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Original paper

Studies on histaminergic compounds VI. Synthesis and structure—activity relationships of a series of cimetidine and impromidine congeners

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Summary — A series of congeners, resulting from the replacement of the 5-methylimidazole group of cimetidine and impromidine by a 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furanyl, 2-pyridyl and a phenyl group have been synthesized and tested for histaminergic activity. From the results, it could be concluded that the 'impromidine extra binding site', which is thought to cause the high activity of impromidine, may not be identical to the binding site for the heterocyclic aromatic part of the H_2-antagonists.

Résumé — **Etudes sur les composés histaminergiques VI. Synthèse et relations structure—activité d'une série de congénères de la cimétidine et de l'impromidine.** *Nous avons préparé une série de congénères en remplaçant le groupe méthyl-5-imidazolyle-4 de la cimétidine et de l'impromidine par un groupe guanidino-2-thiazolyl-4, diméthylaminométhyl-5 furannyle, pyridyl-2 et phényle. Après avoir essayé les composés pour leur activité histaminergique, nous avons conclu que le site de liaison supplémentaire de l'impromidine, censé causer l'activité élevée de l'impromidine n'est pas probablement identique au site de liaison de la partie hétérocyclique des antagonistes H_2.*

cimetidine analogues / impromidine analogues / histamine H_1-activity / histamine H_2-activity

Introduction

Impromidine (*N*-[3-(imidazol-4-yl)propyl]-*N'*-[2-(5-methylimidazol-4-yl)methylthio]ethylguanidine) is known to be a highly potent and selective histamine H_2-agonist [1—3]. Depending upon the test system used, it behaves either as a partial or a full agonist with a potency between about 10 and 600 times that of histamine [1, 4]. By comparing impromidine with compounds containing a part of the impromidine structure, it was shown [1, 2] that most probably the monosubstituted imidazole ring of impromidine has the same function as the imidazole ring of histamine *viz.*: proton-transfer. The protonated guanidino group of impromidine should have the same function as the protonated amino group of histamine, while the methylimidazole part is thought to give the compound its high affinity by interacting with an extra binding site on the histamine H_2-receptor system.

For some time, we have been interested in the nature of this 'impromidine extra binding site' and therefore, we have prepared a number of impromidine analogues in which this methylimidazole group was replaced by other groups [5].

Because it has been suggested that this 'impromidine extra binding site' might be identical to a binding site of the histamine H_2-antagonists [6], we compared the histamine H_2-activity of the impromidine analogues (**9**, Fig. 1) with a series of corresponding cimetidine analogues (**4**). Moreover, we have tested some of the cyanoguanidine analogues of the impromidine like compounds (**8**) for histamine H_2-activity.

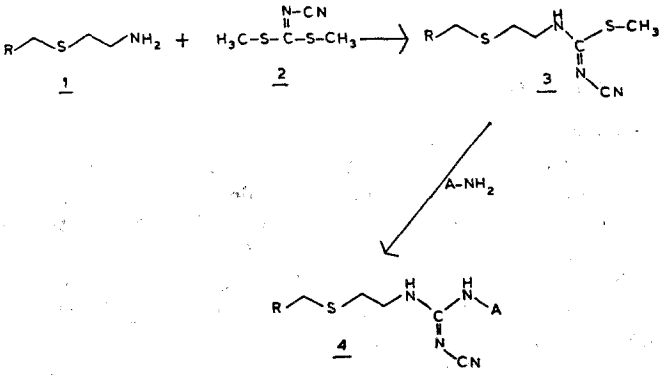

Fig. 1A. Synthesis of cimetidine analogues.

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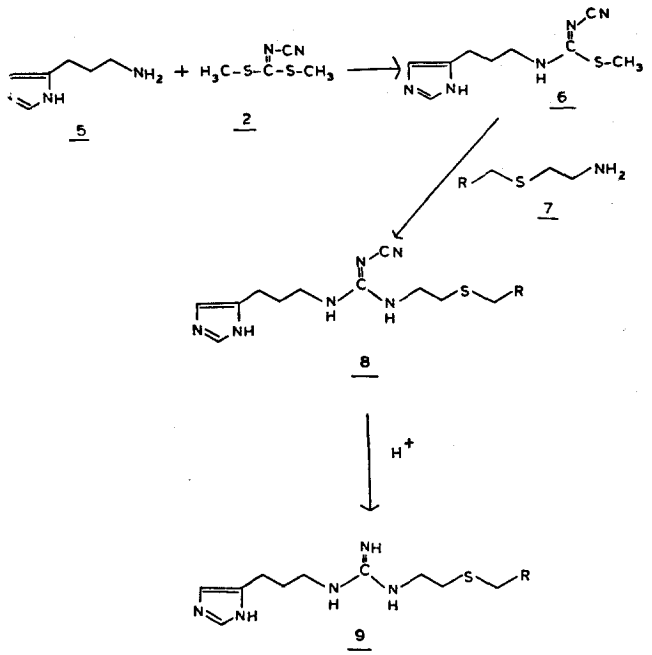


Fig. 1B. Synthesis of impromidine analogues.

Results and Discussion

Synthesis

The general reaction schemes are given in Fig. 1. The cimetidine analogues are readily obtained *via* the indicated pathway (Fig. 1A). The impromidine analogues, however (Fig. 1B) are much harder to obtain, mainly because of the tedious synthesis of aminopropylimidazole [7].

This aminopropylimidazole is converted into the *N*-cyano-S-methylisothiourea **6** which reacts with a primary amine (**7**) to give cyanoguanidine **8**. These cyanoguanidines are obtained in a relatively low yield, which did not improve significantly when the reaction time was extended beyond 48 h (up to 140 h).

The impromidine analogues **9b**, **9c** and **9d** are obtained after acid hydrolysis of the cyanoguanidines and have been purified as their tripicrates. The compounds were titrated with 0.1 M KOH and the results indicated a molecularity within 98% of the theoretical value.

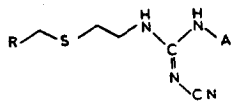
Pharmacology

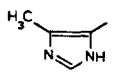
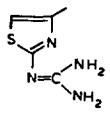
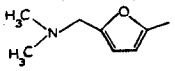
Cimetidine analogues

The histamine H_2-blocking potencies of the cimetidine analogues are summarized in Table I. The H_2-activities of cimetidine and tiotidine agree with those previously reported [20]. **4d**, A = CH_3 was found to be equipotent with cimetidine, whereas **4c**, A = CH_3 has about 50% of the activity of cimetidine. Also the *n*-propyl derivative (**4a**, A = nC_3H_7 and **4d**, A = nC_3H_7) were found to have about 50% of the H_2-blocking potency of their methyl analogues. The phenyl derivative (**4e**, A = CH_3) is devoid of histamine H_2-activity up to a concentration of 10^{-4} M.

These results indicate that changing the methyl substituent at the guanidino part into a *n*-propyl group only slightly affects the H_2-activity, whereas R must be, among other requirements, a heterocyclic aromatic group.

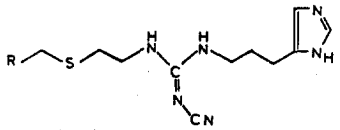
Table I. Antagonistic histamine H_2-activity of some cimetidine analogues (guinea pig right atrium).

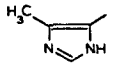
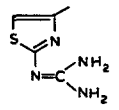


Compound			pA_2 [1]	n
code	name	R		
4a(A=CH_3)	cimetidine		6.3	> 10
4a(A=nC_3H_7)	VUF 8296		6.0	4
4b(A=CH_3)	tiotidine		7.8	8
4c(A=CH_3)	VUF 8294		6.0	4
4d(A=CH_3)	VUF 8298		6.3	4
4d(A=nC_3H_7)	VUF 8297		6.0	4
4e(A=CH_3)	VUF 8299		< 4.0	8

[1]Antagonistic histamine H_2-activity expressed as pA_2 (SD $\leq$ 0.1).

Table II. Antagonistic histamine H_2-activity of some cyano-analogues of impromidine-like compounds (guinea pig right atrium).



Compound			pA_2 [1]	n
code	name	R'		
8a	VUF 8403		6.1	4
8b	VUF 8406		7.8	8
8e	VUF 8295		< 4.0	6

[1]Antagonistic histamine H_2-activity expressed as pA_2 (SD $\leq$ 0.1).

Cyanoguanidino analogues of impromidine-like compounds

The histamine H_2-activity of the cyanoguanidino analogues of the impromidine-like compounds are summarized in Table II. It was found that these compounds are almost equipotent compared with their corresponding cimetidine analogues. The activity found for **8a** corresponds with the results reported for this compound by Durant *et al.* [1].

Impromidine analogues

The results of the pharmacological experiments with impromidine and the impromidine analogues are shown in Table III and are obtained by analyzing the cumulative dose—response curves, using the computer program allfit. From these analyses, it was concluded that the dose—response curves of these impromidine-like compounds are virtually parallel to that of histamine.

The histamine H_1-activities of these compounds are almost identical; a weak but competitive inhibition of the histamine-induced contractions of guinea pig ileum has been found.

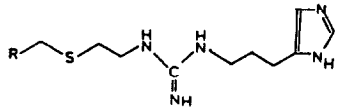
The histamine H_2-activities of these analogues, however, show more differences. Impromidine, **9b** and **9c** are almost equipotent in both H_2-test systems used, but **9d** and **9e** are clearly less potent than impromidine. The histamine H_1-and H_2-activities that we found for impromidine agree with those reported by Durant *et al.* [1]. Also, the H_2-activities of **9b** and **9c** do not disagree with the results found by other groups; for **9b**, Gilman *et al.* [6] reported an 'impromidine-like activity' whereas for **9c**, C. R. Ganellin (personal communication) reports an activity 26 times the activity of histamine on the guinea pig right atrium and an intrinsic activity of 0.82. **9d** has only been mentioned as an H_2-agonist [8].

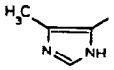
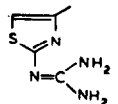
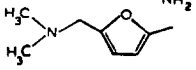
Though the phenyl analogue of impromidine (**9e**) has only about 25% of the activity of impromidine, it still is a very potent H_2-agonist with about 12 times the activity of histamine on the guinea pig right atrium. Preliminary results with an impromidine analogue in which the 5-methylimidazolyl group has been replaced by a methyl group indicated that this compound has an activity of about 0.3% of that of impromidine on the guinea pig right atrium (our results, data not shown).

Therefore it seems that the 'impromidine extra binding site' is specific for an aromatic group; it can not or can only slightly differentiate between these substituted imidazole, thiazole and furan groups and the 2-pyridyl and phenyl groups.

Durant *et al.* [2] deduced that most probably the guanidylpropylimidazole part of impromidine should be responsible for the intrinsic activity of this compound, while its methylimidazole part should be associated with affinity and not with efficacy. It is therefore assumed that this methylimidazole part of impromidine confers the high activity to this compound, most probably by interacting with an

Table III. Histaminergic activity of some impromidine like compounds.



compound			agonistic H_2-activity atrium (2)			fundus (3)			antagonistic H_1-activity ileum (4)	
code	name	R	α	pD_2	n	α	pD_2	n	pA_2	n
9a	impromidine		1.0	7.8	10	1.0	8.5	4	5.5	8
9b	VUF 8407		1.0	7.9	6	1.0	8.2	5	5.6	8
9c	VUF 8413		0.9	7.7	6	0.9	8.5	4	5.5	8
9d	VUF 8532		0.9	7.4	4	0.8	8.0	2	5.5	4
9e	VUF 8405 [18]		1.0	7.2	8	1.0	7.6	4	5.6	4
	histamine		1.0	6.1	> 100	1.0	5.5	9	pD_2=6.9	> 50

(2)Agonistic histamine H_2-activity at the guinea pig right atrium, expressed as pD_2 (SD $\leq$ 0.1).
(3)Agonistic histamine H_2-activity at the guinea pig gastric fundus (acid secretion), expressed as pD_2 (SD $\leq$ 0.2).
(4)Antagonistic histamine H_1-activity at the guinea pig ileum, expressed as pA_2 (SD $\leq$ 0.2).

'affinity related' extra binding site on the H_2-receptor. However, it was found that (in addition to some heterocyclic aromatic groups), this 'affinity related' extra binding site can interact with a simple phenyl group as well.

Furthermore, in cimetidine, the 5-methylimidazole part can only be associated with affinity. Analogous to the results with the impromidine analogues, the H_2-activity of cimetidine is retained, or even improved, when the 5-methylimidazole part is changed into some other heterocyclic aromatic group. However, replacing the aromatic part of the antagonists by a phenyl group results in a complete loss of H_2-activity. Assuming that the 5-methylimidazolyl, 2-guanidinothiazolyl, 2-pyridyl, 5-dimethylaminomethylfuryl, respectively, phenyl group of the agonistic impromidine analogues all interact with the same binding site, we conclude from these results, summarized in the Tables I and III, that the affinity-related extra binding site on the H_2-receptor, with which the 5-methylimidazole part of impromidine is supposed to interact, may not be identical to the binding site for the heterocyclic aromatic part of the cimetidine analogues.

Thin—layer chromatography (TLC)

The purity of all compounds was verified by TLC (Table IV). Though in the cases of **8b**, **8e**, **9b**, **9c**, **9d** and **9e** two spots were detected on TLC, these compounds were considered to be pure because in all instances, the spot with the highest R_f-value was found to be picric acid, maleic acid or oxalic acid (depending upon the compound), while the spot with the lowest R_f-value was found to be the free base of the compound.

The identity of the spots with the highest R_f-values (acids) was verified by comparing their TLC behaviors with the original acid and by ^{1}H NMR (preparative TLC). In two instances the identity of the spot with the lowest R_f-values (free base of the compound) was also verified by ^{1}H NMR (preparative TLC).

Table IV. Thin—layer chromatography results.

Compound	Solvent	R_f
4d (A = CH_3)	ethylacetate (EA)	0.19
4d (A = nC_3H_7)	EA	0.38
4e (A = CH_3)	EA	0.65
8b	50% EA—50% EtOH, with 33% DME[a]	0.63
8e		0.80
9b	90% acetic acid—10% H_2O	0.34
9d		0.43
9e	90% MeOH—10% acetic acid	0.33

[a]Dimethylamine.

Experimental protocols

Chemistry

General

Melting points were determined with a Mettler FP 52 microscope. ^{1}H NMR spectra were measured with a Bruker WH 90 spectrometer. Tetramethylsilane (TMS) was the internal standard in $CDCl_3$ and dimethylsulfoxide d_6 (DMSO d_6), whereas sodium 3-trimethylsilylpropionate was used in D_2O. The compounds (about 0.2 mmol) were potentiometrically titrated with 0.1 M KOH from a calibrated Mettler DV 10 micropetter at 25°C under N_2 using a digital Philips PW 9414 ion activity meter. The volume of the solution was 35—40 ml. Mass spectra were measured with a Finnigan 4000. Impromidine and cimetidine were gifts from SK & F (U.K.) and tiotidine from I.C.I. (U.K.). The purity of all compounds was checked by TLC using pre-coated silica gel plates with fluorescence indicator (F_{254}).

Synthesis

N-*[2-(Benzylthio)ethyl]*-N′-*cyano-S-methylisothiourea* ***3e***

A solution of 10 g of 2-(benzylthio)ethylamine [9] in 100 ml of diethyl ether was added slowly to a stirred solution of 10 g of dimethyl *N*-cyanoiminodithiocarbonate [10] in 100 ml of diethyl ether. After complete addition, the solution was stirred for an additional 30 min after which the solid was filtered off, washed with ether and dried. Yield: 70%; mp = 104—107°C.

^{1}H NMR ($CDCl_3$): 2.46 ppm, singlet (CH_3); 3.0 H; 2.64 ppm, triplet (CH_2—S), J = 6.3 Hz, 2.1 H; 3.46 ppm, quartet (CH_2—N), J = 6.3 Hz, 2.1 H; 3.72 ppm, singlet (benzyl CH_2), 1.9 H; 6.40 ppm, singlet (NH), 1.0 H; 7.28 ppm, singlet (arom H), 5.0 H.

N-*Cyano-S-methyl*-N′-*{2-[(2-pyridyl)methylthio]ethyl}isothiourea* ***3d***

Analogous to the synthesis of **3e** from 2-(2-aminoethylthiomethylpyridine [11]. Yield: 79%; mp = 82—84°C.

^{1}H NMR (DMSO d_6): 2.52 ppm, singlet (CH_3); 2.63 ppm, triplet (CH_2—S), J = 7.1 Hz; + DMSO d_5 together: 7.3 H; 3.44 ppm, triplet (CH_2—N), J = 7.1 Hz, 2.0 H; 3.83 ppm, singlet (pyridyl—CH_2); 2.0 H; 7.14—8.54 ppm, multiplet (arom H + NH), 4.9 H.

N-*Cyano*-N′-*[3-(imidazol-4-yl)propyl]-S-methylisothiourea* ***6***

A solution of 10.1 g of 3-(imidazol-4-yl)propylamine [12] in 500 ml of ethanol was slowly added to a solution of 12.0 g of dimethyl *N*-cyanoiminodithiocarbonate [10] in 200 ml of ethanol. After complete addition, the solution was stirred for an additional hour and subsequently concentrated under reduced pressure. Addition of diethyl ether caused crystallization. The solid was filtered off and recrystallized from 1-propanol—diethyl ether. Yield: 70%; mp = 115—118°C.

^{1}H NMR (DMSO d_6—$CDCl_3$): 1.94 ppm, quintet (CH_2—CH_2—CH_2), J = 0.7 Hz, 2.0 H; 2.64 ppm, multiplet (CH_2—Im + S—CH_3), (+ DMSO d_5) 5.0 H; 3.41 ppm, multiplet (CH_2—N), 2.0 H; 6.83 ppm singlet (Im H4), 1.0 H; 7.72 ppm, singlet (Im H2), 1.0 H; 8.68 ppm, singlet (NH), 0.9 H.

N-*Cyano*-N′-*{2-[(5-methylimidazol-4-yl)methylthio]ethyl}*-N″-*propylguanidine* ***4a*** *(A = nC_3H_7)*

Synthesized according to the method described by Durant *et al.* [7]. mp: found: 108—110°C; reported: 108—110°C [7].

N-*Cyano*-N′-*{2-[(5-dimethylaminomethylfuran-2-yl)methylthio]ethyl}*-N″-*methylguanidine* ***4c*** *(A = CH_3)*

Synthesized according to the method described by Price *et al.* [13]. mp: found: 72—74°C; reported: 73—75°C [13].

N-*Cyano*-N′-*methyl*-N″-*{2-[(2-pyridyl)methylthio]ethyl}guanidine* ***4d*** *(A = CH_3)*

A solution of 2 g of **3d** in 100 ml of methanol was saturated with methylamine and subsequently refluxed for 3 h. After cooling, the solution was evaporated and the residue purified by column chromatography (silica gel 0.2—0.5 mm; 2-propanol). The compound was crystallized from ethyl acetate—diethyl ether. Yield: 74%; mp = 118—120°C.

^{1}H NMR (DMSO d_6): (2.58 ppm, triplet (S—CH_2), J = 6.8 Hz; 2.64 ppm, doublet (N—CH_3), J = 4.9 Hz) together: 5.0 H; 3.06—3.44 ppm, multiplet (CH_2—N), (+ H_2O) 4.7 H; 3.81 ppm, singlet (pyridyl—CH_2) 2.0 H; 6.84—7.88 ppm, multiplet (pyridyl H + 2 NH), 4.5 H; 8.35—8.54 ppm, multiplet (pyridyl H), 0.8 H.

Base *m/e*: calculated: 249.1048; found: 249.1045.

N-*Cyano*-N′-*propyl*-N″-*{2-[(2-pyridyl)methylthio]ethyl}guanidine* ***4d*** *(A = nC_3H_7)*

Synthesized in a manner analogous to **4a** (A = nC_3H_7). Purification by column chromatography (silica gel 0.2—0.5 mm; 2-propanol).

Crystallization from ethyl acetate—diethyl ether. Yield: 72%; mp = 101—103°C.

^{1}H NMR (DMSO d_6): 0.84 ppm, triplet (CH_3), J = 7.2 Hz, 3.0 H; 1.47 ppm, sextet (CH_2—CH_3), J = 7.2 Hz, 2.0 H; 2.59 ppm, triplet (CH_2—S), J = 7.2 Hz, 2.2 H; 2.88—3.52 ppm, multiplet (2 × CH_2 + N—CH_3), (+ H_2O) 8.1 H; 3.85 ppm, singlet (pyridyl—CH_2), 2.1 H; 6.82 —7.16 ppm, multiplet (2 × NH), 1.9 H; 7.18—7.54 ppm, multiplet (pyridyl H), 2.0 H; 7.36—7.90 ppm, multiplet (pyridyl H), 1.0 H; 8.36—8.58 ppm, multiplet (pyridyl H), 1.0 H.

Base *m/e*: calculated: 277.1242; found: 277.1243.

N-[*2-(Benzylthio)ethyl*]-N′-*cyano*-N″-*methylguanidine* ***4e***

Synthesized analogous to **4d** (A = CH_3). Purification by column chromatography (silica gel 0.2—0.5 mm; acetone). Crystallization from chloroform—diethyl ether. Yield: 85%; mp = 77—79°C.

^{1}H NMR ($CDCl_3$): 2.60 ppm, triplet (CH_2—S), J = 6.0 Hz, 2.1 H; 2.78 ppm, doublet (N—CH_3), J = 4.7 Hz, 3.1 H; 3.36 ppm, quartet (CH_2—N), J = 6.0 Hz, 2.1 H; 3.71 ppm, singlet (benzyl CH_2), 2.0 H; 5.77 ppm, triplet (N*H*—CH_2), J = 5.4 Hz, 1.0 H; 6.04 ppm, quartet (N*H*—CH_3), J = 5.1 Hz, 1.0 H; 7.28 ppm, singlet (arom H), 4.8 H.

Base *m/e*: calculated: 248.1102; found: 248.1096.

N-*Cyano*-N′-[*3-(imidazol-4-yl)propyl*]-N″-{*2-*[*(5-methylimidazol-4-yl)-methylthio*]*ethyl*}*guanidine* ***8a***

Synthesized according to the method described by Durant *et al.* [14]. mp: found: 137—140°C; reported: 140—142°C [14].

N-*Cyano*-N′-{*2-*[*(2-guanidylthiazol-4-yl)methylthio*]*ethyl*}-N″-[*3-(imidazol-4-yl)propyl*]*guanidine dihydrogen maleate* ***8b***

A solution of 3 g of **6** and 8 g of 4-[(2-aminoethyl)thiomethyl]-2-guanidinothiazole [15] in 200 ml of ethanol was refluxed for 48 h. The cyanoguanidine was purified by column chromatography (silica gel 0.2—0.5 mm; 2-propanol) and crystallized from 2-propanol ether in the presence of 2 eq. of maleic acid. Yield: 20%; mp = 95—98°C.

^{1}H NMR (DMSO d_6); 180 ppm, quintet (CH_2—CH_2—CH_2), J = 7.0 Hz, 2.0 H; 2.38—2.79 ppm, multiplet, (2 × CH_2), 6.3 H (+ DMSO d_5); 2.97—3.48 ppm, multiplet (2 × CH_2), 4.0 H; 3.74 ppm, singlet (thiazolyl—CH_2), 2.0 H; 6.06 ppm, singlet (maleic acid), 4.0 H; 6.85—7.50 ppm, multiplet (thiazolyl H_4, imidazolyl H_4, 2 NH from cyanoguanidino group + imidazolyl (NH + NH^+) 6.0 H; 7.67—8.40 ppm, broad signals, (NH protons from guanidino group + 3 protons from maleic acid) 7.0 H; 8.88 ppm, doublet, J = 0.8 Hz (imidazolyl H_2), 1.0 H.

N-*(2-Benzylthio)ethyl*-N′-*cyano*-N″-[*3-(imidazol-4-yl)propyl*]*guanidine oxalate* ***8e***

A solution of 10 g of **3e** and 2.5 g of 4-(3-aminopropyl)imidazole [12] in 200 ml of 2-propanol was refluxed for 70 h. After evaporating the reaction mixture, the residue was purified by column chromatography (silica gel 0.2—0.5 mm; 50% mixture of ethyl acetate—ethanol). The compound was crystallized as the oxalate from methanol—diethyl ether. Yield: 8%; mp = 154.5—155.2°C.

^{1}H NMR (D_2O): 1.97 ppm, quintet (CH_2—CH_2—CH_2), J = 7.2 Hz, 2.0 H; 2.58—3.00 ppm, multiplet (2 × CH_2), 4.0 H; 3.15—3.54 ppm, multiplet (2 × CH_2), 4.0 H; 3.78 ppm, singlet (benzyl CH_2), 2.0 H; (7.21 ppm, singlet (Im H5); 7.33 ppm, singlet phenyl H) together: 6.0 H; 8.56 ppm, doublet (Im H2) J = 0.9 Hz, 1.0 H.

N-{*2-*[*(2-Guanidylthiazol-4-yl)methylthio*]*ethyl*}-N′-[*3-(imidazol-4-yl)-propyl*]*guanidine tripicrate* ***9b***

A solution of 2 g of **8b** was refluxed for 2 h in conc. HCl. After evaporating the reaction mixture, the residue was dissolved in ethanol and added to a solution of picric acid in ethanol. The precipitate was filtered off, washed with ethanol and subsequently refluxed for 30 min in 2-butanone. After cooling, the solid was filtered off, washed with acetone and dried. Yield: 75%; mp = 129—132°C.

^{1}H NMR (DMSO d_6): 1.87 ppm, quintet (CH_2—CH_2—CH_2), J = 7.0 Hz, 2.1 H; 2.42—2.81 ppm, multiplet (2 × CH_2), (+ DMSO d_5) 6.1 H; 3.00—3.60 ppm, multiplet (2 × CH_2), (+ H_2O) 10.1 H; 3.80 ppm, singlet (thiazole CH_2), 2.1 H; 7.13 ppm, singlet (thiazole H5), 1.0 H; 7.44 ppm, singlet (central guanidine + Im H5), 5.1 H; 8.20 ppm, singlet (thiazole guanidine), 5.1 H; 8.60 ppm, singlet (picric acid), 6.0 H; 9.03 ppm, doublet (Im H_2), J = 0.9 Hz, 1.0 H.

N-{*2-*[*(5-Dimethylaminomethylfuran-2-yl)methylthio*]*ethyl*}-N′-[*3-(imidazol-4-yl)propyl*]*guanidine tripicrate* ***9c***

A solution of 3 g of **6** and 8 g of 2-[(2-aminoethyl)thiomethyl]-5-(dimethylaminomethyl)furan [13] in 200 ml of 1-propanol was refluxed for 48 h. After evaporating the solvent, the cyanoguadinine was purified by column chromatography (silica gel 0.063—0.200 mm; ethanol). A solution of 500 mg of the purified cyanoguanidine was refluxed for 5 h in 300 ml of 0.5 N HCl. After evaporating the reaction mixture, the residue was dissolved in methanol and added to a solution of picric acid in methanol. The precipitate was filtered off, washed with methanol and recrystallized from ethanol. Yield: 35%; mp = found: 143—146°C; reported [16]: 144—146°C.

N-[*3-(Imidazol-4-yl)propyl*]-N′-[*2-(2-pyridylmethylthio)ethyl*]*guanidine tripicrate* ***9d***

A solution of 3 g of **6** and 7 g of 2-[(2-aminoethyl)thiomethyl]pyridine [11] in 100 ml of ethanol was refluxed for 48 h. After evaporating the mixture, the cyanoguanidine was purified by column chromatography (silica gel 0.2—0.5 mm; 2-propanol). The purified cyanoguanidine was dissolved in 300 ml of 2 N HCl and refluxed for 5 h. After evaporating the reaction mixture, the residue was dissolved in methanol and added to a solution of picric acid in methanol. The precipitate was filtered off, washed with methanol and dried. Yield: 6%; mp = 153—156°C.

^{1}H NMR (DMSO d_6): 1.80 ppm, quintet (CH_2—CH_2—CH_2), J = 7.2 Hz, 2.1 H; 2.40—2.80 ppm, multiplet (2 × CH_2), (+ DMSO d_5) 8.3 H; 3,04—3.50 ppm, multiplet (2 × CH_2), 4.2 H; 4.04 ppm, singlet (pyridyl CH_2), 2.0 H; 7.20 ppm, singlet (b) (guanidine H + Im H5), 5.0 H; 7.62—8.00 ppm, multiplet (pyridyl 2H), 2.0 H; 8.18—8.46 ppm, multiplet (pyridyl H), 1.0 H; 8.60 ppm, singlet (picric acid), 6.0 H; 8.68—8.88 ppm, multiplet (pyridyl H), 1.0 H; 9.00 ppm, singlet (Im H2), 1.0 H.

Pharmacology

Histamine H_2-activity

Guinea pig right atrium

The histamine H_2-activity on the guinea pig right atrium has been determined as described by Sterk *et al.* [17]. The pA_2 of the antagonists was determined from Schild plots using histamine as the agonist. The histamine H_2-specificity of **9b**, **9c** and **9d** was established from Schild plots using cimetidine as the specific H_2-antagonist. The slopes of the Schild plots were not significantly different from one.

Guinea pig gastric acid secretion

The histamine H_2-activity on the isolated gastric fundus of the guinea pig was determined as described by Sterk *et al.* [18].

Histamine H_1-activity

Guinea pig ileum

The histamine H_1-activity on the guinea pig ileum was determined as described by Emmett *et al.* [19].

Test solutions

Test solutions of histamine·2HCl, impromidine·3HCl, **8b** (dimaleate) and **8e** (dioxalate) were prepared in H_2O. Test solutions of the other compounds were prepared in DMSO (10^{-2} or 10^{-3} M) and diluted further with H_2O to desired concentration. **9b**, **9c** and **9d** were tested as their tripicrates and **9e** as its dipicrate. The concentration of DMSO in the organ bath never exceeded 0.2%. DMSO, tested up to a concentration of 0.5%, was found to have no significant effect on the dose—response curves of the compounds under investigation.

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