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Synthesis and *in vitro* pharmacology of dimaprit analogues with histamine H_2-agonistic and H_1-antagonistic activities

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Summary — The synthesis and *in vitro* pharmacology of some dimaprit analogues with histamine H_2-agonistic and additional histamine H_1-antagonistic activities are discussed. 2-Amino-5-(2-aminoethyl)thiazoles can be considered chemically as ring-closed dimaprit analogues, and so the alkylisothiourea structural moiety of dimaprit, *S*-[3-(*N*,*N*-dimethylamino)propyl]isothiourea, could replace the propylthiazole or propylimidazole structural moieties of impromidine-like histamine H_2-agonists. The H_2-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 H_2-agonist / impromidine / amthamine / hybrid molecule / histamine H_1-antagonist

Introduction

The clinical use of compounds active on the histamine H_2-receptor is mainly restricted to histamine H_2-antagonists, which are useful in the treatment of peptic ulcers. However, some efforts have been made with histamine H_2-agonists in the treatment of patients with catecholamine-insensitive congestive heart failure [1, 2].

Histamine H_2-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 H_2-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 H_2-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 H_1-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 H_3-receptor [10] (pA_2 = 7.52; histamine release, rat cerebral cortex).

The H_2-agonist dimaprit **3** (fig 1) is also an antagonist for the histamine H_3-receptor [11] (pA_2 = 5.5; histamine release rat cortex). Structure–activity relationship studies concerning H_2-agonism on dimaprit have revealed that the dimethylamino group has the same function as the amino group of histamine, while the isothiourea group of dimaprit and the imidazole group are regarded as bioisosteric for histamine H_2-agonism [12].

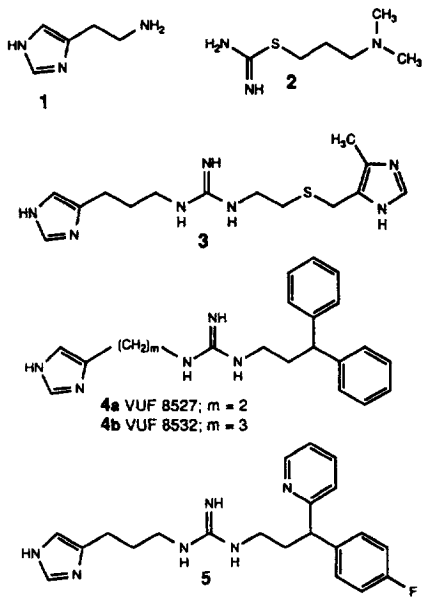

Fig 1. Histamine H_2-agonists.

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).

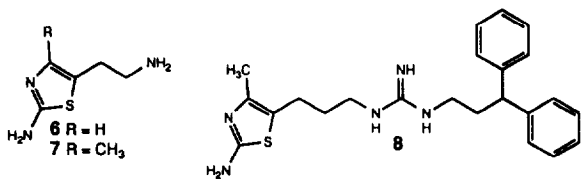

Fig 2. Substituted 2-amino-5-(ω-aminoalkyl)thiazoles.

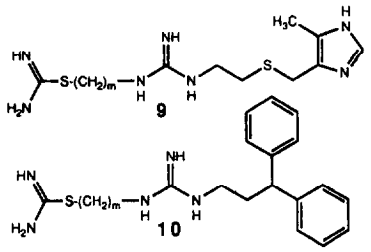

Fig 3. Putative histamine H_2-agonists incorporating impromidine and dimaprit or 3,3-diphenylpropylamine and dimaprit structural moieties.

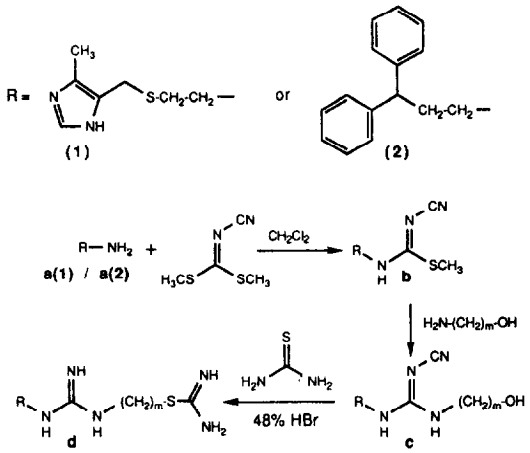

Fig 4. General reaction scheme for compounds **9** and **10**.

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 H_1-antagonistic activities

Histamine H_1-antagonistic activities were determined at the guinea-pig ileum with histamine as agonist (pD_2 = 6.95 ± 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}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-goup of imidazole by trityl chloride (step 1). This protected imidazole derivative was purified by column chromatography (eluents: 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}H-NMR and ^{13}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

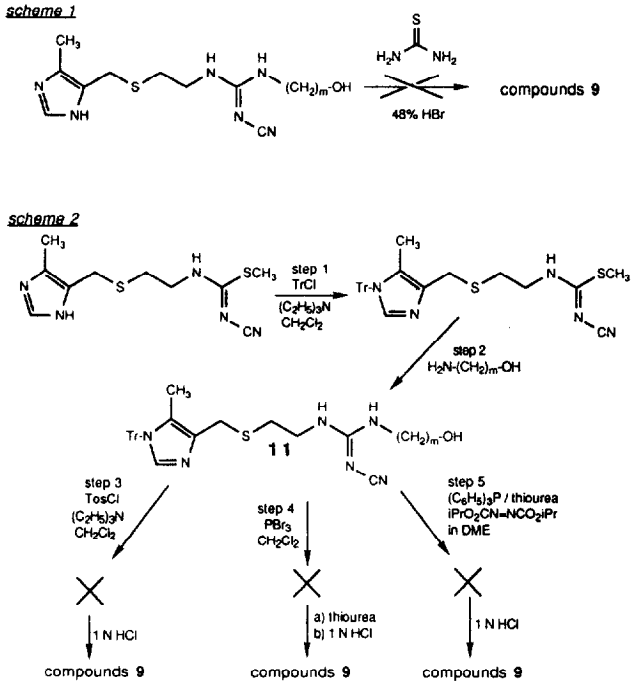

Fig 5. Alternative synthetic routes to obtain compounds with the general structure **9**.

impromidine-like histamine H_2-agonists can be replaced by isothioureidoalkyl structures by synthesizing analogues of the 3,3-diphenylpropylamine-bearing histamine H_2-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 H_1-antagonistic activity, the hybrid molecules obtained are good model compounds to verify whether the ω-isothioureidoethyl moieties display histamine H_2-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 H_2-agonistic activity and intrinsic activity. Moreover, VUF 4642 **10c** is a partial agonist with H_1-antagonistic properties. Furthermore, VUF 4643 **10d** is an H_2-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), pD_2 = 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 H_2-receptor in the series of *N*-(3,3-diphenylpropyl)-*N'*-(ω-isothioureidoalkyl)guanidines would be a butylene chain.

Affinity with the histamine H_2-receptor by **10a–d** reveals an optimum with VUF 4642 **10c** corresponding to a pentylene chain between the isothiourea and guanidine 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 H_2-receptor.

The histamine H_1-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 H_1-antagonistic activities, which is in agreement with the VUF 8532 **4b** and VUF 8527 **4a** (pA_2 = 6.3 and 6.2, respectively).

Conclusion

The histamine H_2-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 H_2-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 H_2-agonistic activity, which is in agreement with the activities of the parent histamine H_2-agonists amthamine, histamine, and dimaprit, respectively. In this series of compounds, the H_2-agonistic activity decreases with elongation of the ω-isothioureidoalkylene chain. VUF 4640 **10a** (propylene chain) is the most potent H_2-agonist in the series of *N*-(3,3-diphenylpropyl)-*N'*-(ω-isothioureidoalkyl)guanidines, while VUF 4643 **10d** (hexylene chain) is a weak H_2-antagonist. Obviously, elongation of the ω-isothioureidoalkylene chain does not affect the histamine H_1-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. ^{1}H-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 $(M + H^+ - HSC(NH)NH_2)^+$ peaks. The new compounds gave one spot upon TLC.

Table I. Histamine H_2-agonistic/H_1-antagonistic activities and H_2-receptor affinities.

Compound	*H_2-activity*			*H_1-antagonism*		
	pD_2	*α*	*pK_d*	*pA_2*	*r*[f]	*Reference*
Histamine **1**	6.14 ± 0.04	1	4.16 ± 0.08[a]	[c]		21
			4.64 ± 0.35[b]			
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][^{3}H]Tiotidine as hot ligand; [b][^{125}I]iodoaminopotentidine as hot ligand; [c]histamine is an agonist; pD_2 = 6.95 ± 0.07; [d]pD_2 determined on electrically stimulated guinea-pig papillary muscle. This compound also shows histamine H_2-antagonistic activity; pA_2 = 6.56 ± 0.22 (papillary muscle); [e]histamine H_2-antagonist; pA_2 = 5.75 ± 0.21 on guinea-pig right atrium and pA_2 = 5.45 ± 0.16 on guinea-pig papillary muscle; [f]*r* = 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. ^{1}H-NMR (DMSO-d_6): 2.22–2.47 ppm (m, 2H, CCH_2C), 2.52 ppm (s, 3H, SCH_3), 3.17–3.23 ppm (m, 2H, CH_2N), 4.00 ppm (t, *J* = 7.8 Hz, 1H, -C*H*CCN), 7.14–7.33 ppm (m, 10H, 10 × phenyl-*H*), 8.31 ppm (bs, 1H, N*H*).

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. ^{1}H-NMR ($CDCl_3$): 2.21–2.32 ppm (m, 2H, CCH_2CN), 3.08–3.15 ppm (m, 4H, 2 × -CH_2N), 3.57–3.62 ppm (m, 2H, -CH_2OH), 3.93 ppm (t, *J* = 7.9 Hz, 1H, -C*H*CCN), 6.03 ppm (bs, 1H, NH), 6.15 ppm (bs, 1H, N*H*), 7.09–7.29 ppm (m, 10H, 10 × phenyl-*H*).

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

Yield: 87%, mp: oil. ^{1}H-NMR ($CDCl_3$): 1.58–1.62 ppm (m, 2H, NCCH_2COH), 2.22–2.32 ppm (m, 2H, CCH_2CN), 3.12–3.16 ppm (m, 4H, 2 × -CH_2N), 3.43–3.58 ppm (m, 2H, -CH_2OH), 3.94 ppm (t, *J* = 7.7 Hz, 1H, -C*H*CCN), 6.01 ppm (bs, 1H, N*H*), 6.18 ppm (bs, 1H, N*H*), 7.07–7.27 ppm (m, 10H, 10 × phenyl-*H*).

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

Yield: 95 %, mp: oil. ^{1}H-NMR ($CDCl_3$): 1.41–1.58 ppm (m, 4H, NCCH_2CH_2COH), 2.20–2.38 ppm (m, 2H, CCH_2CN), 3.00–3.21 ppm (m, 4H, 2 × -CH_2N), 3.48–3.55 ppm (m, 2H, -CH_2OH), 3.91 ppm (t, *J* = 7.7 Hz, 1H, -C*H*CCN), 5.96 ppm (bs, 1H, N*H*), 6.08 ppm (bs, 1H, N*H*), 7.09–7.31 ppm (m, 10H, 10 × phenyl-*H*).

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

Yield: 100 %, mp: oil. ^{1}H-NMR ($CDCl_3$): 1.28–1.50 ppm (m, 6H, NCCH_2CH_2CH_2COH), 2.24–2.35 ppm (m, 2H, CCH_2CN), 2.94–3.05 ppm (m, 2H, -CH_2N), 3.10–3.23 ppm (m, 2H, -CH_2N), 3.51–3.57 ppm (m, 2H, -CH_2OH), 3.94 ppm (t, *J* =

7.8 Hz, 1H, -C*H*CCN), 5.58 ppm (t, *J* = 5 Hz, 1H, NH), 5.64 ppm (t, *J* = 5 Hz, 1H, N*H*), 7.10–7.29 ppm (m, 10H, 10 × phenyl-*H*).

N-Cyano-N'-(3,3-diphenylpropyl)-N''-(6-hydroxyhexyl)guanidine
Yield: 95%, mp: oil. ^{1}H-NMR ($CDCl_3$): 1.18–1.29 ppm (m, 4H, NCCCH_2CH_2CCOH), 1.45–1.51 ppm (m, 4H, NCCH_2C-CCH_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, -C*H*CCN), 5.63 ppm (t, *J* = 5 Hz, 1H, N*H*), 5.79 ppm (t, *J* = 5 Hz, 1H, NH), 7.08–7.28 ppm (m, 10H, 10 × phenyl-*H*).

N-(3,3-Diphenylpropyl)-N'-(ω-isothioureidoalkyl)guanidine
N-Cyano-*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 monopicrate ***10a***
Yield: 33%, mp: 154–158°C. Mass spectrum: (FAB$^+$) 370 (M + H)$^+$, 294 (M + H – HSC(NH)NH_2)$^+$. ^{1}H-NMR (DMSO-d_6): 1.72–1.84 ppm (m, 2H, NCCH_2CS), 2.18–2.32 ppm (m, 2H, CCH_2CN), 2.90–3.24 ppm (m, 6H, 2 × -CH_2N and -CH_2S), 3.99 ppm (t, *J* = 7.7 Hz, 1H, -C*H*CCN), 7.17–7.33 ppm (m, 12H, 10 × phenyl-*H* and 2 × N*H*), 7.59 ppm (bs, 1H, NH), 8.61 ppm (s, 2H, 2 × -C*H*- picric acid), 8.92–9.10 (m, 2H, NH_2).

N-(3,3-Diphenylpropyl)-N'-(4-isothioureidobutyl)guanidine hydrobromide monopicrate ***10b***
Yield: 21%, mp: 169–177°C. Mass spectrum: (FAB$^+$) 384 (M + H)$^+$, 308 (M + H – HSC(NH)NH_2)$^+$. ^{1}H-NMR (DMSO-d_6): 1.85–1.90 ppm (m, 4H, NCCH_2CH_2CS), 2.24–2.36 ppm (m, 2H, -CCH_2CN), 3.10–3.28 ppm (m, 6H, 2 × -CH_2N and -CH_2S), 4.01 ppm (t, *J* = 7.7 Hz, 1H, -C*H*CCN), 7.01–7.21 ppm (m, 2H, 2 × N*H*), 7.25–7.36 ppm (m, 10H, 10 × phenyl-*H*), 8.62 ppm (s, 2H, 2 × -C*H*- picric acid).

N-(3,3-Diphenylpropyl)-N'-(5-isothioureidopentyl)guanidine dipicrate ***10c***
Yield: 18%, mp: 69–72°C. Mass spectrum: (FAB$^+$) 398 (M + H)$^+$, 322 (M + H – HSC(NH)NH_2)$^+$. ^{1}H-NMR (acetone-d_6): 1.55–1.84 ppm (m, 6H, NCCH_2CH_2CH_2CS), 2.42–2.53 ppm (m, 2H, CCH_2CN), 2.95–3.38 ppm (m, 6H, 2 × -CH_2N and -CH_2S), 4.08 ppm (t, *J* = 8 Hz, 1H, -C*H*CCN), 7.12–7.35 ppm (m, 12H, 10 × phenyl-*H* and 2 × N*H*), 8.63 ppm (bs, 1H, NH), 8.77 ppm (s, 4H, 4 × -C*H*- dipicrate).

N-(3,3-Diphenylpropyl)-N'-(6-isothioureidohexyl)guanidine hydrobromide monopicrate ***10d***
Yield: 13%, mp: 74–76°C. Mass spectrum: (FAB$^+$) 412 (M + H)$^+$, 336 (M + H – HSC(NH)NH_2)$^+$. ^{1}H-NMR (DMSO-d_6): 1.37–1.92 ppm (m, 8H, NCCH_2CH_2CH_2CH_2CS), 2.42–2.49 ppm (m, 2H, CCH_2CN), 3.26–3.59 ppm (m, 6H, 2 × -CH_2N and -CH_2S), 4.09 ppm (t, *J* = 8 Hz, 1H, -C*H*CCN), 7.15–7.29 ppm (m, 12H, 10 × phenyl-*H* and 2 × N*H*), 8.72 ppm (s, 2H, 2 × -C*H*- picric acid).

References

1 Felix SB, Buschauer A, Baumann G (1991) *Agents Actions Suppl* 33, 257–269
2 Baumann G, Buschauer A, Felix SB (1992) *In: Agents Actions Special Conference Issue*, Birkhäuser Verlag, Basel, Switzerland, 329–332
3 Durant GJ, Duncan WAM, Ganellin CR, Parsons ME, Blakemore RC, Rasmussen AC (1978) *Nature (Lond)* 276, 403–405
4 Sterk GJ, Van der Goot H, Timmerman H (1987) PCT/WO 87 07 891
5 Buschauer A, Schickaneder H, Schunack W, Szelenyi I, Ahrens KH (1987) Ger Pat, DE 3528214 A1
6 Buschauer A, Schickaneder H, Mörsdorf P, Schunack W, Baumann G, Ahrens KH (1988) Ger Pat, DE 3631334 A1
7 Buschauer A (1989) *J Med Chem* 32, 1963–1970
8 Van der Goot H, Bast A, Timmerman H (1991) *In: Handbook of Experimental Pharmacology; Histamine and Histamine Antagonists* (Uvnäs B, ed) Springer Verlag, Berlin, Germany, 97, 573–748
9 Sterk GJ, Van der Goot H, Timmerman H (1984) *Eur J Med Chem, Chim Ther* 19, 545–550
10 Arrang JM, Garbarg M, Schwartz JC (1983) *Nature (Lond)* 302, 832–837
11 Schwartz JC, Arrang JM, Garbarg M, Pollard H (1990) *Agents Actions* 30, 13–23
12 Durant GJ, Ganellin CR, Parsons ME (1977) *Agents Actions* 7, 39–43
13 Weinstein H, Chou D, Johnson CL, Kang S, Green JP (1976) *Mol Pharmacol* 12, 738–745
14 Green JP, Johnson CL, Weinstein H (1978) *In: Psychopharmacology; A Generation of Progress* (Lipton MA, Di Mascio A, Killam KF, eds), Raven Press, New York, USA, 319–322
15 Donné-Op den Kelder GM, Haaksma EEJ, Timmerman H (1989) *In: Trends in Medicinal Chemistry 1988* (Van der Goot H, Domány G, Pallos L, Timmerman H, eds), Elsevier, Amsterdam, The Netherlands, 365–392
16 Haaksma EEJ, Donné-Op den Kelder GM, Timmerman H (1991) *Agents Actions Suppl* 33, 315–324
17 Vitali T, Impicciatore M, Plazzi PV, Bordi F (1986) *Il Farmaco Ed Sci* 41, 483–498
18 Impicciatore M, Morini G, Chiavarini M *et al* (1987) *Agents Actions* 20, 262–264
19 Haaksma EEJ (1991) PhD thesis, Vrije Universiteit, Amsterdam, The Netherlands
20 Eriks JC, Sterk GJ, Van der Goot H, Timmerman H (1992) *J Med Chem* 35, 3239–3246
21 Eriks JC, Van der Goot H, Timmerman H (1993) *Mol Pharmacol* 44, 886–894
22 Durant GJ, Ganellin CR, Hills DW *et al* (1985) *J Med Chem* 28, 1414–1422
23 Eriks JC, Sterk GJ, Van der Aar EM, Van Acker SABE, Van der Goot H, Timmerman H (1991) *Agents Actions Suppl* 33, 301–314
24 Sterk GJ (1987) PhD thesis, Vrije Universiteit, Amsterdam, The Netherlands
25 Blakemore RC, Ganellin CR, Leigh BK *et al* (1986) *Agents Actions* 19, 18–25
26 Ruat M, Traiffort E, Bouthenet M *et al* (1990) *Proc Natl Acad Sci USA* 87, 1658–1662
27 Christiaans JAM, Windhorst AD, Van der Goot H, Timmerman H (1994) *Eur J Med Chem* 29, 579–593
28 Emmett JC, Durant GJ, Ganellin CR, Roe AM, Turner JL (1982) *J Med Chem* 25, 1168–1174
29 Mitsunobu O, Wada M, Sano T (1972) *J Am Chem Soc* 94, 679
30 Sterk GJ, Koper J, Van der Goot H, Timmerman H (1987) *Eur J Med Chem* 22, 491–498
31 Buschauer A, Baumann G (1991) *Agents Actions Suppl* 33, 231–256