

Design of Potent Non-Thiourea H₃-Receptor Histamine Antagonists[†]

C. Robin Ganellin,* S. Kiumars Hosseini, Yasmin S. Khalaf, Wasyl Tertiuk, Jean-Michel Arrang,[‡] Monique Garbarg,[‡] Xavier Ligneau,[§] and Jean-Charles Schwartz[‡]

Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1H 0AJ, UK, Unité 109 de Neurobiologie et Pharmacologie, Centre Paul Broca de l'INSERM, 2 ter rue d'Alésia, 75014, Paris, France, Laboratoire Bioprojet, 30 rue des Francs-Bourgeois, 75003, Paris, France

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Starting from thioperamide, the first potent and selective H₃-receptor histamine antagonist, analogues have been synthesized and tested *in vitro* on rat cerebral cortex to explore structure-activity relationships. The aim has been to design potent compounds which do not possess the thiourea group of thioperamide and which may have improved brain penetration. In a short series of open chain thiourea analogues, the optimum chain length for H₃-antagonist potency was found to be (CH₂)₃. Compounds derived from histamine and possessing an aromatic nitrogen-containing heterocycle on the side chain amino group in place of thiourea show H₃-antagonist activity. Furthermore, when the heterocycle is 2-pyridyl, electron-withdrawing substituents (e.g. NO₂, CF₃, CO₂Me) in the pyridine 5-position increased potency. The synthesis of 4-[4(5)-imidazolyl]piperidine and its conversion into the (trifluoromethyl)pyridyl analogue **5b** of thioperamide is described; however, **5b** is not as potent as thioperamide. Replacing imidazole by pyridine or substituting imidazole on the remote N considerably reduced potency. Replacing the side-chain NH by S increased potency still further and the most potent compound is 2-[[2-[4(5)-imidazolyl]ethyl]thio]-5-nitropyridine (UCL 1199) which has K_i = 4.8 nM.

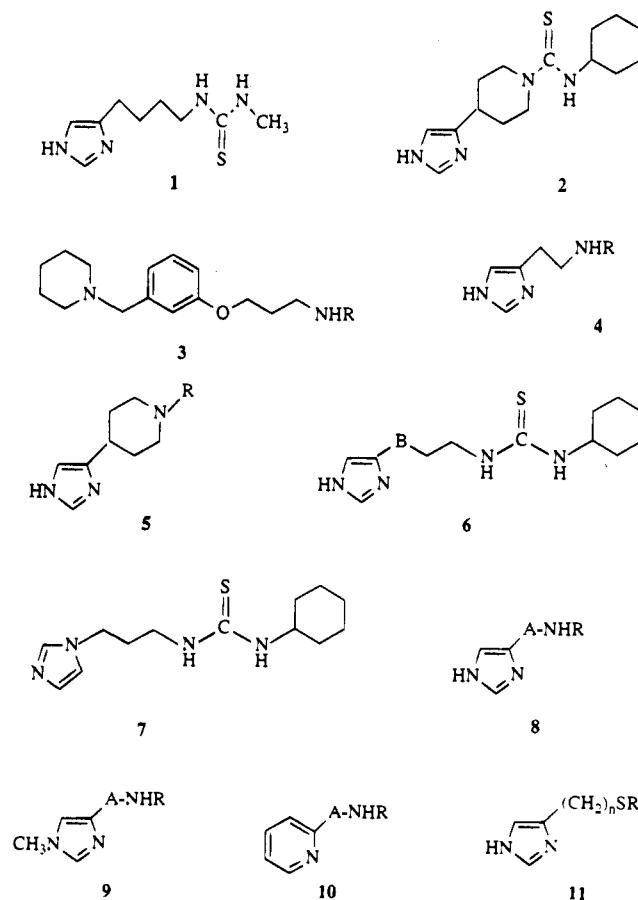
Introduction

The histamine H₃-receptor was first characterized pharmacologically and reported¹ in 1983. It was shown to be located presynaptically on histaminergic neurones in the central nervous system (CNS), where it functions as an autoreceptor to modulate histamine release. The H₃-receptor also modulates the synthesis of histamine from L-histidine.² Thus, activation of the H₃-receptor by histamine leads to a decrease in the concentration of the neurotransmitter histamine released.³ The existence of H₃-receptors in the human brain has also been demonstrated.⁴

The H₃-receptors also appear to occur as heteroreceptors on nonhistaminergic axon terminals, modulating the release of other important neurotransmitters both in the CNS and the periphery.⁵ Thus in the brain, activation of H₃-receptors has been shown to inhibit the release of acetylcholine,⁶ noradrenaline,⁷ dopamine,⁸ and 5-hydroxytryptamine;⁷ in the periphery H₃-receptor activation inhibits the release of acetylcholine,^{9,10} noradrenaline,¹¹ 5-hydroxytryptamine,¹² and NANC transmitters,¹³ probably including neuropeptides such as substance P.

The first substances used to investigate H₃-receptors were drawn from available compounds and especially drugs which were known to act at histamine H₁- or H₂-receptors. In particular it was shown¹ that burimamide (**1**, Chart 1) (the first compound described¹⁴ as a selective H₂-receptor antagonist) was actually active in antagonizing histamine at the putative H₃-receptor at 1/100 of the concentration required for blocking the H₂-receptor. Other H₂-active compounds were also shown to have activity at the H₃-receptor, notably the guani-

Chart 1



dine derivatives impromidine (a potent H₂-receptor agonist) and SK&F 91486 (3-(imidazol-4-yl)propylguanidine). On the other hand, more potent H₂-receptor antagonists such as metiamide, cimetidine, ranitidine, and tiotidine were much less active than burimamide as antagonists at the H₃-receptor.¹

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[‡] Centre Paul Broca de l'INSERM.

[§] Laboratoire Bioprojet.

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None of the above compounds was sufficiently specific for the H₃-receptor and so thioperamide (**2**), a very potent and selective antagonist, was devised to provide confirmatory pharmacological characterization.¹⁵ Thioperamide has become a very useful drug for the investigation of the involvement and role of H₃-receptors in physiology. Although it is very potent *in vitro* ($K_1 = 4.3$ nM)¹⁵ relatively high doses are required *in vivo* (e.g., ED₅₀ *ca.* 2mg/kg ip, *ca.* 5mg/kg po in rats)¹⁶ to enhance histamine release in the brain. This could be due to the pharmacokinetic properties of thioperamide and also might suggest a possible low penetration of the blood-brain barrier. Rather surprisingly, a study in the rat indicated¹⁷ a good brain penetration in which the brain:blood concentration ratio was approximately 0.7 3 h after an ip dose. A more recent study, however, suggests that the brain:peripheral tissue ratio is less than 0.1 in the rat, after bolus intravenous injection.¹⁸

Unfortunately, thioperamide does not appear to be suitable for human studies because of potential liver toxicity. Thus, no H₃-antagonist is yet available for investigation of the role of H₃-receptors in humans to verify the potential therapeutic applications for H₃-receptor histamine antagonists. At present, one may only extrapolate from animal data and speculate. For example, an H₃-antagonist entering the brain would permit an increase in histamine transmission through histaminergic pathways and thereby potentiate the role of histamine in controlling the waking state and so act as a stimulant.^{19a-c} Histamine H₃-receptor antagonists could also increase locomotor activity^{19d} and pituitary hormone^{19e} secretion, act as anticonvulsants^{19f} and antinociceptives,^{19g} and suppress food intake.^{19h}

Structural analogues of thioperamide have been described, e.g., compounds with methyl or amino substituents in the imidazole ring²⁰ and thiourea analogues in which the central piperidine ring has been modified²¹ or replaced²² by an alkylene chain. Ureas and amide analogues of thioperamide have been described in several patents,^{23,24} and amidines have recently been mentioned.²⁵ Amides, esters, ethers, guanidines, and isothiureas substituted by imidazolylalkyl groups have also been reported.²⁶⁻²⁹

We were especially interested in replacing the thiourea group of thioperamide since some thiourea compounds have been associated with toxic side effects.³⁰ The strong similarities in the structures of these H₃-antagonists with H₂-antagonists such as burimamide and SK&F 91486 led us to explore whether the "urea equivalent" groups in the structures of H₂-antagonists³¹ could be used to provide H₃-antagonists.

Groups such as NH-R (where R = an aromatic nitrogen heterocycle) are much weaker hydrogen-bonding groups than amides or thioamides,³² and since hydrogen-bond strength appears to reduce brain penetration, these groups had been used in the design³³ of the brain-penetrating H₂-antagonist zolantidine (**3**, R = 2-benzothiazolyl). Amino-substituted aromatic nitrogen heterocycles (**4**, R = aromatic nitrogen heterocycle) were therefore investigated as possible thiourea replacements for H₃-antagonists,³⁴ based on histamine and higher homologues. Very recently, benzothiazolyl analogues (**5**) of thioperamide have also been reported as cyclized forms of the isothiuronium group.³⁵ More recently still, benzothiazolyl and thiazolyl derivatives

of histamine (**4**, $n = 2$, R = 2-benzothiazolyl, 2-thiazolyl) have been mentioned.³⁶

In order to relate the antagonist structure to histamine for a structure-activity exploration, we first investigated the effect of replacing the piperidine substructure of thioperamide by an open chain. A short series of imidazolylalkyl thioureas (**6**) was therefore synthesized to provide a basis for comparison. The compounds were tested for antagonism of histamine *in vitro* on rat brain cortex slices or synaptosomes (see below).

Chemistry

The aminoheterocyclic derivatives **4**, **5b**, and **8-10** (Tables 1 and 2) were prepared from histamine base or the appropriate amine by displacement of halogen from the halogeno-substituted heterocycle in hot 2-propanol under reflux (Scheme 1). Compounds **4f** and **4g** were prepared in boiling pyridine or 4-picoline, respectively. For the compounds **4k** and **4n**, the reaction was conducted at room temperature in the presence of anhydrous potassium hydrogen carbonate (in THF for **4k**). However, 2-chloro-4-nitropyridine *N*-oxide in 2-propanol led to displacement of the nitro group or the chloro group,⁵⁰ and the 2-chloro-(4-substituted-amino)pyridine (**4m**) was also obtained but, surprisingly, not as the *N*-oxide.^{50b} The products were generally purified chromatographically on a silica-gel column (eluting with gradient mixtures of methanol in chloroform) and converted into a salt form, usually an oxalate. Physical data are given in Tables 1 and 2 and reaction details are in Table 5.

Compound **4l** was synthesized from **4i** by catalytic hydrogenation (Scheme 2). Compound **5b** was prepared from 4-(4(5)-imidazolyl)piperidine³⁷ (**12f**) and 2-chloro-5-(trifluoromethyl)pyridine in boiling 2-propanol in the presence of anhydrous potassium hydrogen carbonate (Scheme 3). Difficulties were experienced in the synthesis³⁷ of **12f** (Scheme 3). The intermediate 4-(aminoacetyl)pyridine (**12c**) was not formed after the Neber rearrangement of 4-acetylpyridine oxime tosylate (**12a**). Treatment of the latter with sodium methoxide in methanol followed by extraction with 2 N HCl as described by Clemo et al.³⁸ gave, instead, a 90% yield of the dimethyl acetal dihydrochloride **12b**. La Mattina and Suleske have commented³⁹ on the use of anhydrous ethanol to prepare diethyl acetals. In the present example, the acetal **12b** was surprisingly stable and required heating in concentrated HCl at 50 °C for 3 h to effect hydrolysis to the ketone **12c**. The latter was converted into the imidazole thione **12d** which was then desulfurized with Raney nickel. It was critical to ensure that no sulfur remained, otherwise, the rhodium catalyst in the final stage was poisoned and failed to effect the reduction to **12f**. A portion of **12f** was also converted into thioperamide maleate (**2**). Compounds **9a** and **9b** were made in boiling ethanol in the presence of anhydrous potassium hydrogen carbonate.

The *N,N*¹-disubstituted thioureas (**6** and **7**, Table 3) were synthesized from the appropriate amine and cyclohexyl isothiocyanate in boiling ethanol (Scheme 4). Two of these compounds (**6c,d**) were converted into oxalate salts in order to provide crystalline solids.

The (imidazolylalkyl)thio heterocycles (**11**, Table 4) were synthesized via alkylation of the heterocyclic

Table 1. Heteroaryl Derivatives of Histamine and their Potencies as H₃-Receptor Antagonists (in Vitro on Rat Cerebral Cortex) and Physical Data

	Het	K _i ± SEM nM	formula	salt form ^a	mp, °C	recrystn solv
4a		~2100	C ₉ H ₁₁ N ₅ ·C ₂ H ₂ O ₄ ·H ₂ O	ox	200–202	2-PrOH:Et ₂ O
4b		200 ± 20	C ₉ H ₁₁ N ₅ ·1.5C ₂ H ₂ O ₄ ·0.75H ₂ O ^b	2ox	200–202	2-PrOH:Et ₂ O
4c		~1300	C ₁₁ H ₁₅ N ₅ ·C ₄ H ₄ O ₈ ·H ₂ O	2ox	164–165	EtOH
4d		330 ± 100	C ₁₂ H ₁₂ N ₄ S·C ₆ H ₄ O ₄	m	137–138 ^c	2-PrOH
4e		340 ± 70	C ₈ H ₁₀ N ₄ S·C ₄ H ₄ O ₈	2ox	198–199	EtOH
4f		~11000	C ₁₂ H ₁₃ N ₇	base	272–273	EtOH
4g		200 ± 60	C ₁₀ H ₁₂ N ₄ ·2.2C ₄ H ₄ O ₄	2m	137–138	EtOH
4h		240 ± 120	C ₁₀ H ₁₁ N ₅ O ₂	base	178–180	aqEtOH
4i		29 ± 11	C ₁₀ H ₁₁ N ₅ O ₂	base	162–163	EtOH
4j		17 ± 3	C ₁₁ H ₁₁ F ₃ N ₄ ·C ₄ H ₄ O ₈ ·0.5H ₂ O	2m	174–175	2-PrOH:Et ₂ O
4k		42 ± 6	C ₁₂ H ₁₄ N ₄ O ₂ ·1.7C ₂ H ₂ O ₄	ox	209–210	MeOH:Et ₂ O
4l		186 ± 37	C ₁₀ H ₁₃ N ₅ ·2C ₂ H ₂ O ₄ ·H ₂ O	2ox	178–179	EtOH
4m		160 ± 50	C ₁₀ H ₁₁ ClN ₄ ·0.2H ₂ O	base	164–165	2-PrOH:Et ₂ O
4n		53 ± 16	C ₁₀ H ₁₁ N ₅ O ₃ ·1.45CF ₃ CO ₂ H	tfa	193–194	<i>d</i>

^a Salt form: ox = oxalate; m = maleate; tfa = trifluoroacetate. ^b C, 0.6% low; N, 0.7 high. ^c Base. ^d Purified by HPLC.

thiones (**11a,d**) or via the (imidazolylalkyl)isothiureas (**11b,c**) through nucleophilic displacement of the activated chloro group in 2-chloro-4-nitropyridine (Scheme 5).

Pharmacology

The compounds were tested in vitro for their antagonism of histamine at H₃-receptors in an assay with K⁺-evoked depolarization-induced release of [³H]histamine from slices or synaptosomes of rat brain cortex.

Rats were killed by decapitation and slices (0.3 mm thick) or synaptosomes were obtained from the cerebral cortex, washed, and resuspended in modified Krebs-Ringer's bicarbonate medium. The slices or synaptosomes were allowed to synthesize [³H]histamine during 30 min incubation at 37 °C in the presence of 3–4 × 10⁻⁷ M [³H]histidine, and then they were washed to remove excess [³H]histidine and to obtain a constant spontaneous [³H]histidine efflux, as described.¹ Slices or synaptosomes were incubated for 2 min with 30 mM K⁺. Unlabelled histamine (1 μM) alone, or together with test compounds, was added 5 min before the start of

incubations, at the end of which [³H]histamine was assayed in tissue and medium after isolation by ion-exchange chromatography on Amberlite CG 50 columns.¹

Inhibition–response curves were analyzed for determination of IC₅₀ values of antagonists by fitting the data with an iterative computer least-squares method derived from Parker and Waud. The apparent dissociation constants (K_i) of the antagonists were calculated from the IC₅₀ values, assuming a competitive antagonism and neglecting the effect of endogenous histamine according to the equation of Cheng and Prusoff,⁴⁰ K_i = IC₅₀/(1 + S/EC₅₀), where S represents the concentration of exogenous histamine (1 μM) and EC₅₀ the histamine concentration (62 nM) eliciting a half-maximal inhibitory effect on K⁺-evoked release of [³H]histamine.

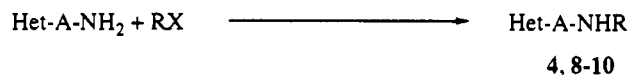
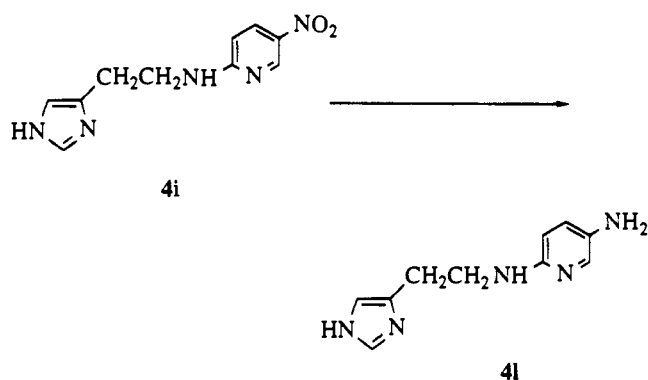
Results and Discussion

Among the cyclohexyl-substituted (imidazolylalkyl)-thiureas, H₃-antagonist potency was found to be dependent on the chain length (Table 3); the most potent compound (**6b**) possessing a three-methylene chain

Table 2. Heteroaryl Derivatives of Amines Other Than Histamine and Their Potencies as H₃-Receptor Antagonists (in Vitro on Rat Cerebral Cortex) and Physical Data

compd	Het-A-NHR			K _i ± SEM nM	formula	salt form ^a	mp, °C	recrystn solv
	Het	A	NHR					
5b				42 ± 22	C ₁₄ H ₁₅ F ₃ N ₄	base	154–155	Et ₂ O:CHCl ₃
8a		(CH ₂) ₃		170 ± 40	C ₁₁ H ₁₃ N ₅ O ₂ ·C ₂ H ₂ O ₄	ox	181–182	EtOH
8b		CH ₂ SCH ₂ CH ₂		1300 ± 200	C ₁₁ H ₁₃ N ₅ O ₂ S·0.25H ₂ O	base	145–147	EtOH
9a		CH ₂ CH ₂		~2500	C ₁₁ H ₁₃ N ₅ O ₂	base	189–190	2-PrOH
9b		CH ₂ CH ₂		~1300	C ₁₂ H ₁₃ F ₃ N ₄ ·2C ₂ H ₂ O ₄	2ox	179–180	EtOH
10a		CH ₂ CH ₂		>10,000	C ₁₁ H ₁₂ N ₄ ·C ₄ H ₄ O ₄	m	132–133	2-PrOH
10b		CH ₂ CH ₂		~3100	C ₁₄ H ₁₃ N ₃ S·2C ₄ H ₄ O ₄	2m	114–116	2-PrOH: Et ₂ O
10c		CH ₂ CH ₂		~1000	C ₁₂ H ₁₂ N ₄ O ₂	base	143–146	2-PrOH

^a For salt forms, see footnote a of Table 1.

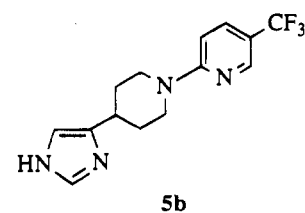
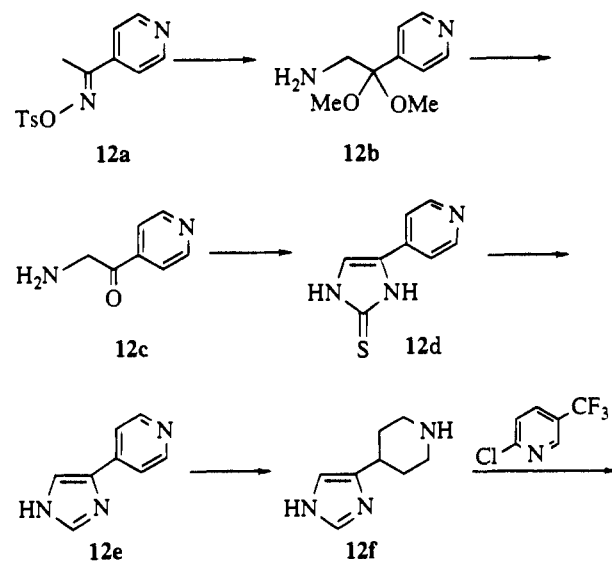
Scheme 1**Scheme 2**

corresponds to the "ring-opened" analogue of thioperamide and has approximately one-third of its potency.

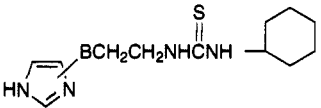
The higher homologue (**6c**) is the cyclohexyl analogue of burimamide (the first described H₂-receptor histamine antagonist)¹⁴ and is approximately 5 times less potent than thioperamide as an H₃-antagonist, whereas burimamide is about 16 times less potent than thioperamide.¹ Comparing these structures one may infer that the cyclohexyl group contributes additional affinity at H₃-receptors through hydrophobic interaction with lipophilic regions of the receptor and that the piperidine ring contributes selectivity by reducing the affinity for H₂-receptors.

These are important findings because they indicate that it is not necessary to restrict the side-chain conformation of the antagonist in order to confer antagonist potency at H₃-receptors (see below).

Various aromatic azaheterocycles were substituted for

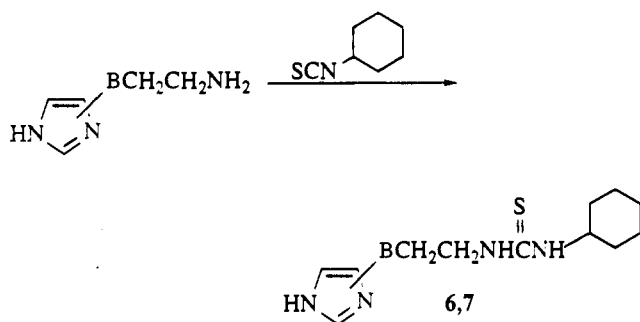
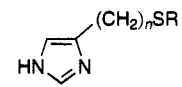
Scheme 3


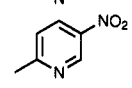
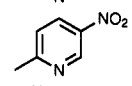

the thiocarbonyl moiety to provide compounds (**4**) which had activity in vitro with K_i in the range 0.02–2 μM (Table 1). In particular, the 2-pyridyl and 2-pyrazinyl compounds derived from histamine were equipotent with the corresponding cyclohexylthiourea analogue. This demonstrates very clearly that, as with H₂-antagonists, amino heterocycles can be used to replace the thiourea structural unit in H₃-antagonists. Among the heterocycles investigated, the contribution to po-

Table 3. Cyclohexylthiourea Derivatives and Their Potencies as H₃-Receptor Antagonists (in Vitro on Rat Cerebral Cortex) and Physical Data


compd	imidazolyl ^a	B	K _i , nM	formula	salt form ^b	mp, °C	recrystn solv
6a	4(5)		~200	C ₁₂ H ₂₀ N ₄ S	base	138–140	2-PrOH:Et ₂ O
6b	4(5)	CH ₂	13 ± 3	C ₁₃ H ₂₂ N ₄ S	base	114–115	EtOAc
6c	4(5)	CH ₂ CH ₂	20 ± 7	C ₁₄ H ₂₄ N ₄ S·0.85C ₂ H ₂ O ₄	ox	107–108	2-PrOH
6d	4(5)	CH ₂ S	~500	C ₁₃ H ₂₂ N ₄ S ₂ ·0.9C ₂ H ₂ O ₄	ox	148–150	2-PrOH
7	1	CH ₂	NA ^c	C ₁₃ H ₂₂ N ₄ S	base	117–118	EtOH
1, burimamide			70				
2, thioperamide			4.3				

^a Position of attachment of side chain to imidazole ring. ^b For salt forms, see footnote *a* of Table 1. ^c Tested up to 1000 nM.

Scheme 4**Table 4.** (Imidazolylalkyl)thio heterocycles and Their Potencies as H₃-Receptor Histamine Antagonists (in Vitro on Rat Cerebral Cortex)


compd	n	R	K _i ± SEM, nM
11a	2		92 ± 22
11b	1		~600
11c ^a	2		4.8 ± 0.9
11d	2		400 ± 100 ^b

^a UCL 1199. ^b Bordi et al report³⁶ 58 nM.

tency was 2-pyridyl = 2-pyrazinyl ≥ 2-thiazolyl = 2-benzothiazolyl > 2-pyrimidinyl. These results may be compared with the contribution to potency when the heterocycles were incorporated into the (piperidino-methyl)phenoxypropyl structure of H₂-antagonists. The potency order of the heterocycles was then 2-thiazolyl = 2-benzothiazolyl > 2-pyridyl,³³ with the thiazole and benzothiazole being some 10 times more potent at H₂-receptors. Surprisingly, the results obtained for compounds **4d** and **4e** differ markedly from the activities reported very recently by Bordi et al;^{35,36} they reported $-\log K_i = 7.7$ for **4d** and $-\log K_i < 6$ for **4e**.

To improve the potential for brain penetration a nitro group was introduced at the 3-position of the 2-aminopyridine derivative (giving **4h**) in the expectation that this would form an intramolecular hydrogen bond with the NH group and so limit its general availability for intermolecular hydrogen bonding. This structural fea-

Table 5. Reaction Details for Compounds 4–10

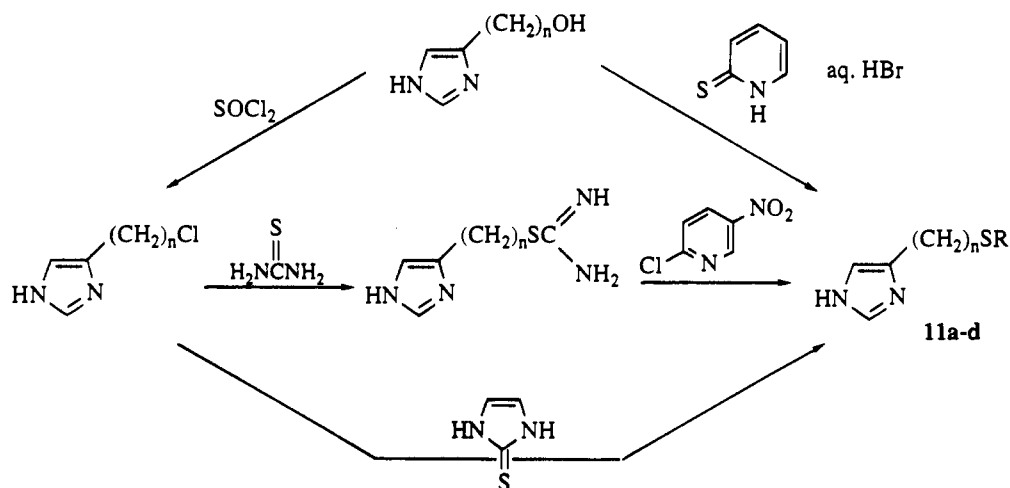
compd	reaction solvent	time, h	temp, °C	X (in RX)	base	% yield
4a	2-PrOH	36	reflux	Cl		27
4b	2-PrOH	72	reflux	Cl		26
4c	2-PrOH	72	reflux	Cl		33
4d	2-PrOH	48	reflux	Cl		67
4e	2-PrOH	96	reflux	Br		31
4f	pyridine	5	80	Cl		13
4g	4-picoline	26	reflux	Br		6
4h	2-PrOH	3	reflux	Cl		65
4i	2-PrOH	48	reflux	Cl		21
4j	2-PrOH	3	reflux	Cl		55
4k	THF	24	reflux	Cl	KHCO ₃	25
4l	EtOH	4	21	hydrogenation		95
4m	2-PrOH	72	21	NO ₂	KHCO ₃	87
4n	2-PrOH	72	21	Cl	KHCO ₃	15
5b	2-PrOH	12	reflux	Cl	KHCO ₃	57
6a	EtOH	1	reflux	CNS		80
6b	EtOH	0.7	reflux	CNS		72
6c	EtOH	3	reflux	CNS		58
6d	EtOH	0.7	reflux	CNS		81
7	EtOH	3	reflux	CNS		43
8a	2-PrOH	21	reflux	Cl		11
8b	2-PrOH	18	reflux	Cl		9
9a	EtOH	4	reflux	Cl	KHCO ₃	72
9b	EtOH	24	reflux	Cl	KHCO ₃	9
10a	2-PrOH	19	reflux	Cl		32
10b	2-PrOH	30	reflux	Cl		46
10c	2-PrOH	2	50	Cl		44

ture had little effect, however, in changing activity. Of greater interest was the finding that a 5-nitro group (giving **4i**) led to an increase in potency of an order of magnitude. Other 2-aminopyridines substituted by electronegative groups at the 5-position, namely CF₃ (**4j**) or CO₂Me (**4k**), were also found to be more active. On the other hand, the electron-releasing 5-NH₂ group (**4l**) did not affect potency.

Increasing the chain length of the active 5-nitropyridine by homologation (**8a**) and then via additional -S- insertion (**8b**) (Table 2) successively reduced potency. Thus the activity pattern does not parallel that found with the thioureas **6** (Table 3).

Another approach to improving brain penetration is to reduce the hydrogen-bonding potential of the imidazole ring by, for example, replacing NH with NMe (**9**), introducing the side chain on the imidazole N (**7**), or replacing imidazole by pyridine (**10**). Several such compounds were synthesized (Table 2) and tested, but they were found to be much less active than the parent 4(5)-imidazole compound. These findings are consistent with other structure-activity studies which suggest²¹ that the unsubstituted imidazole ring is an important structural feature of compounds acting at H₃-

Scheme 5



receptors. Some non-imidazoles such as betahistine,⁴¹ phenacyclidine,⁴² and dimaprit⁴³ have some activity as H₃-antagonists, but they are very much less potent than similar imidazole derivatives.

In the compounds **4**, the NH amino group corresponds to the tertiary N of the thiourea moiety in thioperamide. Hence it seemed likely that the H was not needed for activity. This was demonstrated by replacing NH by S (compounds **11**). This structural modification applied to **4i** led to a further 6-fold increase in potency and compound **11c** (Table 4), (UCL 1199, 2-[[2-[4(5)-imidazolyl]ethyl]thio]-5-nitropyridine) has $K_i = 4.8$ nM, i.e. is equipotent with thioperamide.

Since the 2-amino-5-(trifluoromethyl)pyridyl group (in compound **4j**) increased the potency by 10-fold relative to the corresponding cyclohexylthiourea (**6a**), the same replacement was made in thioperamide to give compound **5b** in the expectation that this would be a very potent compound. In this case, however, the compound was not more potent but actually some 10-fold less potent than thioperamide. This again suggests that the thioureas and these amino heterocycles do not bind in the same manner to the H₃-receptor.

Experimental Section

General Methods. All melting points (mp) were taken in open capillaries on an Electrothermal apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian XL-200 (200 MHz). Mass spectra were recorded on a VG 7070H double-focusing spectrometer with a Finnigan Inco data system using electron-impact at 70 eV. IR spectra were obtained on a Perkin-Elmer 983 spectrometer. The NMR, MS, and IR spectral data of all compounds were consistent with the assigned structures. All final products had satisfactory (within $\pm 0.4\%$) C, H, and N analyses unless otherwise indicated. Elemental analyses were performed by A. A. Stones in the Department of Chemistry, University College London.

Analytical thin-layer chromatography (TLC) was performed using Merck Kieselgel 60F-254 plates using NH₄OH:MeOH:EtOAc (1:1:5) as the solvent system. Analytical high-pressure liquid chromatography (HPLC) was performed on a Gilson binary gradient apparatus with UV detection at 254 nm and a (4 × 4 + 250 × 4 mm) Lichrosorb RP Select B 5 mm column with a flow rate of 1 mL/min.

Starting Materials. Histamine dihydrochloride, 4-(hydroxymethyl)imidazole hydrochloride, 1-(3-aminopropyl)imidazole, and 2-(2-pyridyl)ethylamine were from Aldrich Chemical Co. The latter amine was purified via crystallization of the dihydrochloride. 3-[4(5)-Imidazolyl]propylamine,⁴⁴ 4-[4(5)-imidazolyl]butylamine,⁴⁵ and 2-[[4(5)-imidazolylmethyl]thio]-

ethylamine⁴⁶ were synthesized as published. *N*-Methylhistamine [2-(1-methylimidazol-4-yl)ethylamine] was prepared by hydrolysis of 2-methyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidinium iodide⁴⁷ (mp 225–228 °C) in concentrated HCl followed by neutralization with aqueous NaOH. The reaction mixture was evaporated to dryness under reduced pressure and extracted with CHCl₃ to afford pure *N*-methylhistamine as an oil.

Synthesis of Compounds 4a–n. Histamine base was liberated from the dihydrochloride with NaOEt in ethanol by heating under reflux for 1 h, filtering, and evaporating under reduced pressure. The residue was suspended in 2-propanol and filtered hot and the extract was evaporated to yield histamine. The halogeno-substituted heterocycles RX (Scheme 1) were obtained from Aldrich Chemical Co except for 6-chloro-3-carbomethoxy-pyridine, which was prepared from 6-chloro-nicotinic acid and diazomethane in THF, and 2-chloro-4-nitropyridine *N*-oxide, which was prepared by nitration of 2-chloropyridine *N*-oxide. The compounds were generally synthesized according to the conditions indicated for **4c** or **4d**.

2-[[2-[4(5)-Imidazolyl]ethyl]amino]-3,6-dimethylpyrazine Dioxalate (4c). Histamine (1 g, 8.9 mmol) and 2-chloro-3,6-dimethylpyrazine (1.28 g, 8.9 mmol) in 2-PrOH (10 mL) were heated under reflux for 3 days, the mixture was evaporated, and the residue was subjected to column chromatography on silica gel with successive mixtures of MeOH in CHCl₃ (1, 10, and 20% respectively) to give the title compound as an oil. This was converted into the dioxalate monohydrate salt which was crystallized from 2-PrOH:Et₂O (1:1): mp 164–165 °C; yield 1.2 g, 33%. Anal. (C₁₁H₁₅N₅·2C₂H₂O₄·H₂O) C, H, N.

2-[[2-[4(5)-Imidazolyl]ethyl]amino]benzothiazole Maleate (4d). 2-Chlorobenzothiazole (1.65 g, 9.7 mmol) and histamine base (1.08 g, 9.7 mmol) in 2-PrOH (20 mL) were stirred and heated under reflux for 48 h, and then the mixture was evaporated to dryness. The solid residue was stirred for 1 h in water and the pure product collected by filtration: mp 185–187 °C, yield 1.58 g, (67%). The maleate salt was prepared in EtOH with addition of Et₂O; recrystallized (EtOH) mp 137–138 °C. Anal. (C₁₂H₁₂N₄S·C₄H₄O₄) C, H, N.

2-[[2-[4(5)-Imidazolyl]ethyl]amino]pyridine Dimaleate (4g). A solution of histamine base (2.40 g, 21 mmol) and 2-bromopyridine (3.41 g, 21 mmol) in 4-picoline (5 mL) was heated under reflux for 26 h. The mixture was evaporated under reduced pressure and the oily residue was subjected to column chromatography on silica gel, being eluted with a gradient mixture of CHCl₃:MeOH (1:20%). The resulting product was converted into the dimaleate in EtOH, precipitated with Et₂O, and then recrystallized (EtOH): mp 137–138 °C; yield 0.55 g, (6%). Anal. (C₁₀H₁₂N₄·2.2C₄H₄O₄) C, H, N.

2-[[2-[4(5)-Imidazolyl]ethyl]amino]-5-aminopyridine Dioxalate Monohydrate (4i). 2-[[2-(4(5)-Imidazolyl)ethyl]amino]-5-nitropyridine (**4i**) (1.54 g, 6.6 mmol) in 100 mL of

absolute EtOH containing a few drops of AcOH and palladium on charcoal (10%, 0.75 g) was shaken under hydrogen (1.5 bar) at 21 °C for 4 h. The catalyst was removed and the solvent was evaporated under reduced pressure. The oxalate salt was prepared in EtOH followed by addition of Et₂O and was recrystallized from EtOH: mp 178–179 °C; yield 95%. Anal. (C₁₀H₁₃N₃·2C₂H₂O₄·H₂O) C, H, N.

4-[[2-[4(5)-Imidazolyl]ethyl]amino]-2-chloropyridine (4m). Histamine (38 mg, 0.34 mmol) and 2-chloro-4-nitropyridine *N*-oxide (55 mg, 0.31 mmol) in 2-PrOH (15 mL) were stirred with potassium bicarbonate at 21 °C for 3 days. The mixture was then filtered and evaporated. The resulting solid residue was subjected to column chromatography on silica gel using CHCl₃:MeOH (10:1). The main fraction was evaporated under reduced pressure to give the product which was crystallized from 2-PrOH:Et₂O (1:1): mp 164–165 °C; yield 61 mg (87%). Anal. (C₁₀H₁₁ClN₄·0.2H₂O) C, H, Cl, N. In a repeat of this experiment, one of the fractions afforded compound **4n**; see Tables 1 and 5.

2-[[N-{4-[4(5)-Imidazolyl]piperidyl}]-5-(trifluoromethyl)pyridine (5b). 4-[4(5)-Imidazolyl]piperidine base (**12f**) (0.5 g, 3.3 mmol), KHCO₃ (0.6 g), and 2-chloro-5-(trifluoromethyl)pyridine (0.66 g, 3.6 mmol) were heated together in 2-PrOH (50 mL) under reflux for 12h, and the inorganic residue was filtered off. The filtrate was concentrated under reduced pressure to an oily residue. This residue was purified by silica gel column chromatography using CHCl₃:MeOH (5:1) as eluent. The pure fractions of the product were combined and the solvent was removed under reduced pressure to give a white hygroscopic solid. The product was recrystallized from ether: CHCl₃ to give **5b**: mp 154–155 °C; yield 0.56 g, 57%. Anal. (C₁₄H₁₅F₃N₄) C, H, N.

N'-[2-[4(5)-Imidazolyl]ethyl]-N²-cyclohexylthiourea (6a). Histamine (3.16 g, 27 mmol) was heated with cyclohexyl isothiocyanate (3.81 g, 27 mmol) in absolute EtOH (50 mL) under reflux for 1 h. The solvent was then removed under reduced pressure and the resulting white solid residue was crystallized from 2-PrOH with addition of Et₂O to give the product as a white solid: mp 138–140 °C; yield 5.50 g, 80%. Anal. (C₁₂H₂₀N₄S) C, H, N, S.

Thioureas **6b–d** and **7** were likewise prepared from the appropriate amine and cyclohexyl isothiocyanate in boiling EtOH. Compounds **6c** and **6d**, however, were very hygroscopic and were therefore converted into stable oxalates which were crystallized from 2-propanol.

2-[[2-[1-Methyl-4-imidazolyl]ethyl]amino]-5-(trifluoromethyl)pyridine Dioxalate (9b). 2-(1-Methyl-4-imidazolyl)ethylamine (0.4 g, 3.2 mmol) and 2-chloro-5-(trifluoromethyl)pyridine (0.58 g, 3.2 mmol) were heated with KHCO₃ (0.32 g) in EtOH (5 mL) under reflux for 24 h. Removal of the solvent under reduced pressure and purification of the dark red oily residue by silica gel column chromatography using MeOH:CHCl₃ (1: 5) afforded an oil. This was converted into the dioxalate salt in EtOH (5 mL), precipitated by Et₂O (10 mL), and recrystallized from EtOH: mp 179–180 °C; yield 130 mg (9%). Anal. (C₁₂H₁₃F₃N₄·2C₂H₂O₄) C, H, N.

2-[[2-[4(5)-Imidazolyl]ethyl]thio]pyridine Dihydrobromide Hydrate (11a). 4(5)-(2-Hydroxyethyl)imidazole (0.5 g, 4.4 mmol) and 2-mercaptopyridine (0.49 g, 4.4 mmol) were heated in 47% aqueous HBr (5 mL) under reflux for 24 h. The solvent was azeotropically removed with 2-PrOH under reduced pressure to yield the title compound as the dihydrobromide monohydrate salt which was crystallized from 2-PrOH: mp 189–190 °C; yield 0.81 g (48%). Anal. (C₁₀H₁₁N₃S·2HBr·H₂O) C, H, N.

2-[4(5)-Imidazolyl]methylthio]-5-nitropyridine (11b). A mixture of 4(5)-(chloromethyl)imidazole hydrochloride (0.6 g, 3.9 mmol) and an equimolar equivalent of thiourea (0.3 g) in EtOH (10 mL) were heated under reflux for 30 min. To this was added EtOH (5 mL), water (20 mL), and 1.2 mol equiv of 2-chloro-5-nitropyridine (0.74 g) in hot EtOH (5 mL). The clear solution was cooled to 0–10 °C in an ice bath and a solution of NaOH (0.49 g) in water (10 mL) was added dropwise under N₂ at 0–10 °C followed by stirring for an additional 3 h at 21 °C. The precipitate was collected, washed with water, and chromatographed on silica gel with a gradient

mixture of CHCl₃:MeOH (1–20%) to give the product: mp 155–156 °C (from 2-PrOH); yield 130 mg (4%). Anal. (C₉H₈N₄O₂S) C, H, N indicated the presence of 2% inorganic material.

2-[[2-[4(5)-Imidazolyl]ethyl]thio]-5-nitropyridine (11c). To a solution of *S*-[2-[4(5)-imidazolyl]ethyl]isothiourea dihydrobromide (0.2 g, 0.6 mmol) in water (2 mL) was added a hot solution of 2-chloro-5-nitropyridine (0.2 g, 1.3 mmol) in EtOH (5 mL), and the resulting suspension was stirred under N₂. The reaction mixture was cooled to 0–5 °C and a solution of 4 mol equiv of NaOH (0.16 g) in water (2 mL) was added dropwise under N₂. The reaction mixture was stirred for 1 h at 0–5 °C and for 3 h at 21 °C and then evaporated to dryness; the resulting residue was subjected to column chromatography (silica gel) eluted with a gradient mixture of CHCl₃:MeOH (1–10%) to afford the product which was crystallized from 2-PrOH, to yield 75 mg (50%); mp 147–148 °C. Anal. (C₁₀H₁₀N₄O₂S·0.25H₂O) C, H, N.

2-[[2-[4(5)-Imidazolyl]ethyl]thio]imidazole Oxalate (11d). 4(5)-(2-Chloromethyl)imidazole hydrochloride (183 mg, 1.1 mmol), 2-mercaptoimidazole (110 mg, 1.1 mmol), and solid KOH (200 mg, 3.26 mmol) were heated together in 2-PrOH (10 mL) under reflux for 4 h. The mixture was then evaporated and the semisolid residue was chromatographed on silica gel with CHCl₃:MeOH (5:1). The resulting product was treated with oxalic acid in EtOH to yield the title compound as the oxalate salt: mp 224–226 °C (from EtOH: Et₂O, 10:1); yield 110 mg, 30%. Anal. (C₈H₁₀N₄S·1.6C₂H₂O₄) C, H, N.

4-[4(5)-Imidazolyl]piperidine (12f). 4-Acetylpyridine oxime tosylate^{39b} (29.5 g, 140 mmol) in MeOH (100 mL) was added dropwise to potassium methoxide (from 5.05 g of potassium) in MeOH (250 mL) with stirring. After 1 h the mixture was filtered from potassium tosylate, acidified with concentrated HCl (80 mL), again filtered, and then diluted with Et₂O to furnish 2-(4-pyridyl)-2,2-dimethoxyethylamine (**12b**) dihydrochloride: mp 215 °C; yield 23.2 g (90%). Anal. (C₉H₁₄N₂O₂·2HCl) C, H, Cl, N.

The above acetal, **12b** (20 g, 0.07 mmol), was heated in concentrated HCl (100 mL) at 50 °C for 4h and then the mixture was concentrated under reduced pressure to give 4-(2-aminoacetyl)pyridine dihydrochloride (**12c**): mp 218–220 °C (lit.³⁷ mp 217 °C); yield 14.0 g, 95%.

The above amino ketone (**12c**) (20 g, 0.095 mmol) was heated with KCNS (46.5 g, 0.47 mol) in water (25 mL) at 90 °C for 4 h and then left overnight. The resulting crystalline product was collected to afford 4-(4-pyridyl)imidazole-2-thione hydrochloride (**12d**): mp 254–256 °C; yield 14.3 g, 70%.

The thione hydrochloride **12d** (10 g, 40 mmol) was heated with Raney nickel (50 g) in EtOH (500 mL) under reflux for 6 h. The mixture was then filtered from catalyst and evaporated. The resulting solid product was crystallized from MeOH: Et₂O (1:1) to give 4(5)-(4-pyridyl)imidazole (**12e**): mp 179–180 °C (lit.^{37,48} mp 188 °C, 189–191 °C); yield 3.0 g, 44%.

4(5)-(4-Pyridyl)imidazole (3 g, 20 mmol) was stirred with 5%-rhodium on carbon catalyst (1.5 g) in 2 N HCl (15 mL) under a hydrogen atmosphere (30 atm) for 6 h at 21 °C. Filtration of the catalyst and evaporation of the filtrate afforded 4-[4(5)-imidazolyl]piperidine dihydrochloride (**12f**): mp 289–292 °C (lit.³⁷ mp 292–295 °C). The free base was liberated by neutralizing to pH 9 with KHCO₃ in a minimum of water; the mixture was then concentrated under reduced pressure and the residual moisture was removed azeotropically by distillation with 2-propanol. The resulting residue was extracted with hot 2-propanol and filtered hot. Evaporation of the filtrate under reduced pressure yielded 4-[4(5)-imidazolyl]piperidine base as a white solid: mp 185–186 °C.

A portion of the above base (1.06 g) was heated with cyclohexyl isothiocyanate (1.08 g, 7.7 mmol) in dry toluene (50 mL) under reflux for 2 h. The mixture was cooled and the resulting solid collected and recrystallized from toluene to give thioperamide (**2**): mp 167–168 °C (lit.⁴⁹ mp 170 °C); yield 1.77 g, 87%. The maleate was prepared in EtOH and recrystallized: mp 116–117 °C. Anal. (C₁₅H₂₄N₄S·1.3C₄H₄O₄) C, H, N.

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