# Design, Synthesis, and Structure−Activity Relationships of Novel Non-Imidazole Histamine H₃ Receptor Antagonists

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Novel, potent, and selective non-imidazole histamine H₃ receptor antagonists have been prepared based on the low-affinity ligand dimaprit (p$K_I$ 7.32 ± 0.12, p$K_B$ 5.93 ± 0.17). Detailed structure−activity studies have revealed that *N*-(4-chlorobenzyl)-*N*-(6-pyrrolidin-1-ylhexyl)-guanidine (p$K_I$ 8.38 ± 0.21, p$K_B$ 8.39 ± 0.13), **30**, and *N*-(4-chlorobenzyl)-*N*-(7-pyrrolidin-1-ylheptyl)guanidine (p$K_I$ 8.78 ± 0.12, p$K_B$ 8.38 ± 0.10), **31**, exhibit high affinity for the histamine H₃ receptor. Antagonists **30** and **31** demonstrate significant selectivity over the other histamine, H₁ and H₂, receptor subtypes and a 100-fold selectivity in the $\sigma_1$ binding assay. Compounds **30** and **31** are the most potent, selective non-imidazole histamine H₃ receptor antagonists reported in the literature to date.

## Introduction

The blockade of the monoamine autacoid and neurotransmitter, histamine, acting through its receptor has been of great therapeutic utility throughout the latter half of the twentieth century. The commercially available 'anti-histamine' drug molecules act through the histamine H₁ and H₂ receptor subtypes. The discovery of a third receptor subtype, designated H₃,[1] has renewed interest in the field of histamine research, with the cloning of a human histamine H₃ receptor recently reported.[2] Considerable advances have been achieved in the medicinal chemical[3] understanding of histamine H₃ receptor pharmacology.[4] The therapeutic utility, however, of selective histamine H₃ receptor antagonists has yet to be defined.[5]

The majority of the previously described potent histamine H₃ receptor ligands consist of a 4(5)-substituted imidazole separated from a lipophilic moiety by a suitable chain, which may or may not be interrupted by a polar linkage.[2] This lack of structural diversity has led to a congested field in the search for novel ligands, and the need for non-imidazole histamine H₃ ligands has been recognized by many groups.[6−10] In addition, the lack of an imidazole group may confer potentially advantageous pharmacokinetic and metabolic in vivo properties to such an antagonist.[11]

Early attempts to replace the imidazole moiety in existing H₃ receptor ligands with other nitrogen-containing hetereocycles have met with limited success.[6−8] The reexamination of previously derived drug entities led to the discovery of a variety of weakly active non-imidazole H₃ receptor ligands such as clozapine,[12] phencyclidine,[13] and sabeluzole.[9,14] The utilization of one such low-affinity ligand, sabeluzole, as a potential lead led to the discovery of the active benzothiazole **1** (Chart 1).[9] An alternative approach, in which the imidazole was removed from a previously

## Chart 1. Non-Imidazole Histamine H₃ Receptor Antagonists



(1)
pA₂ 7.67±0.13
pK_I 8.2±0.2

UCL1972
K_I 39±11nm
ED₅₀ 1.1±0.6 mg/kg po

Dimaprit
pK_I' 7.32±0.12 (5)
pK_B' 5.93±0.17
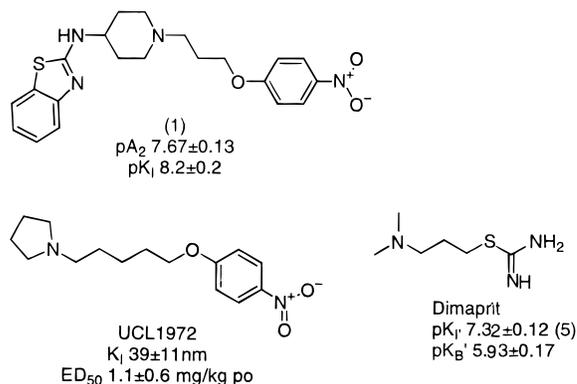
described ligand with only a limited reduction in activity, has been reported.[10] A systematic structure−activity survey resulted in the discovery of UCL 1972, a potent, non-imidazole, histamine H₃ receptor antagonist (Chart 1).[10]

In light of this preceding work we wish to report our findings in this area of non-imidazole H₃ receptor antagonists.[15] The starting point for our investigation was the recognition that dimaprit,[16] a histamine H₂ partial agonist, acts as a ligand at the histamine H₃ receptor (Chart 1).[4] The replacement of the potentially toxic isothiourea moiety with a similarly polar linkage, alterations to the dimethylamino unit, and spatial variations of dimaprit were undertaken. This synthetic approach and the subsequent in vitro histamine H₃ receptor activity of these dimaprit-derived ligands are now presented.

## Chemistry

The sulfonamide-based ligands **2**−**4** were readily prepared by combining one of the two commercially available diamines (R = Me and R = −(CH₂)₄−) with 2-naphthalenesulfonyl chloride or 4-chlorobenzylsulfonyl chloride, respectively (Scheme 1).

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**Scheme 1.** Synthetic Pathways for Initial Ligands[a]
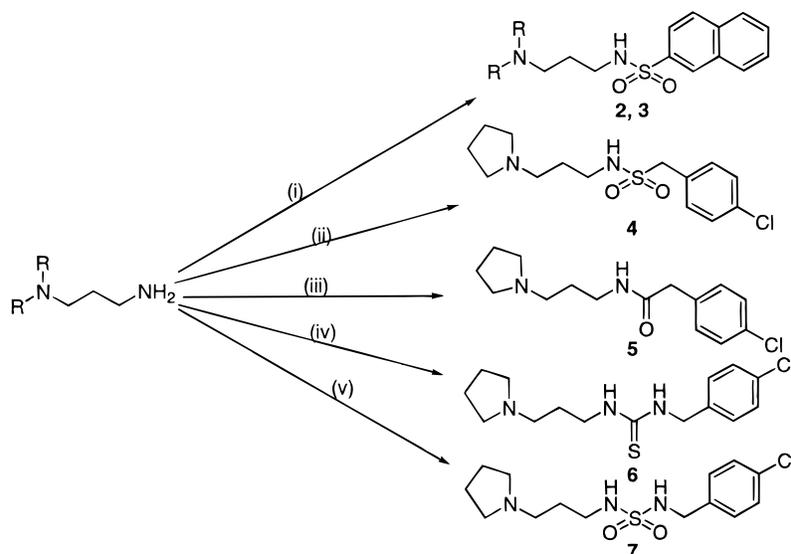


[a] (i) 2-Naphthalenesulfonyl chloride, Et3N, DCM, 20 °C, 18 h; (ii) 4-chlorobenzylsulfonyl chloride, Et3N, DCM, −78 to 20 °C, 18 h; (iii) 4-chlorophenylacetic acid, DCC, DCM, 0−20 °C, 1 h; (iv) 4-chlorobenzyl isothiocyanate, DCM, 20 °C, 18 h; (v) 4-chlorobenzylamine, sulfamide, reflux, 2 h.

**Scheme 2.** Synthetic Route for Preparation of the Initial Guanidines[a]
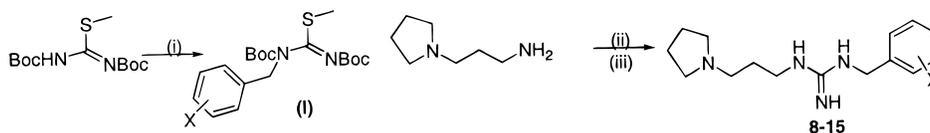


[a] (i) Sodium hydride, DMF, followed by substituted benzyl bromide, 0−20 °C, 16 h, or diethyl azodicarboxylate, substituted benzyl alcohol, Ph3P, THF, 0−20 °C, 18 h; (ii) 10% aq THF, reflux, 1 h; (iii) HCl−1,4-dioxan, 20 °C, 18 h.

**Scheme 3.** Synthesis of **16**[a]
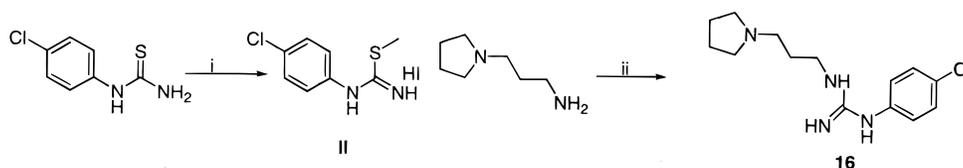


[a] (i) Iodomethane, acetone, reflux, 1 h; (ii) ethanol, reflux, 16 h.

The amide **5** and thiourea **6** ligands were prepared in analogous fashion with the appropriate activated acid and isothiocyanate replacing the sulfonyl chloride. The reaction of 1-(3-aminopropyl)pyrrolidine and 4-chlorobenzylamine with sulfamide in the absence of solvent resulted in the formation of the corresponding *N,N*-sulfamide **7** (Scheme 1).[17]

The preparation of the *N,N*-disubstituted guanidines **8**−**15** required the formation of a suitably substituted guanylating reagent **I**. The formation of this reagent was achieved by one of two methods: deprotonation of the commercially available 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea with sodium hydride, followed by alkylation with an appropriate benzyl bromide, or Mitsunobu reaction of a suitably substituted benzyl alcohol with the thiopseudourea, resulting in the generation of the required reagent **I**. The treatment of **I** with an excess of 1-(3-aminopropyl)pyrrolidine in refluxing aqueous THF,[18] followed by acid deprotection, furnished the initial guanidines **8**−**15** (Scheme 2).

Compound **16** was prepared by the reaction of 1-(3-aminopropyl)pyrrolidine with isothiouronium salt, **II**,

which was formed by the reaction between 4-chlorophenylthiourea and iodomethane (Scheme 3).

The extended guanidines **17**−**27** required a modification to the previous synthetic route. The thiopseudourea was treated with a ω-hydroxyalkene under Mitsunobu conditions to generate a suitably functionalized guanylating reagent **III** which upon treatment with an excess of the required primary amine gave rise to the protected *N,N*-disubstituted guanidine **IV**. The ozonolysis of the alkene followed by reductive amination, utilizing the appropriate cyclic amine, furnished the fully protected guanidine **V**. Acid deprotection afforded the final ligands for pharmacological evaluation **17**−**27** (Scheme 4).

Utilizing a related synthetic methodology the isomeric *N,N*-disubstituted guanidines were prepared. The key step in this synthesis was the mercury(II) chloride-promoted reaction between a suitable diamine **VI** and the thiopseudourea.[19] The requisite diamines were readily prepared by the alkylation of the respective *tert*-butoxycarbonylamines **VII** with an excess of a α,ω-dibromide, followed by displacement of the second bromine with the necessary cyclic amine. Acidic depro-

**Scheme 4.** Synthesis of the Extended Guanidines
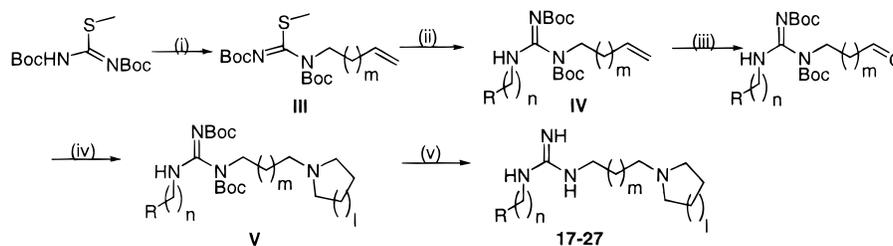


*a* (i) HC≡CH(CH₂)ₘCH₂OH, diethyl azodicarboxylate, Ph₃P, THF, 0−20 °C, 16 h; (ii) R(CH₂)ₙNH₂, 10% aq THF, reflux, 24 h; (iii) ozone, methanol, −78 °C followed by Me₂S, −78 to 20 °C, 2 h; (iv) NaB(OAc)₃H, pyrrolidine or piperidine, 1,2-DCE, 0−20 °C, 2 h; (v) HCl−1,4-dioxan, 20 °C, 16 h.

**Scheme 5.** Preparation of the *N,N*-Disubstituted Guanidines*a*
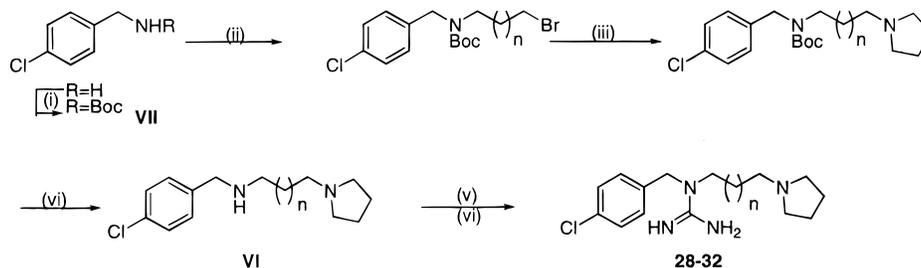


*a* (i) Boc₂O, dioxan, 20 °C, 45 min; (ii) NaH, BrCH₂(CH₂)ₙCH₂Br, DMF, 0−20 °C, 18 h; (iii) pyrrolidine, acetonitrile, 20 °C, 18 h; (iv) HCl−1,4-dioxan, 20 °C, 1 h; (v) Hg(II)Cl₂, Et₃N, guanylating agent, DCM, 0−20 °C, 18 h; (vi) HCl−1,4-dioxan, 20 °C, 16 h.

tection gave the required diamine for the subsequent mercury(II) chloride-promoted guanylation reaction. Acid deprotection of the product from the guanylation gave the *N,N*-disubstituted ligands **28**−**32** for in vitro testing (Scheme 5).

## Pharmacological Results and Discussion

The affinities of the ligands at the histamine $H_3$ receptor were evaluated in two different assays. The pharmacological behavior ($pK_B$ or $p[A]_{50}$) and the affinity ($pK_B$) of the compounds at the histamine $H_3$ receptor were determined in the isolated guinea-pig ileum functional bioassay, in which histamine $H_3$ receptors mediate the inhibition of cholinergic neurogenic contractions.[20] The apparent affinity ($pK_I$) of the compounds at the histamine $H_3$ receptor was evaluated in a radioligand binding assay in guinea-pig cerebral cortex homogenates utilizing the selective histamine $H_3$ agonist [³H]-(*R*)-α-methylhistamine as the radioligand.[21]

Radioligand binding assays can provide misleading affinity estimates if the assumptions on which they are based are not satisfied.[22] Therefore, there may be numerous explanations for any difference between functional $pK_B$ and radioligand binding $pK_I$ affinity estimates. However, if the radioligand binding assay has been established so that it satisfies the criteria upon which the assumptions are based,[22] then the number of possible explanations for these discrepancies is reduced. One possible remaining reason is that the tested ligands retain varying degrees of intrinsic efficacy which, while undetected as agonism in the functional bioassay, can be detected as a high $pK_I$ in the radioligand binding assay. There is ample literature precedent for this complex behavior.[23] Further possibilities could be related to the ligand pharmacologically distinguishing between putative multiple histamine $H_3$ receptor subtypes, either in the guinea-pig cerebral cortex[24,25] or

between the two different guinea-pig tissues. It would not be possible to distinguish which of these various proposals could give rise to any interassay discrepancy in this series using the routine assays described above.

Given the numerous possible reasons underlying any potential interassay discrepancy, any of which may have serious consequences in the potential drug usage of these compounds, the major aim of the current work was to derive a non-imidazole, selective histamine $H_3$ receptor antagonist, which exhibited no significant difference (Δ) between the functional and radioligand binding histamine $H_3$ receptor assays.

The initial replacement of the isothiourea and the dimethylamino moieties from dimaprit for naphthlene-sulfonamide[26] and pyrrolidine,[10] respectively, resulted in **3** (Table 1). Ligand **3** exhibited comparable affinity to dimaprit (Δ ≈ 1.4 log units) in the guinea-pig ileum functional bioassay but a lower apparent affinity in the radioligand binding assay (Δ for **3** ≈ 0.5 log unit). The importance of the 4-chlorobenzyl substituent for high-affinity histamine $H_3$ receptor antagonists has been established in previous studies.[27] The incorporation of this unit resulted in an improved compound, **4**, which exhibited comparable affinity in both assays. In an attempt to increase the affinity of the series, a number of structurally diverse linkers were examined. The polar guanidine[28] linkage **8** (Δ ≈ 0.8 log unit) exhibited the highest affinity in both assays (Table 1).

In contrast to previously reported histamine $H_3$ ligands, no significant sensitivity to the nature of the aromatic substitution was observed in the ileum bioassay (**8**−**14**, Table 1).[27] The variation in the observed $pK_I$ was difficult to rationalize. The 4-chlorobenzyl substituent exhibited the smallest interassay difference (Δ ≈ 0.8 log unit). We, therefore, investigated the effect of increasing the length of the various chains upon affinity. An increase in affinity was observed upon chain exten-

**Table 1.** In Vitro Structure−Activity Profile for the First-Generation Non-Imidazole Antagonists
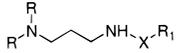
| compd | R | R_1 | X | GP cortex, $pK_I \pm$ SEM $(n)^a$ | GP ileum, $pK_B \pm$ SEM$^b$ |
|---|---|---|---|---|---|
| dimaprit | | | | 7.32 ± 0.12 (5) | 5.93 ± 0.17 |
| **2** | Me | 2-naphthyl | SO_2 | 6.00 ± 0.05 (5) | 5.52 ± 0.14 |
| **3** | −(CH_2)_4− | 2-naphthyl | SO_2 | 6.49 ± 0.09 (4) | 5.96 ± 0.06 |
| **4** | −(CH_2)_4− | 4-chlorobenzyl | SO_2 | 6.27 ± 0.19 (5) | 6.24 ± 0.14 |
| **5** | −(CH_2)_4− | 4-chlorobenzyl | C=O | 5.77 ± 0.07 (4) | NT$^c$ |
| **6** | −(CH_2)_4− | 4-chlorobenzyl | (C=S)NH | 6.39 ± 0.22 (4) | 5.66 ± 0.21 |
| **7** | −(CH_2)_4− | 4-chlorobenzyl | SO_2NH | 6.64 ± 0.12 (4) | 6.21 ± 0.14 |
| **8**$^d$ | −(CH_2)_4− | 4-chlorobenzyl | (C=NH)NH | 7.25 ± 0.28 (4) | 6.42 ± 0.17 |
| **9**$^d$ | −(CH_2)_4− | benzyl | (C=NH)NH | 7.70 ± 0.16 (5) | 6.20 ± 0.13 |
| **10**$^d$ | −(CH_2)_4− | 4-bromobenzyl | (C=NH)NH | 8.33 ± 0.09 (4) | 6.45 ± 0.20 |
| **11**$^d$ | −(CH_2)_4− | 3-bromobenzyl | (C=NH)NH | 7.59 ± 0.10 (5) | 6.46 ± 0.24 |
| **12**$^d$ | −(CH_2)_4− | 2-bromobenzyl | (C=NH)NH | 7.37 ± 0.10 (4) | 6.27 ± 0.11 |
| **13**$^d$ | −(CH_2)_4− | 4-iodobenzyl | (C=NH)NH | 7.27 ± 0.09 (4) | 6.43 ± 0.20 |
| **14**$^d$ | −(CH_2)_4− | 4-trifluoromethylbenzyl | (C=NH)NH | 7.00 ± 0.09 (4) | 6.10 ± 0.09 |
| **15**$^d$ | −(CH_2)_4− | 4-methoxybenzyl | (C=NH)NH | 7.08 ± 0.07 (4) | 6.08 ± 0.10 |

$^a$ $pK_I \pm$ SEM values were estimated from $n$ separate competition experiments in which [³H]-(*R*)-α-methylhistamine was used to label histamine H₃ binding sites in guinea-pig (GP) cerebral cortex homogenates. $^b$ $pK_B \pm$ SEM values were estimated from single shifts of (*R*)-α-methylhistamine concentration−effect curves in the isolated, electrically stimulated, guinea-pig (GP) ileum assay, in at least four separate tisssues, in which the compounds behaved as surmountable antagonists. $^c$ NT = not tested. $^d$ Tested as the dihydrochloride salt.

**Table 2.** Modifications to **8**$^a$
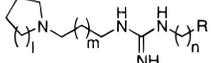
| compd$^b$ | R | $l$ | $m$ | $n$ | histamine H₃ GP cortex, $pK_I \pm$ SEM $(n)$ | histamine H₃ GP ileum, $pK_B \pm$ SEM | $\sigma_1$ GP cortex,$^c$ $pK_I \pm$ SEM $(n)$ |
|---|---|---|---|---|---|---|---|
| **8** | 4-chlorophenyl | 1 | 1 | 1 | 7.25 ± 0.28 (4) | 6.42 ± 0.17 | 6.1 |
| **16** | 4-chlorophenyl | 1 | 1 | 0 | 7.27 ± 0.12 (5) | 6.03 ± 0.11 | NT |
| **17** | 4-chlorophenyl | 1 | 2 | 1 | 8.29 ± 0.13 (5) | 7.32 ± 0.19 | 6.63 ± 0.07 (3) |
| **18** | 4-chlorophenyl | 1 | 3 | 1 | 8.27 ± 0.07 (4) | 7.30 ± 0.11 | 7.05 ± 0.03 (3) |
| **19** | 4-chlorophenyl | 1 | 1 | 2 | 9.03 ± 0.17 (4) | 6.68 ± 0.14 | 7.15 ± 0.04 (3) |
| **20** | 4-chlorophenyl | 1 | 2 | 2 | 8.17 ± 0.07 (4) | 6.24 ± 0.12 | 6.47 ± 0.09 (3) |
| **21** | 4-chlorophenyl | 1 | 3 | 2 | 8.12 ± 0.08 (4) | 7.06 ± 0.06 | 7.21 ± 0.05 (3) |
| **22** | cyclohexyl | 1 | 3 | 1 | 8.85 ± 0.05 (4) | 7.52 ± 0.28 | 8.30 ± 0.11 (3) |
| **23** | cycloheptyl | 1 | 3 | 1 | 8.45 ± 0.05 (5) | 7.67 ± 0.18 | 8.24 ± 0.11 (3) |
| **24** | 1-adamantyl | 1 | 3 | 1 | 8.45 ± 0.14 (4) | 7.90 ± 0.09 | 8.19 ± 0.17 (4) |
| **25** | 1-adamantyl | 2 | 3 | 1 | 7.97 ± 0.18 (5) | 8.14 ± 0.14 | 8.11 ± 0.03 (3) |
| **26** | 1-adamantyl | 3 | 3 | 1 | 8.10 ± 0.14 (5) | 7.84 ± 0.16 | 8.17 ± 0.02 (3) |
| **27** | 1-adamantyl | 4 | 3 | 1 | 7.52 ± 0.11 (4) | 7.37 ± 0.23 | 8.02 ± 0.06 (3) |

$^a$ For explanation of terms in the table, see footnotes to Table 1. $^b$ All compounds were tested as their dihydrochloride salts. $^c$ $pK_I \pm$ SEM values were estimated from $n$ separate competition experiments in which [³H]-(+)-pentazocine was used to label $\sigma_1$ binding sites in guinea pig (GP) cerebral cortex homogenates.

**Table 3.** In Vitro Receptor Results for the *N,N*-Disubstituted Guanidines$^a$
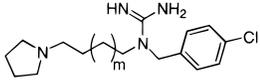
| compd$^b$ | $m$ | histamine H₃ GP cortex $pK_I \pm$ SEM $(n)$ | histamine H₃ GP ileum $pK_B \pm$ SEM | $\sigma_1$ GP cortex$^c$ $pK_I \pm$ SEM $(n)$ |
|---|---|---|---|---|
| **28** | 1 | 8.10 ± 0.15 (5) | 7.34 ± 0.12 | 6.12 ± 0.07 (3) |
| **29** | 2 | 8.97 ± 0.10 (4) | 7.91 ± 0.05 | 6.54 ± 0.04 (3) |
| **30** | 3 | 8.38 ± 0.21 (4) | 8.39 ± 0.13 | 6.29 ± 0.24 (4) |
| **31** | 4 | 8.70 ± 0.12 (3) | 8.38 ± 0.10 | 6.59 ± 0.03 (3) |
| **32** | 5 | 8.33 ± 0.08 (4) | 8.09 ± 0.08 | 6.34 ± 0.24 (3) |

$^a$ For explanation of terms in the table, see footnotes to Table 1. $^b$ All compounds were tested as their dihydrochloride salts. $^c$ See footnote to Table 2.

sion between the pyrrolidine and guanidine moieties from propyl **8** to butyl **17** (Tables 1 and 2). No additional increase in affinity was observed upon further chain extension, nor was there a reduction in the interassay difference ($\Delta \approx 1.0$ log unit). Furthermore, there was no substantial increase in the $pK_B$ value obtained on the functional ileum bioassay with variations in the chain length between the aromatic ring and the guanidine (**8**, **16**, **19**−**21**), although **19** exhibited particularly high affinity in the radioligand binding assay ($\Delta \approx 2.3$ log units). As previously described, **19** could potentially either be imbued with high residual efficacy, still undetected in the ileum functional bioassay, or be particularly able to distinguish between possible receptor subtypes either within or between tissues.

In an attempt to reduce the interassay difference, aliphatic lipophilic units were introduced resulting in compounds **22**−**24**. Of these compounds the change to the more sterically demanding adamantyl moiety,[29] **24**, resulted in a modest increase in affinity in the ileum bioassay, with respect to **18**, and a concomitant reduction in the interassay variance ($\Delta \approx 0.6$ log unit).

In a bid to increase the affinity at the histamine H₃ receptor, an increase in the size of the cyclic amine moiety from a five- to a six-membered ring resulted in **25**. Although this alteration gave no significant increase in affinity, a reduction in the interassay variance to a nonsignificant level ($\Delta \approx 0.2$ log unit) was observed. Further expansion in the ring size resulted in some loss

of affinity for the $H_3$ receptor, but interestingly the low interassay variance was maintained.

Early receptor selectivity screening had shown that **8** expressed an affinity for the $\sigma_1$ binding site ($pK_I$ 6.1), as labeled by [³H]-(+)-pentazocine in guinea-pig cerebral cortex homogenates.[30] Prompted by this finding all the compounds of this series were routinely assessed in a $\sigma_1$ radioligand binding assay. The aliphatic lipophilic substituted guanidines universally exhibited affinities in the nanomolar range at this particular site (Table 2). In contrast the corresponding 4-chlorobenzyl-substituted guanidines displayed significantly lower affinity for this $\sigma_1$ binding site.

The aim of a negligible interassay difference, with respect to the histamine $H_3$ receptor assays, had been achieved. However, the lack of selectivity of **25** over the $\sigma_1$ binding site caused attention to refocus upon the 4-chlorobenzyl-substituted guanidines. These compounds exhibited interassay variance, which could, as previously described, be attributed to either receptor heterogeneity or functionally undetected residual efficacy. It was, therefore, necessary that this property be eliminated. With regard to one of these possibilities, that the interassay variance was caused by residual efficacy, we speculated that the guanidine functional group bound to the site on the histamine $H_3$ receptor normally occupied by the imidazole moiety in the parent hormone. A possible mechanism for receptor activation at the histamine $H_3$ receptor lies in the ability of the imidazole group in agonists to tautomerize, hence facilitating a proton transfer from one residue in the receptor to another, thus triggering a response. It was postulated that the ability of the guanidine to tautomerize could fulfill this role, allowing some of these non-imidazole ligands to possess a degree of undetected residual efficacy. Previous work had suggested that any perturbation in the ability of the imidazole to tautomerize had a beneficial reduction in efficacy while maintaining receptor affinity.[31] Therefore, in this new series it was proposed that any disruption to the ability of the guanidine to tautomerize might result in a reduction in potential receptor activation. Thus, if the interassay difference was due to residual efficacy, a reduction in the interassay difference might be observed.

In an attempt to influence the nature of tautomerization of the guanidine, attention was turned toward the isomeric $N,N$-disubstituted guanidines. These isomeric guanidine ligands would be expected to experience potentially different inter- and intramolecular hydrogen-bonding interactions, raising the possibility of a change in the tautomeric nature of the guanidine moiety with respect to the initial $N,N$-disubstituted compounds, as exemplified by **25**.

The initial compound prepared, **28**, exhibited a similar in vitro profile to the corresponding $N,N$-disubstituted guanidine **17**. Further homologation, resulting in compounds **30**–**32**, gave rise to ligands with increased affinity at the histamine $H_3$ receptor, combined with an insignificant interassay variance.

Ligands **30** and **31** were shown to be simple, competitive histamine $H_3$ receptor antagonists when analyzed over a range of concentrations in the ileum functional bioassay and under Schild analysis exhibited a slope not significantly different from unity.[32]

Antagonists **30** and **31**, when assayed against the $\sigma_1$ binding site ($pK_I$ 6.29 ± 0.24 and 6.59 ± 0.03, respectively), histamine $H_1$ receptor[33] ($pK_B$ 5.41 ± 0.17 and 5.46 ± 0.16, respectively), and histamine $H_2$ receptor[34] (inactive at $1 \times 10^{-6}$ M and $pK_B$ 5.26 ± 0.10, respectively) showed excellent selectivity for the histamine $H_3$ receptor.

## Conclusions

The systematic modification of the low-affinity $H_3$ receptor ligand dimaprit ($pK_I$ 7.32 ± 0.12, $pK_B$ 5.93 ± 0.17) has resulted in the identification of $N$-(4-chlorobenzyl)-$N$-(6-pyrrolidin-1-ylhexyl)guanidine, **30**, and $N$-(4-chlorobenzyl)-$N$-(7-pyrrolidin-1-ylheptyl)guanidine (log $P_{pH7.4}$ octanol/Krebs buffer −0.21), **31**, as potent, competitive, non-imidazole $H_3$ receptor antagonists. These antagonists exhibit excellent selectivity over the other histamine receptor subtypes and over the $\sigma_1$ binding site.

## Experimental Section

All reagents were obtained from commercial suppliers and were used without further purification. Solvents used were of either AR or HPLC grade. Thin-layer chromatography was carried out on Merck Kieselgel 60 $F_{254}$ glass-backed plates. Preparative flash column chromatography was performed on Merck Kieselgel 60 (particle size 0.063−0.040) under pressure. ¹H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer. Chemical shifts are reported in ppm ($\delta$) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.26 ppm and DMSO in DMSO-$d_6$ at 2.54). Signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. All $J$ values are given in hertz (Hz). Elemental analyses were performed at the London School of Pharmacy. All reactions were carried out under a positive pressure of argon unless otherwise stated.

**General Procedure for the Preparation of Naphthalenesulfonamides 2 and 3.** To an ice-cooled solution of 3-(dimethylamino)propylamine or 1-(3-aminopropyl)pyrrolidine (4.41 mmol) and NEt₃ (0.61 mL, 4.41 mmol) in DCM (10 mL) was added portionwise 2-naphthalenesulfonyl chloride (1.00 g, 4.41 mmol). The coolant was removed and the mixture was stirred at 20 °C for 18 h. The reaction mixture was washed with water and brine. The organic phase was dried (MgSO₄) and filtered and the filtrate evaporated to yield the required compound.

$N$-**(3-Dimethylaminopropyl)-2-naphthalenesulfonamide (2):** ¹H NMR (300 MHz, CDCl₃) 8.43 (m, 1H), 7.99− 7.82 (m, 4H), 7.67−7.61 (m, 2H), 7.61−7.27 (br s, 1H), 3.09 (t, $J$ = 5.7 Hz, 2H), 2.29 (t, $J$ = 5.7 Hz, 2H), 2.19 (s, 6H), 1.63− 1.56 (m, 2H). Anal. ($C_{15}H_{20}N_2O_2S$) C, H, N.

$N$-**(3-Pyrrolidin-1-ylpropyl)-2-naphthalenesulfonamide (3):** ¹H NMR (300 MHz, CDCl₃) 8.43 (s, 1H), 7.99−7.59 (m, 7H), 3.11 (t, $J$ = 5.7 Hz, 2H), 2.54−2.49 (m, 6H), 1.81 (m, 4H), 1.68−1.63 (m, 2H). Anal. ($C_{17}H_{22}N_2O_2S$) C, H, N.

$N$-**(3-Pyrrolidin-1-ylpropyl)(4-chlorophenyl)methanesulfonamide (4).** To a cooled (−78 °C) solution of 1-(3-aminopropyl)pyrrolidine (0.20 g, 1.56 mmol) and NEt₃ (0.28 mL, 1.57 mmol) in DCM (3 mL) was added dropwise a solution of (4-chlorophenyl)methanesulfonyl chloride[35] (0.34 g, 1.50 mmol) in DCM (5 mL). The resultant solution was allowed to warm to 20 °C while stirring was continued for 18 h. The solution was washed (H₂O), dried (MgSO₄), and filtered and the filtrate was evaporated. The material was purified by flash column chromatography (DCM:EtOAc, 90:10) to afford the product (0.19 g, 39%): ¹H NMR (300 MHz, CDCl₃) 7.36 (s, 4H), 4.19 (s, 2H), 3.10 (m, 2H), 2.60 (m, 2H), 2.47 (br s, 4H), 1.68 (m, 6H). Anal. ($C_{14}H_{21}ClN_2O_2S$) C, H, N.

**2-(4-Chlorophenyl)-$N$-(4-pyrrolidin-1-ylbutyl)acetamide (5).** To an ice-cooled solution of DCC (3.28 g, 15.90 mmol) in DCM (10 mL) was added a solution of 4-chlorophe-

nylacetic acid (2.02 g, 11.84 mmol) in DCM (10 mL). The coolant was removed and the resultant suspension stirred at 20 °C for 10 min. 1-(3-Aminopropyl)pyrrolidine (1.00 mL, 7.91 mmol) was added dropwise and the reaction stirred at 20 °C for 1 h. The suspension was filtered and the filtrate was extracted with 10% aqueous citric acid. The organic phase was discarded and the aqueous phase washed (DCM). The aqueous phase was basified with NH₄OH and extracted with DCM. The solvent was removed in-vacuo to yield the title compound (1.98 g, 89%): ¹H NMR (300 MHz, CDCl₃) 7.34−7.02 (m, 4H), 7.02 (br s, 1H), 3.49 (s, 2H), 3.36 (m, 2H), 2.52 (t, $J = 6.6$ Hz, 2H), 2.46 (m, 4H), 1.77−1.62 (m, 6H). Anal. (C₁₅H₂₁ClN₂O) C, H, N.

**N-(4-Chlorobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)sulfamide (6).** A solution of 4-chlorobenzylamine (0.610 mL, 5.00 mmol), 1-(3-aminopropyl)pyrrolidine (0.63 mL, 5.00 mmol) and sulfamide (480 mg, 4.99 mmol) was heated at reflux for 2 h. The reaction was allowed to cool and partitioned between EtOAc and H₂O. The aqueous phase was discarded and the organic phase washed with H₂O and brine. The organic phase was dried (MgSO₄) and filtered and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (100/10/1 DCM/MeOH/NH₄OH) to obtain the title compound (365 mg, 22%): ¹H NMR (300 MHz, CDCl₃) 7.35−7.28 (m, 4H), 4.18 (s, 2H), 3.15 ($J = 6$ Hz, 2H), 2.61 (t, $J = 6$ Hz, 2H), 2.51 (br m, 4H), 1.82−1.67 (m, 6H). Anal. (C₁₄H₂₂ClN₃O₂S·0.26H₂O) C, H, N.

**1-(4-Chlorobenzyl)-3-(3-pyrrolidin-1-ylpropyl)thiourea (7).** To an ice-cooled solution of 4-chlorobenzyl isothiocyanate (3.67 g, 20.0 mmol) in DCM (20 mL) was added a solution of 1-(3-aminopropyl)pyrrolidine (2.65 mL, 21.0 mmol) in DCM (20 mL). The coolant was removed and the reaction stirred at 20 °C for 18 h. The reaction mixture was washed with H₂O and brine, dried (MgSO₄), and filtered and the filtrate evaporated. The residue was purified by flash column chromatography (90/10/1 DCM/MeOH/NH₄OH) to yield the title compound (4.65 g, 75%): ¹H NMR (300 MHz, CDCl₃) 9.50 (br s, 1H), 7.32−7.26 (m, 4H), 6.20 (br s, 1H), 3.46 (br s, 2H), 2.55 (br s, 2H), 2.40 (br s, 4H), 1.73 (br s, 2H), 1.57 (br s, 4H). The compound was further analyzed as the hydrochloride salt. Anal. (C₁₅H₂₂ClN₃S·HCl) C, H, N.

**N-(4-Chlorobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine Bis-hydrochloride Salt (8). Step a.** To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.00 g, 3.45 mmol) in DMF (10 mL) was added sodium hydride (60% dispersion in mineral oil, 167 mg, 4.18 mmol) in a single portion. The resultant suspension was stirred at this temperature for 1 h and then treated in a single portion with 4-chlorobenzyl bromide (780 mg, 3.80 mmol). The cooling bath was removed and the reaction mixture stirred at 20 °C for 16 h. H₂O was added and the aqueous phase was extracted with EtOAc. The aqueous phase was discarded and the organic phase was washed with brine (×2) and dried (MgSO₄). The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (9/2 hexane/EtOAc) to give 1,3′-bis(*tert*-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea as a colorless oil (987 mg, 69%): ¹H NMR (300 MHz, CDCl₃) 7.30 (s, 4H), 4.74 (s, 2H), 2.31 (s, 3H), 1.53 (s, 9H), 1.42 (s, 9H).

**Step b.** A solution of the product from step a (920 mg, 2.00 mmol) and 1-(3-aminopropyl)pyrrolidine (669 mg, 5.22 mmol) in THF (20 mL) and water (2 mL) was heated at reflux for 1 h. The solvent was evaporated at reduced pressure and the residue was dissolved in EtOAc. The organic phase was washed sequentially with H₂O and brine and dried (MgSO₄). The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90/10/1 DCM/MeOH/NH₄OH) to give N,N-bis(*tert*-butoxycarbonyl)-N′-(4-chlorobenzyl)-N′′-(3-pyrrolidin-1-ylpropyl)guanidine as a colorless oil (1.14 g, q): ¹H NMR (300 MHz, CDCl₃) 7.27 (br s, 4H), 4.78 (s, 2H), 3.16 (m, 2H) 2.43−2.37 (br s, 6H), 1.76 (m, 4H), 1.57−1.50 (m, 2H), 1.50 (s, 9H), 1.43 (s, 9H).

**Step c.** A solution of the product from step b (1.14 g, 2.00 mmol) in dioxan (5 mL) was treated with hydrogen chloride−

dioxan (4 M, 15 mL, 60 mmol) and the reaction mixture stirred at 20 °C for 16 h. The solvent was evaporated at reduced pressure and the residue evaporated from DCM to give the title compound as a foam (700 mg, 95%): ¹H NMR (300 MHz, DMSO-*d₆*) 10.97 (br s, 1H), 8.29 (br s, 1H), 8.07 (t, $J = 6$ Hz, 1H), 7.69 (br s, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 4.37 (s, 2H), 3.48−3.45 (m, 2H), 3.24−3.20 (m, 2H), 3.08−3.03 (m, 2H), 2.94−2.91 (m, 2H), 2.00−1.84 (m, 6H). Anal. (C₁₅H₂₃ClN₄·2HCl) C, H, N.

The following compounds (**9**−**14**) were prepared in a similar fashion with the requisite benzyl bromide.

**N-Benzyl-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (9):** ¹H NMR (300 MHz, DMSO-*d₆*) 11.10 (br s, 1H), 8.36 (br s, 1H), 8.16 (s, 1H), 7.76 (br s, 2H), 7.39−7.26 (m, 5H), 4.37 (d, $J = 6$ Hz, 2H), 3.47−3.27 (m, 4H), 3.10−2.92 (m, 4H), 1.96−1.86 (m, 6H). Anal. (C₁₅H₂₄N₄·2HCl) C, H, N.

**N-(4-Bromobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (10):** ¹H NMR (300 MHz, DMSO-*d₆*) 10.92 (br s, 1H), 8.26 (br s, 1H), 8.03 (br s, 1H), 7.68 (br s, 2H), 7.56 (d, $J = 9$ Hz, 2H), 7.28 (d, $J = 9$ Hz, 2H), 4.40−4.42 (m, 2H), 3.52−3.46 (m, 2H), 3.37−3.10 (m, 2H), 3.11−2.94 (m, 4H), 1.93−1.86 (m, 6H). Anal. (C₁₅H₂₃BrN₄·2HCl) C, H, N.

**N-(3-Bromobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (11):** ¹H NMR (300 MHz, DMSO-*d₆*) 11.0 (br s, 1H), 8.32 (br s, 1H), 8.08 (br s, 1H), 7.72 (br s, 2H), 7.55−7.47 (m, 2H), 7.35−7.29 (m, 2H), 4.45−4.44 (m, 2H), 3.47−3.30 (m, 4H), 3.13−3.08 (br s, 2H), 2.96 (br s, 2H), 1.94−1.87 (m, 6H). Anal. (C₁₅H₂₃BrN₄·2HCl·3H₂O) C, H, N.

**N-(2-Bromobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (12):** ¹H NMR (300 MHz, DMSO-*d₆*) 11.11 (br s, 1H), 8.17 (br s, 2H), 7.79 (br s, 2H), 7.67−7.64 (m, 1H), 7.43−7.25 (m, 3H), 4.53−4.44 (m, 2H), 3.50−3.45 (m, 2H), 3.31 (m, 2H), 3.17−3.11 (m, 2H), 2.99−2.95 (m, 2H), 1.97−1.88 (m, 6H). Anal. (C₁₅H₂₃BrN₄·2HCl·3H₂O) C, H, N.

**N-(4-Iodobenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (13):** ¹H NMR (300 MHz, DMSO-*d₆*) 11.04 (br s, 1H), 8.32 (br s, 1H), 8.13 (t, $J = 6$ Hz, 1H), 7.75−7.72 (m, 4H), 7.17 (d, $J = 9$ Hz, 2H), 4.41 (d, $J = 6$ Hz, 2H), 3.49−3.44(m, 2H), 3.31−3.29 (m, 2H), 3.09−3.06 (m, 2H), 2.93−2.92 (br m, 2H), 1.97−1.86 (m, 6H). Anal. (C₁₅H₂₃N₄I·2HCl·4H₂O) C, H, N.

**N-(4-(Trifluoromethyl)benzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride salt (14):** ¹H NMR (300 MHz, DMSO-*d₆*) 11.06 (br s, 1H), 8.47 (br s, 1H), 8.21−8.18 (br m, 1H), 7.77−7.73 (m, 4H), 7.57 (d, $J = 9$ Hz, 2H), 4.58 (d, $J = 6$ Hz, 2H), 3.49−3.44 (m, 4H), 3.35−3.29 (m, 2H), 3.13−3.07 (m, 2H), 2.94 (br s, 2H), 1.96−1.88 (m, 6H). Anal. (C₁₆H₂₃N₄F₃·2HCl) C, H, N.

**N-(4-Methoxybenzyl)-N′-(3-pyrrolidin-1-ylpropyl)guanidine Bis-hydrochloride (15). Step a.** To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.45 g, 5.00 mmol), 4-methoxybenzyl alcohol (759 mg, 5.50 mmol) and PPh₃ (1.97 g, 5.50 mmol) in THF (20 mL) was added diethyl azodicarboxylate (1.29 mL, 5.50 mmol). The coolant was removed and the reaction was stirred at 20 °C for 16 h. The solvent was removed at reduced pressure, and the residue purified by flash column chromatography (90/10 hexane/EtOAc) to give 1,3′-bis(*tert*-butoxycarbonyl)-1-(4-methoxybenzyl)-2-methyl-2-thiopseudourea as a colorless oil (1.11 g, 54%): ¹H NMR (300 MHz, CDCl₃) 7.30−7.27 (m, 2H), 6.87−6.84 (m, 2H), 4.71 (s, 2H), 3.80 (s, 3H), 2.27 (s, 3H), 1.53 (s, 9H), 1.44 (s, 9H).

**Step b.** A solution of the product of step a (1.10 g, 2.24 mmol) and 1-(3-aminopropyl)pyrrolidine (0.850 mL, 6.79 mmol) in THF (20 mL) and water (2 mL) was heated at reflux for 2 h. The reaction mixture was diluted with EtOAc, washed with water (×2) and dried (MgSO₄). The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (90/10/1 DCM/MeOH/NH₄OH) to give N,N-bis(*tert*-butoxycarbonyl)-N′-(4-methoxybenzyl)-N′′-(3-pyrrolidin-

1-ylpropyl)guanidine as a colorless oil (1.04 g, 79%): $^1$H NMR (300 MHz, CDCl$_3$) 10.00–9.50 (br s, 1H), 7.27–7.22 (m, 2H), 6.82–6.80 (m, 2H), 4.73 (s, 2H), 3.77 (s, 3H), 3.09 (br s, 2H), 2.40 (br s, 4H), 2.31 (br m, 2H), 1.73 (s, 4H), 1.49 (s, 9H), 1.42 (s, 9H).

**Step c**. A solution of the product of step b (1.04 g, 2.12 mmol) in chloroform (15 mL) was treated with hydrogen chloride−dioxan (4 M, 15 mL, 60 mmol) and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated at reduced pressure and the residue evaporated from DCM (×2) to give the title compound as a yellow foam (850 mg, 100%): $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 8.25 (br s, 1H), 8.11 (t, $J$ = 6 Hz, 1H), 7.71 (br s, 2H), 7.29 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 8.4 Hz, 2H), 4.36 (s, 2H), 3.73 (s, 3H), 3.55–3.26 (m, 4H), 3.07 (m, 2H), 2.93 (s, 2H), 1.96–1.86 (m, 6H). Anal. (C$_{16}$H$_{26}$N$_4$O·2HCl·1.5H$_2$O) C, H, N.

Compound **19** was prepared in analogous fashion with 4-chlorophenethyl alcohol replacing 4-methoxybenzyl alcohol in step a.

**$N$-(2-(4-Chlorophenyl)ethyl)-$N'$-(3-pyrrolidin-1-ylpropyl)guanidine bis-hydrochloride (19):** $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 7.92 (br s, 1H), 7.80 (br s, 1H), 7.59 (br s, 2H), 7.38–7.30 (m, 4H), 3.50–3.23 (m, 6H), 3.11–3.08 (m, 2H), 2.98–2.92 (m, 2H), 2.79 (t, $J$ = 7.5 Hz, 2H), 2.00–1.82 (m, 6H). Anal. (C$_{16}$H$_{25}$ClN$_4$·2HCl) C, H, N.

**$N$-(4-Chlorophenyl)-$N'$-(3-pyrrolidin-1-ylpropyl)guanidine (16). Step a.** To ice-cooled stirred aqueous NH$_4$OH (20 mL) was added dropwise a solution of 4-chlorophenyl isothiocyanante (3.39 g, 20.0 mmol) in dioxan (20 mL). The coolant was removed and the resultant suspension was stirred at 20 °C for 2 h. The solid was removed by filtration and the filter-cake was washed with H$_2$O (50 mL). The filter-cake was dried in vacuo (50 °C) for 16 h to give (4-chlorophenyl)thiourea as a white solid (2.90 g, 78%): $^1$H NMR (300 MHz, DMSO-$d_6$) 9.72 (br s, 1H), 7.61–7.32 (br m, 6H).

**Step b.** To a solution of the product of step a (2.82 g, 15.1 mmol) in acetone (30 mL) was added iodomethane (1.41 mL, 22.65 mmol) and the resultant solution was heated at reflux for 1 h. The solvent was removed at reduced pressure and the residue suspended in EtOAc. The solid was removed by filtration and the filter-cake washed with further EtOAc and dried in vacuo to give 1-(4-chlorophenyl)-2-methylisothiourea hydroiodide (4.53 g, 91%): $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00–9.00 (br s, 3H), 7.57 (d, $J$ = 8.7 Hz, 2H), 7.36 (d, $J$ = 8.7 Hz, 2H), 2.68 (s, 3H).

**Step c.** A solution of the product from step b (986 mg, 3.00 mmol) and 1-(3-aminopropyl)pyrrolidine (0.948 mL, 7.50 mmol) in ethanol (10 mL) was heated at reflux for 16 h. The solvent was removed at reduced pressure and the residue suspended in aqueous NH$_4$OH. The solid was removed by filtration and the filter-cake washed sequentially with H$_2$O and Et$_2$O to give the title compound as a white solid (585 mg, 69%): $^1$H NMR (300 MHz, DMSO-$d_6$) 7.18–7.12 (m, 2H), 6.76–6.66 (m, 2H), 5.80–4.80 (br s, 3H), 3.12 (t, $J$ = 6.9 Hz, 2H), 2.43–2.36 (m, 6H), 1.69–1.56 (m, 6H). Anal. (C$_{14}$H$_{21}$ClN$_4$) C, H, N.

**$N$-(4-Chlorobenzyl)-$N'$-(4-pyrrolidin-1-ylbutyl)guanidine Bis-hydrochloride (17). Step a.** To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (5.00 g, 17.2 mmol), 4-penten-1-ol (2.67 mL, 25.5 mmol) and PPh$_3$ (6.78 g, 25.48 mmol) in THF (35 mL) was added diethyl azodicarboxylate (4.43 mL, 25.5 mmol). The coolant was removed and the reaction stirred at 20 °C for 16 h. The solvent was removed at reduced pressure and the residue was purified by flash column chromatography (5/1 hexane/EtOAc) to give 1,3'-bis(*tert*-butoxycarbonyl)-1-(1-pent-4-enyl)-2-methyl-2-thiopseudourea as a colorless oil (6.23 g, 100%): $^1$H NMR (300 MHz, CDCl$_3$) 5.88–5.74 (m, 1H), 5.08–4.97 (m, 2H), 3.54–3.49 (m, 2H), 2.39 (s, 3H), 2.11–2.04 (m, 2H), 1.83–1.70 (m, 2H), 1.51 (s, 9H), 1.49 (s, 9H).

**Step b**. A solution of the product of step a (1.56 g, 4.36 mmol) and 4-chlorobenzylamine (1.20 mL, 9.83 mmol) in THF (20 mL) and H$_2$O (2 mL) was heated at reflux for 24 h. The solution was diluted with EtOAc and washed sequentially with H$_2$O, 10% aqueous citric acid and brine. The organic phase

was dried (MgSO$_4$) and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (4/1 hexane/EtOAc) to give the $N,N'$-bis(*tert*-butoxycarbonyl)-$N$-(4-chlorobenzyl)-$N''$-(1-pent-4-enyl)guanidine as a colorless oil (1.46 g, 74%): $^1$H NMR (300 MHz, CDCl$_3$) 7.36–7.23 (m, 4H), 5.82–5.73 (m, 1H), 5.03–4.96 (m, 2H), 4.40 (br s, 2H), 3.68 (br t, $J$ = 7.2 Hz, 2H), 2.08–2.01 (m, 2H), 1.68–1.54 (m, 2H), 1.49 (s, 9H), 1.48 (s, 9H).

**Step c.** Ozone gas was bubbled through a solution of the product of step b (500 mg, 1.11 mmol) in MeOH (10 mL) at −78 °C for 5 min. The blue solution was purged of color with nitrogen and then treated at this temperature with Me$_2$S (0.81 mL, 11.0 mmol). The reaction mixture was allowed to warm to 20 °C and stirred at this temperature for 2 h. The solvent was evaporated at reduced pressure and the residue purified by flash column chromatography (1/1 hexane/EtOAc) to give $N,N'$-bis(*tert*-butoxycarbonyl)-$N$-(4-chlorobenzyl)-$N''$-(1-butan-4-al)guanidine as an oil (403 mg, 80%): $^1$H NMR (300 MHz, CDCl$_3$) 9.75 (s, 1H), 9.50 (br s, 1H), 7.34 (d, $J$ = 8.4 Hz, 2H), 7.24 (d, $J$ = 8.4 Hz, 2H), 4.40 (s, 2H), 3.70 (t, $J$ = 7.2 Hz, 2H), 2.48 (t, $J$ = 7.2 Hz, 2H), 1.93–1.83 (m, 2H), 1.54 (s, 9H), 1.49 (s, 9H).

**Step d.** To an ice-cooled suspension of the product of step c (400 mg, 0.88 mmol) and pyrrolidine (0.080 mL, 0.96 mmol) in 1,2-dichloroethane (3 mL) was added sodium triacetoxyborohydride (280 mg, 1.32 mmol) in a single portion. The coolant was removed and the resultant suspension stirred at 20 °C for 2 h. The reaction was quenched with saturated aqueous NaHCO$_3$ and extracted with EtOAc (×2). The combined organics were dried (MgSO$_4$) and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (90/10/1 DCM/MeOH/NH$_4$OH) to give $N,N'$-bis(*tert*-butoxycarbonyl)-$N$-(4-chlorobenzyl)-$N''$-(4-pyrrolidin-1-ylbutyl)guanidine as an oil (389 mg, 87%): $^1$H NMR (300 MHz, CDCl$_3$) 9.50 (br s, 1H), 7.33 (d, $J$ = 7.8 Hz, 2H), 7.24 (d, $J$ = 7.8 Hz, 2H), 4.42–4.41 (m, 2H), 3.68 (m, 2H), 2.51 (br s, 6H), 1.78 (m, 4H), 1.69–1.55 (m, 4H), 1.49 (s, 9H), 1.48 (s, 9H).

**Step e.** A solution of the product of step d (389 mg, 0.77 mmol) in chloroform (5 mL) was treated with hydrogen chloride−dioxan (4 M, 5 mL, 20 mmol) and the reaction stirred at 20 °C for 16 h. The solvent was removed at reduced pressure and the residue was evaporated from CHCl$_3$ (×2) to give the title compound as a foam (312 mg, 100%): $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 8.26 (br s, 1H), 8.03 (br s, 1H), 7.64 (m, 2H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 4.42 (d, $J$ = 6 Hz, 2H), 3.49–3.44 (m, 2H), 3.20–3.16 (m, 2H), 3.11–3.06 (m, 2H), 2.95–2.91 (m, 2H), 1.97–1.86 (m, 4H), 1.73–1.63 (m, 2H), 1.56–1.49 (m, 2H). Anal. (C$_{16}$H$_{25}$ClN$_4$·2HCl·1.61H$_2$O) C, H, N.

The following compounds (**18**, **20**–**27**) were prepared in a similar manner utilizing the appropriate $\omega$-hydroxyalkene, amine, and cyclic secondary amine in steps a, b, and d, respectively.

**$N$-(4-Chlorobenzyl)-$N'$-(5-pyrrolidin-1-ylpentyl)guanidine bis-hydrochloride (18):** $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 8.28 (br s, 1H), 8.00 (br s, 1H), 7.64 (m, 2H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 4.42 (d, $J$ = 6 Hz, 2H), 3.50–3.45 (m, 2H), 3.20–3.13 (m, 2H), 3.06–2.93 (m, 4H), 1.97–1.86 (m, 4H), 1.71–1.61 (m, 2H), 1.53–1.43 (m, 2H), 1.35–1.28 (m, 2H). Anal. (C$_{17}$H$_{27}$ClN$_4$·2HCl·1.57H$_2$O) C, H, N.

**$N$-(2-(4-Chlorophenyl)ethyl)-$N'$-(4-pyrrolidin-1-ylbutyl)guanidine bis-hydrochloride (20):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.90 (br s, 1H), 7.81 (br s, 1H), 7.69 (br s, 1H), 7.51 (m, 2H), 7.37 (d, $J$ = 8.7 Hz, 2H), 7.29 (d, $J$ = 8.7 Hz, 2H), 3.48–3.35 (m, 4H), 3.14–3.06 (m, 4H), 2.97–2.93 (m, 2H), 2.78 (t, $J$ = 7.2 Hz, 2H), 2.00–1.87 (m, 4H), 1.73–1.63 (m, 2H), 1.53–1.43 (m, 2H). Anal. (C$_{17}$H$_{27}$ClN$_4$·2HCl·3H$_2$O) C, H, N.

**$N$-(2-(4-Chlorophenyl)ethyl)-$N'$-(5-pyrrolidin-1-ylpentyl)guanidine bis-hydrochloride (21):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.80 (br s, 1H), 7.78 (br s, 1H), 7.69 (br s, 1H), 7.49 (br s, 2H), 7.38–7.29 (m, 4H), 3.51–3.37 (m, 4H), 3.14–3.03 (m, 4H), 2.98–2.90 (m, 2H), 2.78 (t, $J$ = 7.2 Hz, 2H), 1.99–

1.84 (m, 4H), 1.72−1.62 (m, 2H), 1.48−1.41 (m, 2H), 1.36−1.29 (m, 2H). Anal. ($C_{18}H_{29}ClN_4$·2HCl) C, H, N.

**$N$-Cyclohexylmethyl-$N$-(5-pyrrolidin-1-ylpentyl)guanidine bis-hydrochloride (22):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.90 (br s, 1H), 7.78 (br s, 1H), 7.72 (br s, 1H), 7.45 (m, 2H), 3.50−3.44 (m, 2H), 3.17−2.90 (m, 8H), 1.99−1.83 (m, 4H), 1.70−1.63 (m, 7H), 1.51−1.31 (m, 5H), 1.20−1.06 (m, 3H), 0.95−0.87 (m, 2H). Anal. ($C_{17}H_{34}N_4$·2HCl) C, H, N.

**$N$-Cycloheptylmethyl-$N$-(5-pyrrolidin-1-ylpentyl)guanidine bis-hydrochloride (23):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.90 (br s, 1H), 7.78−7.74 (m, 2H), 7.46 (s, 2H), 3.50−3.44 (m, 2H), 3.17−2.94 (m, 8H), 1.99−1.83 (m, 4H), 1.70−1.38 (m, 17H), 1.19−1.09 (m, 2H). Anal. ($C_{18}H_{36}N_4$·2HCl·4H₂O) C, H, N.

**$N$-Adamantan-1-ylmethyl-$N$-(5-pyrrolidin-1-ylpentyl)-guanidine bis-hydrochloride (24):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.80 (br s, 1H), 7.84 (br s, 1H), 7.63 (br s, 1H), 7.49 (br s, 2H), 3.49−3.44 (m, 2H), 3.17−3.90 (m, 6H), 2.82 (d, $J$ = 5.7 Hz, 2H), 1.94−1.86 (m, 7H), 1.73−1.49 (m, 16H), 1.40−1.35 (m, 2H). Anal. ($C_{21}H_{38}N_4$·2HCl·2.6H₂O) C, H, N.

**$N$-Adamantan-1-ylmethyl-$N$-(5-piperidin-1-ylpentyl)-guanidine bis-hydrochloride (25):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.40 (br s, 1H), 7.89 (br s, 1H), 7.68 (br s, 1H), 7.51 (br s, 2H), 3.32 (br s, 3H), 3.15 (q, $J$ = 6.3 Hz, 2H), 2.94 (m, 2H), 2.83 (m, 4H), 1.93 (br s, 3H), 1.83−1.45 (m, 20H), 1.34 (m, 3H). Anal. ($C_{22}H_{40}N_4$·2HCl·4H₂O) C, H, N.

**$N$-Adamantan-1-ylmethyl-$N$-(5-azepan-1-ylpentyl)-guanidine bis-hydrochloride (26):** $^1$H NMR (DMSO-$d_6$) 10.50 (br s, 1H), 7.88 (br s, 1H), 7.67 (br s, 1H), 7.50 (br s, 2H), 3.29 (br s, 2H), 3.15 (q, $J$ = 6.4 Hz, 2H), 3.02 (m, 4H), 2.83 (d, $J$ = 6 Hz, 2H), 1.94 (br s, 3H), 1.80−1.40 (m, 24H), 1.34 (m, 2H). Anal. ($C_{23}H_{42}N_4$·2HCl·4H₂O) C, H, N.

**$N$-Adamantan-1-ylmethyl-$N$-(5-azocan-1-ylpentyl)-guanidine bis-hydrochloride (27):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.50 (br s, 1H), 7.88 (br s, 1H), 7.66 (br s, 1H), 7.50 (br s, 2H), 3.30 (br s, 2H), 3.16−2.98 (m, 6H), 2.83 (d, $J$ = 6 Hz, 2H), 1.94 (br s, 3H), 1.83−1.40 (m, 26H), 1.34 (m, 2H). Anal. ($C_{24}H_{44}N_4$·2HCl·4H₂O) C, H, N.

**$N$-(4-Chlorobenzyl)-$N$-(4-pyrrolidin-1-ylbutyl)guanidine Bis-hydrochloride (28). Step a.** To a stirred solution of 4-chlorobenzylamine (9.86 g, 69.6 mmol) in 1,4-dioxan (100 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (15.2 g, 69.6 mmol) in 1,4-dioxan (50 mL). The solution was stirred at 20 °C for 45 min and then the solvent was evaporated at reduced pressure. The residue was suspended in hexane and the solid recovered by filtration. The solid was washed with further hexane and dried in vacuo at 50 °C to give (4-chlorobenzyl)carbamic acid *tert*-butyl ester (13.5 g, 80%): $^1$H NMR (300 MHz, CDCl₃) 7.31−7.20 (m, 4H), 4.80 (br s, 1H), 4.27 (d, $J$ = 5.7 Hz, 2H), 1.46 (s, 9H).

**Step b.** To an ice-cooled stirred solution of the product from step a (725 mg, 3.00 mmol) in DMF (9 mL) was added, in a single portion, sodium hydride (60% dispersion in mineral oil, 144 mg, 3.60 mmol). The coolant was removed and the suspension was stirred at 20 °C for 30 min. The suspension was cooled in ice and 1,5-dibromobutane (1.23 mL, 9.03 mmol) was added in three portions. The coolant was removed and the reaction mixture was stirred at 20 °C for 18 h. The reaction was quenched with H₂O and then extracted with EtOAc. The aqueous phase was discarded and the organic phase washed with brine (×2). The organic phase was dried (MgSO₄) and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (5/1 hexane/EtOAc) to afford (4-bromo-butyl)(4-chlorobenzyl)carbamic acid *tert*-butyl ester.

**Step c.** To a stirred solution of the product from step b in acetonitrile (4 mL) was added pyrrolidine (1.27 mL, 15.2 mmol) and the resultant solution was stirred at 20 °C for 18 h. The reaction mixture was diluted with EtOAc, washed sequentially with H₂O and brine, and dried (MgSO₄). The filtrate was evaporated at reduced pressure and the residue treated with hydrogen chloride in 1,4-dioxan (4 M, 10 mL, 40 mmol). The solution was stirred at 20 °C for 1 h and the solvent removed at reduced pressure to afford (4-chlorobenzyl)(4-pyrrolidin-1-

ylbutyl)amine bis-hydrochloride (655 mg, 62%): $^1$H NMR (DMSO-$d_6$) 11.00 (br s, 1H), 9.50 (br s, 2H), 7.61 (d, $J$ = 8.4 Hz, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 4.11 (s, 2H), 3.44 (br s, 2H), 3.08−2.87 (m, 6H), 1.92 (br s, 4H), 1.73 (br s, 4H).

**Step d.** To an ice-cooled suspension of the product of step c (1.24 g, 3.65 mmol) in DCM (30 mL) were added sequentially NEt₃ (2.54 mL, 18.3 mmol), 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.16 g, 4.00 mmol) and mercury(II) chloride (1.09 g, 4.00 mmol). The coolant was removed and the resultant solution was stirred at 20 °C for 18 h to give a suspension. The suspension was filtered through a plug of Celite and the filter-cake was washed with further DCM. The filtrate was washed sequentially with H₂O and brine. The organic phase was dried (MgSO₄) and the filtrate was evaporated at reduced pressure. The crude residue was purified by flash column chromatography (100/10/1 DCM/MeOH/NH₄OH) to afford $N,N$-bis(*tert*-butyoxycarbonyl)-$N'$-(4-chlorobenzyl)-$N'$-(4-pyrrolidin-1-ylbutyl)guanidine (1.19 g, 64%): $^1$H NMR (300 MHz, CDCl₃) 9.97 (br s, 1H), 7.32−7.22 (m, 4H), 4.67 (s, 2H), 3.34−3.29 (m, 2H), 2.51−2.36 (m, 6H), 1.76−1.70 (m, 4H), 1.50−1.41 (m, 22H).

**Step e.** A solution of the product of step d (1.18 g, 2.31 mmol) in chloroform (10 mL) was treated with hydrogen chloride−dioxan (4 M, 10 mL, 40 mmol) and the reaction stirred at 20 °C for 16 h. The solvent was removed at reduced pressure and the residue was evaporated twice from CHCl₃ (×2) to give the title compound as a foam (889 mg, 100%): $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 7.73 (br s, 4H), 7.46 (d, $J$ = 6 Hz, 2H), 7.27 (d, $J$ = 6 Hz, 2H), 4.64 (s, 2H), 3.47−3.28 (m, 4H), 3.05−2.89 (m, 4H), 1.95−1.86 (m, 4H), 1.62−1.58 (m, 4H). Anal. ($C_{16}H_{25}ClN_4$·2HCl·2H₂O) C, H. N.

The following compounds (**29−32**) were prepared in a similar manner utilizing the appropriate dibromide in step b.

**$N$-(4-Chlorobenzyl)-$N$-(5-pyrrolidin-1-ylpentyl)guanidine bis-hydrochloride (29):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.90 (br s, 1H), 7.67−7.61 (br m, 4H), 7.46 (d, $J$ = 6 Hz, 2H), 7.27 (d, $J$ = 6 Hz, 2H), 4.62 (s, 2H), 3.46−3.44 (m, 2H), 3.27−3.24 (m, 2H), 3.03−2.90 (m, 4H), 1.96−1.86 (m, 4H), 1.65−1.52 (m, 4H), 1.30−1.27 (m, 2H). Anal. ($C_{17}H_{27}ClN_4$·2HCl·2H₂O) C, H, N.

**$N$-(4-Chlorobenzyl)-$N$-(6-pyrrolidin-1-ylhexyl)guanidine bis-hydrochloride (30):** $^1$H NMR (300 MHz, DMSO-$d_6$) 11.00 (br s, 1H), 7.68 (br s, 4H), 7.47 (d, $J$ = 9 Hz, 2H), 7.27 (d, $J$ = 9 Hz, 2H), 4.62 (s, 2H), 3.48−3.38 (m, 2H), 3.29−3.24 (m, 2H), 3.05−2.88 (m, 4H), 1.98−1.80 (m, 4H), 1.66−1.58 (m, 2H), 1.50 (br s, 2H), 1.27−1.26 (m, 4H). Anal. ($C_{18}H_{29}ClN_4$·2HCl·1.5H₂O) C, H, N.

**$N$-(4-Chlorobenzyl)-$N$-(7-pyrrolidin-1-ylheptyl)guanidine bis-hydrochloride (31):** $^1$H NMR (300 MHz, DMSO-$d_6$) 11.10 (br s, 1H), 7.72 (br s, 4H), 7.46 (d, $J$ = 9 Hz, 2H), 7.27 (d, $J$ = 9 Hz, 2H), 4.62 (s, 2H), 3.48−3.41 (m, 2H), 3.26 (t, $J$ = 7.5 Hz, 2H), 3.05−2.86 (m, 4H), 1.98−1.82 (m, 4H), 1.64 (m, 2H), 1.48 (br m, 2H), 1.24 (br s, 6H). Anal. ($C_{19}H_{31}ClN_4$·2HCl·2H₂O) C, H, N.

**$N$-(4-Chlorobenzyl)-$N$-(8-pyrrolidin-1-yloctyl)guanidine bis-hydrochloride (32):** $^1$H NMR (300 MHz, DMSO-$d_6$) 10.90 (br s, 1H), 7.62 (br s, 4H), 7.47−7.43 (m, 2H), 7.26−7.24 (m, 2H), 4.60 (s, 2H), 3.46−3.44 (m, 2H), 3.28−3.23 (m, 2H), 3.04−2.92 (m, 4H), 1.95−1.85 (m, 4H), 1.64 (br s, 2H), 1.48 (br s, 2H), 1.23 (br s, 8H). Anal. ($C_{20}H_{33}ClN_4$·2HCl·1.55H₂O) C, H, N.

**$\sigma_1$ Binding Assay.** Guinea-pig cerebral cortical homogenates[24] membranes (400 µL, 10 mg mL$^{-1}$ original weight) were incubated for 48 h at 21 ± 3 °C in a final volume of 500 µL with 20 mM Hepes-NaOH buffer containing [$^3$H]-(+)-pentazocine (50 µL, 10 nmol) and the test compound. Total and nonspecific binding of [$^3$H]-(+)-pentacozine were defined using 50 µL of Hepes-NaOH buffer and 50 µL of 100 µM 1,3-di(2-tolyl)guanidine (DTG), respectively. The assay was terminated by rapid filtration through presoaked (0.1% PEI) Whatman GF/B filters using a Brandell cell harvester. Bound radioactivity was determined by liquid scintillation counting. Competition experiments were analyzed and $K_I$'s were determined using the equation $K_I = IC_{50}/1 + ([ligand]/K_D)$. The $K_d$ is the

equilibrium dissociation constant of [³H]-(+)-pentazocine (p$K_d$ = 9.00 ± 0.12) determined by saturation analysis in the cortex.

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