

Synthesis and *in vitro* pharmacology of dimaprit analogues with histamine H₂-agonistic and H₁-antagonistic activities

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Summary — The synthesis and *in vitro* pharmacology of some dimaprit analogues with histamine H₂-agonistic and additional histamine H₁-antagonistic activities are discussed. 2-Amino-5-(2-aminoethyl)thiazoles can be considered chemically as ring-closed dimaprit analogues, and so the alkylisothiurea structural moiety of dimaprit, *S*-[3-(*N,N*-dimethylamino)propyl]isothiurea, could replace the propylthiazole or propylimidazole structural moieties of impromidine-like histamine H₂-agonists. The H₂-agonistic activities of a number of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines indicate that 2-amino-5-(2-aminoethyl)thiazole can indeed be considered as a ring-closed dimaprit analogue.

dimaprit / histamine H₂-agonist / impromidine / amthamine / hybrid molecule / histamine H₁-antagonist

Introduction

The clinical use of compounds active on the histamine H₂-receptor is mainly restricted to histamine H₂-antagonists, which are useful in the treatment of peptic ulcers. However, some efforts have been made with histamine H₂-agonists in the treatment of patients with catecholamine-insensitive congestive heart failure [1, 2].

Histamine H₂-agonists can be divided in three structural classes: histamine analogues, dimaprit, and impromidine [3] and its analogues [4–7] (reviewed by Van der Goot *et al* [8]). Histamine **1** and dimaprit **2** (fig 1) both show moderate histamine H₂-agonistic activity ($pD_2 = 6.10$ [4] and 5.95 [9], respectively, at guinea-pig right atrium). Impromidine **3** (fig 1) and its analogues VUF 8532 **4b** and the racemic arpromidine **5** (fig 1) are potent histamine H₂-agonists ($pD_2 = 7.80$ [4], 7.70 [4] and 8.01 [7], respectively, at guinea-pig right atrium). Furthermore, the hybrid molecules VUF 8532 **4b** and arpromidine **5** also have a histamine H₁-antagonistic activity ($pA_2 = 6.30$ and 7.65 at guinea-pig ileum, respectively). Impromidine also turned out to be a potent antagonist at the histamine H₃-receptor [10] ($pA_2 = 7.52$; histamine release, rat cerebral cortex).

The H₂-agonist dimaprit **3** (fig 1) is also an antagonist for the histamine H₃-receptor [11] ($pA_2 = 5.5$; histamine release rat cortex). Structure–activity relationship studies concerning H₂-agonism on dimaprit have revealed that the dimethylamino group has the same

function as the amino group of histamine, while the isothiurea group of dimaprit and the imidazole group are regarded as bioisosteric for histamine H₂-agonism [12].

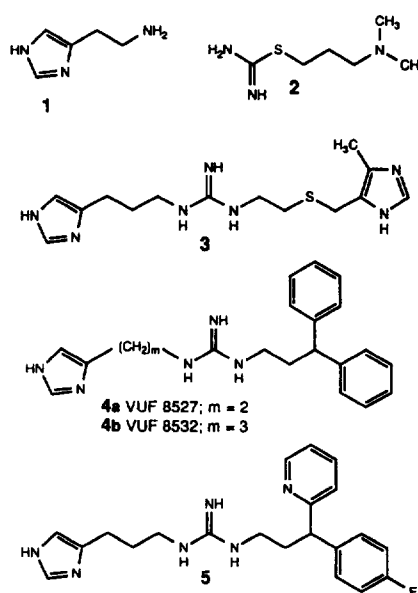


Fig 1. Histamine H₂-agonists.

Two models have been proposed for the interaction of the monocation of dimaprit with the histamine H_2 -receptor, viz the N-fit and the S-fit [12–14]. Quantum chemical calculations have suggested that the S-fit, which includes the interaction of the NH-group and the S-atom of the isothiourea moiety with the H_2 -receptor, is the most favourable [12–16].

Furthermore, similar calculations on 2-amino-5-(2-aminoethyl)thiazole [17] **6** (fig 2) revealed that this compound can be considered as a ring-closed dimaprit analogue [18, 19]. Several substituted 2-aminothiazole derivatives have indeed been shown to be active at the histamine H_2 -receptor; amthamine [20, 21] **7** (fig 2) is the most potent H_2 -agonist in this series ($pD_2 = 6.30$; guinea-pig right atrium).

In impromidine, the 3-[4(5)-imidazolyl]propylguanidine moiety is important for triggering the histamine H_2 -receptor [22]. Replacement of the 3-[4(5)-imidazolyl]propyl structural moiety of impromidine by a number of substituted 3-(5-thiazolyl)propyl moieties afforded N' -substituted N -[3-(5-thiazolyl)]propylguanidines [23] as potent histamine H_2 -agonists, such as VUF 8960 **8** (fig 2; $pD_2 = 7.30$; guinea-pig right atrium).

A number of structural modifications have been carried out on dimaprit [24]. Variations in the alkylene chain length of dimaprit or alkylation of the amidino group drastically reduces the histamine H_2 -agonistic activity [9, 12, 25].

The results of the structure–activity relationship studies on dimaprit analogues and the findings that 2-amino-5-(2-aminoethyl)thiazoles can be considered as ring-closed dimaprit analogues and that substituted 2-amino-5-(3-aminopropyl)thiazoles can replace the 3-[4(5)-imidazolyl]propylamine structural moiety, raised the question whether the alkylisothiourea structural moiety of dimaprit can replace the propylimidazole or propylthiazole structural moieties of impromidine and **4b** (fig 1) or **8** (fig 2). Therefore, we decided to synthesize a series of N,N' -substituted guanidines with 2-[(5-methylimidazol-4-yl)methylthio]ethyl **9** or 3,3-diphenylpropyl groups **10** and the dimaprit structural moiety (fig 3).

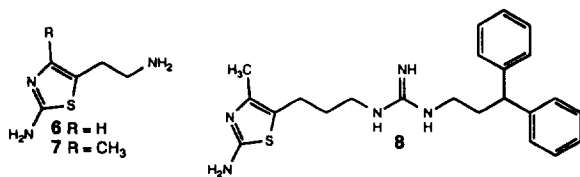


Fig 2. Substituted 2-amino-5-(ω -aminoalkyl)thiazoles.

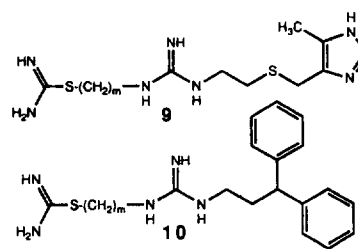


Fig 3. Putative histamine H_2 -agonists incorporating impromidine and dimaprit or 3,3-diphenylpropylamine and dimaprit structural moieties.

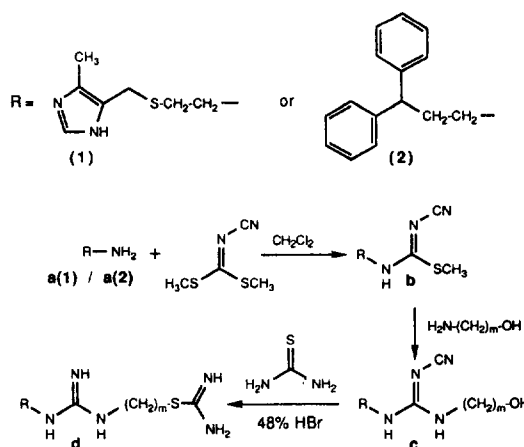


Fig 4. General reaction scheme for compounds **9** and **10**.

General synthetic method

A scheme for the synthesis of compounds **9** and **10** is given in figure 4. The primary amines 2-[(5-methylimidazol-4-yl)methylthio]ethylamine **a(1)** or 3,3-diphenylpropylamine **a(2)** were converted into the *S*-methylisothiourea **b** by reaction with dimethyl *N*-cyanoiminodithiocarbonate [22]. Condensation of **b** with the appropriate aminoalcohol afforded the cyanoguanidines **c**. Finally reaction of the cyanoguanidines **c** with thiourea in hydrobromic acid gave the *N*-(ω -isothioureidoalkyl)guanidines **d**.

Pharmacology

In vitro histamine H_2 -agonistic activities and affinities

Histamine H_2 -agonistic activities were determined as positive chronotropic activities on spontaneously

beating guinea-pig right atrium; radioligand binding studies were performed on guinea-pig cerebral cortex membranes using [125 I]iodoaminopotentidine as the hot ligand [26], as previously described by Christiaans *et al* [27]. Test solutions of **10a–d** were prepared from 10^{-2} M solutions in DMSO followed by dilution with Krebs buffer.

In vitro histamine H₁-antagonistic activities

Histamine H₁-antagonistic activities were determined at the guinea-pig ileum with histamine as agonist ($pD_2 = 6.95 \pm 0.07$), as described by Emmett *et al* [28]. Test solutions of **10a–d** were prepared from 10^{-2} M solutions in DMSO followed by dilution with Krebs buffer.

Results and discussion

Attempts to synthesize compounds 9

The synthetic route to obtain the series of compounds with the general structure **9** (fig 3) proceeds *via* the *N*-cyano-*N'*-[ω -hydroxyalkyl]-*N''*-[2-[(5-methyl-1*H*-imidazol-4-yl)methylthio]ethyl]guanidine intermediates (**c**; fig 4), which are readily prepared in high yields from *N*-cyano-*S*-methyl-*N'*-[2-[(5-methyl-1*H*-imidazol-4-yl)methylthio]ethyl]isothiourea (**b**; fig 4) and the appropriate ω -hydroxyalkylamine. The next step concerns the introduction of thiourea and the hydrolysis of the cyano group to obtain the isothioureas (**d**; fig 4, see also scheme 1; fig 5). This reaction was carried out with 2 equivalents of thiourea at 100°C and at 20°C in 48% HBr. Under the two different sets of reaction conditions the thioether was hydrolyzed, resulting in a 5-methyl-4-hydroxymethylimidazole fragment, as shown by $^1\text{H-NMR}$.

These findings forced us to look for other synthetic routes as shown in figure 5 (scheme 2). A trityl group was introduced at the NH-group of imidazole by trityl chloride (step 1). This protected imidazole derivative was purified by column chromatography (eluent: dichloromethane/ethyl acetate/triethylamine 4:1:0.5 v/v/v). The trityl group was partially removed during column chromatography, if triethylamine was not added to the eluents. The coupling of aminopropanol to the tritylated imidazole moiety and subsequent purification by column chromatography afforded the *N*-cyano-*N'*-(3-hydroxypropyl)-*N''*-[2-[(5-methyl-1-tritylimidazol-4-yl)methylthio]ethyl]guanidine **11** in 50% yield. At this stage of the reaction scheme, we tried three different methods to obtain the isothiourea derivative with the general structure **9** (fig 3).

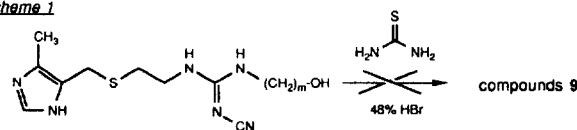
In step 3 (fig 5), we tried to tosylate the hydroxyl group of **11** but tosyl chloride replaced the trityl group

from the imidazole moiety. This method cannot therefore afford compound **9**. In step 4 (fig 5), bromination of the alcohol **11** with phosphorus tribromide also resulted in the removal of the trityl group. The third route (step 5; fig 5) was performed according to the so-called Mitsunobu reaction [29], using triphenylphosphine and diisopropyl azodicarboxylate to prepare thioethers starting from an alcohol and thiourea. After addition of the reagents in dimethoxyethane, the yellow colour of diisopropyl azodicarboxylate vanished; thin-layer chromatography indicated that triphenylphosphine had disappeared. After work-up of the reaction mixture, however, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ showed that the hydroxyl group in compound **11** was still intact. No signals for thiourea or isothiourea were observed in the NMR. Moreover, when *n*-butanol was used instead of alcohol **11**, no reaction was observed with thiourea. Therefore, we must conclude that the Mitsunobu reaction is not of any use for the synthesis of isothioureas, such as compounds **9** (fig 3).

Synthesis of compounds 10

Because of the difficulties we encountered in the syntheses of the series of compounds with general structure **9**, we decided to prove the validity of our idea that the imidazolylpropyl structural moiety in

scheme 1



scheme 2

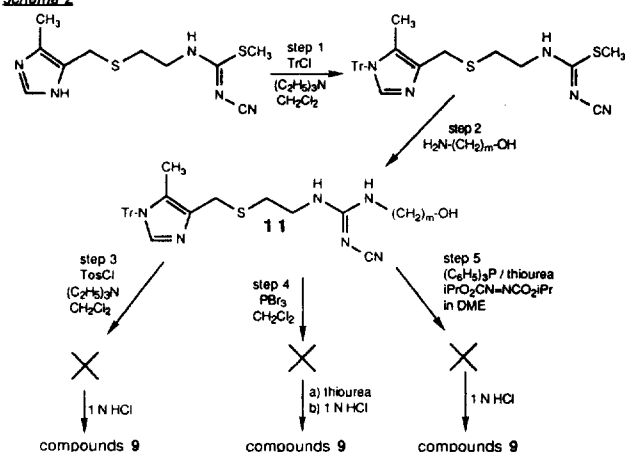


Fig 5. Alternative synthetic routes to obtain compounds with the general structure **9**.

impromidine-like histamine H₂-agonists can be replaced by isothioureidoalkyl structures by synthesizing analogues of the 3,3-diphenylpropylamine-bearing histamine H₂-agonist, **4b** (fig 1) and **8** (fig 2). These hybrid molecules with general structure **10** (fig 3) are easily obtained as described in figure 4. Despite the fact that the 3,3-diphenylpropylamine structure is not optimal for histamine H₁-antagonistic activity, the hybrid molecules obtained are good model compounds to verify whether the ω -isothioureidoethyl moieties display histamine H₂-agonistic activity. The synthesis of the compound with an isothioureidoethyl moiety did not succeed. By reacting *N*-cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(2-hydroxyethyl)guanidine with thiourea in 48% HBr, we could only isolate the hydrobromic salt of 3,3-diphenylpropylamine.

Biological activities of compounds 10 and qualitative structure-activity relationships

The histaminergic activities of a number of dimaprit analogues with the 3,3-diphenylpropylamine structural moiety (general structure **10**; fig 3) are given in table I.

Structure-activity relationship studies on histamine and dimaprit analogues reveal that the optimal alkylene chain length between the amino group and the group responsible for proton-accepting/electrostatic interaction, amounts to two methylene groups in histamine and three methylene groups in dimaprit. In impromidine, the optimal alkylene chain length between the guanidino group and the imidazole group is three methylene groups, *ie* one more than in histamine [22].

In the series of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines **10** (fig 3) increasing the alkylene chain length from propylene to hexylene generally decreases the histamine H₂-agonistic activity and intrinsic activity. Moreover, VUF 4642 **10c** is a partial agonist with H₁-antagonistic properties. Furthermore, VUF 4643 **10d** is an H₂-antagonist, which is in line with the results Sterk [24] described for the corresponding *N,N'*-bis(ω -isothioureidoalkyl)guanidines.

The *N*-(3,3-diphenylpropyl)-*N'*-[ω -[imidazol-4(5)-yl]alkyl]guanidine with a propylene chain (VUF 8532 **4b**; fig 1) is more potent than the one with an ethylene chain (VUF 8527 **4a**; fig 1), pD₂ = 7.7 and 5.6, respectively. A similar structure-activity relationship has been observed for impromidine analogues. It is thus expected that the optimal alkylene chain for stimulation of the H₂-receptor in the series of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines would be a butylene chain.

Affinity with the histamine H₂-receptor by **10a-d** reveals an optimum with VUF 4642 **10c** corresponding to a pentylene chain between the isothioureia and guani-

dine groups. Although the optimum was predicted for VUF 4641 **10b** with the butylene chain, this result is reasonable if one takes into account that the presence of the bulky and hydrophobic diphenylmethyl part in these molecules may influence the binding to the H₂-receptor.

The histamine H₁-antagonistic activities within this series of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines are all similar. We cannot explain the deviation of unity of the slope in the Schild plot for VUF 4641. Variations in the isothioureidoalkylene chain length do not affect the histamine H₁-antagonistic activities, which is in agreement with the VUF 8532 **4b** and VUF 8527 **4a** (pA₂ = 6.3 and 6.2, respectively).

Conclusion

The histamine H₂-agonistic activities of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines confirm that 2-amino-5-(2-aminoethyl)thiazole derivatives can be considered as substituted dimaprit analogues. Replacement of the 3-(5-thiazolyl)propyl or 3-[4(5)-imidazolyl]propyl moiety in the impromidine analogues, such as VUF 8960 **8** and VUF 8532 **4b**, by an ω -isothioureidoalkylene moiety, affords substituted dimaprit analogues which are more potent histamine H₂-agonists than dimaprit. Compared with VUF 8960 **8** and VUF 8532 **4b**, the *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines here have a lower H₂-agonistic activity, which is in agreement with the activities of the parent histamine H₂-agonists amthamine, histamine, and dimaprit, respectively. In this series of compounds, the H₂-agonistic activity decreases with elongation of the ω -isothioureidoalkylene chain. VUF 4640 **10a** (propylene chain) is the most potent H₂-agonist in the series of *N*-(3,3-diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidines, while VUF 4643 **10d** (hexylene chain) is a weak H₂-antagonist. Obviously, elongation of the ω -isothioureidoalkylene chain does not affect the histamine H₁-antagonistic activities of these compounds.

Experimental protocols

Where indicated, the crude reaction products were purified by flash chromatography on silica gel (JT Baker 70242). Melting points were determined on a Mettler FP 52 apparatus with a microscope. ¹H-NMR spectra were recorded on a Bruker AC 200 and were verified by HH-cosy NMR experiments. The chemical shifts are quoted in ppm relative to tetramethylsilane. Mass spectra were determined on a Mat 90 (Finnigan Mat) mass spectrometer with fast atom bombardment ionization (matrix: thioglycerol, Ion Tech saddlefield gun, 8 keV xenon with xenon ioncurrent 0.2 mA). All VUF compounds gave the expected (M + H)⁺ and (M + H⁺ - HSC(NH)NH₂)⁺ peaks. The new compounds gave one spot upon TLC.

Table I. Histamine H₂-agonistic/H₁-antagonistic activities and H₂-receptor affinities.

Compound	H ₂ -activity			H ₁ -antagonism		Reference
	pD ₂	α	pK _d	pA ₂	r ^f	
Histamine 1	6.14 ± 0.04	1	4.16 ± 0.08 ^a 4.64 ± 0.35 ^b	^c		21
Dimaprit 2	5.67 ± 0.12	1	4.58 ± 0.11 ^a			21
Impromidine 3	7.80	1	7.89 ± 0.15	5.47		3
VUF 8527 4a	5.6 ± 0.1	0.9	nt	6.2 ± 0.2		30
VUF 8532 4b	7.7 ± 0.1	1	nt	6.3 ± 0.2		30
Arpromidine 5	8.01	1	nr	7.65		31
VUF 9149 6	5.53 ± 0.10	1	4.82 ± 0.10 ^a	na		23
Amthamine 7	6.30 ± 0.04	1	5.30 ± 0.08 ^a	na		23
VUF 8960 8	7.30 ± 0.04	1	nt	nt		23
VUF 4640 10a , m = 3	6.71 ± 0.16	1	5.66 ± 0.14 ^b	6.69 ± 0.14	0.82	
VUF 4641 10b , m = 4	6.02 ± 0.25	1	5.41 ± 0.05 ^b	6.25 ± 0.44	0.52	
VUF 4642 10c , m = 5	6.24 ± 0.10	0.7	6.42 ± 0.32 ^b	6.82 ± 0.24	0.81	
	5.91 ± 0.08 ^d	0.7				
VUF 4643 10d , m = 6	Antagonist ^e	0	5.98 ± 0.31 ^b	6.38 ± 0.36	0.81	

^a[³H]Tiotidine as hot ligand; ^b[¹²⁵I]iodoaminopotentidine as hot ligand; ^chistamine is an agonist; pD₂ = 6.95 ± 0.07; ^dpD₂ determined on electrically stimulated guinea-pig papillary muscle. This compound also shows histamine H₂-antagonistic activity; pA₂ = 6.56 ± 0.22 (papillary muscle); ^ehistamine H₂-antagonist; pA₂ = 5.75 ± 0.21 on guinea-pig right atrium and pA₂ = 5.45 ± 0.16 on guinea-pig papillary muscle; ^fr = slope of Schild plot; nt: not tested; nr: not reported; na: not active up to 10⁻⁴ M. For structure of **10a**, **10b**, **10c** and **10d** and definition of m see figure 3.

N-Cyano-*N'*-(3,3-diphenylpropyl)-*S*-methylisothiourea

A solution of 50 mmol 3,3-diphenylpropylamine in 100 ml dichloromethane was added slowly to a stirred solution of 1 equiv dimethyl *N*-cyanodithiocarbonimidate in 50 ml dichloromethane. After complete addition, the reaction mixture was stirred for an additional 30 min. Addition of diethyl ether gave a precipitate, which was filtered off, washed with diethyl ether and dried.

Yield: 94%, mp: 187–189°C. ¹H-NMR (DMSO-*d*₆): 2.22–2.47 ppm (m, 2H, CCH₂C), 2.52 ppm (s, 3H, SCH₃), 3.17–3.23 ppm (m, 2H, CH₂N), 4.00 ppm (t, *J* = 7.8 Hz, 1H, -CHCCN), 7.14–7.33 ppm (m, 10H, 10 × phenyl-*H*), 8.31 ppm (bs, 1H, NH).

N-Cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(ω-hydroxyalkyl)guanidine

One equivalent of *N*-cyano-*N'*-(3,3-diphenylpropyl)-*S*-methylisothiourea and 1.25 equiv of the appropriate aminoalcohol were refluxed overnight in absolute ethanol under a nitrogen atmosphere. The solvent was evaporated and the residue was dissolved in dichloromethane and washed three times with water. After evaporation of the organic solvent, the compounds were obtained as oils.

N-Cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(2-hydroxyethyl)guanidine

Yield: 71%, mp: oil. ¹H-NMR (CDCl₃): 2.21–2.32 ppm (m, 2H, CCH₂CN), 3.08–3.15 ppm (m, 4H, 2 × -CH₂N), 3.57–

3.62 ppm (m, 2H, -CH₂OH), 3.93 ppm (t, *J* = 7.9 Hz, 1H, -CHCCN), 6.03 ppm (bs, 1H, NH), 6.15 ppm (bs, 1H, NH), 7.09–7.29 ppm (m, 10H, 10 × phenyl-*H*).

N-Cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(3-hydroxypropyl)guanidine

Yield: 87%, mp: oil. ¹H-NMR (CDCl₃): 1.58–1.62 ppm (m, 2H, NCCH₂COH), 2.22–2.32 ppm (m, 2H, CCH₂CN), 3.12–3.16 ppm (m, 4H, 2 × -CH₂N), 3.43–3.58 ppm (m, 2H, -CH₂OH), 3.94 ppm (t, *J* = 7.7 Hz, 1H, -CHCCN), 6.01 ppm (bs, 1H, NH), 6.18 ppm (bs, 1H, NH), 7.07–7.27 ppm (m, 10H, 10 × phenyl-*H*).

N-Cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(4-hydroxybutyl)guanidine

Yield: 95 %, mp: oil. ¹H-NMR (CDCl₃): 1.41–1.58 ppm (m, 4H, NCCH₂CH₂COH), 2.20–2.38 ppm (m, 2H, CCH₂CN), 3.00–3.21 ppm (m, 4H, 2 × -CH₂N), 3.48–3.55 ppm (m, 2H, -CH₂OH), 3.91 ppm (t, *J* = 7.7 Hz, 1H, -CHCCN), 5.96 ppm (bs, 1H, NH), 6.08 ppm (bs, 1H, NH), 7.09–7.31 ppm (m, 10H, 10 × phenyl-*H*).

N-Cyano-*N'*-(3,3-diphenylpropyl)-*N''*-(5-hydroxypentyl)guanidine

Yield: 100 %, mp: oil. ¹H-NMR (CDCl₃): 1.28–1.50 ppm (m, 6H, NCCH₂CH₂CH₂COH), 2.24–2.35 ppm (m, 2H, CCH₂CN), 2.94–3.05 ppm (m, 2H, -CH₂N), 3.10–3.23 ppm (m, 2H, -CH₂N), 3.51–3.57 ppm (m, 2H, -CH₂OH), 3.94 ppm (t, *J* =

7.8 Hz, 1H, $-CHCCN$), 5.58 ppm (t, $J = 5$ Hz, 1H, NH), 5.64 ppm (t, $J = 5$ Hz, 1H, NH), 7.10–7.29 ppm (m, 10H, 10 \times phenyl-H).

N-(3,3-diphenylpropyl)-*N'*-(6-hydroxyhexyl)guanidine

Yield: 95%, mp: oil. 1H -NMR ($CDCl_3$): 1.18–1.29 ppm (m, 4H, $NCCCH_2CH_2COH$), 1.45–1.51 ppm (m, 4H, $NCCCH_2CCH_2COH$), 2.23–2.34 ppm (m, 2H, $-CCH_2CN$), 2.95–3.05 ppm (m, 2H, $-CH_2N$), 3.06–3.19 ppm (m, 2H, $-CH_2N$), 3.48–3.55 ppm (m, 2H, $-CH_2OH$), 3.94 ppm (t, $J = 7.8$ Hz, 1H, $-CHCCN$), 5.63 ppm (t, $J = 5$ Hz, 1H, NH), 5.79 ppm (t, $J = 5$ Hz, 1H, NH), 7.08–7.28 ppm (m, 10H, 10 \times phenyl-H).

N-(3,3-Diphenylpropyl)-*N'*-(ω -isothioureidoalkyl)guanidine

N-(3,3-diphenylpropyl)-*N'*-(ω -hydroxyalkyl)guanidine and 2 equiv of thiourea were added to 50 ml 48% HBr. The resulting solution was refluxed overnight and then evaporated. The compounds were isolated as dihydrobromic acid salts and purified as picrates. The first four recrystallizations were carried out in the presence of an excess of picric acid. Final recrystallizations (3–6 times) were carried out in methanol/water until the ratio between the picrate signal and the other signals in the NMR spectrum remained unchanged and the melting range became constant and TLC (CH_3OH) gave one spot.

N-(3,3-Diphenylpropyl)-*N'*-(3-isothioureidopropyl)guanidine hydrobromide monopicate **10a**

Yield: 33%, mp: 154–158°C. Mass spectrum: (FAB $^+$) 370 ($M + H$) $^+$, 294 ($M + H - HSC(NH)NH_2$) $^+$. 1H -NMR ($DMSO-d_6$): 1.72–1.84 ppm (m, 2H, $NCCCH_2CS$), 2.18–2.32 ppm (m, 2H, CCH_2CN), 2.90–3.24 ppm (m, 6H, 2 \times $-CH_2N$ and $-CH_2S$), 3.99 ppm (t, $J = 7.7$ Hz, 1H, $-CHCCN$), 7.17–7.33 ppm (m, 12H, 10 \times phenyl-H and 2 \times NH), 7.59 ppm (bs, 1H, NH), 8.61 ppm (s, 2H, 2 \times $-CH$ -picric acid), 8.92–9.10 (m, 2H, NH_2).

N-(3,3-Diphenylpropyl)-*N'*-(4-isothioureidobutyl)guanidine hydrobromide monopicate **10b**

Yield: 21%, mp: 169–177°C. Mass spectrum: (FAB $^+$) 384 ($M + H$) $^+$, 308 ($M + H - HSC(NH)NH_2$) $^+$. 1H -NMR ($DMSO-d_6$): 1.85–1.90 ppm (m, 4H, $NCCCH_2CH_2CS$), 2.24–2.36 ppm (m, 2H, $-CCH_2CN$), 3.10–3.28 ppm (m, 6H, 2 \times $-CH_2N$ and $-CH_2S$), 4.01 ppm (t, $J = 7.7$ Hz, 1H, $-CHCCN$), 7.01–7.21 ppm (m, 2H, 2 \times NH), 7.25–7.36 ppm (m, 10H, 10 \times phenyl-H), 8.62 ppm (s, 2H, 2 \times $-CH$ -picric acid).

N-(3,3-Diphenylpropyl)-*N'*-(5-isothioureidopentyl)guanidine dipicate **10c**

Yield: 18%, mp: 69–72°C. Mass spectrum: (FAB $^+$) 398 ($M + H$) $^+$, 322 ($M + H - HSC(NH)NH_2$) $^+$. 1H -NMR (acetone- d_6): 1.55–1.84 ppm (m, 6H, $NCCCH_2CH_2CH_2CS$), 2.42–2.53 ppm (m, 2H, CCH_2CN), 2.95–3.38 ppm (m, 6H, 2 \times $-CH_2N$ and $-CH_2S$), 4.08 ppm (t, $J = 8$ Hz, 1H, $-CHCCN$), 7.12–7.35 ppm (m, 12H, 10 \times phenyl-H and 2 \times NH), 8.63 ppm (bs, 1H, NH), 8.77 ppm (s, 4H, 4 \times $-CH$ -dipicate).

N-(3,3-Diphenylpropyl)-*N'*-(6-isothioureidoohexyl)guanidine hydrobromide monopicate **10d**

Yield: 13%, mp: 74–76°C. Mass spectrum: (FAB $^+$) 412 ($M + H$) $^+$, 336 ($M + H - HSC(NH)NH_2$) $^+$. 1H -NMR ($DMSO-d_6$): 1.37–1.92 ppm (m, 8H, $NCCCH_2CH_2CH_2CH_2CS$), 2.42–2.49 ppm

(m, 2H, CCH_2CN), 3.26–3.59 ppm (m, 6H, 2 \times $-CH_2N$ and $-CH_2S$), 4.09 ppm (t, $J = 8$ Hz, 1H, $-CHCCN$), 7.15–7.29 ppm (m, 12H, 10 \times phenyl-H and 2 \times NH), 8.72 ppm (s, 2H, 2 \times $-CH$ -picric acid).

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