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New products

Pyridine and reduced pyridine analogues of cimetidine as histamine H_2-receptor antagonists

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H_2-receptor antagonists / alkyl thiourea / cyanoguanidine derivatives

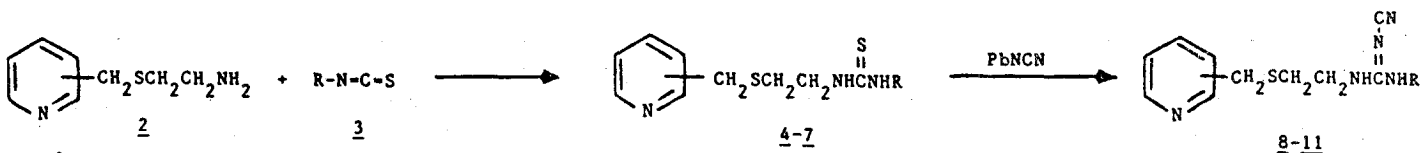
Introduction

The search for improved histamine H_2-receptor antagonists, stimulated by the clinical success of cimetidine, has resulted in the discovery of longer acting highly potent non-imidazole H_2-receptor antagonists possessing a variety of heterocyclic rings and 'urea equivalents' of general structure **1**, Het—$CH_2SCH_2CH_2Y$. The most common aromatic heterocyclic ring (Het) systems include the [(dimethylamino)methyl]-furanyl and guanidinothiazole moieties present in ranitidine [1] and tiotidine [2], respectively, in conjunction with acyclic cyanoguanidine, 1-nitro-2,2-diaminoethene and cyclic isocytosine [3] or 1,2,5-thiadiazole oxide [4, 5] moieties. Histamine H_2-receptor antagonists must therefore interact with the H_2-receptor in different ways and activity is dependent upon the Het and the 'urea equivalent' Y [1—5].

Recently, we prepared compounds **1** in which the Het group was a pyridinyl or 1,2-dihydropyridinyl ring system and Y was —CH(=$CHNO_2$)N— and —NHC(=X, X=O, S, NCN)NHMe. The pharmacological test results suggested that the charge distribution in the Het was an important determinant of activity [6, 7]. It was, therefore, of interest to determine what effect the incorporation of *N*-alkyl 'urea equivalents' would have on H_2-antagonistic activity. We now describe the synthesis and H_2-antagonistic activity of **1** having a pyridinyl or 1,2-dihydropyridinyl Het system and *N*-alkyl(cycloalkyl)thiourea and cyanoguanidine moieties Y.

Chemistry

The synthesis of the target *N*-alkyl(cycloalkyl)-*N'*-[2-(pyridinylmethylthio) ethyl]thioureas **4**—**7** and cyanoguanidines **8**—**11** is outlined in Scheme 1 and summarized in Table I. Thus, reaction of the [(2-aminoethyl)thiomethyl]pyridines **2a**—**c** with cyclopentyl-, *n*-butyl-, *n*-propyl- or ethylisothiocyanate gave the respective thiourea analogues **4**—**7a**—**c** in good yield. The subsequent reaction of the thiourea derivatives **4**—**7** with lead cyanamide gave the corresponding cyanoguanidine analogues **8**—**11a**—**c**. The sodium borohydride reduction of the pyridine derivatives **4c** and **8c** in the presence of methylchloroformate in methanol at — 65°C [8] yielded the respective 1,2-dihydropyridinyl products **12** and **13** in 60 and 68% yields, respectively (Scheme 2).

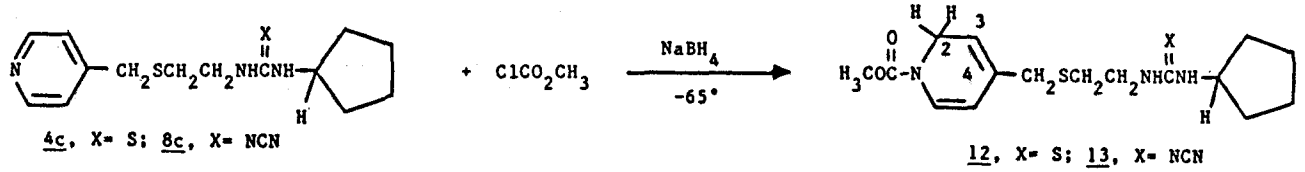


2 3 4-7 8-11

a, 2-Pyridyl; b, 3-Pyridyl; c, 4-Pyridyl; 4-8, R= c-C_5H_9; 5,9, R= n-C_4H_9; 6,10, R= n-C_3H_7; 7,11, R= C_2H_5

Scheme 1.

**Author to whom correspondence should be addressde.*



Scheme 2.

Table I. *N*-Alkyl(cycloalkyl)-*N'*-[2-(2-(3-,4-)pyridinylmethylthio)ethyl]thioureas **4—7** and cyanoguanidines **8—11**.

Het—$CH_2SCH_2CH_2NHC(=X)NHR$

No.	Het	X	R	Reaction time (h)	Yield (%)	R_f[a]	Formula[b]
4a	2-pyridyl	S	c-C_5H_9—	18	81	0.58	$C_{14}H_{21}N_3S_2$
4b	3-pyridyl	S	c-C_5H_9—	18	79	0.50	$C_{14}H_{21}N_3S_2$
4c	4-pyridyl	S	c-C_5H_9—	18	84	0.54	$C_{14}H_{21}N_3S_2$
5a	2-pyridyl	S	*n*-C_4H_9—	14	75	0.60	$C_{13}H_{21}N_3S_2$
5b	3-pyridyl	S	*n*-C_4H_9—	14	73	0.60	$C_{13}H_{21}N_3S_2$
5c	4-pyridyl	S	*n*-C_4H_9—	14	76	0.60	$C_{13}H_{21}N_3S_2$
6a	2-pyridyl	S	*n*-C_3H_7—	14	70	0.62	$C_{12}H_{19}N_3S_2$
6b	3-pyridyl	S	*n*-C_3H_7—	14	70	0.60	$C_{12}H_{19}N_3S_2$
6c	4-pyridyl	S	*n*-C_3H_7—	14	74	0.60	$C_{12}H_{19}N_3S_2$
7a	2-pyridyl	S	C_2H_5—	10	65	0.55	$C_{11}H_{17}N_3S_2$
7b	3-pyridyl	S	C_2H_5—	10	62	0.60	$C_{11}H_{17}N_3S_2$
7c	4-pyridyl	S	C_2H_5—	10	69	0.58	$C_{11}H_{17}N_3S_2$
8a	2-pyridyl	NCN	c-C_5H_9—	48	70	0.60	$C_{15}H_{21}N_5S$
8b	3-pyridyl	NCN	c-C_5H_9—	48	69	0.65	$C_{15}H_{21}N_5S$
8c	4-pyridyl	NCN	c-C_5H_9—	48	72	0.60	$C_{15}H_{21}N_5S$
9a	2-pyridyl	NCN	*n*-C_4H_9—	48	72	0.60	$C_{14}H_{21}N_5S$
9b	3-pyridyl	NCN	*n*-C_4H_9—	48	70	0.60	$C_{14}H_{21}N_5S$
9c	4-pyridyl	NCN	*n*-C_4H_9—	48	73	0.60	$C_{14}H_{21}N_5S$
10a	2-pyridyl	NCN	*n*-C_3H_7—	48	74	0.58	$C_{13}H_{19}N_5S$
10b	3-pyridyl	NCN	*n*-C_3H_7—	48	70	0.60	$C_{13}H_{19}N_5S$
10c	4-pyridyl	NCN	*n*-C_3H_7—	48	74	0.60	$C_{13}H_{19}N_5S$
11a	2-pyridyl	NCN	C_2H_5—	48	68	0.60	$C_{12}H_{17}N_5S$
11b	3-pyridyl	NCN	C_2H_5—	48	65	0.60	$C_{12}H_{17}N_5S$
11c	4-pyridyl	NCN	C_2H_5—	48	70	0.60	$C_{12}H_{17}H_5S$
12	4-(1-methoxy-carbonyl-1,2-dihydropyridinyl)	S	c-C_5H_9—	4	60	0.70[c]	$C_{16}H_{25}N_3O_2S_2$
13	4-(1-methoxy-carbonyl-1,2-dihydropyridinyl)	NCN	c-C_5H_9—	4	68	0.72[d]	$C_{17}H_{25}N_5O_2S$

[a]Chloroform:methanol (8:1, v/v) as the development solvent.
[b]All compounds were analyzed for C, H, N, O and S using high—resolution mass spectrometry.
[c]Chloroform:methanol (16:1, v/v) as the development solvent.
[d]Methylene chloride:methanol (16:1, v/v) as the development solvent.

Pharmacological Results and Discussion

A number of selected thiourea and cyanoguanidine analogues was investigated to determine the effect that a pyridinyl ring and its point of attachment, and a 1-methoxycarbonyl-1,2-dihydropyridinyl ring in conjunction with a variety of terminal *N*-cycloalkyl and *N*-alkyl substituents have upon H_2-antagonist activity. It is known that there is a reasonable correlation between *in vitro* H_2-antagonist activity and a lipophilicity parameter (octanol/water log *P* value) for most cyanoguanidine and related 'urea equivalents'. Terminal *N*-methylcyanoguanidine derivatives are consistently more active than their *N*-desmethyl analogues due to their increased lipophilicity [9]. It has been speculated that cyanoguanidine and related moieties may interact with the H_2-receptor by hydrogen bonding and that the strength of this interaction is determined by the dipole's ability to align with the receptor [10]. The physicochemical properties of the terminal *N*-cycloalkyl(alkyl) substituent are therefore expected to be determinants of lipophilicity, steric effects that influence hydrogen-bonding to the H_2-receptor, the bond angle (geometry) of the N—C—N guanidino moiety and the *E*/*Z* conformation of the cyanoguanidino group. Furthermore, it is feasible for compounds **8—11**

to adopt an intramolecularly folded structure stabilized by a hydrogen bond between the pyridine nitrogen and the terminal nitrogen of the cyanoguanidino group [11], similar to that observed for the clinically useful histamine H_2-receptor antagonist cimetidine [12, 13].

The test results indicate the terminal *N*-alkyl(cycloalkyl) substituent is a determinant of activity. A comparison of the activities of the *N*-alkyl(cycloalkyl)-*N'*-2-[2-(pyridinylmethylthio)ethyl]thiourea analogues indicated the relative activities were *N*-methyl **14** > *N*-cyclopentyl **4a** > *N*-*n*-propyl **6a**. A similar activity profile was observed for the related cyanoguanidine analogues where *N*-methyl **15** > *N*-cyclopentyl **8a** > *N*-*n*-propyl **10a**, but the differences in potency were small. In contrast, the activity sequence for the *N''*-cyano-*N*-alkyl(cycloalkyl)-*N'*-2-[4-(pyridinylmethylthio)ethyl]guanidine analogues was *N*-*n*-propyl **10c** > *N*-methyl **16** > *N*-cyclopentyl **8c** but the differences in activity were not significant. Compound **8c** induced a small non-parallel shift in the dose—response curve at a concentration of 10^{-4} M, presumably due to slow reversible binding to the histamine H_2-receptor [11] and the maximum response to histamine was suppressed. The thiourea analogues were more potent than the corresponding cyanoguanidine analogues in the *N*-cyclopentyl (**4a** > **8a**), *N*-*n*-propyl (**6a** > **10a**) and *N*-methyl (**14** > **15**) series of compounds. Elaboration of the 4-pyridinyl ring of **8c** to a 4-(1-methoxycarbonyl-1,2-dihydropyridinyl) ring **13** abolished activity.

Experimental protocols

Chemistry

Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform unless otherwise stated with tetramethylsilane (TMS) as the internal standard with a Varian EM-360A cr Bruker AM-300 spectrometer. Mass spectra were measured with an AEI MS-50 high resolution mass spectrometer.

General synthesis of N-*alkyl (cycloalkyl)*-N'-[2-*(pyridinylmethylthio) ethyl]thioureas 4—7*

The alkyl(cycloalkyl)isothiocyanate **3** (R = cyclopentyl, *n*-butyl, *n*-propyl or ethyl) (30 mmol) was added to a solution of the [(2-aminoethyl)thiomethyl]pyridine **2a—c** [7] in 70 ml of isopropanol and the mixture was heated at reflux for 10—18 h as specified in Table I. The solvent was removed *in vacuo*, the residue dissolved in acetone, filtered and the solvent removed *in vacuo* to yield the respective products **4—7**. The products were purified on silica gel G plates, 1.0 mm thick, using chloroform: methanol (8:1, v/v) as the development solvent. Extraction of the product band (see R_f values listed in Table I) with warm absolute ethanol yielded **4—7** as oils. Alternatively, products **4—7** could also be purified by elution from a 2.5 × 20 cm silica gel column with chloroform:methanol (8:1, v/v) as the eluant. Removal of the solvent from the 100—450 ml of eluant gave **4—7**. The spectrometric data for **4a** which is representative of the little compounds is listed below.

N-*Cyclopentyl*-N'-[2-*(2-pyridinylmethylthio)ethyl]thiourea* ***4a***. IR (KBr): 1090 (C=S) and 3256 (NH) cm^{-1}. ^1H NMR δ: 1.4—2.3 (m, 8H, cyclopentyl H-2 to H-5); 2.7 (t, J = 7 Hz, 2H, CH_2CH_2N); 3.7 (t, J = 7 Hz, 2H, SCH_2CH_2); 3.9 (s, 2H, pyridinyl—CH_2—S—); 4.25 (m, 1H, cyclopentyl H-1); 5.9—7.03 (m, 2H, two NH protons, exchange with deuterium oxide); 7.0—7.46 (m, 2H, pyridinyl H-3, H-5); 7.66 (d, $J_{3,4}$ = 8 Hz of d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 2 Hz, 1H, pyridinyl H-4); 8.46 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 2 Hz, 1H, pyridinyl H-6). Exact Mass calcd. for $C_{14}H_{21}N_3{}^{32}S_2$: 295.1177; found (high resolution MS): 295.1184.

General synthesis of N''-*cyano*-N-*alkyl(cycloalkyl)*-N'-[2-*(pyridinylmethylthio)ethyl]guanidines 8—11*

Lead cyanamide (52 mmol) was added to a solution of **4—7** (24 mmol) in 260 ml of acetonitrile and 26 ml of dimethylformamide. The mixture was heated under reflux with stirring for 48 h, during which time, additional lead cyanamide (7.8 g) was added in aliquots. The solids were filtered and the solvent was removed *in vacuo* to give the respective products **8—11** which were purified by elution from a 7.5 × 50 cm silica gel column using ethyl acetate:isopropanol (1:1, v/v) as the eluant. The initial 50 ml fraction was discarded. Further elution (500 ml) gave **8—11**. Alternatively, products **8—11** could be purified on silica gel G plates, 1.0 mm thick, using chloroform:methanol (8:1, v/v) as the development solvent. Extraction of the product band (see R_f value listed in Table I) with chloroform:methanol (1:1, v/v) afforded **8—11** as oils. The spectrometric data for **8a** which is representative of the title compounds is listed below.

N''-*Cyano*-N-*cyclopentyl*-N'-[2-*(2-pyridinylmethylthio)ethyl]guanidine* ***8a***. IR (KBR): 2120 (CN) and 3480 (NH) cm^{-1}. ^1H NMR δ: 1.4—2.3 (m, 8H, cyclopentyl H-2 to H-5); 2.7 (t, J = 7 Hz, CH_2CH_2N); 3.7 (t, J = 7 Hz, 2H, SCH_2CH_2); 3.9 (s, 2H, pyridinyl—CH_2—S); 4.25 (m, 1H, cyclopentyl H-1); 6.2—7.03 (m, two NH protons, exchange with deuterium oxide); 7.0—7.46 (m, 2H, pyridinyl H-3, H-5); 7.66 (d, $J_{3,4}$ = 8 Hz of d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 2 Hz, 1H, pyridinyl H-4); 8.46 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 2 Hz, 1H, pyridinyl H-6). Exact Mass calcd. for $C_{15}H_{21}N_5{}^{32}S$: 303.1518; found (high resolution MS): 303.1508.

Table II. Antagonism of histamine-induced guinea pig atria chronotropic response.

No.	Het	X	R	H_2-receptor antagonist activity, pA_2 (± SE)	Slope of Schild plot
4a	2-pyridyl	S	c-C_5H_9—	5.33 (0.142)	0.684
6a	2-pyridyl	S	*n*-C_3H_7—	4.76 (0.124)	0.862
8a	2-pyridyl	NCN	c-C_5H_9—	4.78 (0.06)	1.061
8c	4-pyridyl	NCN	c-C_5H_9—	< 4	
10a	2-pyridyl	NCN	*n*-C_3H_7—	4.66 (0.106)	1.488
10c	4-pyridyl	NCN	*n*-C_3H_7—	4.83 (0.115)	0.910
13	4-(1-methoxycarbonyl-1,2-dihydropyridinyl)	NCN	c-C_5H_9—	inactive	
14	2-pyridyl	S	CH_3	5.71 (0.135)[a]	
15	2-pyridyl	NCN	CH_3	5.05 (0.070)[a]	
16	4-pyridyl	NCN	CH_3	4.67 (0.112)[a]	
Cimetidine				6.1[a]	

[a]Literature value [7].

N-Cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl) methylthio]ethyl} thiourea **12**

Sodium borchydride (0.227 g, 6 mmol) was added to a solution of **4c** (0.295 g, 1 mmol) in absolute methanol (10 ml) precooled in a dry ice—isopropanol bath. A solution of methylchloroformate (0.189 g, 2 mmol) in 3 ml of dry diethylether was added at such a rate that the temperature of the reaction did not rise above —69°C. The reaction was allowed to proceed with stirring at < —69°C for 4 h, after which the reaction mixture was poured onto ice—water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4×100 ml), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform *in vacuo* gave the 1-methoxycarbonyl-1,2-dihydropyridinyl product **12**. The product **12** was purified on silica gel G plates, 1.0 mm thick, using chloroform: methanol (16:1, v/v) as the development solvent. Extraction of the product band (R_f 0.7) with the same solvent gave **12** (0.213 g, 60%) as an oil. IR (KBr): 1090 (C=S), 1710 (CO_2) and 3280 (NH) cm^{-1}. ^1H NMR δ: 1.25—2.22 (m, 8H, cyclopentyl H-2 to H-5); 2.6 (t, J = 7 Hz, 2H, CH_2CH_2N); 3.07 (s, 2H, dihydropyridinyl—CH_2—S); 3.57 (t, J = 7 Hz, 2H, SCH_2CH_2N); 3.75 (s, 3H, OCH_3); 3.9—4.2 (m, 1H, cyclopentyl H-1); 4.27 (d, J_{gem} = 3 Hz, 2H, dihydropyridinyl H-2); 5.2 (m, 1H, dihydropyridinyl H-5); 5.35 (m, 1H, dihydropyridinyl H-3); 6.32 (m, 2H, two NH protons, exchange with deuterium oxide); 6.7 (d, $J_{5,6}$ = 8 Hz, 1H, dihydropyridinyl H-6). Exact Mass calcd. for $C_{16}H_{25}N_3O_2{}^{32}S_2$: 355.1389; found (high resolution MS): 355.1389.

Compound **13** was prepared in a manner similar to that used for **8c**.

Pharmacology

The compounds listed in Table II were evaluated using the previously reported procedure to determine antagonism of the histamine-induced guinea pig atria chronotropic response [7].

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