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New Analogs of Burimamide as Potent and Selective Histamine H_3 Receptor Antagonists: The Effect of Chain Length Variation of the Alkyl Spacer and Modifications of the *N*-Thiourea Substituent

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Burimamide was one of the first compounds reported to antagonize the activation of the histamine H_3 receptor by histamine. We have prepared a large series of burimamide analogs by variation of the alkyl spacer length of burimamide from two methylene groups to six methylene groups and also by replacement of the *N*-methyl group with other alkyl and aryl groups. All analogs are reversible, competitive H_3 antagonists as determined on the guinea pig intestine. Elongation of the alkyl chain from an ethylene chain to a hexylene chain results in an increase of the H_3 antagonistic activity. The H_3 selective pentylene and hexylene analogs of burimamide are about 10 times more potent than burimamide. The *N*-thiourea substituents, however, have no beneficial influence on the affinity.

Introduction

The existence of a third histamine receptor subtype, inhibiting the synthesis and release of histamine, located presynaptically in histaminergic nerve endings in rat cerebral cortex, was suggested in 1983 by Arrang *et al.*[1] Confirmation of the existence of this new histamine receptor subtype was provided by the development of the H_3 selective agonist (*R*)-α-methylhistamine and the H_3 selective antagonist thioperamide.[2] The H_3 receptor has since been shown to play an important regulatory role in the release of other neurotransmitters in the central nervous system[3−6] and the periphery.[7−12]

A few years before the identification of the H_3 receptor, the antagonistic effect of the H_2 antagonist burimamide on the inhibitory action of histamine on electrically evoked contractions of guinea pig intestine preparations was described.[13] This inhibitory effect of histamine was reversible and not mediated by adrenergic nor H_1 receptors.[14] The histamine H_2 antagonist burimamide was able to block this inhibitory effect of histamine, but insensitivity of the evoked contractions to H_2 agonists made it doubtful that this effect was mediated by the H_2 receptor. Further evidence for the distinct difference between the "classical" H_2 receptors in the heart and these histamine-stimulated, contraction-inhibiting receptors on the guinea pig ileum was given by Fjalland *et al.*[15] The antagonistic effect of burimamide on the inhibitory guinea pig ileum receptors was described to be about 25 times higher than that of another H_2 antagonist, cimetidine, whereas on the H_2 receptor in the heart, cimetidine was described to be at least 10 times more potent as an H_2 antagonist than burimamide.

After the discovery of the histamine H_3 receptor and the description of the H_3 antagonistic effect of burimamide, the inhibitory histamine receptors on the guinea pig intestine were suggested to be of the H_3 subtype as well.[16] Burimamide was therefore one of the first compounds discovered to antagonize the H_3 receptor and played a major role in its elucidation. The compounds' lack of selectivity, however, makes it less attractive as a pharmacological tool for this receptor.

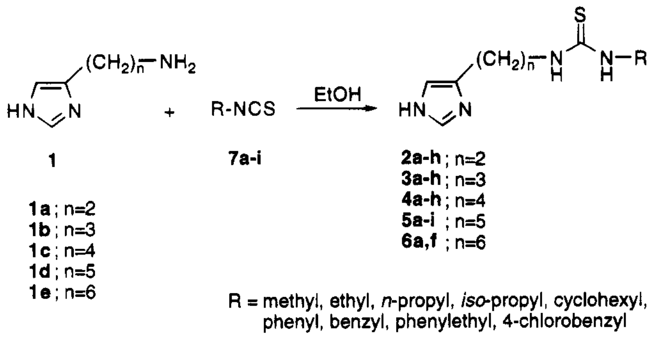
The first potent and selective antagonist for the histamine H_3 receptor was thioperamide, as derived from a series of rigid analogs of histamine.[2] This compound possesses several distinct structural features, which are also present in the structure of burimamide: an *N*-alkyl-substituted thiourea group and an alkyl spacer on the 4(5)-position of an imidazole ring. The cyclohexyl group in the structure of thioperamide has been reported to be optimal for high affinity on the H_3 receptor.[17]

Thioperamide can be seen as a rigid analog of burimamide but is more potent and selective as an H_3 antagonist. Two important differences in the structure of burimamide and thioperamide are the length of the alkyl spacer between the imidazole and the thiourea group (a butylene chain in the structure of burimamide and a propylene chain in the structure of thioperamide) and the *N*-alkyl substituent on the thiourea group (a methyl group for burimamide and a cyclohexyl group for thioperamide).

This raises the question of whether burimamide has the optimal structure for its H_3 antagonistic properties and whether the antagonistic activity and its selectivity for the H_3 receptor can be increased with some structural modifications. Not many structural variations of burimamide and their activity on the histamine H_3 receptor are known. A strong influence of the chain length of the alkyl spacer of burimamide on the H_3 activity has been demonstrated, since a burimamide analog with a propylene chain (norburimamide) is only a weak antagonist, with a pA_2 value of 6.1 for the H_3 receptor, compared to a pA_2 value of 7.2 of burimamide (both on rat cortex).[18]

We wanted to study the influence of the chain length of the alkyl spacer in the structure of burimamide derivatives on the H_3 activity. We additionally wished to evaluate the influence of the *N*-thiourea substituents

Scheme 1. Synthesis of Burimamide Analogs **2–6** from 4(5)-(*ω*-Aminoalkyl)-1*H*-imidazoles **1**



the H_3 activity of these compounds functionally on an *in vitro* test system using guinea pig jejunum preparations.[11] In this series we varied the length of the alkyl spacer of burimamide from two to six methylene groups and additionally replaced the methyl group by other alkyl and aryl groups. We investigated the selectivity of the most potent analogs as well, by determining their affinity for the H_1 and H_2 receptors.

Chemistry

The burimamide analogs **2–6** were prepared by reaction of the corresponding 4(5)-(*ω*-aminoalkyl)-1*H*-imidazoles with a series of alkyl or aryl isothiocyanates (see Scheme 1). The 4(5)-(*ω*-aminoalkyl)-1*H*-imidazoles **1b–e** were prepared using a method described earlier by our group.[19,20] All isothiocyanates (**7a–i**) were commercially available. Most of the compounds were isolated as oxalates because of better stability and isolation.

Pharmacology

The H_3 activity of the compounds was determined on an *in vitro* test system, on the basis of the concentration-dependent inhibitory effect of histamine H_3 agonists on the electrically evoked contractile response of isolated guinea pig jejunum segments.[11] The affinity of the selected compounds for the H_1 receptor was determined by the displacement of [^{3}H]mepyramine bound to membranes of CHO cells expressing guinea pig H_1 receptors.[21] The affinity of the selected compounds for the H_2 receptor was established by displacement of [^{125}I]-iodoaminopotentidine bound to membranes of CHO cells expressing human H_2 receptors.[22]

Results and Discussion

All the synthesized analogs of burimamide are reversible, competitive antagonists on the histamine H_3 receptor, as determined on guinea pig jejunum, with Schild slopes not significantly different from unity (see Table 1).

The burimamide analogs **2a–h**, with an ethylene chain, which can be seen as derivatives of histamine, are only weak H_3 antagonists. This means that replacement of the positively charged, protonated amino group (at physiological pH) of histamine, by a neutral *N*-substituted thiourea group, results in loss of intrinsic activity on the H_3 receptor. This might be due to steric hindrance, since N^α-methylhistamine is a potent agonist for the H_3 receptor and the replacement of the *N*-methyl

Table 1. Histamine H_3 Antagonistic Activity of Burimamide Analogs **2–6** as Determined on the *in Vitro* Test System on Guinea Pig Jejunum

compd	name or code[a]	*n*[b]	R[c]	pA_2[d]	slope[e]	*N*[f]
2a	VUF 4577	2	methyl	5.5 ± 0.2	1.0 ± 0.1	3
2b	VUF 4578	2	ethyl	5.3 ± 0.2	1.1 ± 0.2	4
2c	VUF 4579	2	*n*-propyl	5.4 ± 0.2	1.0 ± 0.1	4
2d	VUF 4580	2	isopropyl	4.8 ± 0.1	0.9 ± 0.1	3
2e	VUF 4581	2	cyclohexyl	5.9 ± 0.2	1.1 ± 0.1	3
2f	VUF 4582	2	phenyl	5.2 ± 0.2	1.0 ± 0.1	3
2g	VUF 4583	2	benzyl	5.8 ± 0.2	1.1 ± 0.2	3
2h	VUF 4584	2	phenylethyl	5.9 ± 0.1	1.0 ± 0.1	3
3a	norburimamide	3	methyl	6.4 ± 0.2	1.0 ± 0.1	4
3b	VUF 4631	3	ethyl	7.1 ± 0.2	1.0 ± 0.1	4
3c	VUF 4632	3	*n*-propyl	7.0 ± 0.2	1.2 ± 0.1	4
3d	VUF 4633	3	isopropyl	7.1 ± 0.2	1.0 ± 0.1	4
3e	VUF 4634	3	cyclohexyl	6.9 ± 0.2	1.1 ± 0.1	4
3f	VUF 4635	3	phenyl	6.9 ± 0.1	1.1 ± 0.1	4
3g	VUF 4636	3	benzyl	6.7 ± 0.2	1.1 ± 0.1	4
3h	VUF 4637	3	phenylethyl	6.7 ± 0.2	1.1 ± 0.1	4
4a	burimamide	4	methyl	7.0 ± 0.2	1.0 ± 0.1	5
4b	VUF 4681	4	ethyl	7.4 ± 0.2	1.1 ± 0.2	4
4c	VUF 4682	4	*n*-propyl	7.3 ± 0.3	1.2 ± 0.3	4
4d	VUF 4683	4	isopropyl	7.5 ± 0.1	1.0 ± 0.3	4
4e	VUF 4684	4	cyclohexyl	7.1 ± 0.2	1.1 ± 0.3	4
4f	VUF 4685	4	phenyl	7.6 ± 0.2	1.0 ± 0.3	4
4g	VUF 4686	4	benzyl	7.1 ± 0.3	1.2 ± 0.3	4
4h	VUF 4687	4	phenylethyl	7.0 ± 0.2	1.3 ± 0.1	3
5a	VUF 4613	5	methyl	8.0 ± 0.1	1.0 ± 0.1	3
5b	VUF 4614	5	ethyl	8.0 ± 0.1	1.0 ± 0.1	4
5c	VUF 4615	5	*n*-propyl	7.7 ± 0.1	1.2 ± 0.1	4
5d	VUF 4616	5	isopropyl	7.7 ± 0.1	1.2 ± 0.1	4
5e	VUF 4617	5	cyclohexyl	7.5 ± 0.1	1.0 ± 0.1	4
5f	VUF 4618	5	phenyl	7.6 ± 0.2	1.0 ± 0.2	3
5g	VUF 4619	5	benzyl	7.7 ± 0.2	1.0 ± 0.1	3
5h	VUF 4620	5	phenylethyl	7.5 ± 0.2	1.1 ± 0.2	3
5i	VUF 4742	5	4-Cl-benzyl	8.1 ± 0.2	0.9 ± 0.1	3
6a	VUF 4740	6	methyl	7.9 ± 0.1	1.0 ± 0.1	5
6f	VUF 4741	6	phenyl	8.0 ± 0.2	0.9 ± 0.2	3

[a] Compound code number. [b] Alkyl chain length of **2–6** (number of methylene units). [c] Substituent of **2–6**. [d] Antagonistic parameter as determined on the described *in vitro* H_3 assay representing the negative logarithm of the abscissal intercept from the Schild plot ± SD. [e] Slope of Schild plot ± SD, not significantly different from unity. [f] Number of different animal preparations.

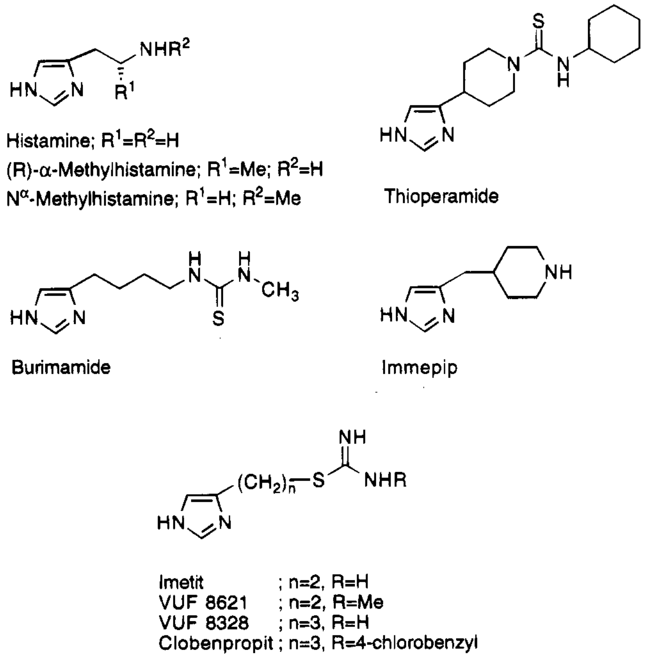


Figure 1. Several discussed structures.

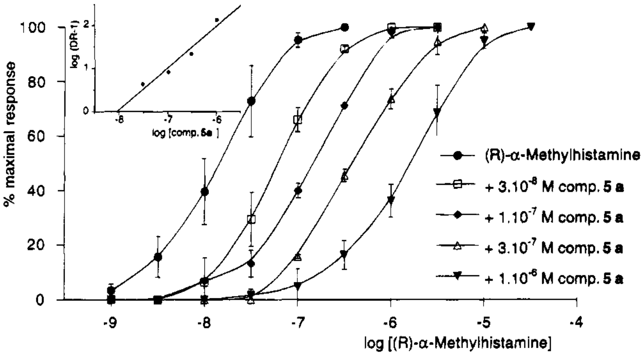


Figure 2. Concentration–response curves of (*R*)-α-methylhistamine, with a rightward parallel shift upon addition of compound **5a** (VUF 4613) (corrected to 100%). The Schild plot of these results is shown in the inset.

Table 2. Selectivity of the Pentylene Analogs of Burimamide **5a–i**, Compared to That of Burimamide Itself (**4a**), for the Histamine H_3 Receptor

compd	n[a]	R[b]	pK_i H_1[c]	pK_i H_2[d]	pA_2 H_3[e]
4a	4	methyl	3.5 ± 0.5[f]	5.4 ± 0.1	7.0 ± 0.2
5a	5	methyl	4.7 ± 0.1	4.7 ± 0.1	8.0 ± 0.1
5b	5	ethyl	4.8 ± 0.1	5.0 ± 0.1	8.0 ± 0.1
5c	5	*n*-propyl	5.5 ± 0.1	5.3 ± 0.1	7.7 ± 0.1
5d	5	isopropyl	4.9 ± 0.1	5.0 ± 0.1	7.7 ± 0.1
5e	5	cyclohexyl	5.1 ± 0.1	5.4 ± 0.1	7.5 ± 0.1
5f	5	phenyl	5.6 ± 0.1	4.9 ± 0.1	7.6 ± 0.2
5g	5	benzyl	5.4 ± 0.1	5.8 ± 0.2	7.7 ± 0.2
5h	5	phenylethyl	5.5 ± 0.1	5.5 ± 0.3	7.5 ± 0.2
5i	5	4-Cl-benzyl	5.8 ± 0.1	5.8 ± 0.2	8.1 ± 0.2

[a] Alkyl chain length of **5** (number of methylene units). [b] Substituent of **5**. [c] log value of the binding affinity for the histamine H_1 receptor ± SEM. [d] log value of the binding affinity for the histamine H_2 receptor ± SEM. [e] Antagonistic parameter as determined on the described *in vitro* H_3 assay representing the negative logarithm of the abscissal intercept from the Schild plot ± SD. [f] Apparent -log K_b as determined by Black *et al.*[29] on a conventional *in vitro* assay on guinea pig ileum, using histamine as agonist; however, since the Schild slope was significantly different from unity, it is doubtful that this is an H_1 antagonistic effect.

with an imidazole ring and an amino group (*e.g.*, (*R*)-α-methylhistamine and immepip), separated by an alkyl spacer.

The imidazole ring seems to be essential for activation, since replacement of the imidazole ring by other heterocyclic rings resulted in less active compounds or compounds deprived of any agonistic activity.[23,24] The amino group of histamine, however, which is protonated at physiological pH, has been replaced with other basic groups, like an isothiourea group, resulting in potent H_3 agonists (*e.g.*, imetit[25–28]). The pK_a of the isothiourea group (pK_a = 9–10) has been described to be similar to that of aliphatic amines (pK_a = 9–11).[27] Monomethylation of the isothiouronium moiety in imetit does not drastically affect the agonistic activity on the H_3 receptor (pD_2 value of VUF 8621 is 7.3, compared to a pD_2 value of 8.1 for imetit on the guinea pig ileum),[9,25,27] whereas the ethylene homolog of burimamide **2a** is a weak H_3 antagonist. Because the thiourea group of **2a** is uncharged at physiological pH, it seems that a specific ionic binding site at the H_3 receptor for cationic groups of H_3 agonists, probably a carboxylate (*e.g.*, an aspartate residue), exists.

Elongation of the alkyl chain of the burimamide

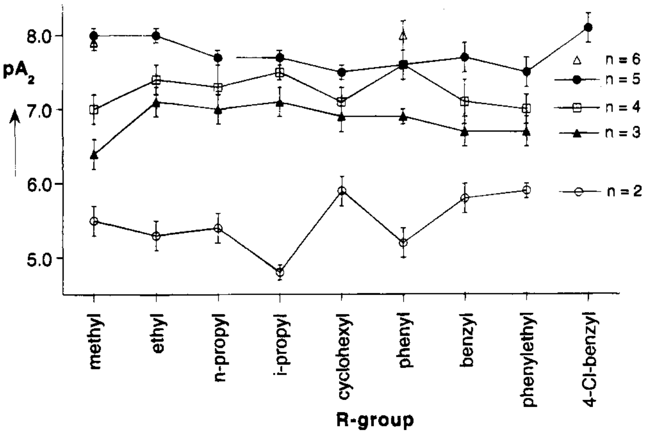


Figure 3. Influence of the alkyl chain length (n) and the *N*-thiourea substituent (R) of burimamide analogs **2–6** on the pA_2 value on the histamine H_3 receptor. Lines have been drawn for easy recognition of these influences.

results in an increase of the H_3 antagonistic activity. The pentylene chain seems to be optimal in length for H_3 antagonistic activity for these analogs. Replacement of the pentylene chain of **5a**, for instance, by a hexylene chain, does not lead to increased H_3 activity (see **6a**).

The affinity for the H_1 and H_2 receptors is determined for these potent pentylene analogs (**5a–i**) (see Table 2). Clearly these compounds are selective for the H_3 receptor, although the *N*-methyl-substituted pentylene analog **5a** is more selective than the more lipophilic *N*-(4-chlorobenzyl)-substituted analog **5i**. This pentylene homolog of burimamide **5a** is 10 times more potent and about 50 times more selective than burimamide itself.

The large influence of the length of the alkyl spacer (up to five methylene units) on the H_3 activity of the burimamide analogs is clearly visible in Figure 3. From this figure, the lack of influence of the *N*-thiourea substituent on the H_3 activity, however, is also apparent. If we consider the analogs **5a–i** with a pentylene chain (n = 5), there is not a great difference in the pA_2 value between the compounds containing a small alkyl group, a large alkyl group, or an aromatic substituent. This suggests that the receptor binding of this part of the burimamide analogs is not through a hydrophobic interaction nor through an electrostatic π–π interaction between aromatic systems. These results are rather surprising, since it has been proposed that an H_3 antagonist should consist of an N-containing heterocycle linked to a polar group by an alkyl chain with a lipophilic residue attached to the polar group for enhancement of the affinity.[24] A clear example of the affinity-enhancing effect of lipophilic residues can be observed in the series of analogs of imetit, as described by Van der Goot *et al.*[25] In this series, derivatization of the potent H_3 antagonist VUF 8328 (pA_2 value of 8.0 on guinea pig ileum) leads to compounds with even higher affinity for the H_3 receptor. The introduction of a *p*-chlorobenzyl group on the isothiourea group of VUF 8328 resulted in the most potent H_3 antagonist described so far (clobenpropit), with a pA_2 value of 9.9 on the guinea pig ileum. The introduction of lipophilic residues on the thiourea group of the burimamide analogs, however, does not enhance the H_3 antagonistic activity. This seems to rule out a possible interaction isothiourea derivatives of Van der Goot.[24] Thioperamide also binds in a distinct manner to the H_3 receptor, other than the burimamide analogs, since **3e** is about 100 times less potent as an H_3 antagonist than thioperamide, which can be seen as its rigid analog. Since there is no large influence of the *N*-thiourea substituents of the burimamide analogs on the pA_2 value, only an interaction of the thiourea group with the receptor via hydrogen bonding seems likely.

It can be concluded that the intrinsic activity of histamine on the H_3 receptor is lost when the amino group is replaced by an *N*-substituted thiourea group. Elongation of the alkyl spacer up to five methylene units leads to an increase of affinity. Replacement of the pentylene chain of **5a** by a hexylene chain does not lead to increased H_3 activity (see **6a**) indicating an additional binding site for the pentylene and higher analogs of burimamide. The chain length of the alkyl spacer has a large influence on the H_3 antagonistic activity, with **5a** being 10 times more potent than burimamide. The *N*-thiourea substituents, however, have no great influence on the affinity. The results indicate a binding behavior for the burimamide analogs in a nonlipophilic environment different from other H_3 antagonists like thioperamide and clobenpropit. Although burimamide was originally described as an H_2 antagonist, the pentylene analogs of burimamide are more potent and selective for the histamine H_3 receptor.

Experimental Section

Chemistry. ^1H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer with tetramethylsilane or sodium 3-(trimethylsilyl)propionate as an internal standard. Mass spectra were recorded on a Finnigan MAT-90 spectrometer. Melting points were measured on a Mettler FP-5 + FP-52 apparatus and are uncorrected. Elemental analyses was performed by MHW Laboratories, Phoenix, AZ. Histamine dihydrochloride (**1a**) was purchased from Janssen Chimica. 4-(5)-(3-Aminopropyl)-1*H*-imidazole dihydrobromide (**1b**), 4(5)-(4-aminobutyl)-1*H*-imidazole dihydrobromide (**1c**), and 4(5)-(5-aminopentyl)-1*H*-imidazole dihydrobromide (**1d**) were prepared as described earlier by our group.[19] 4(5)-(6-Aminohexyl)-1*H*-imidazole (**1e**) was prepared using the same method.[20] Methyl (**7a**) and ethyl (**7b**) isothiocyanate were purchased from Aldrich; *n*-propyl (**7c**), isopropyl (**7d**), benzyl (**7g**), and phenylethyl (**7h**) isothiocyanate were from Maybridge Chemical Co. (MCC); cyclohexyl (**7e**) and phenyl (**7f**) isothiocyanate were from Janssen Chimica, and chlorobenzyl isothiocyanate (**7i**) was purchased from Lancaster. The isothiocyanates were used without purification. The purity of the products was checked on thin layer chromatography (Merck silica gel 60, F254, 0.25 mm). The free bases of all compounds gave one spot using either ethyl acetate ($R_f \approx 0-0.1$), methanol ($R_f \approx 0.9-1.0$), or $CHCl_3$ ($R_f \approx 0.5$). The yields of the purified salts are given.

General Procedure. The required 4(5)-(ω-aminoalkyl)-1*H*-imidazole **1**, either as dihydrochloride or as dihydrobromide, was added to 2 equiv of sodium ethanolate in absolute ethanol. This solution was refluxed for 30 min and cooled to room temperature. The formed precipitate was removed by filtration, and 3 equiv of the needed isothiocyanate **7** was added to the filtrate. The ethanol was removed under reduced pressure, after 2 h of refluxing. The residue was purified by column chromatography, by washing with ethyl acetate as eluent (isothiocyanate eluted R_f = 1.0). The product was subsequently eluted with methanol as eluent (unreacted amine remained on column). After removal of the methanol under reduced pressure, the free base was converted into a hydrobromide or an oxalate.

The hydrobromides were prepared by the solvation of the

vacuo, triturated three times with absolute ethanol, and recrystallized from ethanol/ethyl acetate.

The oxalates were prepared by solvation of the free base in ethyl acetate and the addition of an excess of a saturated solution of oxalic acid in ethyl acetate (slowly). The formed precipitate was collected by centrifugation, washed with ethyl acetate (three times), and recrystallized from absolute ethanol.

***N*-Methyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea hydrobromide (2a):** mp 99.9−100.8 °C; yield 49%. ^1H NMR (D_2O): δ 2.87 (s, 3H, CH_3), 3.03 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.78 (t, 2H, J = 7 Hz, CH_2NH), 7.30 (s, 1H, imidazole-5(4)H), 8.62 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 184 (M^+, 57), 153 ($M^+ - CH_3NH_2$, 47), 150 ($M^+ - H_2S$, 54), 95 ($[ImC_2H_4]^+$, 100), 81 ($[ImCH_2]^+$, 84). HRMS: m/z 184.0782; calcd for $C_7H_{12}N_4S$, 184.0783. Anal. ($C_7H_{12}N_4S{\cdot}2HBr$) C, H, N.

***N*-Ethyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea hydrobromide (2b):** mp 164.5−165.0 °C; yield 74%. ^1H NMR (D_2O): δ 1.12 (t, 3H, J = 7 Hz, CH_3), 3.03 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.32 (q, 2H, J = 7 Hz, CH_2CH_3), 3.78 (t, 2H, J = 7 Hz, CH_2NH), 7.39 (s, 1H, imidazole-5(4)H), 8.62 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 198 (M^+, 50), 164 ($M^+ - H_2S$, 32), 153 ($M^+ - C_2H_5NH_2$, 18), 95 ($[ImC_2H_4]^+$, 100), 81 ($[ImCH_2]^+$, 51). HRMS: m/z 198.0940; calcd for $C_8H_{14}N_4S$, 198.0939. Anal. ($C_8H_{14}N_4S{\cdot}1.96HBr$) C, H, N.

***N*-*n*-Propyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea hydrobromide (2c):** mp 172.6−173.1 °C; yield 36%. ^1H NMR (D_2O): δ 0.88 (t, 3H, J = 7 Hz, CH_3), 1.53 (m, 2H, CH_2CH_3), 3.04 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.10−3.45 (m, 2H, CH_2-CH_2CH_3), 3.70−3.92 (m, 2H, CH_2NH), 7.30 (s, 1H, imidazole-5(4)H), 8.64 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 212 (M^+, 62), 178 ($M^+ - H_2S$, 5), 153 ($M^+ - C_3H_7NH_2$, 13), 95 ($[ImC_2H_4]^+$, 100), 81 ($[ImCH_2]^+$, 35). HRMS: m/z 212.1100; calcd for $C_9H_{16}N_4S$, 212.1096. Anal. ($C_9H_{16}N_4S{\cdot}HBr$) C, H, N.

***N*-Isopropyl)-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea oxalate (2d):** mp 123.1 °C; yield 53%. ^1H NMR (D_2O): δ 1.01 (d, 6H, J = 7 Hz, 2*CH_3), 2.90 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.58−3.75 (m, 2H, CH_2NH), 3.75−4.10 (b s, 1H, CH), 7.16 (s, 1H, imidazole-5(4)H), 8.49 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 212 (M^+, 59), 178 ($M^+ - H_2S$, 12), 153 ($M^+ - C_3H_7NH_2$, 19), 95 ($[ImC_2H_4]^+$, 100), 81 ($[ImCH_2]^+$, 52). HRMS: m/z 212.1090; calcd for $C_9H_{16}N_4S$, 212.1096. Anal. ($C_9H_{16}N_4S{\cdot}C_2H_2O_4$) C, H, N.

***N*-Cyclohexyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea oxalate (2e):** mp 161.7 °C; yield 92%. ^1H NMR (D_2O): δ 0.99−1.85 (m, 10H, cyclohexyl-CH_2's), 2.97 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.50−3.90 (m, 3H, CH + CH_2NH), 7.22 (s, 1H, imidazole-5(4)H), 8.53 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 252 (M^+, 57), 218 ($M^+ - H_2S$, 12), 153 ($M^+ - C_6H_{11}NH_2$, 30), 95 ($[ImC_2H_4]^+$, 100), 81 ($[ImCH_2]^+$, 72). HRMS: m/z 252.1401; calcd for $C_{12}H_{20}N_4S$, 252.1409. Anal. ($C_{12}H_{20}N_4S{\cdot}0.5C_2H_2O_4$) C, H, N.

***N*-Phenyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea hydrobromide (2f):** mp 148.6−148.9 °C; yield 74%. ^1H NMR (D_2O): δ 2.94−3.03 (m, 2H, imidazole-CH_2), 3.75−3.97 (m, 2H, CH_2NH), 7.11−7.57 (m, 6H, phenyl-H + imidazole-5(4)H), 8.61 (s, 1H, imidazole-2H). MS (EI, rel intensity): m/z 246 (M^+, 3), 212 ($M^+ - H_2S$, 7), 153 ($M^+ - C_6H_5NH_2$, 41), 135 ($[C_6H_5NCS]^+$, 100), 93 ($[C_6H_5NH_2]^+$, 62), 95 ($[ImC_2H_4]^+$, 12), 81 ($[ImCH_2]^+$, 72), 77 ($[C_6H_5]^+$, 51). HRMS: m/z 246.0931; calcd for $C_{12}H_{14}N_4S$, 246.0939. Anal. ($C_{12}H_{14}N_4S{\cdot}HBr$) C, H, N.

***N*-Benzyl-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea oxalate (2g):** mp 153.7−155.0 °C; yield 18%. ^1H NMR (DMSO-d_6): δ 2.89 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.59−3.83 (m, 2H, CH_2-NH), 4.53−4.77 (m, 2H, CH_2-phenyl), 7.18−7.38 (m, 6H, phenyl-H + imidazole-4(5)H), 7.85−8.00 (m, 1H, NH), 8.72 (t, 1H, J = 6 Hz, NH), 8.72 (s, 1H, imidazole-2H), 11.15−11.85 (m, NH + oxalate). MS (EI, rel intensity): m/z 260 (M^+, 28), 226 ($M^+ - H_2S$, 8), 153 ($M^+ - C_7H_7NH_2$, 20), 95 ($[ImC_2H_4]^+$, 44), 91 ($[C_7H_7]^+$, 100), 81 ($[ImCH_2]^+$, 38). HRMS: m/z 260.1101; calcd for $C_{13}H_{16}N_4S$, 260.1096. Anal. ($C_{13}H_{16}N_4S{\cdot}C_2H_2O_4$) C, H, N.

***N*-(2-Phenylethyl)-*N'*-[2-(4(5)-imidazolyl)ethyl]thiourea oxalate (2h):** mp 145.1−145.5 °C; yield 18%. ^1H NMR

7.10–7.34 (m, 5H, phenyl-H), 8.47 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 274 (M$^+$, 39), 220 (M$^+$ − H_2S, 2), 153 (M$^+$ − $C_8H_9NH_2$, 22), 105 ([C_8H_9]$^+$, 42), 95 ([ImC_2H_4]$^+$, 100), 91 ([C_7H_7]$^+$, 64), 81 ([$ImCH_2$]$^+$, 43). HRMS: *m/z* 274.1253; calcd for $C_{14}H_{18}N_4S$, 274.1252. Anal. ($C_{14}H_{18}N_4S{\cdot}C_2H_2O_4$) C, H, N.

***N*-Methyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3a):** mp 126.1–128.9 °C; yield 49%. ^{1}H NMR (D_2O): δ 1.96 (m, 2H, CH_2CH_2NH), 2.77 (t, J = 7 Hz, 2H, imidazole-CH_2), 2.86 (b s, 3H, CH_3), 3.30–3.67 (m, 2H, CH_2NH), 7.23 (s, 1H, imidazole-5(4)H), 8.57 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 198 (M$^+$, 20), 167 (M$^+$ − CH_3NH_2, 6), 164 (M$^+$ − H_2S, 5), 109 ([ImC_3H_6]$^+$, 12), 95 ([ImC_2H_4]$^+$, 94), 82 ([$ImCH_3$]$^+$, 100). HRMS: *m/z* 198.0929; calcd for $C_8H_{14}N_4S$, 198.0939. Anal. ($C_8H_{14}N_4S{\cdot}0.84C_2H_2O_4$) C, H, N.

***N*-Ethyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3b):** mp 116.1 °C; yield 44%. ^{1}H NMR (D_2O): δ 1.12 (t, 3H, J = 7 Hz, CH_3), 1.95 (m, 2H, CH_2CH_2NH), 2.77 (t, 2H, J = 8 Hz, imidazole-CH_2), 3.15–3.62 (m, 4H, 2*CH_2NH), 7.23 (s, 1H, imidazole-5(4)H), 8.57 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 212 (M$^+$, 53), 178 (M$^+$ − H_2S, 10), 167 (M$^+$ − $C_2H_5NH_2$, 4), 109 ([ImC_3H_6]$^+$, 31), 95 ([ImC_2H_4]$^+$, 85), 82 ([$ImCH_3$]$^+$, 100). HRMS: *m/z* 212.1092; calcd for $C_9H_{16}N_4S$, 212.1096. Anal. ($C_9H_{16}N_4S{\cdot}C_2H_2O_4$) C, H, N.

***N*-*n*-Propyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3c):** mp 123.2–125.2 °C; yield 24%. ^{1}H NMR (D_2O): δ 0.87 (t, 3H, J = 7 Hz, CH_3), 1.53 (m, 2H, CH_2CH_3), 1.97 (m, 2H, CH_2CH_2NH), 2.77 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.10–3.65 (m, 4H, 2*CH_2NH), 7.23 (s, 1H, imidazole-5(4)H), 8.56 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 226 (M$^+$, 9), 192 (M$^+$ − H_2S, 4), 167 (M$^+$ − $C_3H_7NH_2$, 4), 109 ([ImC_3H_6]$^+$, 9), 95 ([ImC_2H_4]$^+$, 100), 82 ([$ImCH_3$]$^+$, 33). HRMS: *m/z* 226.1265; calcd for $C_{10}H_{18}N_4S$, 226.1252. Anal. ($C_{10}H_{18}N_4S{\cdot}0.8C_2H_2O_4$) C, H, N.

***N*-Isopropyl)-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3d):** mp 146.0 °C; yield 43%. ^{1}H NMR (D_2O): δ 1.13 (d, 6H, J = 7 Hz, CH_3), 1.94 (m, 2H, CH_2CH_2NH), 2.77 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.37–3.58 (m, 2H, CH_2NH), 3.89–4.17 (m, 1H, CH), 7.23 (s, 1H, imidazole-5(4)H), 8.57 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 226 (M$^+$, 30), 192 (M$^+$ − H_2S, 6), 167 (M$^+$ − $C_3H_7NH_2$, 7), 109 ([ImC_3H_6]$^+$, 23), 95 ([ImC_2H_4]$^+$, 79), 82 ([$ImCH_3$]$^+$, 66). HRMS: *m/z* 226.1271; calcd for $C_{10}H_{18}N_4S$, 226.1252. Anal. ($C_{10}H_{18}N_4S{\cdot}0.8C_2H_2O_4$) C, H, N.

***N*-Cyclohexyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3e):** mp 102.2 °C; yield 50%. ^{1}H NMR (D_2O): δ 0.93–1.97 (m, 12H, CH_2CH_2NH + cyclohexyl-CH_2's), 2.70 (t, 2H, J = 8 Hz, imidazole-CH_2), 3.23–3.90 (m, 3H, CH_2NH + $CHNH$), 7.18 (s, 1H, imidazole-5(4)H), 8.52 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 266 (M$^+$, 29), 232 (M$^+$ − H_2S, 8), 167 (M$^+$ − $C_6H_{11}NH_2$, 6), 109 ([ImC_3H_6]$^+$, 24), 95 ([ImC_2H_4]$^+$, 73), 82 ([$ImCH_3$]$^+$, 100). HRMS: *m/z* 266.1572; calcd for $C_{13}H_{22}N_4S$, 266.1565.

***N*-Phenyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3f):** mp 126.7 °C; yield 47%. ^{1}H NMR (D_2O): δ 1.90 (m, 2H, CH_2CH_2NH), 2.70 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.39–3.65 (m, 2H, CH_2NH), 7.27 (m, 6H, imidazole-5(4)H + phenyl-H's), 8.50 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 260 (M$^+$, 2), 226 (M$^+$ − H_2S, 3), 135 ([C_6H_5NCS]$^+$, 63), 108 ([ImC_3H_5]$^+$, 19), 95 ([ImC_2H_4]$^+$, 68), 93 ([$C_6H_5NH_2$]$^+$, 74), 82 ([$ImCH_3$]$^+$, 100), 77 ([C_6H_5]$^+$, 30). HRMS: *m/z* 260.1108; calcd for $C_{13}H_{16}N_4S$, 260.1096. Anal. ($C_{13}H_{16}N_4S{\cdot}0.8C_2H_2O_4$) C, H, N.

***N*-Benzyl-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3g):** mp 117.2 °C; yield 33%. ^{1}H NMR (D_2O): δ 1.84 (m, 2H, CH_2CH_2NH), 2.39–2.79 (m, 2H, imidazole-CH_2), 3.30–3.57 (m, 2H, CH_2NH), 4.42–4.73 (m, 2H, CH_2-phenyl), 7.10 (s, 1H, imidazole-5(4)H), 7.29 (m, 5H, phenyl-H), 8.47 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 274 (M$^+$, 50), 240 (M$^+$ − H_2S, 2), 168 (M$^+$ − C_7H_7NH, 10), 109 ([ImC_3H_6]$^+$, 31), 95 ([ImC_2H_4]$^+$, 79), 91 ([C_7H_7]$^+$, 100), 82 ([$ImCH_3$]$^+$, 94). HRMS: *m/z* 274.1250; calcd for $C_{14}H_{18}N_4S$, 274.1252. Anal. ($C_{14}H_{18}N_4S{\cdot}0.84C_2H_2O_4$) C, H, N.

***N*-(2-Phenylethyl)-*N*′-[3-(4(5)-imidazolyl)propyl]thiourea oxalate (3h):** mp 125.5 °C; yield 27%. ^{1}H NMR (D_2O): δ … CH_2), 2.82 (t, 2H, J = 7 Hz, CH_2-phenyl), 3.10–3.44 (m, 2H, CH_2NH), 3.44–3.79 (m, 2H, CH_2CH_2-phenyl), 7.12 (s, 1H, imidazole-5(4)H), 7.16–7.36 (m, 5H, phenyl-H), 8.49 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 288 (M$^+$, 0.2), 95 ([ImC_2H_4]$^+$, 8), 91 ([C_7H_7]$^+$, 47), 82 ([$ImCH_3$]$^+$, 18), 45 ([$C_2H_5NH_2$]$^+$, 100). HRMS: *m/z* 288.1414; calcd for $C_{15}H_{20}N_4S$, 288.1409. Anal. ($C_{15}H_{20}N_4S{\cdot}0.8C_2H_2O_4$) C, H, N.

***N*-Methyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4a):** mp 120.1–122.6 °C; yield 18%. ^{1}H NMR (D_2O): δ 1.61 (m, 4H, central CH_2's), 2.72 (t, 2H, J = 7 Hz, imidazole-CH_2), 2.82 (m, 3H, CH_3), 3.22–3.62 (m, 2H, CH_2NH), 7.17 (s, 1H, imidazole-5(4)H), 8.52 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 212 (M$^+$, 79), 181 (M$^+$ − CH_3NH_2, 20), 179 (M$^+$ − HS, 9), 123 ([ImC_4H_8]$^+$, 42), 109 ([ImC_3H_6]$^+$, 43), 95 ([ImC_2H_4]$^+$, 100), 81 ([$ImCH_2$]$^+$, 69). HRMS: *m/z* 212.1091; calcd for $C_9H_{16}N_4S$, 212.1096. Anal. ($C_9H_{16}N_4S{\cdot}0.8C_2H_2O_4$) C, H, N.

***N*-Ethyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4b):** mp 120.3 °C; yield 29%. ^{1}H NMR (D_2O): δ 1.08 (t, 3H, J = 7Hz, CH_3), 1.61 (m, 4H, central CH_2's), 2.72 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.22–3.51 (m, 4H, 2*CH_2NH), 7.17 (s, 1H, imidazole-5(4)H), 8.52 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 226 (M$^+$, 81), 193 (M$^+$ − HS, 7), 181 (M$^+$ − $C_2H_5NH_2$, 25), 123 ([ImC_4H_8]$^+$, 47), 109 ([ImC_3H_6]$^+$, 40), 95 ([ImC_2H_4]$^+$, 100), 81 ([$ImCH_2$]$^+$, 75). HRMS: *m/z* 226.1250; calcd for $C_{10}H_{18}N_4S$, 226.1252. Anal. ($C_{10}H_{18}N_4S{\cdot}1.8C_2H_2O_4$) C, H, N.

***N*-*n*-Propyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4c):** mp 146.9 °C; yield 55%. ^{1}H NMR (D_2O): δ 0.84 (t, 3H, J = 7 Hz, CH_3), 1.42–1.78 (m, 6H, central CH_2's + CH_2CH_3), 2.73 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.10–3.62 (m, 4H, 2*CH_2NH), 7.18 (s, 1H, imidazole-5(4)H), 8.53 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 240 (M$^+$, 69), 207 (M$^+$ − HS, 7), 181 (M$^+$ − $C_3H_7NH_2$, 23), 123 ([ImC_4H_8]$^+$, 55), 109 ([ImC_3H_6]$^+$, 38), 95 ([ImC_2H_4]$^+$, 100), 81 ([$ImCH_2$]$^+$, 80), 45 ([$C_2H_5NH_2$]$^+$, 71). HRMS: *m/z* 240.1409; calcd for $C_{11}H_{20}N_4S$, 240.1409. Anal. ($C_{11}H_{20}N_4S{\cdot}C_2H_2O_4$) C, H, N.

***N*-Isopropyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4d):** mp 151.3 °C; yield 64%. ^{1}H NMR (D_2O): δ 1.16 (d, 6H, J = 7 Hz, 2*CH_3), 1.65 (m, 4H, central CH_2's), 2.76 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.43 (m, 2H, CH_2NH), 4.08 (m, 1H, CH), 7.21 (s, 1H, imidazole-5(4)H), 8.55 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 240 (M$^+$, 60), 207 (M$^+$ − HS, 5), 181 (M$^+$ − $C_3H_7NH_2$, 17), 123 ([ImC_4H_8]$^+$, 51), 109 ([ImC_3H_6]$^+$, 25), 95 ([ImC_2H_4]$^+$, 70), 81 ([$ImCH_2$]$^+$, 52), 45 ([$C_2H_5NH_2$]$^+$, 100). HRMS: *m/z* 240.1401; calcd for $C_{11}H_{20}N_4S$, 240.1409. Anal. ($C_{11}H_{20}N_4S{\cdot}1.76C_2H_2O_4$) C, H, N.

***N*-Cyclohexyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4e):** mp 109.5 °C; yield 24%. ^{1}H NMR (DMSO-d_6): δ 1.00–1.95 (m, 14H, central CH_2's + cyclohexyl-CH_2's), 2.64 (m, 2H, imidazole-CH_2), 3.37 (m, 2H, CH_2NH), 3.93 (m, 1H, CH), 7.20 (s, 1H, imidazole-5(4)H), 7.28–7.62 (m, 4H, NH + CO_2H), 8.50 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 280 (M$^+$, 66), 247 (M$^+$ − HS, 7), 181 (M$^+$ − $C_6H_{11}NH_2$, 28), 123 ([ImC_4H_8]$^+$, 62), 109 ([ImC_3H_6]$^+$, 32), 95 ([ImC_2H_4]$^+$, 100), 81 ([$ImCH_2$]$^+$, 76), 45 ([$C_2H_5NH_2$]$^+$, 65). HRMS: *m/z* 280.1724; calcd for $C_{14}H_{24}N_4S$, 280.1722. Anal. ($C_{14}H_{24}N_4S{\cdot}1.15C_2H_2O_4$) C, H, N.

***N*-Phenyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4f):** mp 153.7 °C; yield 42%. ^{1}H NMR (D_2O): δ 1.59 (m, 4H, central CH_2's), 2.70 (t, 2H, imidazole-CH_2), 3.49 (m, 2H, CH_2NH), 7.31 (m, 6H, imidazole-5(4)H + phenyl-H), 8.50 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 274 (M$^+$, 4), 241 (M$^+$ − HS, 2), 181 (M$^+$ − $C_6H_5NH_2$, 10), 135 ([C_6H_5NCS]$^+$, 100), 95 ([ImC_2H_4]$^+$, 61), 93 ([$C_6H_5NH_2$]$^+$, 78), 77 ([C_6H_5]$^+$, 47). HRMS: *m/z* 274.1251; calcd for $C_{14}H_{18}N_4S$, 274.1252. Anal. ($C_{14}H_{18}N_4S{\cdot}1.4C_2H_2O_4$) C, H, N.

***N*-Benzyl-*N*′-[4-(4(5)-imidazolyl)butyl]thiourea oxalate (4g):** mp 109.1 °C; yield 42%. ^{1}H NMR (DMSO-d_6): δ 1.53 (m, 4H, central CH_2's), 2.59 (t, 2H, J = 7 Hz, imidazole-CH_2), 3.40 (m, 2H, CH_2NH), 4.63 (m, 2H, CH_2-benzyl), 7.13 (s, 1H, imidazole-5(4)H), 7.28 (m, 5H, phenyl-H), 7.71 (m, 1H, N-H), 7.99 (m, 1H, N-H), 8.39 (s, 1H, imidazole-2H). MS (EI, rel intensity): *m/z* 288 (M$^+$, 42), 255 (M$^+$ − HS, 3), 181 (M$^+$ − $C_7H_7NH_2$, 14), 123 ([ImC_4H_8]$^+$, 28), 109 ([ImC_3H_6]$^+$, 15), 106

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