3806 *J. Med. Chem.* **1996,** *39,* 3806−3813

A Novel Series of (Phenoxyalkyl)imidazoles as Potent H_3-Receptor Histamine Antagonists[†]

C. Robin Ganellin,* Abdellatif Fkyerat, Benny Bang-Andersen, Salah Athmani, Wasyl Tertiuk,
Monique Garbarg,[‡] Xavier Ligneau,[§] and Jean-Charles Schwartz[‡]

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

Received February 13, 1996[⊗]

[[(4-Nitrophenyl)X]alkyl]imidazole isosteres (where X = NH, S, CH_2S, O) of previously described [[(5-nitropyrid-2-yl)X]ethyl]imidazoles (where X = NH, S) have been synthesized and evaluated for H_3-receptor histamine antagonism in vitro (K_i for [^{3}H]histamine release from rat cerebral cortex synaptosomes) and in vivo (ED_{50} per os in mice on brain *tele*-methylhistamine levels). Encouraging results led to the synthesis and testing of a novel series of substituted (phenoxyethyl)- and (phenoxypropyl)imidazoles. From the latter, 4-[3-(4-cyanophenoxy)propyl]-1*H*-imidazole (**10a**, UCL 1390; K_i = 12 nM, ED_{50} = 0.54 mg/kg) and 4-[3-[4-(trifluoromethyl)-phenoxy]propyl]-1*H*-imidazole (**10c**, UCL 1409; K_i = 14 nM, ED_{50} = 0.60 mg/kg) have been selected as potential candidates for drug development. For 16 [(aryloxy)ethyl]imidazoles the relationship between in vitro and in vivo potency is described by the equation log ED_{50} = 0.47 log K_i + 0.20 (r = 0.78).

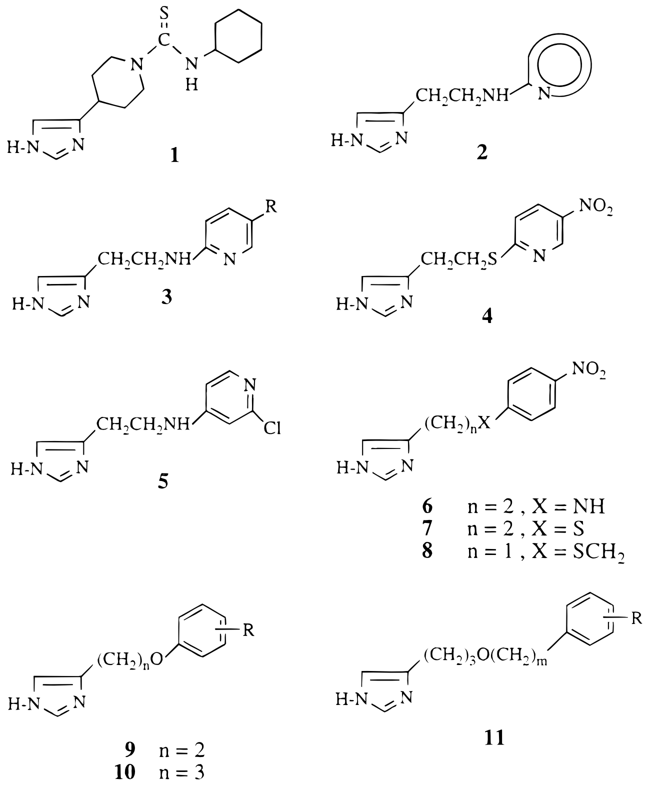
Introduction

Histamine H_3-receptors are presynaptic autoreceptors which modulate the synthesis[2] and release[3] of histamine in histaminergic neurones in the central nervous system (CNS). The H_3-receptors also appear to occur as heteroreceptors on nonhistaminergic axon terminals,[4] modulating the release of other important neurotransmitters both in the CNS and the periphery (see previous paper[5] for an extensive list of references).

The first potent and highly selective H_3-receptor histamine antagonist to be described[6] was thioperamide (**1**) (Chart 1), which has been widely used for investigation of the involvement and role of H_3-receptors in physiology. Although **1** is very potent in vitro (K_i = 4.3 nM),[6] relatively high doses are required in vivo (e.g., ED_{50} ca. 2 mg/kg ip, ca. 5 mg/kg po in rats)[7] 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.

Unfortunately, thioperamide is not suitable for human studies because of potential liver toxicity, and no H_3-antagonist is yet available for investigation of the role of H_3-receptors in humans to confirm the potential therapeutic applications for H_3-receptor histamine antagonists. 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.[8,9] Histamine H_3-receptor antagonists could also increase locomotor activity[10] and pituitary hormone[11] secretion, act as anticonvulsants[12] and antinociceptives,[13] and suppress food intake.[14]

Chart 1



We recently described[5] a structure−activity analysis of thioperamide analogues. It was demonstrated that replacement of the central piperidine ring of thioperamide by a two-methylene chain gave the cyclohexylthiourea derived from histamine which was some 50 times less active than thioperamide.[15] We demonstrated that in such structures derived from histamine it was possible to replace the cyclohexylthioureido group by an aminoheterocycle (**2**) (Chart 1) with retention of activity. It was also shown that introducing an electron-withdrawing group into the heterocycle, e.g., nitropyridyl or (trifluoromethyl)pyridyl (**3**, R = NO_2 or CF_3),

---

[†] Presented in part at the 13th International Meeting on Medicinal Chemistry, Paris, France, September 21, 1994, and at the 2nd European Congress of Pharmaceutical Sciences,[1] Berlin, Germany, September 30, 1994.

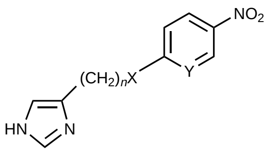
[‡] Centre Paul Broca de l'INSERM.

[§] Laboratoire Bioprojet.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

S0022-2623(96)00138-0 CCC: $12.00

Table 1. [[(5(4)-Nitrophenyl)X]alkyl]imidazoles and Their Potencies as H_3-Receptor Histamine Antagonists (K_i in Vitro for [^{3}H]Histamine Release from Rat Cerebral Cortex Synaptosomes, and ED_{50} in Vivo in Mice for Effect on Brain *tele*-Methylhistamine Levels)



no.	*n*	X	Y	$K_i \pm$ SEM (nM)	$ED_{50} \pm$ SEM (mg/kg)[a]
1	thioperamide			4 ± 1[b]	1.0 ± 0.5
3	2	NH	N	29 ± 11[c]	nd[d]
4	2	S	N	4.8 ± 0.9[c]	2.6 ± 1.0
6	2	NH	CH	23 ± 9	10.7 ± 2.8
7	2	S	CH	9 ± 3	2.7 ± 0.7
8	1	SCH_2	CH	313 ± 58	≥10
9a	2	O	CH	35 ± 6	0.66 ± 0.11

[a] Calculated as the base. [b] Reference 6. [c] Reference 5. [d] Not determined.

enhanced potency. Furthermore, replacing the amino group attached to nitropyridine by thio gave a compound (**4**, UCL 1199) which is as active in vitro as thioperamide. Although it was hoped that **4** would penetrate the CNS more readily than thioperamide (since it has one less N-H group) it was subsequently found to actually be less active than thioperamide in vivo in the mouse (Table 1).

In structure **2** the side chain is attached through an amino group to the 2-position of pyridine (or other heterocycle), maintaining the 1,3 relationship of nitrogen atoms (N−C−N) that exists in thiourea. One compound (**5**), however, had the side chain attached to the pyridine 4-position and yet was active (K_i = 160 nM), indicating that antagonists do not have to necessarily retain the N−C−N relationship. This result established a precedent for replacing =N by =CH, and it therefore seemed worthwhile to replace the pyridine ring by phenyl. In pursuance of this idea, 4-[(4-nitrophenyl)heteroalkyl]-1*H*-imidazole isosteres (**6**−**8**) of compounds **3** and **4** were synthesized, and this was followed by a series[16] of substituted (phenoxyethyl)imidazoles (**9**). The compounds have been tested for antagonism of histamine inhibition of histamine release in vitro from rat cerebral cortex synaptosomes (see below) and in vivo in mice for their effect on the levels of the histamine catabolite, *tele*-methylhistamine, in the brain. The results are reported herein.

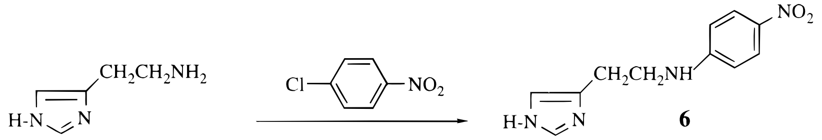
Chemistry

N^α-(4-Nitrophenyl)histamine (**6**) was synthesized from histamine and 4-chloronitrobenzene (Scheme 1). 4-[2-[(4-Nitrophenyl)thio]ethyl]-1*H*-imidazole (**7**) was prepared from 4-(2-chloroethyl)-1*H*-imidazole[17] and sodium 4-nitrophenylthiolate in dry DMF (Scheme 2). 4-[[[(4-Nitrophenyl)methyl]thio]methyl]-1*H*-imidazole (**8**) was synthesized from *S*-(imidazol-4-ylmethyl)isothiourea[18] by displacement with 4-nitrobenzyl chloride (Scheme 3).

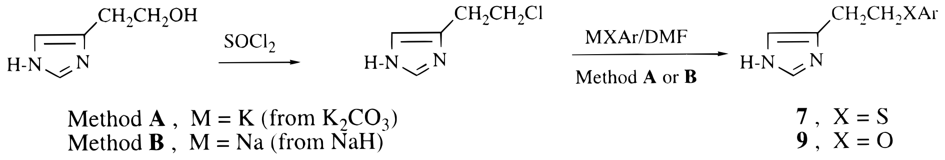
Most of the substituted phenoxyethylimidazoles (**9**) were prepared in a Williamson synthesis (Scheme 2) from 4-(2-chloroethyl)-1*H*-imidazole and the appropriate phenoxide (generated with K_2CO_3 (method A) or NaH (method B)) in dry DMF as indicated in Table 2. These alkylation methods were not always satisfactory, however, and to obtain a more reproducible procedure it was necessary to protect the imidazole ring. This was effected in two ways, either by using trityl (triphenylmethyl) as for compounds **9p**, **r** (Scheme 5) or by using *N*,*N*-dimethylsulfamoyl (Scheme 6) exemplified by **9l**. Both routes involve a Mitsunobu type coupling[19] between the N-protected 4(or 5)-(2-hydroxyethyl)imidazole and the appropriate substituted phenol using triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF (Scheme 5). The trityl or sulfamoyl groups were subsequently cleaved off using aqueous HCl in hot THF.

The requisite 1-(triphenylmethyl)-4-(2 hydroxyethyl)imidazole was obtained by tritylation of 4-(2-hydroxy-

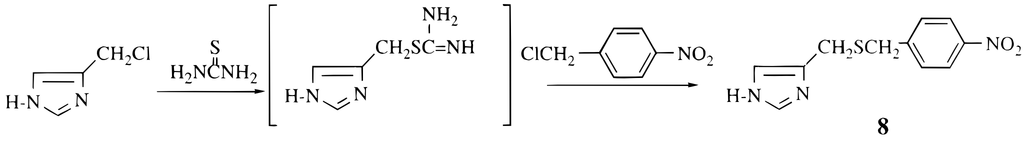
Scheme 1



Scheme 2



Scheme 3



Scheme 4

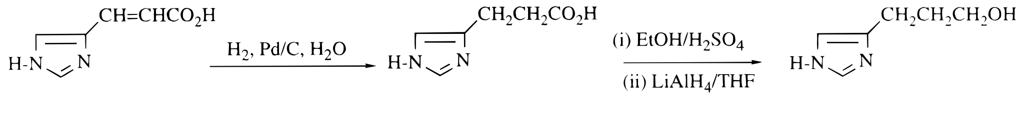
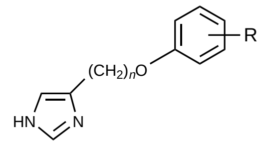


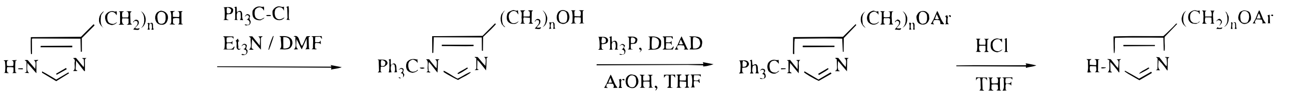
Table 2. Aryloxyalkylimidazoles and Their Potencies as H_3-Receptor Histamine Antagonists (K_i in Vitro for [^{3}H]Histamine Release from Rat Cerebral Cortex Synaptosomes and ED_{50} in Vivo in Mice for Effect on Brain *tele*-Methylhistamine Levels) and Physical Data



no.	R	K_i ± SEM (nM)	ED_{50} ± SEM (mg/kg)[a]	formula[b]	mp (°C)	crystn solvent	synth scheme
n = 2							
9a	4-NO_2	35 ± 6	0.66 ± 0.11	$C_{11}H_{11}N_3O_3$	197−200	MeOH	2A
9b	3-NO_2	12 ± 2	0.9 ± 0.4	$C_{11}H_{11}N_3O_3 \cdot 0.75C_2H_2O_4$	174−178	EtOH	2B
9c	4-CN	9 ± 5	1.2 ± 0.3	$C_{12}H_{11}N_3O$	181−183	H_2O:MeOH[c]	2A
9d	3-CN	39 ± 6	2.9 ± 2.0	$C_{12}H_{11}N_3O \cdot C_2H_2O_4$	189−190	EtOH:Et_2O[d]	2B
9e	2-CN	483 ± 95	≥10	$C_{12}H_{11}N_3O \cdot 0.95C_2H_2O_4$	170−171	EtOH:Et_2O[d]	2B
9f	4-CO_2Me	5.1 ± 1.7	>>3	$C_{13}H_{14}N_2O_3 \cdot CF_3CO_2H \cdot 0.3H_2O$	116−118	H_2O	2A
9g	4-CO_2Et	6 ± 1	>10	$C_{14}H_{16}N_2O_3 \cdot 0.8C_2H_2O_4$	160−162	2-PrOH:Et_2O	2A
9h	4-COMe	23 ± 5	3.2 ± 1.4	$C_{13}H_{14}N_2O_2 \cdot C_2H_2O_4$	178−182	MeOH:Et_2O[e]	2A
9i	4-COEt	3.7 ± 0.6	0.95 ± 0.08	$C_{14}H_{16}N_2O_2 \cdot 0.9C_2H_2O_4$	185−187	2-PrOH:Et_2O	5
9j	4-COPh	54 ± 13	2.6 ± 0.5	$C_{18}H_{16}N_2O_2 \cdot 1.3C_2H_2O_4$	193−194	MeOH:Et_2O[d]	2B
9k	4-CON(CH_2)$_5$[f]	338 ± 135	>10	$C_{17}H_{21}N_3O_2 \cdot 1.3C_2H_2O_4$	130−131	EtOH:Et_2O[g]	2B
9l	4-Cl	21 ± 3	0.78 ± 0.21	$C_{11}H_{11}ClN_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$	197−199	2-PrOH	6
9m	3,5-Cl_2	>500	>10	$C_{11}H_{10}Cl_2N_2O \cdot CF_3CO_2H$	115−116	*h*	2B
9n	4-Br	24 ± 10	2.9 ± 0.5	$C_{11}H_{11}BrN_2O \cdot 1.1C_2H_2O_4$	162−165	EtOH:Et_2O	2B
9o	2,3,4,5,6-F_5	>500	~10	$C_{11}H_7F_5N_2O \cdot 1.2C_2H_2O_4 \cdot 0.2H_2O$	163−164	EtOH:Et_2O[d]	2B
9p	4-CF_3	68 ± 18	>10	$C_{12}H_{11}F_3N_2O$	105−109	H_2O	5
9q	4-OMe	38 ± 12	2.9 ± 1.5	$C_{12}H_{14}N_2O_2 \cdot 0.85C_2H_2O_4$	178−181	EtOH	2B
9r	4-Me	56 ± 23	2.3 ± 0.7	$C_{12}H_{14}N_2O \cdot 0.8C_2H_2O_4$	188−189	2-PrOH:Et_2O	5
9s	4-Et	80 ± 16	>10	$C_{13}H_{16}N_2O \cdot 0.85C_2H_2O_4$	178	EtOH:Et_2O	2B
9t	4-Pr	19 ± 9	1.6 ± 0.6	$C_{14}H_{18}N_2O \cdot 1.1C_2H_2O_4$	168−171	EtOH:Et_2O	2B
9u	3,4-C_4H_4[i]	90 ± 27	1.5 ± 0.4	$C_{15}H_{14}N_2O \cdot 0.1H_2O$	157−158[j]	H_2O:MeOH[g]	2B
9v	2,3-C_4H_4[k]	137 ± 20	3.4 ± 1.1	$C_{15}H_{14}N_2O \cdot 0.75C_2H_2O_4$	187−189	EtOH	2B
n = 3							
10a	4-CN	12 ± 3	0.54 ± 0.23	$C_{13}H_{13}N_3O \cdot 0.1H_2O$	194−195	EtOH:Et_2O	5
10b	4-F	11 ± 2	4.9 ± 1.1	$C_{12}H_{13}FN_2O \cdot 0.07CHCl_3$	135−137	$CHCl_3$	5
10c	4-CF_3	14 ± 6	0.6 ± 0.2	$C_{13}H_{13}F_3N_2O \cdot 1.1C_2H_2O_4$	201−204	EtOH:Et_2O	5

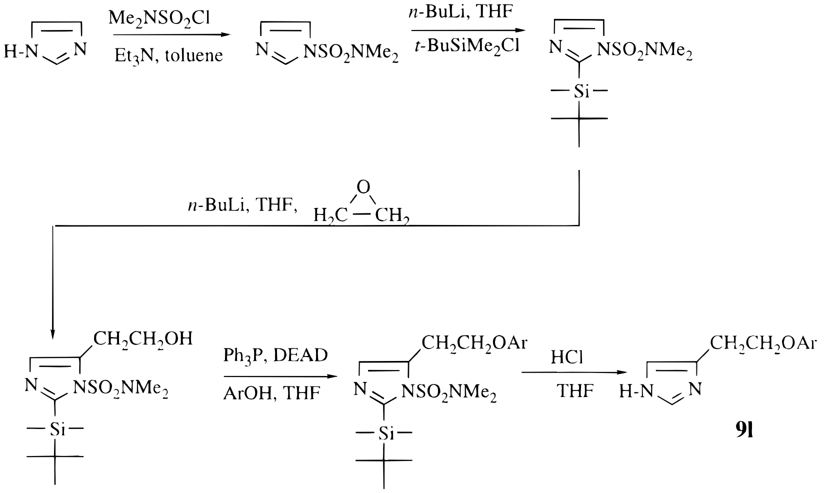
[a] Calculated as the base. [b] $C_2H_2O_4$ = oxalic acid. [c] 1:3. [d] 2:1. [e] 10:1. [f] Piperidinyl. [g] 1:2. [h] Purified by preparative HPLC. [i] *β*-Naphthyl. [j] Lit.[28] mp 151−152 °C. [k] α-Naphthyl.

Scheme 5



9, n = 2
10, n = 3

Scheme 6



ethyl)-1*H*-imidazole (Scheme 5), the latter being synthesized by the published method.[20] As an alternative, which directly furnished the protected (hydroxyethyl)-imidazole, 1-(*N*,*N*-dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole[21] was lithiated and treated with ethylene oxide (Scheme 6).

The Williamson synthesis was not successful when applied to the higher homologues **10** since the requisite

4-(3-chloropropyl)-1*H*-imidazole[23] underwent intramolecular cyclization under the conditions of the reaction. Instead, the (phenoxypropyl)imidazoles (**10**) were prepared using the trityl-protected imidazole derivative 1-(triphenylmethyl)-4-(3-hydroxypropyl)imidazole in a Mitsunobu type synthesis (Scheme 5). 1-(Triphenylmethyl)-4-(3-hydroxypropyl)imidazole was synthesized from the commercially available urocanic acid (Scheme 4) via hydrogenation,[22] followed by esterification with ethanol in sulfuric acid, then reduction with $LiAlH_4$ to 4-(3-hydroxypropyl)-1*H*-imidazole,[23] and finally tritylation (Scheme 5).

Pharmacology

In Vitro. 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 $[^3H]$histamine from synaptosomes of rat cerebral cortex.

Rats were killed by decapitation, and synaptosomes were obtained from the cerebral cortex, washed, and resuspended in modified Krebs-Ringer's bicarbonate medium. The synaptosomes were allowed to synthesize $[^3H]$histamine during a 30 min incubation at 37 °C in the presence of $(3-4) \times 10^{-7}$ M L-$[^3H]$histidine, and then they were washed to remove excess $[^3H]$histidine and to obtain a constant spontaneous $[^3H]$histamine efflux, as described.[3] Synaptosomes were incubated for 2 min with 30 mM K^+. Unlabeled 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 by liquid scintillation counting of the supernatant liquid after isolation by ion-exchange chromatography on Amberlite CG 50 columns.[3]

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.[24] 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,[25] $K_i = IC_{50}/(1 + S/EC_{50})$, where S represents the concentration of exogenous histamine (1 μM) and EC_{50} represents the histamine concentration (62 nM) eliciting a half-maximal inhibitory effect on K^+-evoked release of $[^3H]$histamine.

In Vivo. The compounds were tested in vivo by administration as the salt form indicated in Table 2 as a suspension in 1% methylcellulose per os to groups of at least six male Swiss mice (weighing 18−22 g) as described by Garbarg et al.[26] The compounds were first given at 10 mg/kg (calculated as free base), and then further doses were selected based on the initial results. The brain histamine turnover was determined by measuring the level of the main metabolite of histamine, *tele*-methylhistamine. Mice were fasted for 24 h before po treatment, and 90 min after treatment, animals were decapitated and the cerebral cortex was dissected out. The cortex was homogenized in 10 volumes of ice-cold perchloric acid (0.4 M). The *tele*-methylhistamine level was measured by a radioimmunoassay described by Garbarg et al.[27] Treatment with 10 mg/kg thioperamide furnished the maximal *tele*-methylhistamine level for comparison with the level reached after the administered drug, and the ED_{50} value was calculated.[24]

Results and Discussion

The *N*-(4-nitrophenyl)histamine analogue **6** is active (Table 1) as an H_3-receptor histamine antagonist in vitro ($K_i = 23 \pm 9$ nM) and is not significantly different from the corresponding pyridyl derivative *N*-(5-nitropyrid-2-yl)histamine **3** (R = NO_2) ($K_i = 29 \pm 11$ nM).[5] This finding establishes that it is not necessary to retain a heterocycle for activity in the structural type represented by **3**. This is also the case for the nitropyridyl thioether **4** ($K_i = 4.8 \pm 0.9$ nM) in which the corresponding nitrophenyl thioether **7** ($K_i = 9 \pm 3$ nM) is slightly less active as an H_3 antagonist in vitro but is equiactive in vivo. The isomer **8**, in which the S and CH_2 groups attached to the benzene ring are interchanged, is, by contrast, some 30-fold less active ($K_i = 313 \pm 58$ nM) than **7** in vitro and also less active in vivo ($ED_{50} \geq 10$ mg/kg).

These results encouraged us to investigate the corresponding oxygen isostere, 4-[2-(4-nitrophenoxy)ethyl]-1*H*-imidazole, **9a**. This compound was found to be somewhat less active than **7** in vitro ($K_i = 35 \pm 6$ nM), but it is actually as active as thioperamide **1** in vivo ($ED_{50} = 0.66 \pm 0.11$ mg/kg). This last result led us to explore a series of phenoxy compounds in which the effects of a variety of substituents have been examined.

Other electron-withdrawing groups in the 4-position of structure **9**, such as R = CN, CF_3, COR′, and halogen, give compounds whose activities are in the range K_i = 3.7−68 nM, except for the piperidine amide **9k**. The position of substitution has been investigated. There is not a large difference between 3- and 4-substituted compounds (e.g., R = NO_2 or CN, **9b**,**d**). On the other hand a 2-CN-substituted compound **9e** is approximately 50-fold less active than the 4-CN derivative **9c**, and the presence of two substituents, as in the 3,5-dichloro analogue **9m**, also appears to be deleterious for activity.

With the published[5] aminopyridine series **3**, electron-withdrawing substituents R appeared to be much better for activity than electron-releasing groups. In the present phenoxy series, electron-releasing groups (R = OMe, Me, Et, Pr) also give active compounds (**9q**−**t**) (K_i = 19−80 nM). The β-naphthyloxy compound **9u** has previously been investigated for histamine-like effects (H_1 receptor) and was described as having a "momentary spasmodic effect" on the isolated guinea pig ileum.[28] The substituent effects in the 4-position span 2 orders of magnitude in potency in vitro (K_i = 3.7−338 nM), but attempts to obtain meaningful multiparameter correlations between physicochemical properties and antagonist potencies have not been successful.

There is a wide divergence between some of the in vitro and in vivo potencies. The esters **9f** and **9g** which are very active in vitro are not active in vivo, but this probably reflects hydrolysis in vivo to the corresponding acid. Some compounds were not sufficiently active in vivo for an ED_{50} to be determined. For the other 16 active compounds (where $n = 2$), a trend is apparent between K_i and ED_{50} values, shown in Figure 1. The equation $\log ED_{50} = 0.47 \log K_i + 0.20$ ($n = 16$, $r = 0.78$) obtained by regression analysis describes this relationship. The compounds constitute a chemically homogeneous set since they are all imidazolylethoxy derivatives which only vary by the substituent in the phenoxy ring. In general, compounds with low K_i values are the most active in vivo, but there is quite a spread of results. The

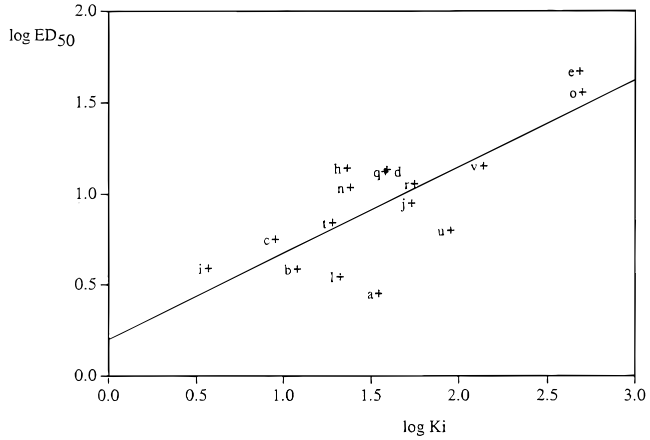


Figure 1. Correlation of oral activity log ED_{50} (μmol/kg) on brain *tele*-methylhistamine levels in mice with in vitro log K_i (nM) on rat cerebral cortex synaptosomes for 16 [(aryloxy)ethyl]imidazoles **9a−e,h−j,l,n,o,q,r,t−v**.

reliability for prediction is not good, however, because the ED_{50} values only span 1 order of magnitude although the K_i values extend over 2 orders.

Analysis of the in vivo data is complex. The compounds are administered perorally, and activity will be affected by their ability to be absorbed and by their biodistribution properties. Included in this is the requirement for the compounds to cross the blood−brain barrier to enter the brain. In this connection, these phenoxy compounds should have a distinct advantage for brain penetration over the previous heterocyclic arylamines since they are less polar and have a lower propensity for hydrogen bonding, factors which are believed to be very important for encouraging brain penetration.[29,30]

Higher homologues, **10a−c**, are also active $K_i \sim 11-14$ nM (Table 2), and two of these have ED_{50}'s 0.5−0.6 mg/kg. Indeed **10a** (UCL 1390, R = 4-CN) and **10c** (UCL 1409, R = 4-CF_3) have been selected for further study as potential candidates for drug development. Compound **10a** appears to be relatively selective for H_3 receptors; in a range of binding assays it was found to have no significant affinity at 10^{-5} M for A_1, β_1, β_2, AT_1, benzodiazepine, D_1, D_2, NMDA, and 5-HT_{1A} receptors or Ca L-channels. It produced <50% inhibition at 10^{-5} M on α_1, M, and opiate receptors but had somewhat more affinity (<50% at 10^{-6} M) at H_1 and (<50% at 10^{-7} M) at α_2 receptors.

Subsequent to this work, homologous *aliphatic* ethers [[(aralkyloxy)propyl]imidazoles, **11**] have been described[31] as H_3-receptor histamine antagonists, the most important of which is the new radiochemically labeled ligand iodoproxyfan[32] (**11**, $m = 1$, R = 4-I) which has $K_i = 5$ nM.

Experimental Section

General Methods. 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) or VXR-400 (400 MHz) spectrometer, and chemical shifts (ppm) are reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm and DMSO in DMSO-d_6 at 2.49 ppm) or relative to TMS. Signals are designated as follows: s, singlet; s_{br}, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; quint, quintet; m, multiplet. Mass spectra were recorded by Dr. M. Mruzek 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. T. 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. Column chromatography was conducted using Merck silica gel 60 (particle size 0.063−0.200 mm).

Starting Materials. Histamine dihydrochloride, 4-(hydroxymethyl)-1*H*-imidazole hydrochloride, and the appropriate substituted phenols were from Aldrich Chemical Co. except for *N*-(*p*-hydroxybenzoyl)piperidine which was synthesized from *p*-hydroxybenzoic acid using acetyl as a protecting group (Scheme 7).

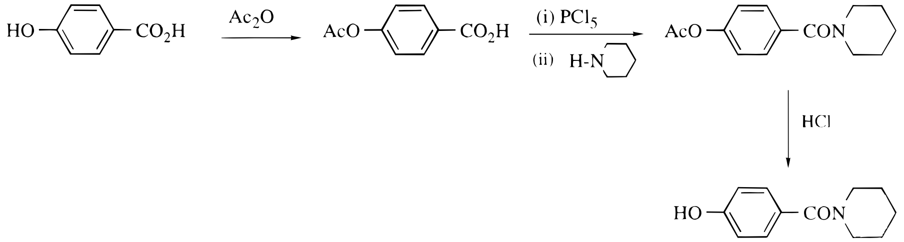
N^{α}-(4-Nitrophenyl)histamine Oxalate (6). Histamine base was liberated from the dihydrochloride with NaOEt in EtOH by heating under reflux for 1 h, filtering, and evaporating under reduced pressure. The residue was suspended in 2-PrOH and filtered hot, and the extract was evaporated to yield histamine. Histamine (1.46 g, 13 mmol), 1-chloro-4-nitrobenzene (2.06 g, 13 mmol), and K_2CO_3 were heated with stirring under reflux in 2-PrOH (10 mL). The mixture was filtered and concentrated under reduced pressure, and the resulting solid residue was chromatographed on silica gel eluted with $CHCl_3$ and MeOH (1:10). The purified product was dissolved in the minimum amount of 2-PrOH (10 mL), cooled, and filtered from silica. The filtrate was then evaporated under reduced pressure to afford a solid: mp 165−168 °C; yield 0.85 g, 28%. The product was converted into the oxalate salt in EtOH followed by addition of ether and then recrystallized from EtOH:$CHCl_3$ (10:1) to yield yellow needles: mp 185−186 °C; UV (MeOH) λ_{max} (nm) (log ϵ_{max}) 380 (4.25); ^1H NMR (200 MHz, DMSO-d_6 + D_2O) δ 8.66 (s, 1H, Im-2), 8.07 (d, $J = 7$ Hz, 2H, Ph), 7.32 (s, 1H, Im-4(5)), 6.54 (d, $J = 7$ Hz, 2H, Ph), 3.53 (t, 2H, CH_2NH), 2.97 (t, 2H, $ImCH_2$). Anal. ($C_{11}H_{12}N_4O_2$, $1.25C_2H_2O_4$) H, N; C: found, 46.4; calcd, 47.0.

4-[2-[(4-Nitrophenyl)thio]ethyl]-1H-imidazole (7). 4-Nitrothiophenol (1.86 g, 12 mmol) in DMF (10 mL) was stirred with NaH (200 mg of 60% in paraffin oil, 5 mmol) at 20 °C for 1 h under N_2, and then 4-(2-chloroethyl)-1*H*-imidazole hydrochloride[17] (200 mg, 1.2 mmol) and Bu_4NI (catalytic amount) were added. The mixture was heated at 80 °C for 1 d, and the solvent was then evaporated under reduced pressure. The resulting residue was stirred in Et_2O, filtered, and extracted with dilute HCl. The aqueous extract was basified with K_2CO_3, and the product was extracted into $CHCl_3$ and then crystallized from EtOH: mp 167−168 °C (yield 135 mg, 45%); ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (m, 2H, Ph-3,5H), 7.55 (s, 1H, Im-2H), 7.49 (m, 2H, Ph-2,6H), 6.87 (s, 1H, Im-4(5)H), 3.35 (t, 2H, CH_2O), 2.85 (t, 2H, Im-CH_2). Anal. ($C_{11}H_{11}N_3O_2S$) C, H, N.

4-[[(4-Nitrobenzyl)thio]methyl]-1*H*-imidazole (8). A mixture of 4-(chloromethyl)-1*H*-imidazole hydrochloride[33] (1.53 g, 10 mmol) and thiourea (0.76 g, 10 mmol) was heated in EtOH (10 mL) under reflux for 15 min. EtOH (5 mL), H_2O (20 mL), and 4-nitrobenzyl chloride (200 mg, 1.16 mmol) were added, and the mixture was cooled to 0−10 °C. A solution of NaOH (1.44 g, 36 mmol) in H_2O (14 mL) was added dropwise under N_2 at 0−10 °C, followed by stirring for 1 h at the same temperature and for an additional 3 h at 20 °C. The precipitate was collected and washed (H_2O) to afford the title compound: mp 88 °C; yield 190 mg, 65%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, Ph-3,5H), 7.56 (s, 1H Im-2H), 7.40 (d, 2H, Ph-2,6H), 6.85 (s, 1H, Im-4(5)H), 3.69 (t, 2H, Im-CH_2), 3.56 (t, 2H, CH_2). Anal. ($C_{11}H_{11}N_3O_2S$) C, H, N.

Synthesis of Compounds 9a−v. The compounds were synthesized according to the schemes and methods indicated

Scheme 7



in Table 2. The conditions for these procedures are exemplified below with compounds **9a** (Scheme 2, method A), **9k** (Scheme 2, method B), **9l** (Scheme 6), and **9p** (Scheme 5).

4-[2-(4-Nitrophenoxy)ethyl]-1*H*-imidazole (9a) (Method A). 4-Nitrophenol (209 mg, 1.5 mmol), 4-(2-chloroethyl)-1*H*-imidazole hydrochloride (251 mg, 1.4 mmol), K_2CO_3 (475 mg, 3 mmol), and NaI (catalyst) were stirred at 80 °C for 5 d in DMF (5 mL). The reaction mixture was cooled, diluted with Et_2O (100 mL), and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was subjected to column chromatography on silica gel (first eluant $CHCl_3$ and second eluant $CHCl_3$:MeOH, 9:1) to give the product which, after crystallization (MeOH), had the following properties: mp 197-200 °C; yield 350 mg, 33%; ^1H NMR (200 MHz, DMSO-d_6) δ 11.83 (s, 1H, NH), 8.16 (d, 2H, Ph-3,5H), 7.64 (s, 1H, Im-2H), 7.13 (d, 2H, Ph-2,6H), 6.94 (s, 1H, Im-4(5)H), 4.28 (t, 2H, CH_2O), 2.48 (t, 2H, Im-CH_2).

4-[2-[4-(1-Piperidinylcarbonyl)phenoxy]ethyl]-1*H*-imidazole Oxalate (9k) (Method B). A suspension of 4-hydroxybenzoic acid (35 g, 0.25 mol) was heated in Ac_2O (46.2 mL) under reflux for 6 h. The Ac_2O was evaporated, and the resulting residue was triturated in Et_2O, filtered, and washed with Et_2O to give 4-acetoxybenzoic acid as a white solid (33.6 g, 75%) (lit.[34] mp 189 °C): ^1H NMR (200 MHz, $CDCl_3$) δ 9.50 (s, 1H, COOH), 8.20 (d, 2H, Ph-3,5H), 7.25 (d, 2H, Ph-2,6H), 2.30 (s, 3H, CH_3).

A mixture of 4-acetoxybenzoic acid (33.6 g, 0.19 mol) and PCl_5 (39.1 g, 0.19 mol) in Et_2O (250 mL) was stirred at 20 °C for 2 h. The solvent and phosphorus oxychloride were then evaporated off, and the residue was dried in vacuo and washed with dry Et_2O to give 4-acetoxybenzoyl chloride (26.3 g, 71%): ^1H NMR (200 MHz, DMSO-d_6) δ 8.20 (d, 2H, Ph-3,5H), 7.25 (d, 2H, Ph-2,6H), 2.20 (s, 3H, CH_3).

4-Acetoxybenzoyl chloride (1.7 g, 8.6 mmol) was added to a solution of piperidine (1.40 g, 18 mmol) in water (5 mL) at 15−25 °C. The mixture was stirred for 2 h, treated with 2 N NaOH (45 mL), stirred for 2 h, acidified at 0 °C with dilute HCl, and stirred for 2 h. The resulting white precipitate of 1-(4-hydroxybenzoyl)piperidine was collected and washed twice with water and had the following properties: mp 215−217 °C (lit.[35] mp 210 °C); yield 1.33 g, 76%; IR ν (cm^{-1}) 3100 (br, OH), 1680 (s, C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 7.14 (d, 2H, Ph-3,5H), 6.70 (s, 2H, Ph-2,6H), 3.40 (m, 4H, NCH_2), 1.48 (m, 6H, CCH_2C).

To 1-(4-hydroxybenzoyl)piperidine (1.23 g, 6 mmol) in dry DMF (10 mL) was added NaH (60% in paraffin oil, 200 mg, 5 mmol). The mixture was stirred at 20 °C for 1 h under N_2, and then 4-(2-chloroethyl)-1*H*-imidazole hydrochloride (200 mg, 1.20 mmol) and Bu_4NI (catalytic amount) were added. The mixture was heated at 100 °C for 2 d, and the solvent was then evaporated under reduced pressure. The oily residue was stirred in Et_2O and filtered. The excess of 1-(4-hydroxybenzoyl)piperidine was extracted in Et_2O under acidic conditions (dilute HCl). The aqueous solution was basified with K_2CO_3 and extracted with $CHCl_3$. The extract was evaporated, and the resulting residue was subjected to chromatography on a silica gel column (first eluant $CHCl_3$, second eluant $CHCl_3$:MeOH, 95:5). The resulting product was converted into the oxalate and recrystallized from EtOH:Et_2O (1:2): mp 130−131 °C; yield 35 mg, 29%; ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, 1H, Im-2H), 7.31 (d, 2H, Ph-3,5H), 7.25 (d, 1H, Im-4(5)H), 6.99 (d, 2H, Ph-2,6H), 4.24 (t, 2H, O-CH_2), 3.46 (m, 4H, piperidine-2,6H), 3.05 (t, 2H, Im-CH_2), 1.60 (m, 6H, piperidine-3,4,5H).

4-[2-(4-Chlorophenoxy)ethyl]-1*H*-imidazole Oxalate (9l). 1-(*N*,*N*-Dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole[21] (2 g, 6.92 mmol) in dry THF (20 mL) was cooled to −78 °C under N_2, and a solution of *n*-butyllithium (1.5 M in hexane) (6 mL, 9 mmol) was added slowly by syringe. The mixture was stirred at −78 °C for 30 min, and then a solution of ethylene oxide (1.52 g, 34 mmol, 5 equiv) in dry THF (10 mL) was added at 0 °C. The mixture was stirred at 20 °C for 16 h, then poured into cold water (20 mL), and evaporated under reduced pressure. The product was extracted into CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which was purified by column chromatography (Et_2O:petroleum ether, 1:1) to afford 1-(*N*,*N*-dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-4-(2-hydroxyethyl)imidazole (1.2 g, 52%): mp 133−134 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, Im-4H), 3.90 (t, 2H, CH_2O), 3.01 (t, 2H, Im-CH_2), 2.99 (s, 6H, $N(CH_3)_2$), 0.99 (s, 9H, $C(CH_3)_3$), 0.76 (s, 6H, $Si(CH_3)_2$).

To the above carbinol (0.70 g, 2.10 mmol) in freshly distilled THF (10 mL) were added triphenylphosphine (0.82 g, 3.15 mmol) and 4-chlorophenol (0.27 g, 2.10 mmol), and the mixture was cooled and stirred for 5 min under N_2. Diethyl azodicarboxylate (0.55 g, 3.15 mmol), in freshly distilled THF (6 mL), was added slowly, and stirring was continued at 20 °C for 16 h. The solvent was then removed in vacuo, and the residue was chromatographed on a column (EtOAc:hexane, 1:2) to give 1-(*N*,*N*-dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-[2-(4-chlorophenoxy)ethyl]imidazole as an oil (0.3 g, 32%). The latter (0.3 g, 0.675 mmol) in THF (10 mL) and 2 N HCl (10 mL) was heated at 80 °C for 5 h. The THF was removed under reduced pressure, and the resulting mixture was washed (Et_2O), basified (K_2CO_3), and extracted with $CHCl_3$. The extract was dried and evaporated, and the resulting product was purified by column chromatography (EtOAc:MeOH, 5:1). The resulting oil (0.1 g, 0.35 mmol) was dissolved in 2-PrOH (4 mL) and treated with oxalic acid (1.5 equiv) in 2-PrOH (3 mL), cooled, and diluted with Et_2O to give the product, as oxalate, which was collected by filtration and crystallized from EtOH: yield 0.044 g, 32%; mp 197−199 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H, Im-2H), 7.32 (d, 2H, Ph-H), 7.20 (d, 2H, Ph-H), 6.98 (d, 1H, Im-4(5)H), 4.18 (t, CH_2O), 3.03 (t, 2H, Im-CH_2).

4-[2-[4-(Trifluoromethyl)phenoxy]ethyl]-1*H*-imidazole (9p). A solution of 4-(2-hydroxyethyl)-1*H*-imidazole hydrochloride[20] (0.5 g, 4.46 mmol) and dry triethylamine (1.25 mL, 9 mmol) in DMF (10 mL) was treated with triphenylmethyl chloride (1.24 g, 4.46 mmol) in DMF (5 mL) under N_2. The reaction mixture was stirred at 20 °C for 2 h and then poured onto crushed ice (50 g). The resulting solid was collected by filtration, washed (H_2O × 3), and crystallized (EtOH:Et_2O) to afford 1-(triphenylmethyl)-4-(2-hydroxyethyl)imidazole: yield 1.10 g, 69%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.12 (m, 16H, Im-2H and Ph_3C), 6.60 (s, 1H, Im-5H), 3.90 (t, 2H, CH_2-O), 3.70 (s, 1H, OH), 2.75 (t, 2H, Im-CH_2).

To 1-(triphenylmethyl)-4-(2-hydroxyethyl)imidazole (708 mg, 2 mmol) under N_2 was added freshly distilled THF (15 mL), 4-(trifluoromethyl)phenol (340 mg, 2.1 mmol), and triphenylphosphine (550 mg, 2.1 mmol). The resulting mixture was cooled and stirred for 5 min, and then diethyl azodicarboxylate (366 mg, 2.1 mmol) in THF (10 mL) was slowly added; stirring was continued at 20 °C for 2 h under N_2. The solvent was then evaporated under reduced pressure, and the resulting residue was subjected to chromatography on a silica gel column using Et_2O as an eluant to give 1-(triphenylmethyl)-4-[2-[4-

(trifluoromethyl)phenoxy]ethyl]imidazole which was recrystallized from water: yield 0.75 g, 75%. A solution of 1-(triphenylmethyl)-4-[2-[4-(trifluoromethyl)phenoxy]ethyl]imidazole (640 mg, 1.28 mmol) in THF (2 mL) and 2 N HCl (5 mL) was heated at 70 °C during 2 h. The THF was then evaporated off under reduced pressure, the resulting residue was washed (Et_2O) and basified (K_2CO_3), and the resulting white solid was filtered off and washed (H_2O × 3) to give 4-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1*H*-imidazole: mp 105−109 °C; yield 281 mg, 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H, Im-2H), 7.50 (d, 2H, Ph-3,5H), 6.93 (d, 2H, Ph-2,6H), 6.89 (s, 1H, Im-4(5)H), 5.90 (s, 1H, Im-NH), 4.25 (t, 2H, CH_2O), 3.10 (t, 2H, Im-CH_2).

4-[3-(4-Cyanophenoxy)propyl]-1*H*-imidazole (10a). Urocanic acid (25 g, 0.18 mol) was hydrogenated[22] with 10% palladium on charcoal (2.5 g) in water (200 mL) at 40 °C for 4 h. The mixture was then cooled, filtered, and evaporated under reduced pressure. The resulting white residue was dissolved in EtOH (1 L), sulfuric acid (10 mL) was added, and the reaction mixture was heated under reflux for 12 h and then cooled and evaporated under reduced pressure to give an oily residue. The latter was basified at 0 °C with saturated $NaHCO_3$ and extracted with $CHCl_3$ (6 × 100 mL). The combined extracts were dried ($MgSO_4$) and then evaporated to give ethyl 2-(imidazol-4-yl)propionate[23] as an oil (29.2 g, 96%): IR ν (cm^{-1}) 3500 (b, N−H), 1730 (s, C=O); ^1H NMR (200 MHz, D_2O) δ 7.70 (s, 1H, Im-2H), 6.40 (s, 1H, Im-4(5)H), 3.31 (q, 2H, OCH_2), 2.20 (t, 2H, Im-CH_2), 1.94 (t, 2H, CH_2CO), 1.10 (t, 3H, CH_3).

The above ester (29.2 g, 0.17 mol) in freshly distilled THF (200 mL) was added dropwise to a cooled suspension of $LiAlH_4$ (7.8 g, 0.2 mol) in THF (100 mL), and the mixture was stirred at 20 °C for 15 h. Then KOH (6 g) in water (24 mL) was added dropwise with cooling; the resulting mixture was heated to reflux, and the hot solution was filtered. The residue was extracted with boiling THF (2 × 200 mL) and filtered. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure, and the resulting 4-(3-hydroxypropyl)-1*H*-imidazole[23] was converted into the oxalate in 2-propanol and then precipitated with Et_2O: yield 28.9 g, 79%; ^1H NMR (200 MHz, D_2O) δ 7.94 (s, 1H, Im-2H), 7.00 (s, 1H, Im-4(5)H), 3.14 (t, 2H, CH_2O), 2.06 (t, 2H, Im-CH_2), 1.14 (quint, 2H, CH_2).

A solution of 4-(3-hydroxypropyl)-1*H*-imidazole (2.0 g, 15.85 mmol) and dry triethylamine (5.5 mL, 54.3 mmol) in dry DMF (15.6 mL) was treated with triphenylmethyl chloride (4.86 g, 17.4 mmol) in DMF (5 mL) under N_2. The reaction mixture was stirred at 20 °C for 2 h and then poured into crushed ice (350 g). The resulting solid was collected by filtration, washed (3×) with water, and purified by column chromatography using $CHCl_3$, followed by $CHCl_3$:MeOH (1:1) as eluant to give 1-(triphenylmethyl)-4-(3-hydroxypropyl)imidazole: mp 132−133 °C.

To 1-(triphenylmethyl)-4-(3-hydroxypropyl)imidazole (184 mg, 0.5 mmol) under N_2 was added freshly distilled THF (5 mL), 4-cyanophenol (71 mg, 0.6 mmol), and triphenylphosphine (157 mg, 0.6 mmol). The resulting mixture was cooled and stirred for 5 min, diethyl azodicarboxylate (104 mg, 0.6 mmol) in THF (3 mL) was slowly added, and stirring was continued at 20 °C for 3 h under N_2. The solvent was then evaporated under reduced pressure, and the residue was subjected to chromatography on a silica gel column (first eluant petroleum spirit: Et_2O (1:1); second eluant Et_2O) to give 1-(triphenylmethyl)-4-[3-(4-cyanophenoxy)propyl]imidazole, which was recrystallized from EtOH:petroleum ether (1:1): mp 187−188 °C; yield 140 mg, 56%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H, Ph-3,5H), 7.47 (s, 1H, Im-2H), 7.32−7.10 (m, 15H, Ph_3C), 6.88 (d, 2H, Ph-2,6H), 6.56 (s, 1H, Im-5H), 4.01 (t, 2H, CH_2O), 2.75 (t, 2H, Im-CH_2), 2.18 (quint, 2H, CH_2).

1-(Triphenylmethyl)-4-[3-(4-cyanophenoxy)propyl]imidazole (96 mg, 0.2 mmol) in THF (2 mL) and 2 N HCl (5 mL) was heated at 70 °C during 6 h. The THF was then removed under reduced pressure, and the residue was washed with Et_2O and basified (K_2CO_3), and the product was extracted into $CHCl_3$ and dried ($MgSO_4$). The combined extracts were evaporated under reduced pressure to give the product, 4-[3-(4-cyanophenoxy)propyl]-1*H*-imidazole, as a white solid which was crystallized from EtOH:Et_2O (1:2): mp 194−195 °C; yield 35 mg, 77%; IR ν (cm^{-1}) 3450 (b, N−H str), 2220 (s, CN str), ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, Ph-3,5H), 7.85 (m, 1H, Im-2H), 7.28 (d, 2H, Ph-2,6H), 7.08 (s, 1H, Im-4(5)H), 4.37 (t, 2H, CH_2O), 3.11 (t, 3H, Im-CH_2 and NH), 2.49 (quint, 2H, CH_2).

Acknowledgment. We thank Dr. J. M. Lecomte for a grant (to A.F., S.A.) from Laboratoire Bioprojet, Paris, and the Commission of the European Communities for a grant from the Biomedical and Health Research Programme Biomed 1 (CT92-1087). We thank the following for synthesis of the compounds indicated: Dr. S. K. Hosseini (**6**), Helen Magnusen (**9j**), and Vincenzo Cannizzaro (**9i,r,u**). We thank Dr. K. Richardson, Pfizer Central Research Sandwich, Kent, for providing binding data on **10a**.

References

(1) Ganellin, C. R.; Fkyerat, A.; Hosseini, S. K.; Tertiuk, W.; Garbarg, M.; Ligneau, X.; Schwartz, J.-C. Design of Non-Thiourea H_3-Receptor Histamine Antagonists. *Eur. J. Pharm. Sci.* **1994**, *2*, 93 (SC 10).

(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) 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.

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

(5) Ganellin, C. R.; Hosseini, S. K.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Schwartz, J.-C. Design of Potent Non-Thiourea H_3-Receptor Histamine Antagonists. *J. Med. Chem.* **1995**, *38*, 3342−3350.

(6) 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.

(7) 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.

(8) 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.

(9) 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.

(10) 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.

(11) 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.

(12) 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.

(13) Malmberg-Aillo, P.; Lamberti, C.; Ghelardini, C.; Giotti, A.; Bartolini, A. Role of Histamine in Rodent Antinociception. *Br. J. Pharmacol.* **1994**, *111*, 1269−1279.

(14) 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.

(15) A similar analysis of burimamide analogues has been carried out by Vollinga et al.: Vollinga, R. C.; Menge, W. M. P. B.; Leurs, R.; Timmerman, H. New Analogs of Burimamide as Potent and Selective Histamine H_3 Receptor Antagonists: The Effect of Chain Length Variation of the Alkyl Spacer and Modifications of the *N*-Thiourea Substituent. *J. Med. Chem.* **1995**, *38*, 2244−2250. It was shown that the cyclohexylthiourea derived from histamine was some 10-fold less active than burimamide as an H_3-receptor antagonist when tested on the guinea pig jejunum.

(16) Schwartz, J.-C.; Arrang, J. M.; Garbarg, M.; Lecomte, J. M.; Ganellin, C. R.; Fykerat, A.; Tertiuk, W.; Schunack, W.; Lipp, R.; Stark, H.; Purand, K. French Patent 2 686 084-A1, 1993.

(17) (a) Turner, R. A. Studies of Imidazole Compounds III. Synthesis of 4-(2-Chloroethyl)-imidazole. *J. Am. Chem. Soc.* **1949**, *71*, 3476−3478. (b) Huebner, C. F. Studies of Imidazole Compounds V. A New and Improved Synthesis of 4-(2-Substituted Aminoethyl)-imidazoles. *J. Am. Chem. Soc.* **1951**, *73*, 4667−4669.

(18) Sterk, G. J.; van der Goot, H.; Timmerman, H. Studies on Histaminergic Compounds III. Synthesis and Histamine H_2-Activity of a Series of Corresponding Histamine and Dimaprit Analogues. *Arch. Pharm. (Weinheim)* **1986**, *319*, 624−630.

(19) (a) Mitsunobu, O. The use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. The Mitsunobu Reaction. *Org. React.* **1992**, *42*, 335−656.

(20) (a) Battersby, A. R.; Nicoletti, M.; Staunton, J.; Vleggaar, R. Studies of Enzyme-mediated Reactions. Part 13. Stereochemical Course of the Formation of Histamine by Decarboxylation of (2S)-Histidine with Enzymes from Clostridium Welchii and Lactobacillus 30a. *J. Chem. Soc., Perkin Trans. 1* **1980**, 43−51. (b) Bruice, T. C.; Sturtevant, J. M. Imidazole Catalysis. V. The Intramolecular Participation of the Imidazolyl Group in the Hydrolysis of Some Esters and the Amide of γ-(4-Imidazolyl)-butyric Acid and 4-(2′-Acetoxyethyl)-imidazole. *J. Am. Chem. Soc.* **1959**, *81*, 2860−2870.

(21) Ngochindo, R. I. 2-Protecting Groups for 5-Lithiation in the Synthesis of Imidazoles. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645−1648.

(22) Schunack, W. Structure-Activity Relationships of Histamine Analogs. 4. Ethers and Esters of 4-(2-Hydroxyethyl)imidazole and Esters of 4-Imidazolepropionic Acid. *Archiv. Pharm. (Weinheim)* **1974**, *307*, 517−523.

(23) Pasini, C.; Coda, S. Murexine and Related Imidazole Derivatives. Part III. Imidazolylacetyl-, Imidazolylpropionyl- and Imidazolylbutyrylcholine; Imidazolylmethoxy- and Imidazolylpropoxycholine. *Gazz. Chim. Ital.* **1957**, *87*, 1464−1477.

(24) Parker, R. B.; Waud, D. R. Pharmacological Estimation of Drug-Receptor Dissociation Constants. Statistical Evaluation. I. Agonists. II. Antagonists. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 1−24.

(25) 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 Raction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(26) Garbarg, M.; Arrang, J.-M.; Rouleau A.; Ligneau, X.; Dam Trung Tuong, M.; Schwartz, J.-C.; Ganellin, C. R. S-[2-(4-Imidazolyl)-ethyl]isothiourea, a Highly Specific and Potent Histamine H_3-Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304−310.

(27) Garbarg, M.; Pollard, H.; Dam Tung Tuong, M.; Schwartz, J.-C.; Gros, C. Sensitive Radioimmunoassay for Histamine and Tele-methylhistamine in the Brain. *J. Neurochem.* **1989**, *53*, 1724−1730.

(28) Huebner, C. F.; Turner, R. A.; Scholz, C. R. Studies of Imidazole Compounds. IV. Derivatives or 4-Ethylimidazole. *J. Am. Chem. Soc.* **1949**, *71*, 3942−3944.

(29) Chadha, H. S.; Abraham, M. H.; Mitchell, R. C. Physicochemical Analysis of the Factors Governing Distribution of Solutes between Blood and Brain. *BioMed. Chem. Lett.* **1994**, *4*, 2511−2516.

(30) 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.

(31) (a) Schunack, W.; Stark, H. Design of Histamine H_3-Receptor Agonists and Antagonists. *Eur. J. Drug Pharmacokinet.* **1994**, *3*, 173−178. (b) Hüls, A.; Purand. K.; Stark, H.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. A New Class of Potent Histamine H_3-Receptor Antagonists. XXIIIrd Annual Meeting of the European Histamine Research Society, Budapest, Hungary, May 18−21, 1994.

(32) 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.

(33) Turner, R. A.; Huebner, C. F.; Scholz, C. R. Studies of Imidazole Compounds. I. 4-Methylimidazole and related compounds. *J. Am. Chem. Soc.* **1949**, *71*, 2801−2803.

(34) Desai, J. M.; Marjadi, S. I.; Desai, C. M.; Synthesis and Study of Mixed-Ligand Complexes of Benzoylacetone with some Schiff Bases. *J. Indian Chem. Soc.* **1993**, *70*, 65−66.

(35) Schotten, C.; The Transformation of Piperidine into δ-Amidovaleric Acid and Piperidone. *Chem. Ber.* **1888**, *21*, 2235−2254.

JM960138L