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

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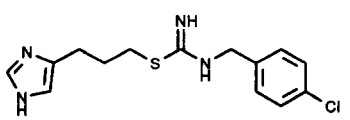
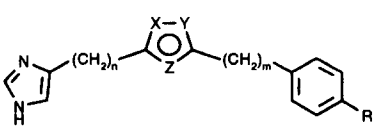
Abstract: Replacement of the isothiourea moiety of known histamine $H_3$ antagonists by certain 5-membered heteroaromatic systems can give compounds with an improved activity profile. One of these, 3-[(4-chlorophenyl)methyl]-5-[2-(1H-imidazol-4-yl)ethyl] 1,2,4-oxadiazole (GR175737) is a potent, selective, 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

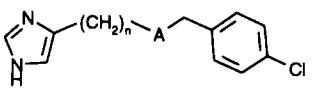



**II** X, Y, Z = O, N, S; n = 1-3, m = 1, 2
R = various

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]**

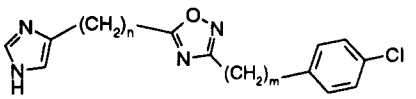



| Compd | n | A | $H_3$ pKi[b] | $H_3$ $pK_B$[c] | $H_2$ $pK_B$[d] | $H_1$ $pK_B$[d] |
|---|---|---|---|---|---|---|
| 1 | 3 |  | 7.6 | 6.8 | <5.0 | <5.0 |
| 2 | 2 |  | 8.2 | 8.1 | <5.0 | <5.0 |
| 3 | 3 |  | 7.9 | 7.4 | <5.0 | <5.0 |
| 4 | 2 |  | 6.7 | 5.7 | NT | NT |
| 5 | 2 |  | 6.9 | 5.8 | NT | NT |
| 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]-$N^{\alpha}$-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**

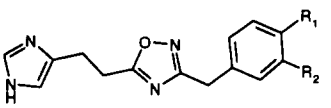


| Compd | n | m | $H_3$ $pK_i$ | $H_3$ $pK_B$ | $H_2$ $pK_B$ | $H_1$ $pK_B$ |
|---|---|---|---|---|---|---|
| 1 | 3 | 1 | 7.6 | 6.8 | <5.0 | <5.0 |
| 2 | 2 | 1 | 8.2 | 8.1 | <5.0 | <5.0 |
| 9 | 2 | 2 | 7.7 | 7.7 | <5.0 | <5.0 |
| 10 | 1 | 2 | 6.6 | NT | NT | NT |
| 11 | 1 | 1 | 7.6 | 7.2 | NT | NT |

[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

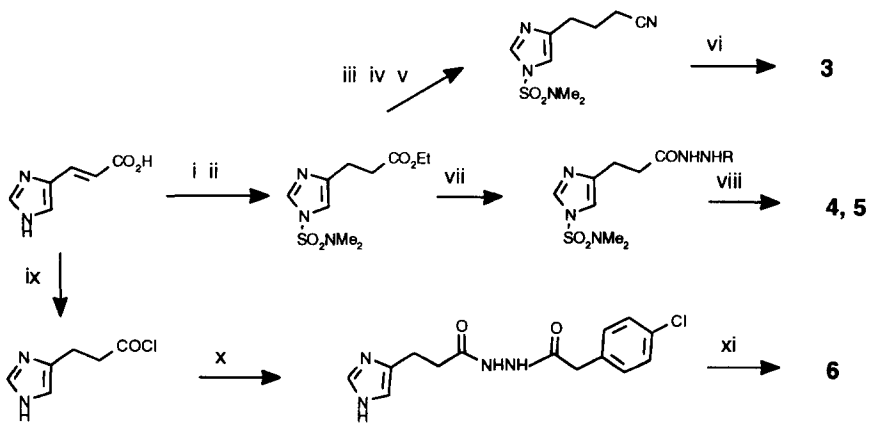
**Table 4 Comparison of *ex vivo* and *in vivo* data for Histamine $H_3$ Antagonists[a]**

| 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]

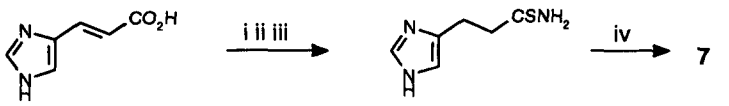
**Scheme 1**




(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%

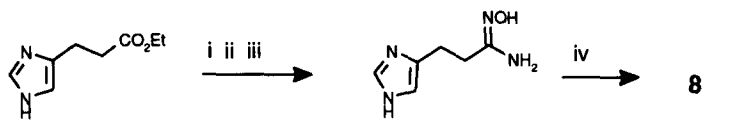
The syntheses of the 1,2,4-oxadiazole, 1,2,4-triazole, thiazole and 1,3,4-thiadiazole systems, from urocanic acid, are summarised in Schemes **1** - **5**.

**Scheme 2**



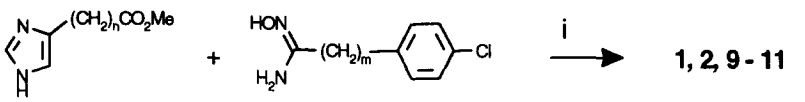

(i) a) $H_2$/Pd-C, b) $SOCl_2$, EtOH, 0°; 92% (ii) $NH_3$, $H_2O$, RT; 42% (iii) Lawesson's reagent; 31%
(iv) 4-$ClCH_2COCH_2C_6H_4Cl$, MeOH, Δ

**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%

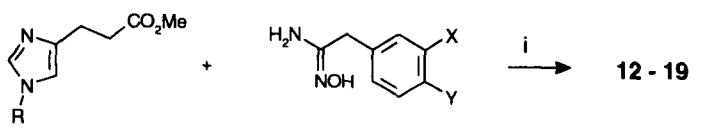
**Scheme 4**




(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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