifluoromethanesulfonate,[11)] K_2CO_3, DMF, room temperature, 6 h, 50% (**2e**), 1-iodoacetonitrile, K_2CO_3, DMF, room temperature, 64 h, 17% (**2f**).

Chart 2



Reagents and conditions: (a) (3-bromopropoxy)-*tert*-butyldimethylsilane, K_2CO_3, 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)trimethylsilane, $NaBH_3CN$, TEA, AcOH, THF, 60 °C, 3 h, 70%; (d) MsCl, TEA, CH_2Cl_2, room temperature, 2 h, 83%; (e) corresponding amine, K_2CO_3, 1,4-dioxane, 80 °C, 12—24 h, 83% (**2c**), 59% (**2l**), 29% (**2m**).

Chart 3

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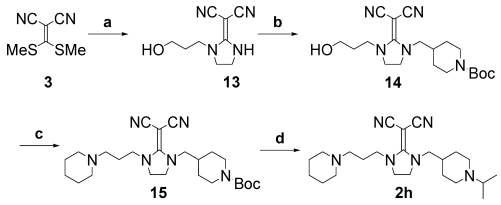
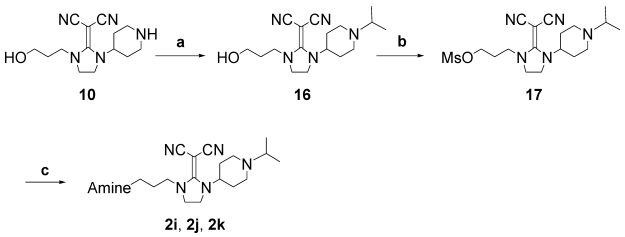


Reagents and conditions: (a) *N*-(3-hydroxypropyl)ethylenediamine, THF, room temperature, 3 h, 82%; (b) 1-*tert*-butoxylcarbonyl-4-methanesulfonyloxymethylpiperidine,[12] K_2CO_3, DMF, 80—100 °C, 46 h, 50%; (c) MsCl, TEA, CH_2Cl_2, room temperature, 5 h, 97%, then piperidine, KI, 1,4-dioxane, 80 °C, 2.5 h, 64%; (d) TFA, CH_2Cl_2, room temperature, 0.5 h, then 2-iodopropane, K_2CO_3, DMF, 50 °C, 5 h, 20% (2 steps).

Chart 4



Reagents and conditions: (a) 2-iodopropane, K_2CO_3, DMF, 60 °C, 23 h, 30%; (b) MsCl, TEA, CH_2Cl_2, room temperature, 1.5 h, 55%; (c) corresponding amine, K_2CO_3, 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 $Na(OAc)_3BH$ gave compound **2b** (R=*iso*-Pr). Furthermore, as illustrated in Chart 2, compound **2a** was treated with corresponding electrophiles and K_2CO_3 in DMF to provide compounds **2d**, **2e**[11] 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 debenzylation 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_3R 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, debenzylation and *iso*-propylation. On the other hand, compound **2h** was synthesized as follows. Compound **13**,[9] obtained from malononitrile **5** and *N*-(3-hydroxypropyl)ethylenediamine, was reacted with 1-*tert*-butoxylcarbonyl-4-methanesulfonyloxymethylpiperidine[12] 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_3Rs 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_3Rs. For example, compound **2b** showed six-fold and nine-fold affinity to human and rat H_3Rs (K_i=0.37 nM and 0.28 nM, respectively) than those of parent compound **1**. Furthermore, compound **2b** showed excellent selectivity over human H_1, H_2 and H_4 receptors (percent inhibition of hH_1R, hH_2R, hH_4R at 10 μM; 20%, −12%, −4%). Compound **2c** also showed high affinities to both H_3Rs (K_i=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_3Rs.

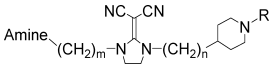
Modification of linker length (*i.e.* compounds **2g**, **2h**) caused decrease in affinity for both human and rat H_3Rs. These results indicate that the distance between two basic nitrogen atoms is important for high affinities to both H_3Rs.

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_3Rs with K_i 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_3Rs than **2b** or **2c**.

Compounds **2b**, **2c**, **2d**, **2i**, **2j**, **2k**, **2l** and **2m** were selected for a functional assay.[13] Among them, compounds **2b** and **2c** reversed NAMH-mediated inhibition of [^{3}H]-histamine release from rat forebrain synaptosomes with IC_{50} 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_3R than compound **1**. Somehow, there is a poor correlation between K_i values and IC_{50} 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_{50} values of 54.1 nM and 3397 nM, respectively, in spite of their similar affinities for rat H_3Rs (K_i; 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 [^{3}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_3R Binding Affinities and H_3R Antagonistic Activities of Compounds **2a**—**m**



Compound	Amine	R	Linker *m*, *n*	K_i (nM)		Synaptosome[b]
				hH_3[a]	rH_3[a]	IC_{50} (nM)
JNJ-7737782				0.48[c]	2.14[c]	[d]
Thioperamide				43.1	5.14	54.1±13.1[f]
Proxyfan				9.14	3.95	3397±713[f]
1				2.4 (78/98)[e]	2.6 (88/96)[e]	27.9±4.2[f]
2a	Piperidino	H	3, 0	(−8/50)[e]	(32/50)[e]	[d]
2b	Piperidino	*iso*-Pr	3, 0	0.37	0.28	10.2±2.9[f]
2c	Piperidino	*cyclo*-Pr	3, 0	0.20	0.23	11.6±1.8[f]
2d	Piperidino	CH_2CH_2F	3, 0	1.48	1.55	63.8±28.3[f]
2e	Piperidino	CH_2CF_3	3, 0	(42/66)[e]	(40/76)[e]	[d]
2f	Piperidino	CH_2CN	3, 0	(18/67)[e]	(40/86)[e]	[d]
2g	Piperidino	*iso*-Pr	2, 0	(72/96)[e]	(54/88)[e]	[d]
2h	Piperidino	*iso*-Pr	3, 1	(60/87)[e]	(70/96)[e]	[d]
2i	Morpholino	*iso*-Pr	3, 0	2.58	2.81	23.8±8.4[f]
2j	Thiomorpholino	*iso*-Pr	3, 0	0.33	0.22	16.9±1.2[f]
2k	4-Oxopiperidino	*iso*-Pr	3, 0	0.51	0.48	18.5±1.1[f]
2l	Morpholino	*cyclo*-Pr	3, 0	1.6	2.3	80.8±14.2[f]
2m	Thiomorpholino	*cyclo*-Pr	3, 0	0.38	0.37	26.7[g]

a) Binding potencies were assessed by displacement of [^{3}H]-N^{α}-methylhistamine (NAMH). The human H_3 values were from cloned human H_3R expressed in COS-7 cells, while rat H_3R values were from rat striatal membranes. *b*) H_3R antagonism was assessed by reverse effect on NAMH-mediated inhibition of [^{3}H]-histamine release from rat forebrain 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_3R ligands possessing a 1-alkylated-4-piperidinyl moiety as a conformationally restricted linker. This shows potent affinity to both human and rat H_3Rs, some of which are proven potent antagonists at H_3Rs in rat cortical synaptosomes. Further structural modification and pharmacological evaluation of these compounds are in progress.

Experimental

^{1}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. ^{1}H-NMR (CD_3OD) 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_2<u>CH_2</u>–OH), 3.52 (2H, s, Ph–<u>CH_2</u>–), 3.62—3.80 (3H, m, –NH–<u>CH_2</u>CH_2–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 ($MgSO_4$), filtered, and concentrated under vacuum to give compound **5** (0.705 g, 40%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.90 (4H, m, piperidine 3-CH_2 and 5-CH_2), 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–<u>CH_2</u>–), 3.55—3.76 (4H, m, imidazolidine ring CH_2×2), 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_2CO_3 (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 ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was triturated with *n*-hexane to afford **6a** (0.694 g, 71%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.72—1.88 (4H, m, piperidine 3-CH_2 and 5-CH_2), 2.08—2.32 (4H, m, piperidine 2-CH and 6-CH and Br–CH_2–<u>CH_2</u>–CH_2–), 2.93—3.03 (2H, m, piperidine 2-CH and 6-CH), 3.45—3.75 (10H, m, Ph–<u>CH_2</u>–, Br–<u>CH_2</u>–CH_2–<u>CH_2</u>–, imidazolidine ring CH_2×2), 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_2CO_3 (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 ($MgSO_4$), 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. ^{1}H-NMR ($CDCl_3$) δ: 1.37—1.93 (12H, m, 3-CH_2, 4-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–<u>CH_2</u>–CH_2–), 2.08—2.22 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 2.29—2.43 (6H, m, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–<u>CH_2</u>–CH_2–CH_2–), 2.9—3.02 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.47—3.65 (8H, m, Ph–<u>CH_2</u>–, piperidino–CH_2–CH_2–<u>CH_2</u>–, imidazolidine ring CH_2×2), 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 ($MgSO_4$), filtered and concentrated *in vacuo* to give compound **2a** (0.134 g, 85%) as brown oil. ^{1}H-NMR (CD_3OD) δ: 1.46—1.54 (2H, m, 4-CH_2 of piperidino group), 1.58—1.96 (10H, m, 3-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–<u>CH_2</u>–CH_2–), 2.08—2.20 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 2.64—2.78 (6H, m, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–<u>CH_2</u>–CH_2–CH_2–), 3.11—3.22 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.60—3.70 (6H, m, piperidino–CH_2–CH_2–<u>CH_2</u>–, imidazolidine ring CH_2×2), 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_2CO_3 aq. and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), 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. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, d, J=6.4 Hz, CH_3 of *iso*-Pr), 1.37—1.50 (2H, m, 4-CH_2 of piperidino group), 1.51—1.93 (10H, m, 3-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–$\underline{CH_2}$–CH_2–), 2.22—2.42 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 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_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.17 (1H, m, piperidine 4-CH). APCI-MS m/z: 385 ($M+H^+$). *Anal.* Calcd for $C_{22}H_{36}N_6$: 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_2CO_3 (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 ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with 10% 2 mol/l NH_3–CH_3OH/$CHCl_3$ 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. ^{1}H-NMR ($CDCl_3$) δ: 1.38—1.50 (2H, m, 4-CH_2 of piperidino group), 1.50—1.93 (10H, m, 3-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–$\underline{CH_2}$–CH_2–), 2.20—2.45 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 2.70 (2H, dt, J=28.4, 5.0 Hz, N–$\underline{CH_2}CH_2F$), 3.00—3.10 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.50—3.67 (6H, m, piperidino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.21 (1H, m, piperidine 4-CH), 4.54 (2H, dt, J=47.5, 5.0 Hz, N–$CH_2\underline{CH_2}F$). APCI-MS m/z: 389 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{33}FN_6\cdot 0.5H_2O$: 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). ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.62 (6H, m, 3-CH_2, 4-CH_2 and 5-CH_2 of piperidino group), 1.73—1.92 (6H, m, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–$\underline{CH_2}$–CH_2–), 2.34—2.57 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 2.88—3.07 (4H, m, 2-CH and 6-CH of 4-piperidinyl group, N–CH_2CF_3), 3.52—3.66 (6H, m, piperidino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.21 (1H, m, piperidine 4-CH). APCI-MS m/z: 425 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{31}F_3N_6$: 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). ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.50 (2H, m, 4-CH_2 of piperidino group), 1.50—2.00 (10H, m, 3-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group, piperidino–CH_2–$\underline{CH_2}$–CH_2–), 2.32—2.56 (8H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 2.90—3.00 (2H, m, 2-CH and 6-CH of 4-piperidinyl group), 3.46 (2H, s, N–CH_2CN), 3.50—3.70 (6H, m, piperidino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.24 (1H, m, piperidine 4-CH). APCI-MS m/z: 382 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{31}N_7$: 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). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J=6.6 Hz, CH_3 of *iso*-Pr), 1.38—1.95 (10H, m, 3-CH_2, 4-CH_2 and 5-CH_2 of piperidino group, 3-CH_2 and 5-CH_2 of 4-piperidinyl group), 2.24—2.50 (6H, m, 2-CH and 6-CH of 4-piperidinyl group, 2-CH_2 and 6-CH_2 of piperidino group), 2.53—2.65 (2H, m, piperidino–$\underline{CH_2}$–CH_2–), 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_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.16 (1H, m, piperidine 4-CH). APCI-MS m/z: 371 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{34}N_6$: 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_2CO_3 (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 ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was triturated with diisopropyl ether to afford **9** (12.3 g, 90%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, 2×CH_3 of TBS), 0.89 (9H, s, *tert*-butyl of TBS), 1.70—1.93 (6H, m, TBSO–$CH_2\underline{CH_2}CH_2$–, piperidine 3-CH_2 and 5-CH_2), 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–$\underline{CH_2}$–), 3.53—3.72 (8H, m, TBSO–$\underline{CH_2}CH_2\underline{CH_2}$–, imidazolidine ring CH_2×2), 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. ^{1}H-NMR (CD_3OD) δ: 1.84—2.15 (6H, m, HO–$CH_2\underline{CH_2}CH_2$–, piperidine 3-CH_2 and 5-CH_2), 3.04—3.15 (2H, m, HO–$\underline{CH_2}CH_2CH_2$), 3.45—3.58 (2H, m, piperidine 2-CH and 6-CH), 3.61—3.80 (8H, m, HO–$CH_2CH_2\underline{CH_2}$–, piperidine 2-CH and 6-CH-, imidazolidine ring CH_2×2), 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_2O (110 ml) and 2 mol/l HCl aq. and washed with ethyl acetate. The aqueous layer was neutralized with K_2CO_3, and then extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), 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. ^{1}H-NMR ($CDCl_3$) δ: 0.34—0.39 and 0.42—0.51 (each 2H, each m, *cyclo*-Pr CH_2×2), 1.63—1.68 (3H, m, HO–$CH_2\underline{CH_2}CH_2$–, *cyclo*-Pr CH), 1.71—1.99 (4H, m, piperidine 3-CH_2 and 5-CH_2), 2.36 (2H, m, piperidine 2-CH and 6-CH), 3.11 (2H, m, HO–$\underline{CH_2}CH_2CH_2$–), 3.54—3.76 (8H, m, HO–$CH_2CH_2\underline{CH_2}$–, piperidine 2-CH and 6-CH-, imidazolidine ring CH_2×2), 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 ($MgSO_4$), filtered and concentrated under reduced pressure to afford the mesylate **12** (520 mg, 83%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.41—0.50 (4H, m, *cyclo*-Pr CH_2×2), 1.64—1.86 (5H, m, piperidine 3-CH and 5-CH, HO–$CH_2\underline{CH_2}CH_2$–, *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_3SO_2–), 3.06—3.15 (2H, m, piperidine 2-CH and 6-CH), 3.57—3.72 (6H, m, MsO–$CH_2CH_2\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.22 (1H, m, piperidine 4-CH), 4.34 (2H, t, J=5.8 Hz, MsO–$\underline{CH_2}CH_2CH_2$–).

Step e The mesylate **12** (0.21 g, 0.52 mmol) was dissolved in 1,4-dioxane (12 ml), and K_2CO_3 (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 ($MgSO_4$), 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. ^{1}H-NMR ($CDCl_3$) δ: 0.34—0.51 (4H, m, *cyclo*-Pr CH_2×2), 1.42—1.44 (2H, m, 4-CH_2 of piperidino group), 1.53—1.73 (8H, m, 3-CH_2 and 5-CH_2 of piperidino group, 3-CH and 5-CH of 4-piperidinyl group, piperidino–CH_2–$\underline{CH_2}$–CH_2–), 1.81—1.91 (2H, m, 3-CH and 5-CH of 4-piperidinyl group), 2.31—2.36 (9H, m, 2-CH_2 and 6-CH_2 of piperidino group, 2-CH and 6-CH of 4-piperidinyl group, piperidino–$\underline{CH_2}$–CH_2–CH_2–, *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_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.27 (1H, m, piperidine 4-CH). APCI-MS m/z: 383 ($M+H^+$). *Anal.* Calcd for $C_{22}H_{34}N_6$: 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-

pound **2c**.

Compound **2l** (White Solid): mp 104—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.34—0.41 and 0.43—0.51 (each 2H, each m, *cyclo*-Pr CH_2×2), 1.65—1.75 (3H, m, morpholino–CH_2–$\underline{CH_2}$–CH_2–, *cyclo*-Pr CH), 1.81—1.91 (4H, m, piperidine 3-CH_2 and 5-CH_2), 2.30—2.45 (8H, m, morpholino–$\underline{CH_2}$–CH_2–CH_2–, morpholine 3-CH_2 and 5-CH_2, piperidine 2-CH and 6-CH), 3.11 (2H, m, piperidine 2-CH and 6-CH), 3.52—3.63 (6H, m, morpholino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.23 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 385 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{32}N_6O$: 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. ^{1}H-NMR ($CDCl_3$) δ: 0.36—0.41 and 0.43—0.51 (each 2H, each m, *cyclo*-Pr CH_2×2), 1.62—1.75 (5H, m, thiomorpholino–CH_2–$\underline{CH_2}$–CH_2–, piperidine 3-CH and 5-CH, *cyclo*-Pr CH), 1.81—1.90 (4H, m, thiomorpholine 2-CH and 6-CH, piperidine 3-CH and 5-CH), 2.31—2.44 (4H, m, thiomorpholino–$\underline{CH_2}$–CH_2–CH_2–, thiomorpholine 2-CH and 6-CH), 2.65—2.72 (6H, m, thiomorpholine 3-CH_2 and 5-CH_2, piperidine 2-CH and 6-CH), 3.11 (2H, m, piperidine 2-CH and 6-CH), 3.51—3.60 (6H, m, thiomorpholino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.22 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 401 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{32}N_6S$: 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%). ^{1}H-NMR (DMSO-d_6) δ: 1.65—1.79 (2H, m, HO–$CH_2\underline{CH_2}CH_2$–), 3.38—3.55 (6H, m, HO–$\underline{CH_2}CH_2\underline{CH_2}$–, imidazolidine ring CH_2), 3.63—3.75 (2H, m, imidazolidine ring CH_2), 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_2CO_3 (1.71 g, 12.4 mmol) in DMF (12 ml) was added 1-*tert*-butoxycarbonyl-4-methanesulfonyloxymethylpiperidine[12] (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 ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with $CH_3OH/CHCl_3$ (from 3 to 8%) to provide compound **14** (1.21 g, 50%). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.40 (2H, m, HO–$CH_2\underline{CH_2}CH_2$–), 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–$\underline{CH_2}CH_2CH_2$–), 3.60—3.78 (8H, m, 4-piperidinyl–$\underline{CH_2}$–, HO–$CH_2CH_2\underline{CH_2}$–, imidazolidine ring CH_2×2), 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 ($MgSO_4$), 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%). ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.28 (2H, m, HO–$CH_2\underline{CH_2}CH_2$–), 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_3SO_2–), 3.30—3.78 (8H, m, 4-piperidinyl–$\underline{CH_2}$–, HO–$CH_2CH_2\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.05—4.24 (2H, m, 2-CH and 6-CH of piperidine), 4.35 (2H, t, *J*=6.0 Hz, MsO–$\underline{CH_2}CH_2CH_2$–).

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 ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (from 1 to 15% $CH_3OH/CHCl_3$) to give compound **15** (490 mg, 64%). ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.29 (2H, m, 4-CH_2 of piperidino group), 1.43—1.52 (11H, m, HO–$CH_2\underline{CH_2}CH_2$–, *tert*-butyl), 1.58—1.75 (6H, m, 3-CH_2 and 5-CH_2 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_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 2.62—2.79 (2H, m, 2-CH and 6-CH of 4-piperidinylmethyl group), 3.28—3.50 (2H, m, piperidino–CH_2–CH_2–$\underline{CH_2}$–), 3.55—3.70 (6H, m, 4-piperidinyl–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 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_2CO_3 (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 ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with 20% 2 mol/l NH_3–$CH_3OH/CHCl_3$ to yield compound **2h** (13 mg, 20%) as a white solid. mp 115—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, d, *J*=6.6 Hz, CH_3 of *iso*-Pr), 1.23—1.50 (2H, m, 4-CH_2 of piperidino group), 1.51—1.63 (6H, m, piperidino–$\underline{CH_2}$–CH_2–CH_2–, 3-CH_2 and 5-CH_2 of piperidino group), 1.68—1.94 (5H, m, 3-CH_2, 4-CH and 5-CH_2 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_2 and 6-CH_2 of piperidino group, piperidino–$\underline{CH_2}$–CH_2–CH_2–), 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_2–CH_2–$\underline{CH_2}$–), 3.53—3.67 (6H, m, 4-piperidinyl–$\underline{CH_2}$–, imidazolidine ring CH_2×2). APCI-MS *m/z*: 399 ($M+H^+$). *Anal.* Calcd for $C_{23}H_{38}N_6$: 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_2CO_3 (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 ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with 10% $CH_3OH/CHCl_3$ to yield compound **16** (1.96 g, 30%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, *J*=6.6 Hz, CH_3 of *iso*-Pr), 1.72—1.98 (6H, m, HO–$CH_2\underline{CH_2}CH_2$–, piperidine 3-CH_2 and 5-CH_2), 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_2×2), 3.66—3.71 (2H, m, HO–$CH_2CH_2\underline{CH_2}$–), 3.74 (2H, t, *J*=6.8 Hz, HO–$\underline{CH_2}CH_2CH_2$–), 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 ($MgSO_4$), filtered and concentrated under reduced pressure to afford the mesylate **17** (1.34 g, 55%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d, *J*=6.6 Hz, CH_3 of *iso*-Pr), 1.75—1.80 (4H, m, piperidine 3-CH_2 and 5-CH_2), 2.13—2.21 (2H, m, MsO–$CH_2\underline{CH_2}CH_2$–), 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_3SO_2–), 3.62 (4H, s, imidazolidine ring CH_2×2), 3.72 (2H, t, *J*=7.2 Hz, MsO–$CH_2CH_2\underline{CH_2}$–), 4.20 (1H, m, piperidine 4-CH), 4.35 (2H, t, *J*=5.9 Hz, MsO–$\underline{CH_2}CH_2CH_2$–).

Step c The mesylate **17** (1.77 g, 4.47 mmol) was dissolved in 1,4-dioxane (20 ml), and K_2CO_3 (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 ($MgSO_4$), 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. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, *J*=6.6 Hz, CH_3 of *iso*-Pr), 1.70—1.93 (6H, m, piperidine 3-CH_2 and 5-CH_2, morpholino–CH_2–$\underline{CH_2}$–CH_2–), 2.24—2.50 (8H, m, piperidine 2-CH and 6-CH, morpholine 3-CH_2 and 5-CH_2, morpholino–$\underline{CH_2}$–CH_2–CH_2–), 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_2 and 6-CH_2, morpholino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.18 (1H, m, piperidine 4-CH). APCI-MS *m/z*: 387 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{34}N_6O$: 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. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, *J*=6.6 Hz, CH_3 of *iso*-Pr), 1.67—1.88 (6H, m, piperidine 3-CH_2 and 5-CH_2, thiomorpholino–CH_2–$\underline{CH_2}$–CH_2–), 2.27—2.37 (2H, m, thiomorpholine 2-CH and 6-CH), 2.41 (2H, t, *J*=7.0 Hz, thiomorpholino–$\underline{CH_2}$–CH–

CH_2–), 2.65—2.79 (9H, m, piperidine 2-CH and 6-CH, thiomorpholine 2-CH, 6-CH, 3-CH_2 and 5-CH_2, CH of *iso*-Pr), 2.94—2.98 (2H, m, piperidine 2-CH and 6-CH), 3.54—3.60 (6H, m, thiomorpholino–CH_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.19 (1H, m, piperidine 4-CH). APCI-MS *m*/*z*: 403 ($M+H^+$). *Anal.* Calcd for $C_{21}H_{34}N_6S$: 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. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J=6.6 Hz, CH_3 of *iso*-Pr), 1.75 (2H, m, 4-oxopiperidino–CH_2–$\underline{CH_2}$–CH_2–), 1.87—1.99 (4H, m, piperidine 3-CH_2 and 5-CH_2), 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–$\underline{CH_2}$–CH_2–CH_2–), 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_2–CH_2–$\underline{CH_2}$–, imidazolidine ring CH_2×2), 4.19 (1H, m, piperidine 4-CH). APCI-MS *m*/*z*: 399 ($M+H^+$). *Anal.* Calcd for $C_{22}H_{34}N_6O$: 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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