Design of Potent Non-Thiourea H_3-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 OAJ, 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

Received March 15, 1995®

Starting from thioperamide, the first potent and selective H_3-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 H_3-antagonist potency was found to be $(CH_2)_3$. Compounds derived from histamine and possessing an aromatic nitrogen-containing heterocycle on the side chain amino group in place of thiourea show H_3-antagonist activity. Furthermore, when the heterocycle is 2-pyridyl, electron-withdrawing substituents (e.g. NO_2, CF_3, CO_2Me) 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.

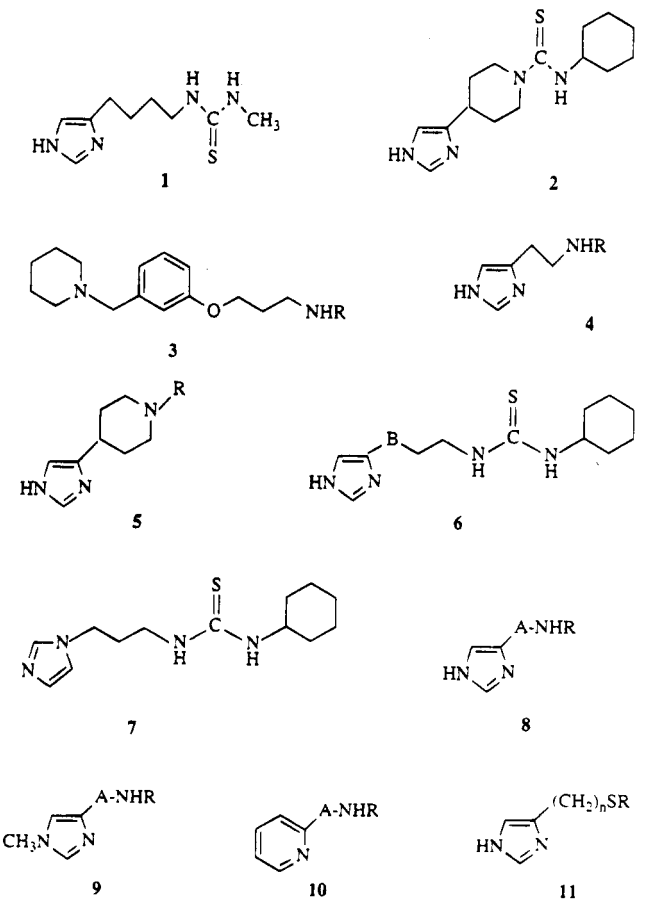
Introduction

The histamine H_3-receptor was first characterized pharmacologically and reported[1] 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 H_3-receptor also modulates the synthesis of histamine from L-histidine.[2] Thus, activation of the H_3-receptor by histamine leads to a decrease in the concentration of the neurotransmitter histamine released.[3] The existence of H_3-receptors in the human brain has also been demonstrated.[4]

The H_3-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 H_3-receptors has been shown to inhibit the release of acetylcholine,[6] noradrenaline,[7] dopamine,[8] and 5-hydroxytryptamine;[7] in the periphery H_3-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 H_3-receptors were drawn from available compounds and especially drugs which were known to act at histamine H_1- or H_2-receptors. In particular it was shown[1] that burimamide (**1**, Chart 1) (the first compound described[14] as a selective H_2-receptor antagonist) was actually active in antagonizing histamine at the putative H_3-receptor at $^1/_{100}$ of the concentration required for blocking the H_2-receptor. Other H_2-active compounds were also shown to have activity at the H_3-receptor, notably the guanidine derivatives impromidine (a potent H_2-receptor agonist) and SK&F 91486 (3-(imidazol-4-yl)propylguanidine). On the other hand, more potent H_2-receptor antagonists such as metiamide, cimetidine, ranitidine, and tiotidine were much less active than burimamide as antagonists at the H_3-receptor.[1]

Chart 1



† Presented in part at the 209th American Chemical Society National Meeting, Anaheim, CA, April 2, 1995 (MEDI 015).
‡ Centre Paul Broca de l'INSERM.
§ Laboratoire Bioprojet.
® Abstract published in *Advance ACS Abstracts*, August 1, 1995.

0022-2623/95/1838-3342$09.00/0

None of the above compounds was sufficiently specific for the H_3-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 H_3-receptors in physiology. Although it is very potent in vitro (K_i = 4.3 nM)[15] relatively high doses are required in vivo (e.g., ED_{50} *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 indicated[17] 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 H_3-antagonist is yet available for investigation of the role of H_3-receptors in humans to verify the potential therapeutic applications for H_3-receptor histamine antagonists. At present, one may only extrapolate from animal data and speculate. For example, an H_3-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 H_3-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 ring[20] and thiourea analogues in which the central piperidine ring has been modified[21] or replaced[22] 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 isothioureas 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 H_3-antagonists with H_2-antagonists such as burimamide and SK&F 91486 led us to explore whether the "urea equivalent" groups in the structures of H_2-antagonists[31] could be used to provide H_3-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 design[33] of the brain-penetrating H_2-antagonist zolantidine (**3**, R = 2-benzothiazolyl). Amino-substituted aromatic nitrogen heterocycles (**4**, R = aromatic nitrogen heterocycle) were therefore investigated as possible thiourea replacements for H_3-antagonists,[34] based on histamine and higher homologues. Very recently, benzothiazolyl analogues (**5**) of thioperamide have also been reported as cyclized forms of the isothiouronium 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

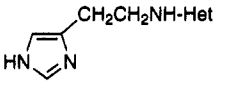
The aminoheterocyclic derivatives **4, 5b,** and **8–10** (Tables 1 and 2) were prepared from histamine base or the appropriate amine by displacement of halogen from the halogeno-substituted heterocycle in hot 2-propanol under reflux (Scheme 1). Compounds **4f** and **4g** were prepared in boiling pyridine 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.

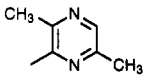
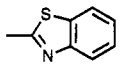
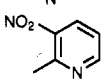
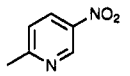
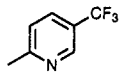
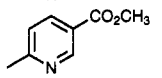
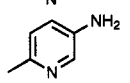
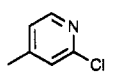
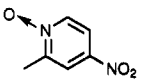
Compound **4l** was synthesized from **4i** by catalytic hydrogenation (Scheme 2). Compound **5b** was prepared from 4-(4(5)-imidazolyl)piperidine[37] (**12f**) and 2-chloro-5-(trifluoromethyl)pyridine in boiling 2-propanol in the presence of anhydrous potassium hydrogen carbonate (Scheme 3). Difficulties were experienced in the synthesis[37] 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 commented[39] 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 H_3-Receptor Antagonists (in Vitro on Rat Cerebral Cortex) and Physical Data



	Het	$K_i \pm$ SEM nM	formula	salt form[a]	mp, °C	recrystn solv
4a		~2100	$C_9H_{11}N_5 \cdot C_2H_2O_4 \cdot H_2O$	ox	200–202	2-PrOH:Et_2O
4b		200 ± 20	$C_9H_{11}N_5 \cdot 1.5C_2H_2O_4 \cdot 0.75H_2O$[b]	2ox	200–202	2-PrOH:Et_2O
4c		~1300	$C_{11}H_{15}N_5 \cdot C_4H_4O_8 \cdot H_2O$	2ox	164–165	EtOH
4d		330 ± 100	$C_{12}H_{12}N_4S \cdot C_6H_4O_4$	m	137–138[c]	2-PrOH
4e		340 ± 70	$C_8H_{10}N_4S \cdot C_4H_4O_8$	2ox	198–199	EtOH
4f		~11000	$C_{12}H_{13}N_7$	base	272–273	EtOH
4g		200 ± 60	$C_{10}H_{12}N_4 \cdot 2.2C_4H_4O_4$	2m	137–138	EtOH
4h		240 ± 120	$C_{10}H_{11}N_5O_2$	base	178–180	aqEtOH
4i		29 ± 11	$C_{10}H_{11}N_5O_2$	base	162–163	EtOH
4j		17 ± 3	$C_{11}H_{11}F_3N_4 \cdot C_4H_4O_8 \cdot 0.5H_2O$	2m	174–175	2-PrOH:Et_2O
4k		42 ± 6	$C_{12}H_{14}N_4O_2 \cdot 1.7C_2H_2O_4$	ox	209–210	MeOH:Et_2O
4l		186 ± 37	$C_{10}H_{13}N_5 \cdot 2C_2H_2O_4 \cdot H_2O$	2ox	178–179	EtOH
4m		160 ± 50	$C_{10}H_{11}ClN_4 \cdot 0.2H_2O$	base	164–165	2-PrOH:Et_2O
4n		53 ± 16	$C_{10}H_{11}N_5O_3 \cdot 1.45CF_3CO_2H$	tfa	193–194	*d*

[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)isothioureas (**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 H_3-receptors in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from slices or synaptosomes of rat brain cortex.

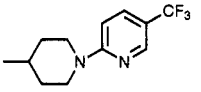
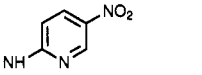
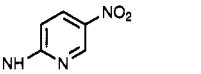
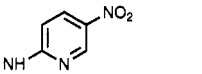
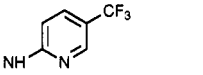
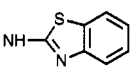
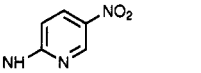
Rats were killed by decapitation and slices (0.3 mm thick) or synaptosomes were obtained from the cerebral cortex, washed, and resuspended in modified Krebs-Ringer's bicarbonate medium. The slices or synaptosomes were allowed to synthesize [^{3}H]histamine during 30 min incubation at 37 °C in the presence of $3-4 \times 10^{-7}$ M [^{3}H]histidine, and then they were washed to remove excess [^{3}H]histidine and to obtain a constant spontaneous [^{3}H]histidine efflux, as described.[1] Slices or synaptosomes were incubated for 2 min with 30 mM K^+. Unlabelled histamine (1μM) alone, or together with test compounds, was added 5 min before the start of incubations, at the end of which [^{3}H]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 IC_{50} 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 IC_{50} values, assuming a competitive antagonism and neglecting the effect of endogenous histamine according to the equation of Cheng and Prusoff,[40] $K_i = IC_{50}/(1 + S/EC_{50})$, where S represents the concentration of exogenous histamine (1 μM) and EC_{50} the histamine concentration (62 nM) eliciting a half-maximal inhibitory effect on K^+-evoked release of [^{3}H]histamine.

Results and Discussion

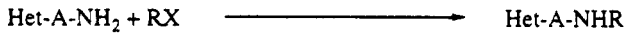
Among the cyclohexyl-substituted (imidazolylalkyl)-thioureas, H_3-antagonist potency was found to be dependent on the chain length (Table 3); the most potent compound (**6b**) possessing a three-methylene chain

Table 2. Heteroaryl Derivatives of Amines Other Than Histamine and Their Potencies as H_3-Receptor Antagonists (in Vitro on Rat Cerebral Cortex) and Physical Data

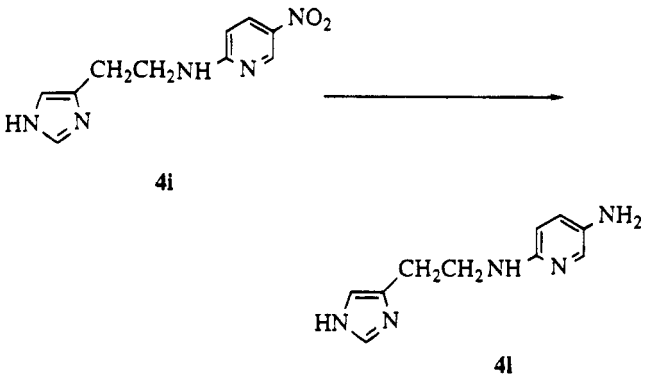
	Het-A-NHR							
compd	Het	A	NHR	$K_i \pm$ SEM nM	formula	salt form[a]	mp, °C	recrystn solv
5b				42 ± 22	$C_{14}H_{15}F_3N_4$	base	154–155	Et_2O:$CHCl_3$
8a		$(CH_2)_3$		170 ± 40	$C_{11}H_{13}N_5O_2 \cdot C_2H_2O_4$	ox	181–182	EtOH
8b		$CH_2SCH_2CH_2$		1300 ± 200	$C_{11}H_{13}N_5O_2S \cdot 0.25H_2O$	base	145–147	EtOH
9a		CH_2CH_2		~2500	$C_{11}H_{13}N_5O_2$	base	189–190	2-PrOH
9b		CH_2CH_2		~1300	$C_{12}H_{13}F_3N_4 \cdot 2C_2H_2O_4$	2ox	179–180	EtOH
10a		CH_2CH_2		>10,000	$C_{11}H_{12}N_4 \cdot C_4H_4O_4$	m	132–133	2-PrOH
10b		CH_2CH_2		~3100	$C_{14}H_{13}N_3S \cdot 2C_4H_4O_4$	2m	114–116	2-PrOH: Et_2O
10c		CH_2CH_2		~1000	$C_{12}H_{12}N_4O_2$	base	143–146	2-PrOH

[a] For salt forms, see footnote *a* of Table 1.

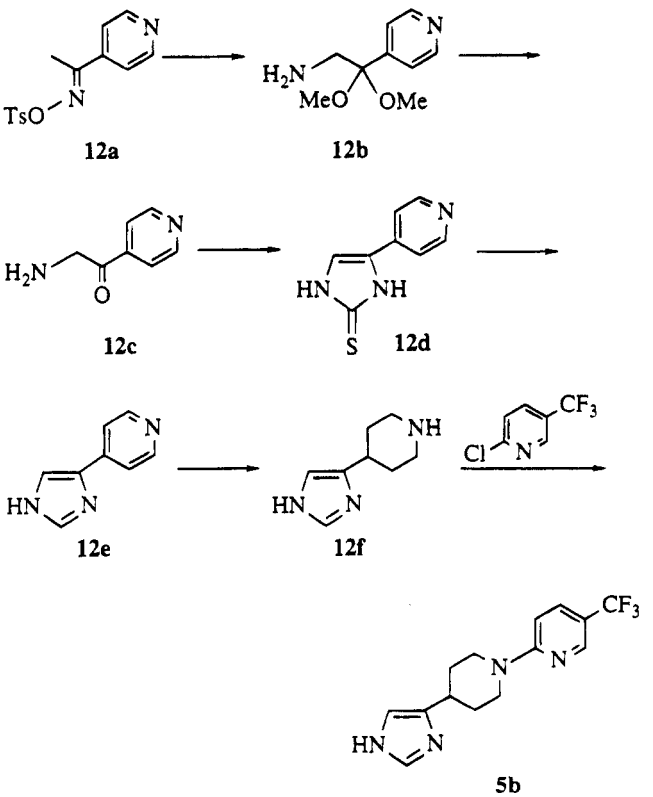
Scheme 1



Scheme 2



Scheme 3



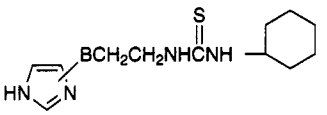
corresponds to the "ring-opened" analogue of thioperamide and has approximately one-third of its potency.

The higher homologue (**6c**) is the cyclohexyl analogue of burimamide (the first described H_2-receptor histamine antagonist)[14] and is approximately 5 times less potent than thioperamide as an H_3-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 H_3-receptors through hydrophobic interaction with lipophilic regions of the receptor and that the piperidine ring contributes selectivity by reducing the affinity for H_2-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 H_3-receptors (see below).

Various aromatic azaheterocycles were substituted for the thiocarbamoyl 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 cyclohexylthioureido analogue. This demonstrates very clearly that, as with H_2-antagonists, amino heterocycles can be used to replace the thiourea structural unit in H_3-antagonists. Among the heterocycles investigated, the contribution to po-

Table 3. Cyclohexylthiourea Derivatives and Their Potencies as H_3-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	$C_{12}H_{20}N_4S$	base	138–140	2-PrOH:Et_2O
6b	4(5)	CH_2	13 ± 3	$C_{13}H_{22}N_4S$	base	114–115	EtOAc
6c	4(5)	CH_2CH_2	20 ± 7	$C_{14}H_{24}N_4S{\cdot}0.85C_2H_2O_4$	ox	107–108	2-PrOH
6d	4(5)	CH_2S	~500	$C_{13}H_{22}N_4S_2{\cdot}0.9C_2H_2O_4$	ox	148–150	2-PrOH
7	1	CH_2	NA[c]	$C_{13}H_{22}N_4S$	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

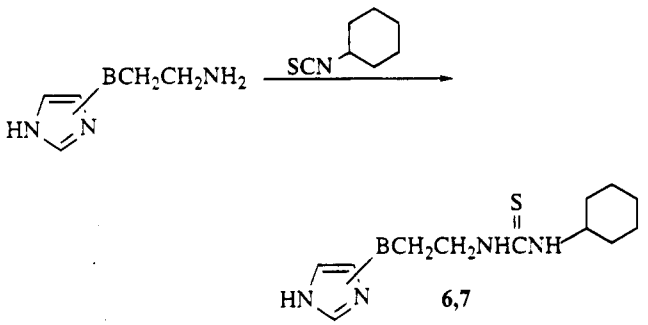
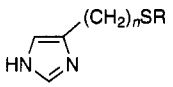
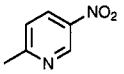
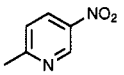


Table 4. (Imidazolylalkyl)thio heterocycles and Their Potencies as H_3-Receptor Histamine Antagonists (in Vitro on Rat Cerebral Cortex)



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 report[36] 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 (piperidinomethyl)phenoxypropyl structure of H_2-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 H_2-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 feature 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 CF_3 (**4j**) or CO_2Me (**4k**), were also found to be more active. On the other hand, the electron-releasing 5-NH_2 group (**4l**) did not affect potency.

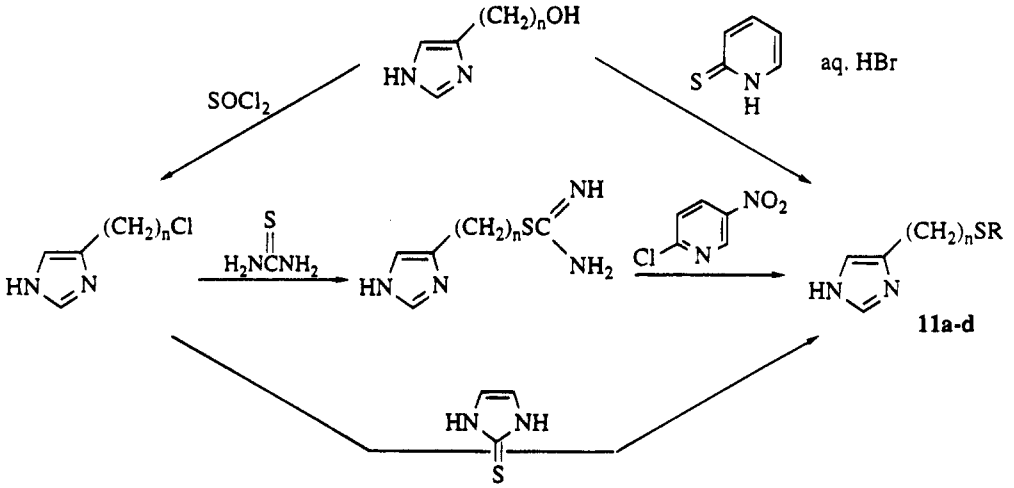
Increasing the chain length of the active 5-nitropyridine by homologation (**8a**) and then via additional −S− insertion (**8b**) (Table 2) successively reduced potency. Thus the activity pattern does not parallel that found with the thioureas **6** (Table 3).

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 suggest[21] that the unsubstituted imidazole ring is an important structural feature of compounds acting at H_3-

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

Scheme 5



receptors. Some non-imidazoles such as betahistine,[41] phencyclidine,[42] and dimaprit[43] have some activity as H_3-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 H_3-receptor.

Experimental Section

General Methods. All melting points (mp) were taken in open capillaries on an Electrothermal apparatus and are uncorrected. ^{1}H 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 Incos 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 ± 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 NH_4OH: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]-ethylamine[46] were synthesized as published. N^τ-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 iodide[47] (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 $CHCl_3$ to afford pure N^τ-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-carbomethoxypyridine, which was prepared from 6-chloronicotinic 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 $CHCl_3$ (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:Et_2O (1:1): mp 164–165 °C; yield 1.2 g, 33%. Anal. ($C_{11}H_{15}N_5 \cdot 2C_2H_2O_4 \cdot H_2O$) 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 Et_2O; recrystallized (EtOH) mp 137–138 °C. Anal. ($C_{12}H_{12}N_4S \cdot C_4H_4O_4$) 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 $CHCl_3$:MeOH (1-20%). The resulting product was converted into the dimaleate in EtOH, precipitated with Et_2O, and then recrystallized (EtOH): mp 137–138 °C; yield 0.55 g, (6%). Anal. ($C_{10}H_{12}N_4 \cdot 2.2C_4H_4O_4$) C, H, N.

2-{[2-[4(5)-Imidazolyl)ethyl]amino}-5-aminopyridine Dioxalate Monohydrate (4l). 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 Et_2O and was recrystallized from EtOH: mp 178–179 °C; yield 95%. Anal. ($C_{10}H_{13}N_5 \cdot 2C_2H_2O_4 \cdot H_2O$) 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 $CHCl_3$:MeOH (10:1). The main fraction was evaporated under reduced pressure to give the product which was crystallized from 2-PrOH:Et_2O (1:1): mp 164–165 °C; yield 61 mg (87%). Anal ($C_{10}H_{11}ClN_4 \cdot 0.2H_2O$) 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), $KHCO_3$ (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 $CHCl_3$: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: $CHCl_3$ to give **5b**: mp154–155 °C; yield 0.56 g, 57%. Anal. ($C_{14}H_{15}F_3N_4$) C, H, N.

***N*¹-[2-[4(5)-Imidazolyl]ethyl]-*N*²-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 Et_2O to give the product as a white solid: mp 138–140 °C; yield 5.50 g, 80%. Anal ($C_{12}H_{20}N_4S$) 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 $KHCO_3$ (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:$CHCl_3$ (1: 5) afforded an oil. This was converted into the dioxalate salt in EtOH (5 mL), precipitated by Et_2O (10 mL), and recrystallized from EtOH: mp 179–180 °C; yield 130 mg (9%). Anal. ($C_{12}H_{13}F_3N_4 \cdot 2C_2H_2O_4$) 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. ($C_{10}H_{11}N_3S \cdot 2HBr \cdot H_2O$) C, H, N.

2-{[4(5)-Imidazolyl]methyl]thio}-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 N_2 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 $CHCl_3$:MeOH (1–20%) to give the product: mp 155–156 °C (from 2-PrOH); yield 130 mg (4%). Anal. ($C_9H_8N_4O_2S$) 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 N_2. 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 N_2. 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 $CHCl_3$:MeOH (1–10%) to afford the product which was crystallized from 2-PrOH, to yield 75 mg (50%); mp 147–148 °C. Anal. ($C_{10}H_{10}N_4O_2S \cdot 0.25H_2O$) 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 $CHCl_3$: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: Et_2O, 10:1); yield 110 mg, 30%. Anal. ($C_8H_{10}N_4S \cdot 1.6C_2H_2O_4$) 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 (80mL), again filtered, and then diluted with Et_2O to furnish 2-(4-pyridyl)-2,2-dimethoxyethylamine (**12b**) dihydrochloride: mp 215 °C; yield 23.2 g (90%). Anal. ($C_9H_{14}N_2O_2 \cdot 2HCl$) 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: Et_2O (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 $KHCO_3$ 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. ($C_{15}H_{24}N_4S \cdot 1.3C_4H_4O_4$) C, H, N.

Acknowledgment. We thank Dr. J. M. Lecomte for a grant (to S.K.H., Y.S.K.) from Laboratoire Bioprojet, Paris, and the Commission of the European Communities for a grant from the Biomedical and Health Research Programme (CT92-1087). We also gratefully acknowledge the excellent technical assistance of Mme N. Defontaine.

References

(1) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-Inhibition of Brain Histamine Release Mediated by a Novel Class (H3) of Histamine Receptor. *Nature (London)* **1983**, *302*, 832–837.

(2) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-inhibition of Histamine Synthesis Mediated by Pre-synaptic H_3-Receptors. *Neuroscience* **1987**, *23*, 149–157.

(3) Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Körner, M. Properties and Roles of the Three Subclasses of Histamine Receptors in Brain *J. Exp. Biol.* **1986**, *124*, 203–224.

(4) Arrang, J.-M.; Devaux, B.; Chodkiewicz, J.-P.; Schwartz, J.-C. H_3-Receptors Control Histamine Release in Human Brain. *J. Neurochem.* **1988**, *51*, 105–108.

(5) Schlicker, E.; Malinowska, B.; Kathmann, M.; Göthert, M. Modulation of Neurotransmitter Release via Histamine H_3 Heteroreceptors. *Fundam. Clin. Pharmacol.* **1994**, *8*, 128–137.

(6) Clapham, J.; Kilpatrick, G. J. Histamine H_3 Receptors Modulate the Release of [^{3}H]-Acetylcholine from Slices of Rat Entorhinal Cortex: Evidence for the Possible Existence of H_3 Receptor Subtypes. *Br. J. Pharmacol.* **1992**, *107*, 919–923.

(7) (a) Smits, R. P. J. M.; Mulder, A. H. Inhibiting Effects of Histamine on the Release of Serotonin and Noradrenaline from Rat Brain Slices. *Neurochem. Int.* **1991**, *18*, 215–220. (b) Schlicker, E.; Betz, R.; Göthert, M. Histamine H_3-Receptor Mediated Inhibition of Serotonin Release in the Rat Brain Cortex. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 588–590.

(8) Schlicker, E.; Fink, K.; Detzner, J.; Göthert, M. Histamine Inhibits Dopamine Release in the Mouse Striatum via Presynaptic H_3 Receptors. *J. Neural. Transm.* [Gen. Sect.] **1993**, *93*, 1–10.

(9) Ichinose, M.; Stretton, C. D.; Schwartz, J.-C.; Barnes, P. J. Histamine H_3 Receptors Inhibit Cholinergic Neurotransmission in Guinea Pig Airways. *Br. J. Pharmacol.* **1989**, *97*, 13–15.

(10) Trzeciakowski, J. P. Inhibition of Guinea Pig Ileum Contractions Mediated by a Class of Receptor Resembling the H_3 Subtype. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 874–880.

(11) (a) Malinowska, B.; Schlicker, E. H_3 Receptor-Mediated Inhibition of the Neurogenic Vasopressor Response in Pithed Rats. *Eur. J. Pharmacol.* **1991**, *205*, 307–310. (b) Koss, M. C.; Hey, J. A. Activation of Histamine H_3 Receptors Produces Presynaptic Inhibition of Neurally Evoked Cat Nictitating Membrane Responses in vivo. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1992**, *346*, 208–212. (c) Endou, M.; Poli, E.; Levi, R. Histamine H_3-Receptor Signalling in the Heart: Possible Involvement of Gi/Go Proteins and N-type Ca^{++} Channels. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 221–229.

(12) Schwörer, H.; Katsoulis, S.; Racké, K. Histamine Inhibits 5-Hydroxytryptamine Release from the Porcine Small Intestine. Involvement of H_3 Receptors. *Gastroenterology* **1992**, *102*, 1908–1912.

(13) (a) Ichinose, M.; Barnes, P. J. Histamine H_3-Receptors Modulate Nonadrenergic Noncholinergic Neural Bronchoconstriction in Guinea-Pig in vivo. *Eur. J. Pharmacol.* **1989**, *174*, 49–55. (b) Taylor, S. J.; Kilpatrick, G. J. Characterization of Histamine-H_3 Receptors Controlling Non- Adrenergic Non-Cholinergic Contractions of the Guinea-Pig Isolated Ileum. *Br. J. Pharmacol.* **1992**, *105*, 667–674.

(14) Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E. Definition and Antagonism of Histamine H_2 Receptors. *Nature (London)* **1972**, *236*, 385–390.

(15) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. Highly Potent and Selective Ligands for Histamine H_3-Receptors. *Nature (London)* **1987**, *327*, 117–123.

(16) Garbarg, M.; Trung Tuong, M. D.; Gros, C.; Schwartz, J.-C. Effects of Histamine H_3-Receptor Ligands on Various Biochemical Indices of Histaminergic Neuron Activity in Rat Brain. *Eur. J. Pharmacol.* **1989**, *164*, 1–11.

(17) Bordi, F.; Mor, M.; Plazzi, P. V.; Silva, C.; Caretta, A.; Morini, G. HPLC Detection of Thioperamide from Biological Samples and its Determination in Rat Blood and Brain After Systemic Administration. *Farmaco* **1992**, *47*, 1093–1103.

(18) Sakurai, E.; Gunji, E.; Iizuka, Y.; Hikichi, N.; Maeyama, K.; Watanabe, T. The Disposition of Thioperamide, A Histamine H_3-Receptor Antagonist, in Rats. *J. Pharm. Pharmacol.* **1994**, *46*, 209–212.

(19) (a) Monti, J. M.; Jantos, H.; Boussard, M.; Altier, H.; Orellana, C.; Olivera, S. Effects of Selective Activation or Blockade of the Histamine H_3 Receptor on Sleep and Wakefulness. *Eur. J. Pharmacol.* **1991**, *205*, 283–287. (b) Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Pollard, H.; and Ruat, M. Histaminergic Transmission in the Mammalian Brain. *Physiol. Rev.* **1991**, *71*, 1–51. (c) Lin, J. S.; Sakai, K.; Vanni-Mercier, G.; Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C.; Jouvet, M. Involvement of Histaminergic Neurons in Arousal Mechanisms Demonstrated with H_3-Receptor Ligands in the Cat. *Brain Res.* **1990**, *523*, 325–330. (d) Sakai, N.; Onodera, K.; Maeyama, K; Yanai, K.; Watanabe, T. Effects of Thioperamide, a Histamine H_3-Receptor Antagonist, on Locomotor Activity and Brain Histamine Content in Mast Cell Deficient W/W^v Mice. *Life Sci.* **1991**, *48* 2397–2404. (e) Soe-Jensen, P.; Knigge, U.; Garbarg, M.; Kjoer, A.; Rouleau, A.; Bach, F. W.; Schwartz, J-C.; Warberg, J. Responses of Anterior Pituitary Hormones and Hypothalamic Histamine to Blockade of Histamine Synthesis and to Selective Activation or Inactivation of Presynaptic Histamine H_3 Receptors in Stressed Rats. *Neuroendocrinology*, **1993**, *57*, 532–540. (f) Yokoyama, H.; Onodera, K.; Iinuma, K.; Watanabe, T. Effect of Thioperamide, a Histamine H_3-Receptor Antagonist, on Electrically Induced Convulsions in Mice. *Eur. J. Pharmacol.* **1993**, *234*, 129–133. (g) Malmberg-Aillo, P.; Lamberti, C.; Ghelardini, C.; Giotti, A.; Bartolini, A. Role of Histamine in Rodent Antinociception. *Br. J. Pharmacol.* **1994**, *111*, 1269–1279. (h) Ookuma, K.; Sakata, T.; Fukagawa, K.; Yoshimatsu, H.; Kurokawa, M.; Machidori, H.; Fujimoto, K. Neuronal Histamine in the Hypothalamus Suppresses Food Intake in Rats. *Brain Res.* **1993**, *628*, 235–242.

(20) Bordi, F.; Mor, M.; Silva, C.; Morini, G.; Caretta, A.; Barocelli, E.; Impicciatore, M.; Plazzi, P. V. Synthesis and Binding Assays of H_3-Receptor Ligands. *Farmaco* **1992**, *47*, 1343–1365.

(21) Ganellin, C. R.; Jayes, D.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J. M.; Defontaine, M.; Schwartz, J.-C. Synthesis of Pyridyl Isosteres of Thioperamide as H_3-Receptor Histamine Antagonists. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2448–2455.

(22) Khalaf, Y. S.; Ganellin, C. R.; Tertiuk, W.; Arrang, J.-M.; Defontaine, N. Partial Structures of Thioperamide and Related H_3-Receptor Histamine Antagonists. XIXth Meeting of the European Histamine Research Society (Abstract, p38). Kuopio, May 16–20, 1990.

(23) (a) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C. M.; Lecomte, J.-M.; Robba, M.-F.; Schwartz, J.-C. (Imidazol-4-yl) pipéridines, their Preparation and their Therapeutic use. *Eur. Pat.* 0 197 840, **1986.** (b) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C. M.; Robba, M.-F.; Schwartz, J.-C. *Eur. Pat.* 0 494 010 A, 1992.

(24) Durant, G. J.; Khan, A. M. 4-(4'-Piperidinyl or 3'-Pyrrolidinyl) Substituted Imidazoles as H_3-Receptor Antagonists and Therapeutic uses thereof. PCT WO93/20061, 1993.

(25) Goto, T.; Sakashita, H.; Murakami, K.; Sugiura, M.; Kondo, T.; Fukaya, C.; Yamanouchi, K. Novel Histamine H_3-Receptor Antagonists: Synthesis and Evaluation of Formamidine and S-Methylisothiourea Derivatives. Abstr. MEDI 117, 208th ACS National Meeting, Washington, DC, August 21–25, 1994.

(26) (a) Lipp, R.; Schunack, W.; Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Synthesis and H_3-Antagonist Activity of N$^{\alpha}$-Substituted Histamine Derivatives. Xth International Symposium on Medicinal Chemistry (Abstract, p 119). Budapest, August 15–19, 1988. (b) Schlicker, E.; Kathmann, M.; Reidemeister, S.; Stark, H.; Schunack, W. Novel Histamine H_3 Receptor Antagonists: Affinities in an H_3 Receptor Binding Assay and Potencies in Two Functional H_3 Receptor Models. *Br. J. Pharmacol.* **1994**, *112*, 1043–1048. (c) Ligneau, X.; Garbarg, M.; Vizuete, M. L.; Diaz, J.; Purand, K.; Stark, H.; Schunack, W.; Schwartz, J. C.: [^{125}I]Iodoproxyfan, a New Antagonist to Label and Visualize Cerebral Histamine H_3 Receptors. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 452–459.

(27) Lipp, R.; Stark, H.; Schunack, W. Pharmacochemistry of H_3-Receptors. In *The Histamine Receptor*; Schwartz, J.-C., Haas, H., Eds.; Wiley-Liss: New York, 1992; pp 57–72.

(28) van der Goot, H.; Schepers, M. J. P.; Sterk, G. J.; Timmerman, H. Isothiourea Analogues of Histamine as Potent Agonists or Antagonists of the Histamine H_3-Receptor. *Eur. J. Med. Chem.* **1992**, *27*, 511–517.

(29) Ganellin, C. R.; Bang-Anderson, B.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Rouleau, A.; Schwartz, J.-C. Imetit and N-Methyl Derivatives. The transition from Potent Agonist to Antagonist at Histamine H_3 Receptors. *BioMed. Chem. Lett.* **1992**, *2*, 1231–1234.

(30) (a) Brimblecombe, R. W.; Duncan, W. A. M.; Walker, T. F. Toxicology of Metiamide In *International Symposium on Histamine H_2-Receptor Antagonists*; Wood, C. J., Simkins, M. A., Eds.; Smith Kine and French Laboratories: Welwyn Garden City, 1973; pp 53–70. (b) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Leslie, G. B.; Parsons, M. E. Characterization and Development of Cimetidine as a Histamine H_2-Receptor Antagonist. *Gastroenterology* **1978**, *74*, 339–347.

(31) Cooper, D. G.; Young, R. C.; Durant, G. J.; Ganellin, C. R. Histamine Receptors In *Comprehensive Medicinal Chemistry;* Emmett, J. C., Ed., Pergamon, Oxford, 1990; Vol. 3, pp 323–421.
(32) Seiler, P. Interconversion of Lipophilicities from Hydrocarbon/Water Systems into Octanol/Water Systems. *Eur. J. Med. Chem.* **1974,** *9,* 473–479.
(33) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R., Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. Development of a New Physicochemical Model for Brain Penetration and its Application to the Design of Centrally Acting H_2 Receptor Histamine Antagonists. *J. Med. Chem.* **1988,** *31,* 656–671.
(34) Schwartz, J. C.; Arrang, J. M.; Garbarg, M.; Lecomte, J. M.; Ganellin, C. R.; Fkyerat, A.; Tertiuk, W.; Schunack, W.; Lipp, R.; Stark, H.; Purand, K. French Patent 2 686 084-A1, 1993.
(35) Bordi, F.; Mor, M.; Morini, G.; Plazzi, P. V.; Silva, C.; Vitali, T.; Caretta, A. QSAR Study on H_3-Receptor Affinity of Benzothiazole Derivatives of Thioperamide. *Il Farmaco* **1994,** *49,* 153–166.
(36) Bordi, F.; Mor, M.; Morini, G.; Plazzi, P. V.; Silva, C.; Ballabeni, V.; Barocelli, E.; Caretta, A. H_3 Antagonistic imidazole derivatives Poster presentation P50, 11th National Meeting of the Medicinal Chemistry Division of the Italian Chemical Society, Bari, Italy, October 2–5, 1994.
(37) Schunack, W. Histamine-like Compounds with Cyclized Side Chains. Part 1. Structure-activity relationships for histamine analogues. *Arch. Pharm.* (Weinheim), **1973,** *306,* 934–942.
(38) Clemo, G. R.; Homles, T.; Leitch, G. C. The Synthesis of Phenyl- and Pyridyl-glyoxalines. *J. Chem. Soc.* **1938,** 753–755.
(39) La Mattina, J. L.; Suleske, R. T. (a) Use of the Neber Rearrangement for the Synthesis of α-Amino Acetals. *Synthesis* **1980,** 329–330. (b) 4-Pyridineethanamine, β,β-diethoxy. *Org. Synth.* **1985,** *64,* 19–24.
(40) Cheng, Y. C.; Prusoff, W. H. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50 per cent Inhibition (I_{50}) of the Enzymatic Reaction. *Biochem. Pharmacol.* **1973,** *22,* 3099–3108.
(41) Arrang, J. M.; Garbarg, M.; Quach, T. T.; Trung Tuong, M. D.; Yeramian, E.; Schwartz, J. C. Actions of Betahistine at Histamine Receptors in the Brain. *Eur. J. Pharmacol,* **1985,** *111,* 73–84.
(42) Arrang, J. M.; Defontaine, N; Schwartz, J. C. Phencyclidine Blocks Histamine H_3-Receptors in Rat Brain. *Eur. J. Pharmacol.* **1988,** *157,* 31–35.
(43) Schwartz, J. C.; Arrang, J. M.; Garbarg, M.; Pollard, H. A Third Histamine Receptor Subtype, Localisation and Functions of the H_3-Receptor. *Agents Actions* **1990,** *30,* 13–23.
(44) Black, J. W.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R. Isothioureas. U.K. Patent, 1,305,547, 1973.
(45) Akabori, S.; Kaneko, T. Synthesis of imidazole derivatives from α-aminoacids. III Synthesis of two higher homologues of histamine. *Bull. Chem. Soc. Jpn.* **1936,** *11,* 208–213.
(46) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. Cyanoguanidine-Thiourea Equivalence in the Development of the Histamine H_2-Receptor Antagonist, Cimetidine. *J. Med. Chem.* **1977,** *20,* 901–906.
(47) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M.; Slater, R. A. Potential Histamine H_2-Receptor Antagonists. 3. Methylhistamines. *J. Med. Chem.* **1976,** *19,* 923–928.
(48) Lipinski, C. A.; La Mattina, J. L.; Oates, P. J. Bioisosteric Prototype Design of Biaryl Imidazolyl and Triazolyl Competitive Histamine H_2-Receptor Antagonists. *J. Med. Chem.* **1986,** *29,* 2154–2163.
(49) Arrang, J. M.; Garbarg, M.; Lancelot, J. C. M.; Lecomte, J. M.; Robba, M. F.; Schwartz, J. C. (Imidazolyl-4)piperidines, their preparation and therapeutic use. *Eur. Pat.* 0 197840, 1986.
(50) (a) Abramovitch, R. A.; Smith, E. M. Pyridine-1-oxides. In *Pyridine and its Derivatives*; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Vol.14, Suppl. Part 2, pp 201–204. (b) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: London, New York, 1971; pp 434–441.

JM950192M