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NOVEL 1, 2, 4-OXADIAZOLES AS POTENT AND SELECTIVE HISTAMINE H_3 RECEPTOR ANTAGONISTS

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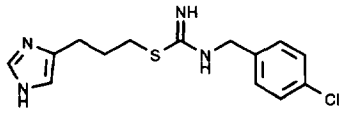
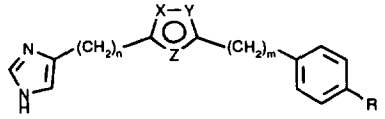
Abstract: Replacement of the isothiourea moiety of known histamine H_3 antagonists by certain 5-membered heteroaromatic systems can give compounds with an improved activity profile. One of these, 3-[(4-chlorophenyl)methyl]-5-[2-(1H-imidazol-4-yl)ethyl] 1,2,4-oxadiazole (GR175737) is a potent, selective, orally active and centally penetrating H_3 antagonist. Copyright © 1996 Elsevier Science Ltd

Histamine H_3 receptors have been reported to play a rôle as a regulating receptor system, controlling not only the release and synthesis of histamine but also the release of other neurotransmitters.[1] Histamine H_3 receptors are widely distributed but in high density in those areas of the brain associated with cognition. Significantly, it has been shown that H_3 receptors exert an inhibitory control on the release of acetylcholine in the CNS.[2] Furthermore, the selective H_3 antagonist thioperamide improves performance in models of cognitive function.[3] A further class of compounds which exhibits potent and selective H_3 antagonist activity are isothioureas of which clobenpropit **I** is a leading example.[4-6] In seeking therapeutically useful H_3 antagonists our priority lay in obtaining structures which lacked the potentially unstable and toxic isothiourea moiety. We now report the synthesis and histamine H_3 receptor activity of a series of compounds **II** and show that certain 5-membered heterocycles can serve as bioisosteres for the isothiourea group. Recently, non-thiourea/isothiourea H_3 antagonists have been described by Ganellin *et al.*[7], Vollinga *et al.*[8] and Ligneau *et al.*[9] In additon, Plazzi *et al.*[10] have reported the histamine H_3 receptor affinity of some thiazolylhistamine derivatives.



I clobenpropit

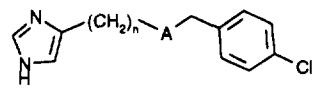


II X, Y, Z = O, N, S; n = 1-3, m = 1, 2
R = various

The effects of replacing the isothiourea group of clobenpropit **I** by heterocyclic ring systems are summarised in Table 1. In general H_3 binding affinity paralleled H_3 antagonist potency. Both 1,2,4-oxadiazole and 1,2,4-triazole ring systems can serve as effective surrogate groups imparting good

H_3 antagonist activity and selectivity (>100 fold) over H_1 and H_2 receptors. Other heterocycles had inferior activity at H_3 receptors although their effectiveness may also be dependent upon the length of the methylene spacers (*vide infra*).

Table I ***In vitro* data for heterocyclic histamine H_3 antagonists[a]**

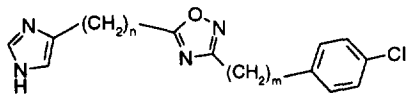


Compd	n	A	H_3 pKi[b]	H_3 pK_B[c]	H_2 pK_B[d]	H_1 pK_B[d]
1	3		7.6	6.8	<5.0	<5.0
2	2		8.2	8.1	<5.0	<5.0
3	3		7.9	7.4	<5.0	<5.0
4	2		6.7	5.7	NT	NT
5	2		6.9	5.8	NT	NT
6	2		7.0	7.0	5.8	NT
7	2		6.7	7.3	NT	NT
8	2		7.7	7.0	5.6	NT
	Thioperamide		8.7	8.3	<5.0	<5.0
	Clobenpropit		9.8	9.9	<6.0	<6.0

[a] Figures quoted are the mean of two independent determinations, each within 0.2 log units of the mean. [b] Binding affinity: [^{3}H]-N^{α}-methylhistamine was used to label H_3 sites in rat cerebral cortex membranes. [c] Antagonist activity at histamine H_3 receptors was assesed on guinea-pig longitudinal muscle strips subjected to electrical field stimulation. [d] Antagonist activity at histamine H_1 receptors was assessed against histamine-induced contractions of guinea-pig isolated whole ileum and at H_2 receptors against histamine-induced tachycardia in guinea-pig isolated atria. See reference 5 for details. NT = Not tested

The promising profile of the oxadiazole **2** (GR175737) led us to examine SAR around this structure. Thus far, our studies in this series indicate that the optimum chain length for H_3 antagonist activity is two methylene groups between the imidazole ring and the oxadiazole moiety and one methylene between the latter and the 4-chlorophenyl group (Table 2). However, in the triazole series (**3**, **4**, Table 1) a longer chain between the imidazole and the triazole appears to be advantageous.

Table 2[a] Modifications to the linkers in the oxadiazole H_3 antagonists

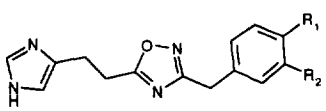


Compd	n	m	H_3 pK_i	H_3 pK_B	H_2 pK_B	H_1 pK_B
1	3	1	7.6	6.8	<5.0	<5.0
2	2	1	8.2	8.1	<5.0	<5.0
9	2	2	7.7	7.7	<5.0	<5.0
10	1	2	6.6	NT	NT	NT
11	1	1	7.6	7.2	NT	NT

[a] See footnotes for Table 1

Electron withdrawing, polar substituents (as in e.g. **18**, **20**, **21**) in the 4-position appear detrimental to H_3 affinity. In contrast, lipophilic groups (as in e.g. **2**, **12**, **14** and **15**) seem to bring high H_3 affinity, although some steric constraints are perhaps indicated by the lower activity of the phenyl substituted analogue **16** (Table 3).

Table 3 Modifications to the benzenoid ring of GR 175737



Compd	R_1	R_2	H_3 pK_i[a]	H_3 pK_B[a]
2, GR175737	Cl	H	8.2	8.1
12	CF_3	H	8.1	8.3
13	F	H	8.0	8.4
14	Cl	Cl	8.5	8.0
15	I	H	8.2	7.1
16	Ph	H	7.2	6.6
17	MeO	H	7.4	6.5
18	$MeSO_2NH$	H	5.9	NT
19	MeS	H	7.6	NT
20	MeSO	H	5.6	NT
21	$MeSO_2$	H	6.5	NT

[a] See footnotes a, b and c, Table 1

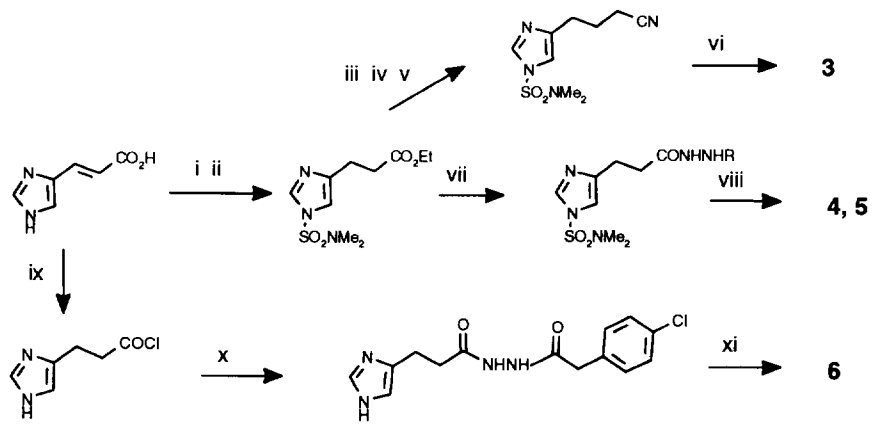
Table 4 Comparison of *ex vivo* and *in vivo* data for Histamine H_3 Antagonists[a]

Compound	*Ex vivo* Binding[b] ED_{50} (mg/kg)		(R)-α-Methylhistamine Drinking[c] ED_{50} (mg/kg)	
GR 175737	1.4 s.c.	1.2 p.o.	1.0 s.c.	NT p.o.
Clobenpropit	10.5 s.c.	> 30 p.o.	1.3 s.c.	2.4 p.o.
Thioperamide	5.1 s.c.	6.0 p.o.	0.8 s.c.	0.8 p.o.

[a] Figures quoted are the mean of two independent determinations, each within 10% of the mean.
[b] Antagonism of *ex vivo* binding: Male rats were injected s.c. or p.o. with the test compounds. One hour later the animals were sacrificed, the cortices and hippocampi removed and homogenised. Radioligand binding was conducted using [^{3}H]-N$^\alpha$-Methylhistamine. [c] Antagonism of (R)-α-methylhistamine-induced dipsogenicity: Measurement of water consumption induced by (R)-α-methylhistamine was performed in male rats. Test compounds were administered s.c. or p.o. and (R)-α-methylhistamine was given at the same time. Following drug treatment the rats were denied access to water. The amount of water consumed over a 10 min period was measured and ED_{50} values were calculated as the dose required to inhibit water consumption by 50% of control. See reference 5 for details.

GR175737 was selected for further pharmacological evaluation. To assess its CNS penetration, *ex vivo* binding to rat cortex/hippocampus was determined. Interestingly, GR175737 was 7 fold more potent than chlobenpropit following s.c. administration and it also showed excellent oral activity. The *in vivo* activity of GR175737 was evaluated using antagonism of (R)-α-methylhistamine induced dipsogenicity[11]: it showed good activity, comparable to that of Clobenpropit. The difference observed with Clobenpropit and GR175737 across the two tests may relate to the relative ease with which they cross the blood brain barrier (BBB). It is possible that the dipsogenic responses are mediated by the circumventricular organs, which reside outside the BBB, and that the ED_{50}s observed in the drinking test are reflective of peripheral and not central activity.[11,12,13]

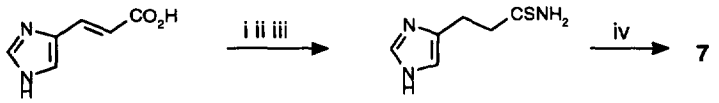
Scheme 1



(i) a) H_2/Pd-C, b) $SOCl_2$, EtOH, 0°; 92% (ii) Me_2NSO_2Cl, Et_3N, CH_2Cl_2, Δ; 80% (iii) $LiAlH_4$, THF, RT;56% (iv) CBr_4, Ph_3P, 0°; 57% (v) KCN, H_2O, $PhCH_2Et_3NCl$; 43% (vi) a) HCl, EtOH b) 4-$H_2NHNOCCH_2C_6H_4Cl$, Et_3N c) 2N HCl, Δ, 42% (vii) $RNHNH_2$, EtOH, Δ; R = H, 65% R = Me, 71% (viii) a) 4-Cl-C_6H_4.C(OEt)=NH.HCl, Et_3N, EtOH, Δ b) 2N HCl, Δ; R = H, 44% R = Me, 39% (ix) a) H_2/Pd-C, b) $SOCl_2$; 100%, used crude (x) 4-$H_2NHNOCCH_2C_6H_4Cl$, Et_3N, $CHCl_3$; 36% (xi) Lawesson's reagent; 71%

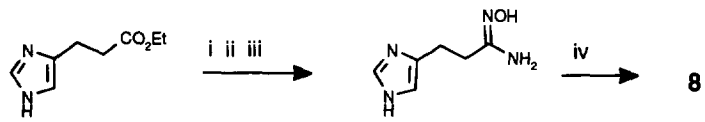
The syntheses of the 1,2,4-oxadiazole, 1,2,4-triazole, thiazole and 1,3,4-thiadiazole systems, from urocanic acid, are summarised in Schemes **1** - **5**.

Scheme 2



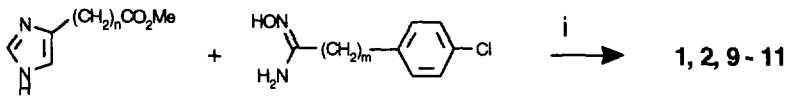
(i) a) H_2/Pd-C, b) $SOCl_2$, EtOH, 0°; 92% (ii) NH_3, H_2O, RT; 42% (iii) Lawesson's reagent; 31%
(iv) 4-$ClCH_2COCH_2C_6H_4Cl$, MeOH, Δ

Scheme 3



(i) NH_3, H_2O, RT; 42% (ii) $SOCl_2$, DMF; 14% (iii) NH_2OH, MeOH; 83% (iv) 4-$Cl.C_6H_4CH_2CO_2Et$, NaOMe, MeOH; 58%

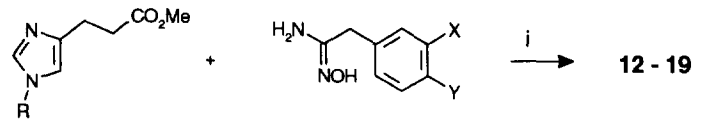
Scheme 4



(i) NaOMe, MeOH (n=3, m=1, 19%; n=2, m=1, 57%; n=m=2, 49%; n=1, m=2, 51%; n=m=1, 63%)

Compounds **12** - **19** were synthesised by methodology similar to that summarised in Scheme 4 starting from either the dihydro derivative of urocanic acid methyl ester (for **13**, **16** and **19**) or its *N,N*-dimethylaminosulfonyl protected version (for **12**, **14**, **15**, **17** and **18**) (Scheme 5). Removal of the *N,N*-dimethylaminosulfonyl protecting group occurred either *in situ* or, in the case of **12** and **18**, following treatment with hydrochloric acid. Oxidation of the methylthio derivative **19** gave a mixture of the corresponding sulphoxide **20** and sulphone **21** which were separated by column chromatography.[14]

Scheme 5



R = H, SO_2NMe_2

(i) NaOMe, MeOH, reflux, 18-24h (27- 49%)

In summary, we have shown that it is possible to replace the isothiourea of potent histamine H_3 antagonists by certain 5-membered heteroaromatic systems. This stategy has led to GR175737, a potent, selective, orally active and centrally penetrating histamine H_3 antagonist. Compounds of this type should aid in the understanding of the potential therapeutic rôle of CNS acting H_3 antagonists.

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