Novel Histamine H_3 Receptor Antagonists: Synthesis and Evaluation of Formamidine and *S*-Methylisothiourea Derivatives

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In order to obtain a new, potent and selective histamine H_3 receptor antagonist, chemical modifications of thioperamide, a well-known H_3 receptor antagonist, were conducted. A new series of compounds has been synthesized by modifying the thiourea and cyclohexyl groups of thioperamide, and tested for H_3 receptor affinity by receptor binding assay using plasma membrane from rat cerebral cortex. The thiourea group of thioperamide was found to be replaceable with a basic moiety such as formamidine or *S*-methylisothiourea. Replacement of the cyclohexyl group in thioperamide by a 1-adamantyl or an *exo*-2-norbornyl group increased the affinity for H_3 receptor. Among the compounds synthesized, *N*-(1-adamantyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]formamidine 3f (AQ0145) showed the highest H_3 receptor affinity, having a potent antagonistic activity. This compound was at least 1000-fold more active towards H_3 than towards H_1 and H_2 receptors.

Key words histamine H_3 receptor antagonist; formamidine derivative; *S*-methylisothiourea derivative; AQ0145

Histamine, besides being a potent autacoid, has been shown to be a neurotransmitter or a neuromodulator in mammalian brain, like other monoamines such as dopamine, noradrenaline and serotonin. It has been suggested that neuronal histamine affects various brain activities, such as sleep–wakefulness, circadian rhythms, feeding and drinking behaviors, locomotor activities, learning and memory, and regulation of the neuroendocrine system, body temperature and circulation.[1] These actions of histamine are believed to be manifested through the activation of histamine receptors. Recently, in addition to two postsynaptic receptor subtypes (H_1, H_2), presynaptic H_3 receptors have been identified in the brain,[2] regulating the release and synthesis of histamine. In addition, it has been reported that the H_3 receptor modulates not only the release of histamine, but also other neurotransmitters, such as acetylcholine,[3–5] serotonin,[6,7] and noradrenaline,[8] in both the central nervous system and peripheral nervous system. Hence, it has been suggested that the H_3 receptor is a potential target for the development of new therapeutic agents.[9]

In order to establish the precise physiological role of the H_3 receptor, it is necessary to develop potent and specific H_3 ligands. So far, some active and selective H_3 agonists ((*R*)-α-methylhistamine,[10,11] α(*R*), β(*S*)-dimethylhistamine,[12,13] imetit,[14] and immepip[15]) and H_3 antagonists (thioperamide,[11,16] clobenpropit,[14] impentamine[17] and UCL1199[18]) have been successfully synthesized (Fig. 1). Among them, (*R*)-α-methylhistamine and thioperamide, the first H_3 receptor ligands, were used to characterize the H_3 receptor definitively,[11] and were also used for various experiments to investigate the physiological role of the H_3 receptor. It was observed that administration of thioperamide in animals induces arousal effects,[19] enhances locomotor activity,[20] and exerts anticonvulsion activity.[21] However, thioperamide does not appear to be suitable for human studies because of potential liver toxicity.

These facts led us to attempt the elaboration of new H_3 antagonists based on thioperamide. Thioperamide is composed of three parts, an imidazole ring, a thiourea group (a neutral polar moiety), and a cyclohexyl group (a hydrophobic moiety). The modification of the imidazole ring of thioperamide results in reduced activities.[22–24] The thiourea was replaced with several other neutral polar moieties,[16,25,26] but these modifications also resulted in insufficient activity. Importantly, another antagonist clobenpropit contains a basic polar moiety isothiourea instead of thiourea, suggesting that thiourea in thioperamide is also replaceable with a basic polar moiety. However, only a few attempts have so far been made at bioisosteric replacement of the thiourea in thioperamide with a basic polar moiety.[16] Here we report the design, synthesis, and evaluation of novel H_3 receptor antagonists focusing on chemical modification of the thiourea moiety and cyclohexyl group in thioperamide.

Chemistry

N-Substituted thiourea, formamidine, and *S*-methylisothiourea derivatives (**2**—**4**) were synthesized according to the routes illustrated in Chart 1. They were prepared from a common intermediate **1**, which was synthesized according to the previous report.[27] The intermediate **1** was treated with the alkyl, aryl, and aralkyl isothiocyanates

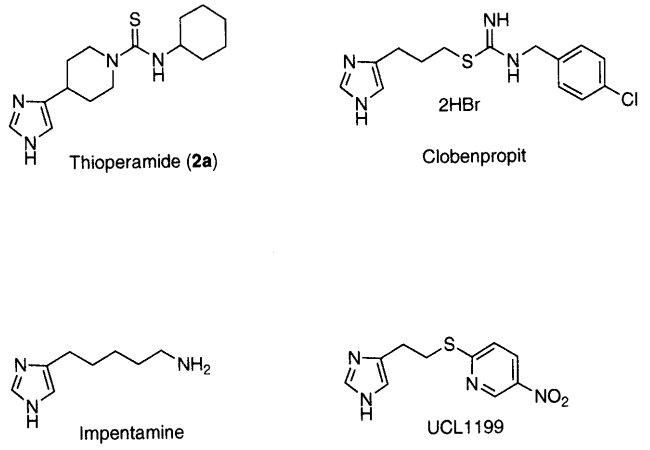

Fig. 1

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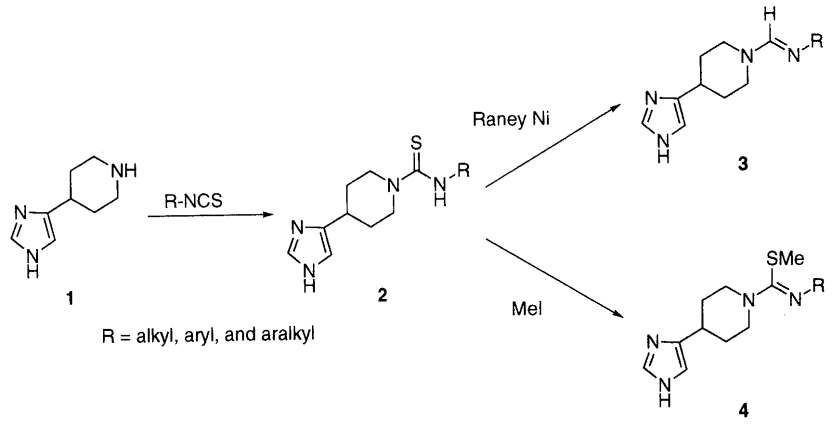


Chart 1

(RNCS) in refluxing toluene to give the corresponding thiourea derivatives.[16] Requisite isothiocyanates were prepared from the corresponding amines by treatment with carbon disulfide and ethyl chloroformate,[28] except for *exo*-2-norbornyl isothiocyanate, which was prepared from 2-norbornene and potassium thiocyanate.[29] Desulfurization of these thiourea derivatives **2** by Raney nickel in ethanol furnished the target formamidine derivatives **3**.[30] The desired *S*-methyl isothiourea derivatives **4** were synthesized by reaction of the corresponding thiourea derivatives **2** with iodomethane in methanol containing excess hydrogen chloride.

Results and Discussion

The affinities of the synthesized compounds for the H_3 receptor *in vitro* were accessed by the receptor binding assay of Arrang *et al.*[11] in which the effects of compounds on the binding of [^{3}H](*R*)α-methylhistamine to plasma membrane from rat cerebral cortex are examined. The affinities of the compounds are expressed as relative values (thioperamide = 100) in Table 1. The affinities of thiourea derivatives **2**, formamidine derivatives **3** that have formamidine instead of thiourea and *S*-methylisothiourea derivatives **4** that have *S*-methylisothiourea instead of thiourea are listed in separate columns.

First, the effects of replacing the thiourea moiety of thioperamide with formamidine and *S*-methylisothiourea were investigated (**2a**, **3a**, **4a**). The formamidine **3a** showed an affinity for H_3 receptor as high as that of thioperamide. The *S*-methylisothiourea **4a** was a third less potent than thioperamide. From these results, it was suggested that formamidine and *S*-methylisothiourea could function as a bioisostere of the thiourea in the H_3 receptor antagonist thioperamide, although formamidine is more effective. Therefore, the effects of various substituents R at the terminal nitrogen in **2a**, **3a**, and **4a** were extensively investigated by introducing alkyl, aryl, and aralkyl groups instead of the cyclohexyl ring.

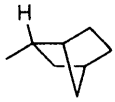
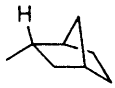
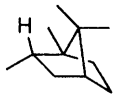
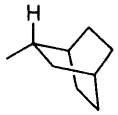
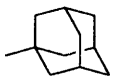
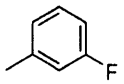
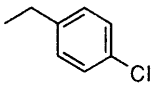
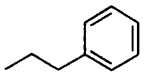
The binding affinities of various cycloalkyl substituents of the thiourea **2**, formamidine derivatives **3**, and *S*-methylisothiourea derivatives **4** are shown in Table 1. The substitution of the cyclohexyl group with an *exo*-2-norbornyl group resulted in an enhancement of the affinity in all of the thiourea derivatives **2**, formamidine derivatives **3**, and *S*-methylisothiourea derivatives **4**. The thiourea **2b**, formamidine **3b**, and *S*-methylisothiourea **4b** showed several times higher affinities than their mother compounds having a cyclohexyl group. The change of R from an *exo*-2-norbornyl group to an *endo*-2-norbornyl group resulted in a marked decrease in the affinity for H_3 receptor in every case (**2c**, **3c**, **4c**). Thus, the affinities were greatly dependent on the *exo*/*endo* stereochemistry. Alkylation of the *endo*-2-norbornyl group caused a marked decrease in the affinity, as shown by **2d**, **3d**, and **4d**. When R was a bicyclo[2.2.2]octyl group, the formamidine **3e** was nearly equipotent to thioperamide, but the *S*-methylisothiourea **4e** and thiourea **2e** showed low affinity. The effect of an adamantyl group on the affinity for the H_3 receptor was examined. The adamantyl-substituted thiourea **2f** was slightly more potent than thioperamide. Importantly, the introduction of an adamantyl group at terminal nitrogen in the formamidine led to **3f**, which was five times more potent than thioperamide and was the most potent derivative among the compounds synthesized in this study. The adamantyl-substituted *S*-methylisothiourea analog **4f** was found to have the highest affinity in the *S*-methylisothiourea series. When a 1,2,2-trimethylpropyl group was introduced, the thiourea **2g** suffered a small drop in affinity, but the formamidine **3g** and *S*-methylisothiourea **4g** showed greatly reduced affinity.

From the above results, *exo*-2-norbornyl and adamantyl groups were shown to be better than a cyclohexyl group as the substituent R at the terminal nitrogen. It was speculated that cycloalkyl groups such as cyclohexyl, *exo*-2-norbornyl and adamantyl could interact better than other substituents with the lipophilic binding site on the receptor.

In the next series of experiments, we synthesized compounds that have aryl groups (phenyl and 3-fluorophenyl groups) as R instead of the non-aromatic cyclohexyl ring and tested their binding to the H_3 receptor. As shown in Table 1 (thioureas **2h—i**, formamidines **3h—i** and *S*-methylisothioureas **4h—i**), the substitution failed to enhance the affinities of the compounds.

In H_3 antagonists of another type, represented by clobenpropit, aralkyl groups such as 4-chlorobenzyl and phenethyl on the isothiourea moiety play an important role in generating high affinity for the H_3 receptor.[27] Therefore, the effects of introduction of these substituents

Table 1. Inhibitory Effects of New H_3 Ligand Derivatives on the Binding of [^{3}H](*R*)α-Methylhistamine to Rat Cerebral Cortex Membranes[a)]

Compd.	Structure of R	2	3	4
a		100	113	31
b		193	300	50
c		44	15	1.6
d		8	2	3
e		30	88	16
f		150	544	75
g		70	21	5
h		21	71	16
i		16	46	11
j		5	16	8
k		20	35	5

a) Value relative to thioperamide (=100).

were examined. Although the substituted formamidine and the substituted *S*-methylisothiourea derivatives (**3j—k**, **4j—k**) were structurally analogous to clobenpropit, these compounds were found to have very weak affinities for the H_3 receptor. In general, the incorporation of aryl and aralkyl groups in all types of compounds (**2—4**) led to a decrease in the affinity for H_3 receptor. From these results, it was suggested that aryl and aralkyl moieties do not fit well into the lipophilic pocket of the receptor.

When the substituent R was the same in the three types of systems, the affinity for H_3 receptor was generally in the following order: formamidine > thiourea > *S*-methylisothiourea. The differences in affinity between formamidine, thiourea and *S*-methylisothiourea might be caused by both steric factors and the electronic effects in each individual system. Among the compounds, **3f** was selected as a potential candidate for further evaluation.

The pharmacological properties of **3f** are summarized in Table 2. Compound **3f** was regarded as a potent H_3 receptor antagonist since this compound antagonized the electrically evoked contractile response of isolated guinea pig ileum segments with the antagonistic dissociation constant K_b value of 7.4 nM. The potency of **3f** was comparable to that of thioperamide (K_b = 5.9 nM). In order to confirm the specificity of **3f** as an H_3 receptor antagonist, the effects of this compound on H_1 and H_2 receptors were

Table 2. Pharmacological Properties of **3f** as a H_3 Receptor Antagonist

Compound	H_3 receptor		H_1 receptor	H_2 receptor
	(K_i; nM)[a]	(K_b; nM)[b]	(K_b; μM)[c]	(K_b; μM)[d]
Thioperamide	32.1	5.9	150	>1000
3f	5.9	7.4	53	>1000

a) Inhibitory effects of H_3 ligands on the binding of [^{3}H](*R*)α-methylhistamine to rat cerebral cortex membranes. *b*) Dissociation constants (K_b) obtained for H_3 ligands of (*R*)α-methylhistamine-induced inhibition of contractile responses to electrical stimulation in guinea pig ileum. *c*) K_b obtained for H_3 ligands of histamine-induced contractile responses in guinea pig ileum. *d*) K_b obtained for H_3 ligands of histamine-induced positive chronotropic responses in guinea pig right atrium.

examined. The K_b values of **3f** for the H_1 and H_2 receptors were 53 μM and >1 mM, respectively. The antagonistic dissociation constant K_b values of thioperamide for H_1 and H_2 receptors were 150 μM and >1 mM, respectively. From these results, it was concluded that **3f** is a potent and selective H_3 receptor antagonist comparable to thioperamide. In addition, it has been reported that **3f** decreases seizure susceptibility of electrically induced convulsions in mice, suggesting the efficacy of this compound *in vivo*.[31]

Conclusion

Starting from the structure of thioperamide, various formamidine and *S*-methylisothourea derivatives were synthesized with the aim of obtaining a new, potent and selective histamine H_3 receptor antagonist. These basic moieties were found to be efficient replacements for thiourea in thioperamide. Of the compounds examined, **3f** (AQ0145) was a potent and selective H_3 receptor antagonist comparable to thioperamide.

Experimental

Reagents were purchased from commercial suppliers and used without further purification. Reaction solvents were distilled from an appropriate drying agent before use. Flash column chromatography was carried out at medium pressure using silica gel (Nacalai Tesque, 230—400 mesh) with the indicated solvent. Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. IR and NMR spectra, which were in agreement with the structures cited, were recorded on a Shimadzu IR-420 instrument for IR and Bruker AC-200 and AM-500 spectrometers (sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) or tetramethylsilane (TMS) as an internal standard) for NMR. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). High-resolution mass (HR-MS) spectra were obtained on a Hitachi M-2000 instrument in a positive secondary ion mass (SI-MS) mode.

***N*-(1-Adamantyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]thiourea (2f)** A solution of 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride[27] (15.0 g, 66.9 mmol) in MeOH (1.2 l) was treated with K_2CO_3 (21.7 g, 157 mmol) at room temperature. The mixture was refluxed for 3 h, insoluble material was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was taken up in 2-propanol (1 l). After gentle heating, insolubles were removed by filtration, and the filtrate was concentrated *in vacuo*. This residue was taken up in benzene, and the mixture was evaporated for azeotropic removal of methanol. A solution of the residue in toluene (280 ml) was treated with 1-adamantyl isothiocyanate (15.5 g, 80.3 mmol) at room temperature. The mixture was refluxed for 6 h, then concentrated *in vacuo*. The residue was chromatographed ($CHCl_3$/MeOH = 10/1→5/1), and the product was recrystallized from MeOH–AcOEt–hexane to give **2f** (13.5 g, 58%). White powder. mp 111.0—113.0 °C. IR (KBr): 3370, 2910, 1530, 1355, 1305, 1175 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.01—11.57 (br, 1H), 7.51 (s, 1H), 6.82 (br s, 0.6H), 6.62 (br s, 0.4H), 6.51 (br s, 0.4H), 6.46 (br s, 0.6H), 4.72—4.42 (m, 2H), 3.00 (t, J = 12 Hz, 2H), 2.89—2.61 (m, 1H), 2.25 (d, J = 2.3 Hz, 6H), 2.10—1.34 (m, 8H). HR-MS *m/z*: Calcd for $C_{19}H_{29}N_4S$ (MH^+), 345.2102; Found, 345.2122. *Anal.* Calcd for $C_{19}H_{28}N_4S \cdot H_2O$: C, 62.95; H, 8.34; N, 15.45. Found: C, 62.91; H, 8.21; N, 15.51.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(*exo*-2-norbornyl)thiourea (2b)** The title compound **2b** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and *exo*-2-norbornyl isothiocyanate by the same procedure as described for **2f**. The product was recrystallized from CH_2Cl_2–ether to give **2b** (82%). White needles. mp 140.5—142.0 °C. IR (KBr): 3400, 2940, 1520, 1340, 1193 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.76—11.10 (br, 1H), 7.51 (s, 1H), 6.96 (d, J = 6.2 Hz, 1H), 6.75 (br s, 1H), 4.86—4.50 (m, 2H), 4.19—3.92 (m, 1H), 3.01 (t, J = 11.4 Hz, 2H), 2.89—2.66 (m, 1H), 2.34—2.16 (m, 2H), 1.86 (d, J = 11.4 Hz, 2H), 1.71—0.97 (m, 10H). HR-MS *m/z*: Calcd for $C_{16}H_{25}N_4S$ (MH^+), 305.1790; Found, 305.1759. *Anal.* Calcd for $C_{16}H_{24}N_4S \cdot 0.5H_2O$: C, 61.31; H, 8.04; N, 17.87. Found: C, 61.29; H, 7.85; N, 17.84.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(*endo*-2-norbornyl)thiourea (2c)** The title compound **2c** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and *endo*-2-norbornyl isothiocyanate by the same procedure as described for **2f**. The product was recrystallized from MeOH–AcOEt–hexane to give **2c** (73%). White powder. mp 168.0—169.5 °C. IR (KBr): 3300, 2950, 1520, 1340 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.02—11.50 (br, 1H), 7.50 (s, 1H), 7.29—6.96 (br, 1H), 6.82 (br s, 0.7H), 6.63 (br s, 0.3H), 4.88—4.57 (m, 2H), 4.55—4.36 (m, 1H), 3.19—2.64 (m, 3H), 2.61—2.45 (m, 2H), 2.30—1.08 (m, 12H). *Anal.* Calcd for $C_{16}H_{24}N_4S$: C, 63.12; H, 7.95; N, 18.40. Found: C, 63.05; H, 8.07; N, 18.26.

***N*-(*endo*-2-Bornyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]thiourea (2d)** The title compound **2d** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and *endo*-2-bornyl isothiocyanate by the same procedure as described for **2f**. The product was recrystallized from MeOH–ether–hexane to give **2d** (79%). White powder. mp 132.0—134.0 °C. IR (KBr): 3400, 2930, 1525, 1350 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.08—11.58 (br, 1H), 7.50 (s, 1H), 7.04—6.85 (br, 1H), 6.82 (br s, 0.7H), 6.65 (br s, 0.3H), 5.10—4.90 (m, 1H), 4.81—4.53 (m, 2H), 3.22—2.68 (m, 3H), 2.37—1.00 (m, 11H), 0.91 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H). *Anal.* Calcd for $C_{19}H_{30}N_4S \cdot 0.4H_2O$: C, 64.51; H, 8.78; N, 15.84. Found: C, 64.44; H, 9.17; N, 15.90.

***N*-(Bicyclo[2.2.2]octan-2-yl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]thiourea (2e)** The title compound **2e** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and bicyclo[2.2.2]octan-2-yl isothiocyanate by the same procedure as described for **2f**. The product was recrystallized from MeOH–ether–hexane to give **2e** (87%). White powder. mp 143.0—146.0 °C. IR (KBr): 2900, 1520, 1360 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.10—11.50 (br, 1H), 7.50 (s, 1H), 7.19—6.90 (br, 1H), 6.82 (br s, 0.7H), 6.64 (br s, 0.3H), 4.91—4.58 (m, 2H), 4.50—4.28 (m, 1H), 3.24—2.62 (m, 3H), 2.03—1.17 (m, 16H). *Anal.* Calcd for $C_{17}H_{26}N_4S \cdot 0.33H_2O$: C, 62.94; H, 8.29; N, 17.27. Found: C, 62.77; H, 8.31; N, 17.00.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(1,2,2-trimethylpropyl)thiourea (2g)** The title compound **2g** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and 1,2,2-trimethylpropyl isothiocyanate by the same procedure as described for **2f**, in 26% yield. Pale yellow solid. mp 167—171 °C. IR (KBr): 3340, 2940, 1525, 1333 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.26—11.50 (br, 1H), 7.51 (s, 1H), 6.92 (d, J = 9.1 Hz, 1H), 6.79 (br s, 1H), 4.85—4.43 (m, 3H), 3.22—2.65 (m, 3H), 2.00—1.75 (m, 2H), 1.69—1.26 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H). HR-MS *m/z*: Calcd for $C_{15}H_{27}N_4S$ (MH^+), 295.1946; Found, 295.1942. *Anal.* Calcd for $C_{15}H_{26}N_4S \cdot 0.25H_2O$: C, 61.19; H, 8.90; N, 19.03. Found: C, 61.02; H, 8.76; N, 18.81.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-phenylthiourea (2h)** The title compound **2h** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and phenyl isothiocyanate by the same procedure as described for **2f**, in 45% yield. Foam. mp 102—108 °C. IR (KBr): 1520, 1493, 1317, 758, 695 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.91—11.04 (br, 1H), 9.28 (s, 1H), 7.53 (s, 1H), 7.41—6.97 (m, 5H), 6.79 (s, 1H), 4.74 (d, J = 12.6 Hz, 2H), 3.20 (t, J = 12.6 Hz, 2H), 2.96—2.73 (m, 1H), 2.06—1.84 (m, 2H), 1.72—1.42 (m, 2H). HR-MS *m/z*: Calcd for $C_{15}H_{19}N_4S$ (MH^+), 287.1322; Found, 287.1313. *Anal.* Calcd for $C_{15}H_{18}N_4S \cdot 0.25H_2O$: C, 61.93; H, 6.41; N, 19.26. Found: C, 61.80; H, 6.43; N, 19.09.

***N*-(3-Fluorophenyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-

thiourea (2i) The title compound **2i** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and 3-fluorophenyl isothiocyanate by the same procedure as described for **2f**, in 91% yield. Pale yellow amorphous solid. mp 92—98 °C. IR (KBr): 3180, 2900, 1595, 1526, 1484, 1316, 775, 760, 708 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.16—11.56 (br, 1H), 9.38 (br s, 1H), 7.53 (s, 1H), 7.42—7.06 (m, 3H), 6.98—6.63 (br, 1H), 6.90 (dt, J=2.1, 8.7 Hz, 1H), 4.72 (d, J=13.2 Hz, 2H), 3.32—3.11 (m, 2H), 3.03—2.68 (m, 1H), 2.07—1.86 (m, 2H), 1.76—1.44 (m, 2H). HR-MS m/z: Calcd for $C_{15}H_{18}FN_4S$ (MH^+), 305.1228; Found, 305.1222. *Anal.* Calcd for $C_{15}H_{17}FN_4S \cdot 0.25H_2O$: C, 58.33; H, 5.71; N, 18.14. Found: C, 58.34; H, 5.72; N, 18.20.

***N*-(4-Chlorobenzyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-thiourea (2j)** The title compound **2j** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and 4-chlorobenzyl isothiocyanate by the same procedure as described for **2f**, in 32% yield. Foam. mp 87—92 °C. IR (KBr): 3200, 1528, 1484, 1320, 1088, 820, 795 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.42—11.13 (br, 1H), 8.23 (t, J=5.5 Hz, 1H), 7.52 (s, 1H), 7.37 (d, J=8.6 Hz, 2H), 7.29 (d, J=8.6 Hz, 2 H), 6.77 (br s, 1H), 4.77 (d, J=5.5 Hz, 2H), 4.69 (d, J=12.0 Hz, 2H), 3.12 (t, J=12.0 Hz, 2H), 2.94—2.70 (m, 1H), 2.03—1.78 (m, 2H), 1.66—1.34 (m, 2H). HR-MS m/z: Calcd for $C_{16}H_{20}ClN_4S$ (MH^+), 335.1088; Found, 335.1108. *Anal.* Calcd for $C_{16}H_{19}ClN_4S \cdot 0.25H_2O$: C, 56.63; H, 5.79; N, 16.51. Found: C, 56.49; H, 5.64; N, 16.32.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(2-phenylethyl)thiourea (2k)** The title compound **2k** was prepared from 4-[4(5)-1*H*-imidazolyl]piperidine dihydrochloride and 2-phenylethyl isothiocyanate by the same procedure as described for **2f**, in 51% yield. Foam. mp 42—45 °C. IR (KBr): 3300, 1520, 747, 696 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.56—11.05 (br, 1H), 7.76 (t, J=5.0 Hz, 1 H), 7.52 (s, 1H), 7.39—7.08 (m, 5H), 6.76 (br s, 1H), 4.64 (d, J=12.6 Hz, 2H), 3.84—3.58 (m, 2H), 3.06 (t, J=12.6 Hz, 2H), 2.85 (t, J=8.3 Hz, 2H), 2.94—2.66 (m, 1H), 2.00—1.76 (m, 2H), 1.63—1.32 (m, 2H). HR-MS m/z: Calcd for $C_{17}H_{23}N_4S$ (MH^+), 315.1634; Found, 315.1633. *Anal.* Calcd for $C_{17}H_{22}N_4S \cdot 0.33H_2O$: C, 63.73; H, 7.13; N, 17.49. Found: C, 63.72; H, 7.00; N, 17.39.

***N*-(1-Adamantyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-formamidine Dihydrochloride (3f)** The thiourea **2f** (13.2 g, 38.3 mmol) was dissolved in EtOH (200 ml), and a suspension of Raney nickel (*ca.* 200 g) in EtOH (200 ml) was added at 0 °C. The mixture was stirred for 1 h at the same temperature, then the supernatant solution was separated by decantation, and the residue was washed with EtOH (5 × 80 ml). The supernatant and washings were combined, and filtered through Celite. The filtrate was mixed with 10% HCl–MeOH (300 ml) at 0 °C. After having been stirred at the same temperature for 0.5 h, the solution was concentrated *in vacuo* to give crude **3f** (10.5 g) as a white amorphous solid. The crude product was purified as the picrate by means of the following procedure. A solution of the crude product (10.5 g) in MeOH (140 ml) was added to a solution of picric acid (20.0 g, 87.1 mmol) in MeOH (350 ml). When water (700 ml) was added to the well-stirred solution, a yellow powder was precipitated. The precipitate was collected by filtration and recrystallized from MeOH–acetone–ether to give the picrate **3f** (8.72 g) as a yellow powder. This salt was converted to its dihydrochloride **3f** as follows. The picrate (8.72 g) was added to 2.4 N aqueous HCl (330 ml), and liberated picric acid was separated by extraction with nitromethane (3 × 100 ml). The aqueous solution was concentrated *in vacuo* and the product was recrystallized from EtOH–ether to give **3f** (3.51 g, 24%). White powder. mp 240 °C (dec). IR (KBr): 2800, 1682, 1602, 1460, 1348, 1065, 950, 795, 600 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ: 8.63 (s, 1H), 7.80 (s, 1H), 7.31 (s, 1H), 4.07 (d, J=13.2 Hz, 1H), 3.92 (d, J=13.2 Hz, 1H), 3.59 (dt, J=2.6, 13.2 Hz, 1H), 3.29 (dt, J=2.6, 13.2 Hz, 1H), 3.23 (t, J=3.7 Hz, 1H), 2.27—2.10 (m, 5H), 1.90 (d, J=2.2 Hz, 6H), 1.88—1.77 (m, 2H), 1.74 (d, J=12.3 Hz, 3H), 1.67 (d, J=12.3 Hz, 3H). HR-MS m/z: Calcd for $C_{19}H_{29}N_4$ (MH^+), 313.2382; Found, 313.2375. *Anal.* Calcd for $C_{19}H_{28}N_4 \cdot 2HCl \cdot 0.85H_2O$: C, 56.95; H, 7.97; N, 13.98. Found: C, 56.97; H, 8.05; N, 14.04.

***N*-Cyclohexyl-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]formamidine Dihydrochloride (3a)** The title compound **3a** was prepared from thioperamide **2a** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride **3a** (42%). White amorphous solid. IR (KBr): 3400, 2920, 1690, 1620, 1450 cm^{-1}. ^{1}H-NMR (200 MHz, MeOH-d_4) δ: 8.89 (s, 1H), 8.09 (br s, 1H), 7.43 (s, 1H), 4.20 (d, J=13.0 Hz, 1H), 3.95 (d, J=13.0 Hz, 1H), 3.61 (t, J=13.0 Hz, 1H), 3.58—3.12 (m, 3H), 2.40—1.00 (m, 14H). HR-MS m/z: Calcd for $C_{15}H_{25}N_4$ (MH^+), 261.2070; Found, 261.2093. *Anal.* Calcd for $C_{15}H_{24}N_4 \cdot 2HCl \cdot 1.5H_2O$: C, 50.00; H, 8.11; N, 15.55. Found: C, 50.03; H, 8.45; N, 15.65.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(*exo*-2-norbornyl)-formamidine Dihydrochloride (3b)** The title compound **3b** was prepared from the thiourea **2b** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride **3b** (52%). Foam. IR (KBr): 3400, 2920, 1680, 1620 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.63 (s, 1H), 7.88 (s, 1H), 7.30 (s, 1H), 4.05 (d, J=14.2 Hz, 1H), 3.86 (d, J=13.6 Hz, 1H), 3.75—3.47 (m, 2H), 3.40—3.12 (m, 2H), 2.42—2.11 (m, 4H), 1.93—1.03 (m, 10H). HR-MS m/z: Calcd for $C_{16}H_{25}N_4$ (MH^+), 273.2070; Found, 273.2098.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(*endo*-2-norbornyl)-formamidine Dihydrochloride (3c)** The title compound **3c** was prepared from the thiourea **2c** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride **3c** (42%). Pale yellow powder. IR (KBr): 3400, 1685, 1620 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 15.50—14.30 (br, 1H), 9.92—9.50 (m, 1H), 9.09 (s, 1H), 8.22 (d, J=13.0 Hz, 1H), 7.50 (br s, 1H), 4.80—4.44 (m, 1H), 4.04—3.60 (m, 2H), 3.55—2.95 (m, 3H), 2.50—0.98 (m, 14H). HR-MS m/z: Calcd for $C_{16}H_{25}N_4$ (MH^+), 273.2070; Found, 273.2062.

***N*-(*endo*-2-Bornyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-formamidine Dihydrochloride (3d)** The title compound **3d** was prepared from the thiourea **2d** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride. Subsequent recrystallization (EtOH–ether) gave **3d** (7.5%). White powder. mp 230 °C (dec.). IR (KBr): 2950, 1690, 1620, 1450, 1370 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 15.30—13.60 (br, 1 H), 9.58—9.37 (m, 1H), 9.04 (s, 1H), 8.14 (d, J=13.2 Hz, 1H), 7.49 (s, 1H), 4.49—4.31 (m, 1H), 4.00—3.02 (m, 5H), 2.49—1.14 (m, 11H), 0.87 (s, 6H), 0.76 (s, 3H). *Anal.* Calcd for $C_{19}H_{30}N_4 \cdot 2HCl \cdot 2H_2O$: C, 53.90; H, 8.57; N, 13.23. Found: C, 53.91; H, 8.32; N, 13.59.

***N*-(Bicyclo[2.2.2]octan-2-yl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]formamidine Dihydrochloride (3e)** The title compound **3e** was prepared from the thiourea **2e** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride. Subsequent recrystallization (EtOH–ether) gave **3e** (23%). White powder. mp 224—228 °C. IR (KBr): 3500, 2920, 1700, 1615, 1470 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 15.30—14.00 (br, 1H), 9.65—9.39 (m, 1H), 9.05 (s, 1H), 8.19 (d, J=13.3 Hz, 1H), 7.49 (s, 1H), 4.68—4.41 (m, 1H), 3.95—3.00 (m, 5H), 2.25—1.22 (m, 16H). HR-MS m/z: Calcd for $C_{17}H_{27}N_4$ (MH^+), 287.2226; Found, 287.2236.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(1,2,2-trimethylpropyl)formamidine Dihydrochloride (3g)** The title compound **3g** was prepared from the thiourea **2g** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride to give **3g** (58%). Foam. IR (Nujol): 1685, 1610, 1120, 995 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.64 (s, 1H), 7.90 (s, 1H), 7.30 (s, 1H), 4.08 (d, J=13.4 Hz, 1H), 3.89 (d, J=13.4 Hz, 1H), 3.71—3.52 (m, 1H), 3.47—3.16 (m, 3H), 2.33—2.13 (m, 2H), 1.96—1.67 (m, 2H), 1.28 (d, J=6.9 Hz, 3H), 0.94 (s, 9H). HR-MS m/z: Calcd for $C_{15}H_{27}N_4$ (MH^+), 263.2226; Found, 263.2239.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-phenylformamidine (3h)** The title compound **3h** was prepared from the thiourea **2h** by the same procedure as described for **3f**, except that the crude product was purified as the free base by column chromatography ($CHCl_3$/MeOH = 10/1→5/1→3/1), in 41% yield. Foam. IR (KBr): 3200, 1616, 1582, 760, 695 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.96—10.67 (br, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.20 (t, J=7.8 Hz, 2H), 6.98—6.86 (m, 3H), 6.78 (br s, 1H), 4.67—2.66 (m, 5H), 2.04—1.83 (m, 2 H), 1.50 (dddd, J=12.2, 12.2, 12.2, 4.1 Hz, 2H). HR-MS m/z: Calcd for $C_{15}H_{19}N_4$ (MH^+), 255.1602; Found, 255.1610. *Anal.* Calcd for $C_{15}H_{18}N_4 \cdot 1.5H_2O$: C, 64.03; H, 7.52; N, 19.91. Found: C, 64.12; H, 7.55; N, 20.06.

***N*-(3-Fluorophenyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-formamidine Dimaleate (3i)** The title compound **3i** was prepared from the thiourea **2i** by the same procedure as described for **3f**, except that the crude product was purified as the dimaleate, instead of the picrate, by precipitation from EtOH–ether in 86% yield. White powder. mp 148—150 °C. IR (KBr): 1690, 1570, 1470, 1360, 1190, 985 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ: 8.67 (s, 1H), 8.47 (s, 1H), 7.58—7.57 (m, 1H), 7.35 (s, 1H), 7.20—7.07 (m, 3H), 6.30 (s, 4H), 4.33 (d, J=12.5 Hz, 1H), 4.12 (d, J=12.5 Hz, 1H), 3.81 (dt, J=2.5, 12.5 Hz, 1H), 3.56 (dt, J=2.5, 12.5 Hz, 1H), 3.32 (tt, J=3.6, 11.6 Hz, 1H), 2.40—2.26 (m, 2H), 2.03—1.86 (m, 2H). *Anal.* Calcd for $C_{15}H_{17}FN_4 \cdot 2C_4H_4O_4 \cdot 0.33H_2O$:

C, 54.12; H, 5.07; N, 10.98. Found: C, 54.06; H, 4.95; N, 11.08.

***N*-(4-Chlorobenzyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-formamidine Dihydrochloride (3j)** The title compound **3j** was prepared from the thiourea **2j** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride. Recrystallization (EtOH–EtOAc) gave **3j** (13%). Pale yellow solid. mp 153—156 °C. IR (KBr): 1680, 1610, 1460, 1090, 800, 620 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.65 (s, 1H), 8.05 (s, 1H), 7.55—7.44 (m, 2H), 7.36 (d, J=8.5 Hz, 2H), 7.31 (s, 1H), 4.63 (s, 2H), 4.12—3.84 (m, 2H), 3.88 (ddd, J=12.8, 12.8, 2.9 Hz, 1H), 3.26 (dddd, J=11.6, 11.6, 3.5, 3.5 Hz, 1H), 2.37—2.18 (m, 2H), 1.99—1.68 (m, 2H). HR-MS *m/z*: Calcd for $C_{16}H_{20}ClN_4$ (MH^+), 303.1368; Found, 303.1345.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*N'*-(2-phenylethyl)-formamidine Dihydrochloride (3k)** The title compound **3k** was prepared from the thiourea **2k** by the same procedure as described for **3f**. The crude product was purified as the picrate and converted to its dihydrochloride to give **3k** (60%). Foam. IR (Nujol): 1690, 1610, 1270, 1155, 995, 965 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.65 (s, 1H), 7.55—7.22 (m, 7H), 3.98—2.80 (m, 9H), 2.32—2.04 (m, 2H), 1.77—1.40 (m, 2H). HR-MS *m/z*: Calcd for $C_{17}H_{23}N_4$ (MH^+), 283.1914; Found, 283.1890.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*S*-methyl-*N'*-(*exo*-2-norbornyl)isothiourea Dihydrochloride (4b)** A solution of the thiourea **2b** (11.6 g, 38.3 mmol) in 10% HCl–MeOH (580 ml) was treated with iodomethane (41 ml, 659 mmol) at 0 °C. After having been stirred for 7 h at room temperature, the reaction mixture was concentrated *in vacuo* to give crude **4b**. The crude product was purified as the picrate and converted to its dihydrochloride by the same procedure as described for **3f**. Recrystallization (EtOH–ether) gave **4b** (8.77 g, 59%). White crystals. mp 170.0—171.0 °C. IR (KBr): 3370, 2850, 1595, 1448, 1387, 1360, 1255, 1093, 824 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ: 8.66 (d, J=1.3 Hz, 1H), 7.33 (s, 1H), 4.24 (d, J=13.6 Hz, 2H), 3.98—3.88 (m, 1H), 3.63—3.48 (m, 2H), 3.27 (dddd, J=3.7, 3.7, 11.7, 11.7 Hz, 1H), 2.62 (s, 3H), 2.42—2.33 (m, 2H), 2.32—2.22 (m, 2H), 1.97—1.80 (m, 3H), 1.66—1.46 (m, 4H), 1.35—1.24 (m, 2H), 1.23—1.14 (m, 1H). HR-MS *m/z*: Calcd for $C_{17}H_{27}N_4S$ (MH^+), 319.1946; Found, 319.1931. *Anal.* Calcd for $C_{17}H_{26}N_4S \cdot 2HCl \cdot H_2O$: C, 49.87; H, 7.39; N, 13.68. Found: C, 49.60; H, 7.43; N, 13.66.

***N*-Cyclohexyl-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea Dimaleate (4a)** A solution of thioperamide **2a** (0.50 g, 1.71 mmol) in MeOH (10 ml) was treated with 10% MeI–CH_2Cl_2 (1.06 ml) at 0 °C. The mixture was stirred for 5 h at the same temperature, then 10% aqueous K_2CO_3 was added. The mixture was extracted with CH_2Cl_2, and the combined extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH = 5/1→2/1) to give the free base of **4a** (0.194 g). A solution of the free base (0.183 g, 0.597 mmol) in EtOH (5 ml) was treated with maleic acid (0.139 g, 1.194 mmol) at 0 °C. The mixture was stirred for 0.5 h at the same temperature, then ether was added. The precipitated powder was collected by filtration to give **4a** (0.179 g, 19%). White powder. mp 138—141 °C. IR (KBr): 2900, 1580, 1490, 1390, 1370, 1200, 1080, 990, 865 cm^{-1}. ^{1}H-NMR (200 MHz, MeOH-d_4) δ: 8.64 (s, 1H), 7.31 (s, 1H), 6.26 (s, 4H), 4.24 (d, J=12.6 Hz, 2H), 4.05—3.90 (m, 1H), 3.53 (dt, J=2.0, 12.6 Hz, 2H), 3.19 (tt, J=4.0, 11.7 Hz, 1H), 2.64 (s, 3H), 2.25—2.15 (m, 2H), 2.08—1.10 (m, 12H). HR-MS *m/z*: Calcd for $C_{16}H_{27}N_4S$ (MH^+), 307.1946; Found, 307.1918. *Anal.* Calcd for $C_{16}H_{26}N_4S \cdot 2C_4H_4O_4$: C, 53.52; H, 6.36; N, 10.40. Found: C, 53.15; H, 6.31; N, 10.41.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*S*-methyl-*N'*-(*endo*-2-norbornyl)isothiourea Dihydrochloride (4c)** The title compound **4c** was prepared from the thiourea **2c** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride. Recrystallization (MeOH–ether) gave **4c** (45%). White powder. mp 187.5—189.0 °C. IR (KBr): 3350, 2880, 1600 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 9.06 (s, 1H), 7.47 (s, 1H), 4.30—4.01 (m, 3H), 3.51 (t, J=13.5 Hz, 2H), 3.29—3.09 (m, 1H), 2.62 (s, 3H), 2.42—1.22 (m, 14H). HR-MS *m/z*: Calcd for $C_{17}H_{27}N_4S$ (MH^+), 319.1946; Found, 319.1907. *Anal.* Calcd for $C_{17}H_{26}N_4S \cdot 2HCl \cdot 0.85H_2O$: C, 50.20; H, 7.36; N, 13.78. Found: C, 50.16; H, 7.58; N, 13.79.

***N*-(*endo*-2-Bornyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea Dihydrochloride (4d)** The title compound **4d** was prepared from thiourea **2d** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride to give **4d** (68%). Pale yellow amorphous solid. IR (KBr): 3350, 1600, 1445, 1370 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 15.50—14.50 (br, 1H), 10.00—9.55 (br, 1H), 9.09 (s, 1H), 7.49 (s, 1H), 4.44—4.05 (m, 3H), 3.88—3.40 (m, 2H), 3.32—3.05 (m, 1H), 2.62 (s, 3H), 2.48—1.17 (m, 11H), 0.92 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H). HR-MS *m/z*: Calcd for $C_{20}H_{33}N_4S$ (MH^+), 361.2414; Found, 361.2375. *Anal.* Calcd for $C_{20}H_{32}N_4S \cdot 2HCl \cdot 1.72H_2O$: C, 51.72; H, 8.12; N, 12.06. Found: C, 51.68; H, 8.36; N, 12.21.

***N*-(Bicyclo[2.2.2]octan-2-yl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea Dihydrochloride (4e)** The title compound **4e** was prepared from the thiourea **2e** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride. Recrystallization (EtOH–ether) gave **4e** (71%). White powder. mp 176.0—178.0 °C. IR (KBr): 3400, 2900, 1600, 1390 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 9.07 (s, 1H), 7.47 (s, 1H), 4.30—4.05 (m, 3H), 3.78—3.06 (m, 3H), 2.65 (s, 3H), 2.25—1.25 (m, 16H). HR-MS *m/z* : Calcd for $C_{18}H_{29}N_4S$ (MH^+), 333.2102; Found, 333.2102. *Anal.* Calcd for $C_{18}H_{28}N_4S \cdot 2HCl \cdot 0.73H_2O$: C, 51.65; H, 7.58; N, 13.39. Found: C, 51.61; H, 7.67; N, 13.37.

***N*-(1-Adamantyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea Dipicrate (4f)** The title compound **4f** was prepared from the thiourea **2f** by the same procedure as described for **4b**, except that the picrate was not converted to its dihydrochloride, in 61% yield. Yellow powder. IR (KBr): 1610, 1562, 1314, 1162, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 14.50—13.66 (br, 2H), 9.04 (s, 1H), 8.84—8.52 (br, 1H), 8.59 (s, 3H), 7.49 (s, 1H), 4.08 (d, J=13.5 Hz, 2H), 3.58—3.24 (m, 2H), 3.24—3.00 (m, 1H), 2.61 (s, 3H), 2.30—1.97 (m, 11H), 1.90—1.60 (m, 8H). HR-MS *m/z*: Calcd for $C_{20}H_{31}N_4S$ (MH^+), 359.2258; Found, 359.2220. *Anal.* Calcd for $C_{20}H_{30}N_4S \cdot 2C_6H_3N_3O_7$: C, 47.06; H, 4.44; N, 17.15. Found: C, 47.00; H, 4.46; N, 17.23.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*S*-methyl-*N'*-(1,2,2-trimethylpropyl)isothiourea Dihydrochloride (4g)** The title compound **4g** was prepared from the thiourea **2g** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride **4g** (98%). Foam. IR (KBr): 1580, 1440, 1380, 815 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.65 (s, 1H), 7.30 (s, 1H), 4.46—4.13 (m, 3H), 3.68—3.46 (m, 2H), 3.38—3.19 (m, 1H), 2.60 (s, 3H), 2.49—2.20 (m, 2H), 1.98—1.71 (m, 2H), 1.30 (d, J=6.9 Hz, 3H), 0.97 (s, 9H). HR-MS *m/z*: Calcd for $C_{16}H_{29}N_4S$ (MH^+), 309.2102; Found, 309.2141.

***N*,*N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*S*-methyl-*N'*-phenylisothiourea (4h)** The title compound **4h** was prepared from the thiourea **2h** by the same procedure as described for **4b**, except that the crude product was purified as the free base by column chromatography ($CHCl_3$/MeOH = 30/1→20/1→10/1), in 78% yield. Pale yellow amorphous solid. IR (KBr): 1570, 1180, 1140, 1092, 972, 763, 693 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.24—11.43 (br, 1H), 7.52 (s, 1H), 7.22 (t, J=7.5 Hz, 2H), 6.93 (t, J=7.5 Hz, 1H), 6.76 (d, J=7.5 Hz, 2H), 4.15 (d, J=7.5 Hz, 2H), 3.00 (d, J=12.5 Hz, 2H), 2.88—2.66 (m, 1H), 2.09 (s, 3H), 1.96 (d, J=12.6 Hz, 2H), 1.58 (dq, J=3.2, 12.3 Hz, 2H). HR-MS *m/z*: Calcd for $C_{16}H_{21}N_4S$ (MH^+), 301.1478; Found, 301.1481. *Anal.* Calcd for $C_{16}H_{20}N_4S \cdot 0.5H_2O$: C, 62.11; H, 6.84; N, 18.11. Found: C, 62.11; H, 6.73; N, 18.00.

***N*-(3-Fluorophenyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea (4i)** The title compound **4i** was prepared from the thiourea **2i** by the same procedure as described for **4b**, except that the crude product was purified as the free base by column chromatography ($CHCl_3$/MeOH = 30/1→15/1), in 31% yield. White amorphous solid. IR (KBr): 3060, 2920, 2830, 1563, 1182, 1116, 772, 748, 692 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 12.16—11.49 (br, 1H), 7.53 (s, 1H), 7.24 (dd, J=8.2, 15.2 Hz, 1H), 6.85 (br s, 1H), 6.73 (dt, J=2.0, 8.2 Hz, 1H), 6.66—6.49 (m, 2H), 4.18 (d, J=12.3 Hz, 2H), 3.04 (t, J=12.3 Hz, 2H), 2.92—2.66 (m, 1H), 2.11 (s, 3H), 2.06—1.86 (m, 2H), 1.75—1.44 (m, 2H). HR-MS *m/z*: Calcd for $C_{16}H_{20}FN_4S$ (MH^+), 319.1384; Found, 319.1395. *Anal.* Calcd for $C_{16}H_{19}FN_4S$: C, 60.35; H, 6.01; N, 17.60. Found: C, 60.25; H, 6.05; N, 17.34.

***N*-(4-Chlorobenzyl)-*N'*,*N'*-[3-(4(5)-1*H*-imidazolyl)pentamethylene]-*S*-methylisothiourea Dihydrochloride (4j)** The title compound **4j** was prepared from the thiourea **2j** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride **4j** (94%). White amorphous solid. IR (KBr): 1590, 1445, 1250, 1200, 830 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.65 (s, 1H), 7.48 (d, J=8.5 Hz, 2H), 7.36 (d, J=8.5 Hz, 2H), 7.31 (s, 1H), 4.30 (d, J=14.0 Hz, 2H), 3.73—3.49 (m, 2H), 3.41—3.18 (m, 1H), 2.55 (s, 3H),

2.37—2.19 (m, 2H), 2.00—1.72 (m, 2H). HR-MS *m/z*: Calcd for $C_{17}H_{22}ClN_4S$ (MH^+), 349.1244; Found, 349.1282.

***N,N*-[3-(4(5)-1*H*-Imidazolyl)pentamethylene]-*S*-methyl-*N'*-(2-phenylethyl)isothiourea Dihydrochloride (4k)** The title compound **4k** was prepared from the thiourea **2k** by the same procedure as described for **4b**. The crude product was purified as the picrate and converted to its dihydrochloride. Recrystallization (EtOH–ether) gave **4k** (37%). White powder. mp 148—150 °C. IR (KBr): 3320, 2800, 1595, 1420, 1350, 1260, 850, 750, 700 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O) δ: 8.64 (s, 1H), 7.51—7.24 (m, 6H), 4.18—3.96 (m, 4H), 3.42 (t, J=12.3 Hz, 2H), 3.30—3.10 (m, 1H), 3.01 (t, J=6.5 Hz, 2H), 2.27—2.11 (m, 2H), 1.85—1.54 (m, 2H). HR-MS *m/z*: Calcd for $C_{18}H_{25}N_4S$ (MH^+), 329.1790; Found, 329.1822. *Anal.* Calcd for $C_{18}H_{24}N_4S \cdot 2HCl \cdot H_2O$: C, 51.55; H, 6.73; N, 13.36. Found: C, 51.33; H, 6.73; N, 13.46.

H_3 Receptor Binding Assay Binding assay was performed according to Arrang *et al.*[11] Rat cerebral cortex was homogenized in 50 volumes of cold 50 mM Na_2HPO_4/KH_2PO_4 buffer, pH 7.5. After two successive centrifugations (500 × *g* for 2 min, 10000 × *g* for 20 min), the final pellets were resuspended in phosphate buffer. Membranes (400 μg of protein) were incubated with 2 nM [^{3}H](*R*)α-methylhistamine and a test compound for 60 min at room temperature. Incubations were terminated by addition of ice-cold phosphate buffer followed by rapid filtration through a glass-fiber filter (GF/C). Radioactivity retained on the filter was measured by liquid scintillation spectrometry. Specific binding was defined as radioactivity bound after subtracting nonspecific binding determined in the presence of 2 μM thioperamide.

H_3 Receptor Assay The effect on H_3 receptor was examined according to the method of Hew et *al.*[4] Isolated ileum of guinea pig was placed in a 20 ml Magnus chamber filled with Krebs–Henseleit solution, continuously gassed with 95% O_2/5% CO_2, at 30 °C. The ileum segments were electrically stimulated with a submaximal voltage at a frequency of 0.1 Hz for 1 ms. H_3 antagonistic effect was assessed after 5 min of pretreatment with a test compound, as the degree of antagonism to suppression of electrically induced ileum contraction by (*R*)α-methylhistamine.

H_1 Receptor Assay Isolated ileum of guinea pig was incubated in a 20 ml Magnus chamber filled with Tyrode solution, continuously gassed with 95% O_2/5% CO_2 at 30 °C. The H_1 antagonistic effect was assessed after 3 min of pretreatment with a test compound, as the degree of antagonism to histamine-induced ileum contraction.

H_2 Receptor Assay Isolated right atrium of guinea pig was incubated in a 20 ml Magnus chamber filled with Krebs–Henseleit solution, continuously gassed with 95% O_2/5% CO_2 at 33 °C. The H_2 antagonistic effect of a test compound was assessed as the degree of antagonism to histamine-induced positive chronotropic action.

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