Meta-Substituted Aryl(thio)ethers as Potent Partial Agonists (or Antagonists) for the Histamine H_3 Receptor Lacking a Nitrogen Atom in the Side Chain§

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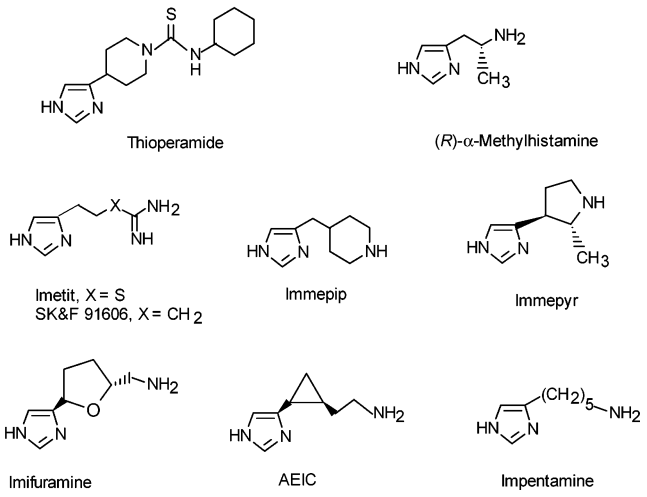
4-(3-Aryloxypropyl)-1*H*-imidazoles, which possess a meta-positioned substituent in the aryl ring, have been synthesized and tested for activity at histamine H_3 receptors. The compounds having a CN, Me, or Br substituent were found to be antagonists, whereas CF_3, Et, *i*-Pr, *t*-Bu, $COCH_3$, or NO_2 substituents remarkably afforded partial agonists when tested in vitro on rat cerebral cortex synaptosomes for inhibition of [^{3}H]histamine release. The compounds were also active in vivo, and furthermore, the CF_3-substituted compound trifluproxim (UCL 1470, **7**) acted as a potent full agonist in vivo, having $ED_{50} = 0.6 \pm 0.3$ mg/kg per os in mice for inhibition of brain N^{τ}-methylhistamine formation. Related structures have also been investigated; homologues 4-[4-(3-(trifluoromethyl)phenoxy)butyl]-1*H*-imidazole and 4-[2-(3-(trifluoromethyl)-phenylthio)ethyl]-1*H*-imidazole are shown to be partial agonists, whereas the O isostere 4-[2-(3-(trifluoromethyl)phenoxy)ethyl]-1*H*-imidazole is an antagonist as is the S homologue 4-[3-(3-(trifluoromethyl)phenylthio)propyl]-1*H*-imidazole and its CH_2 isostere 4-[4-(3-(trifluoromethyl)phenyl)butyl]-1*H*-imidazole.

Introduction

Histamine H_3 receptors were first indicated in 1983 by Arrang et al.[1] and subsequently definitively characterized[2] in 1987 with the antagonist thioperamide (Chart 1). They act as presynaptic autoreceptors that inhibit the synthesis[3] and release[1] of histamine in histaminergic neurons in the central nervous system (CNS). They also function as heteroreceptors[4] in modulating the release of other important neurotransmitters in the CNS and periphery. The classification of histamine receptors has been thoroughly discussed,[5] although there are now four subtypes of histamine receptors (H_1, H_2, H_3, and H_4) that have been characterized.[5b] Various ligands for the histamine H_3 receptor have been reviewed,[6a−c] and potential therapeutic applications for drugs acting at histamine H_3 receptors have been reported.[6c,d] Agonists might have application in the treatment of several inflammatory disorders.

The first potent selective H_3 receptor agonist to be described[2] was (*R*)-α-methylhistamine (Chart 1), and it has since been investigated in human studies in the form of a prodrug.[7] Other potent agonists are imetit,[8a] SK&F 91606,[8d] and various conformationally restricted

Chart 1. Structures of Thioperamide (the Reference H_3 Receptor Histamine Antagonist) and Various H_3 Receptor Agonists



forms of histamine and homologues of histamine such as immepip,[9a] immepyr,[9b] imifuramine,[10a] and the cyclopropane analogue AEIC.[10b] Impentamine,[11] a histamine homologue, was originally identified as a potent antagonist[11a] on neurogenic contractions of guinea pig jejunum but was subsequently shown to be a partial agonist[11b] on H_3-receptor-mediated inhibition of [^{3}H]-noradrenaline release from mouse brain. All these agonists comprise an imidazole ring with a side chain in the 4(5)-position ending in a nitrogen-containing base that at the physiological neutral pH is protonated and positively charged. The cationic moiety is presumed to interact Coulombically with an aspartic acid residue in

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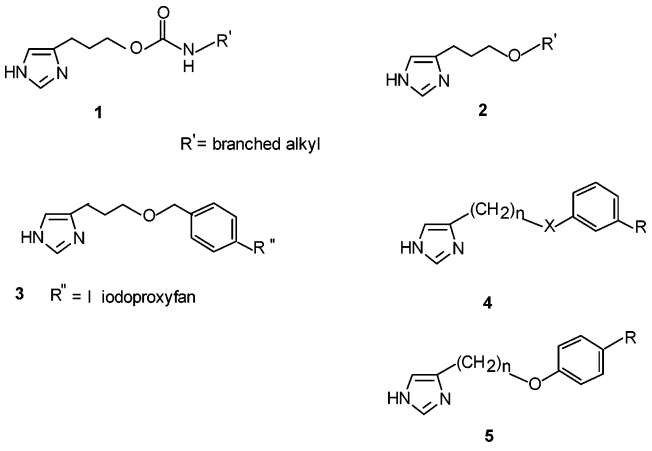
Chart 2. Structures of Carbamates and Ethers as H_3 Receptor (Partial) Agonists or Antagonists



the putative third transmembrane region of the G-protein-coupled receptor, thus leading to a change in receptor conformation and resulting in an agonist response.[12] The protonated cationic moiety could also act as a hydrogen-bond donor. As with the H_1,[13a,b] H_2,[13c] and H_4[13d] histamine receptors, the presence of an aspartic acid residue in the third transmembrane domain has also been inferred[13e] for the H_3 receptor.

Recently, however, partial agonists have been described (Chart 2) that are carbamates[14,15] (**1**) or ethers[14−17] (**2**, **3**). These compounds do not have cationic side chains and therefore lack a fundamentally important physicochemical property. Accordingly it is remarkable that they show agonist effects. These compounds have been tested for their actions at H_3 receptors, but their effects are tissue-sensitive. Three main functional procedures have been used: an in vitro assay on rat cerebral cortex synaptosomes[8a] using K^+-evoked depolarization-induced release of [^{3}H]histamine; an in vitro assay on guinea pig ileum[18] measuring the concentration-dependent inhibition of electrically evoked twitches; an in vivo test involving administration of the compounds per os to mice[8a] and measurement of the cerebral cortex level of the main histamine metabolite N^τ-methylhistamine.

The carbamates (**1**) carry a branched aliphatic alkyl group on the carbamoyl N, and their H_3 receptor activity is surprisingly sensitive to small structural changes in the branching.[14a] Thus, when R′ is isopropyl (**1**, R′ = *i*-Pr), the compound is a weak antagonist, whereas an additional methyl group to give the *tert*-butyl homologue (**1**, R′ = *t*-Bu) provides a partial agonist when tested in vivo in mice. Homologues show similar differentiation. The isobutyl analogue (**1**, R′ = CH_2CHMe_2) is a relatively weak antagonist, whereas the neopentyl compound (**1**, R′ = CH_2CMe_3) is a potent partial agonist and its methyl homologue (**1**, R′ = $CH(Me)CMe_3$) is a full agonist in vivo.[14b] All of the compounds, however, were antagonists when tested on the guinea pig ileum.

The activity of the ethers (**2**) is also extremely sensitive to structural variation.[14a] In structure **2**, R′ is a branched alkyl group; the isobutyl ether (**2**, R′ = CH_2-$CHMe_2$) is a potent antagonist in vivo, whereas the isopentyl (**2**, R′ = $CH_2CH_2CHMe_2$) and 3,3-dimethyl (**2**, R′ = $CH_2CH_2CMe_3$) homologues are potent full agonists in vivo while being partial agonists in vitro on rat synaptosomes and antagonists on the guinea pig ileum. The benzylic ethers **3** show partial agonist activity depending on the para substituent in the phenyl ring. Iodoproxyfan[19] (**3**, R″ = I) was the first nonaminergic compound to be reported[17b] as a partial agonist when tested on guinea pig ileum and mouse brain cortex, but it was purely an antagonist on rat synaptosomes. Proxyfan itself (**3**, R″ = H) also acts as a partial agonist and has been examined on many different test systems; it has been reported[17a,b] to act as a partial agonist on mitogen-activated protein kinase activity, [^{35}S]GTPγ-[S] binding, and inhibition of cAMP formation mediated by recombinant rat H_3 receptors expressed in Chinese hamster ovary (CHO) cells,[17a] as well as on inhibition of 20 mM K^+-evoked [^{3}H]histamine release[17a] and electrically evoked [^{3}H]noradrenaline release[17b] mediated in rat and mouse brain, respectively, by native H_3 receptors. Proxyfan was even shown[17a,c] to behave as a full agonist on inhibition of cAMP formation mediated by recombinant rat and human H_3 receptors expressed in human embryonic kidney (HEK) cells[17c] as well as in vivo on inhibition of cyclophosphamide-induced cystitis in the mouse and the modulation of the sleep−wake cycle in the cat.[17a] However, the effects of proxyfan were reported to be strongly dependent on the level of constitutive activity displayed by H_3 receptors in each test sytem and proxyfan could also act as a neutral antagonist or inverse agonist on other responses, leading to the new concept of protean agonism.[17a] Besides iodoproxyfan, the other halogeno derivatives of proxyfan (**3**, R″ = F, Cl, Br) were also shown[17d,e] to behave as partial agonists. More recently, chloroproxyfan (**3**, R″ = Cl) was reported[17f,g] to act as a full agonist on inhibition of forskolin-stimulated adenylate cyclase in SK-N-MC neuroblastoma cells expressing the rat H_3 receptor protein[17f] and on release of calcium in HEK cells transiently cotransfected with human H_3 receptor cDNA and the Gq_{i5} plasmid.[17g]

We now report a series of substituted 4-[ω-(phenyl-(oxy/thio))alkyl]-1*H*-imidazoles (**4**, n = 2−4, X = O or S) that also demonstrate partial agonist activity when tested in vitro on rat synaptosomes and especially in vivo in the mouse. The activities of these compounds are also remarkably sensitive to chemical structure and particularly to the nature of the substituent in the phenyl ring. Indeed, it appears that the substituent has to be in the meta position. Previously we have described[20] a series of 4-[ω-(aryloxy)alkyl]-1*H*-imidazoles (**5**, n = 2 or 3) (Chart 2) acting as potent antagonists at the histamine H_3 receptor; these compounds were substituted in the para position of the aryloxy ring. Two aryloxypropylimidazoles were of special interest, being more potent in vivo than the standard reference H_3 receptor antagonist/inverse agonist thioperamide (Chart 1). Thus, **5a** (R = *p*-CN, n = 3) and **5b** (R = *p*-CF_3, n = 3) had ED_{50} values in vivo per os in mice (Table 1) of 0.54−0.60 mg/kg (calculated for the free base form of the compound) for increasing brain N^τ-methylhistamine levels and had K_i values in vitro of 12−14 nM for [^{3}H]-histamine release from rat cerebral cortex synaptosomes (cf. thioperamide ED_{50} = 1.0 mg/kg po and K_i = 4 nM).[2] Further developments from this series led to the potent

Scheme 1

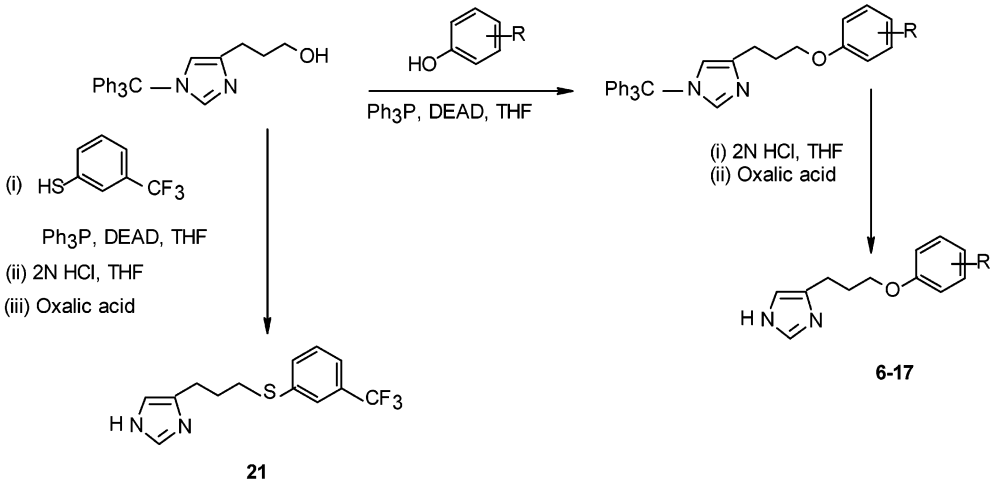
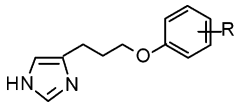


Table 1. Aryloxypropylimidazoles and Their Potencies as H_3 Receptor Histamine Antagonists or Partial Agonists (K_i and Intrinsic Activities in Vitro for [^{3}H]Histamine Release from Rat Cerebral Cortex Synaptosomes, and ED_{50} per Os and Intrinsic Activities in Vivo in Mice for Modulation of Brain N^{τ}-Methylhistamine Formation)



		in vitro		in vivo	
compd	R	ia [a]	$K_i \pm$ SEM (nM)	$ED_{50} \pm$ SEM po (mg/kg)[b]	ia [a]
5a	*p*-CN	<0.1[c]	12 ± 3	0.54 ± 0.23[d,e]	0[d]
5b	*p*-CF_3	<0.1[c]	14 ± 6	0.6 ± 0. 2[d,e]	0[d]
6	*m*-CN	<0.1[c]	108 ± 22	>10	
7	*m*-CF_3	0.40[f]	8.4 ± 2.5	0.6 ± 0.3	1.0
8	*o*-CF_3	<0.1[c]	~500	>10	
9	3,5-$(CF_3)_2$	<0.1[c]	116 ± 21	4.8 ± 2.8[d]	0[d]
10	H	<0.1[c]	55 ± 11	>10	
11	*m*-Me	<0.1[c]	37 ± 8	>10	
12	*m*-Et	0.20	15 ± 3	~1	0.85
13	*m*-*i*-Pr	0.30	29 ± 7	0.5 ± 0.1	0.82
14	*m*-*t*-Bu	0.28	22 ± 4	0.8 ± 0.2	0.78
15	*m*-Br	<0.1[c]	19 ± 8	>10	
16	*m*-$COCH_3$	0.15	20 ± 2	0.4 ± 0.2	0.90
17	*m*-NO_2	0.10	9.4 ± 1.5	1.1 ± 0.6	0.61

[a] Intrinsic activity = maximal effect relative to the maximal effect of histamine (ia = 1.0) in vitro and imetit in vivo. [b] Calculated as the base. [c] ia < 0.1, no detectable agonism. [d] Antagonist. [e] Reference 20. [f] Trifluproxim (UCL 1470).

antagonists ciproxifan (**5**, R = *p*-CO-cyclopropyl, *n* = 3)[20b,c] and imoproxifan (**5**, R = *p*-C(=NOH)CH_3, *n* = 3).[20d]

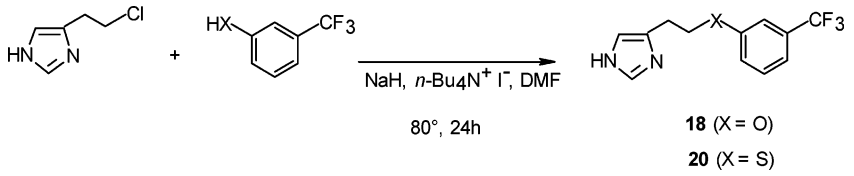
The corresponding meta-substituted compounds, however, gave surprising results. The *m*-cyano compound **6** (Table 1) still acted as an H_3 antagonist but was found to be much less potent (ED_{50} > 10 mg/kg po, K_i = 108 nM). The *m*-trifluoromethyl compound **7**, however, was found to act as a partial agonist, *reducing* the release of histamine from rat cortical synaptosomes in vitro (EC_{50} = 98 ± 32 nM) although it only reached 40% of the maximal reduction effected by histamine, which is presumed to act as a full agonist. This unexpected finding led us to investigate other meta-substituted analogues (**9**−**22**) as listed in Tables 1−3 and to explore the structure−activity relationships for the transition between antagonist and partial agonist structures.

Chemistry

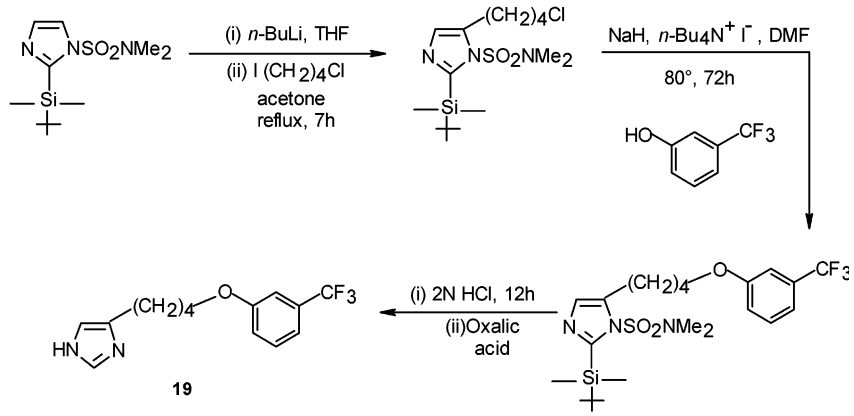
The synthesis of compounds **6**−**17** and **21** (Scheme 1) uses the key intermediate 1-(triphenylmethyl)-4-(3-hydroxypropyl)imidazole, which was prepared as previously described.[20a] This intermediate was treated with the appropriately substituted phenol or thiophenol (as described for **7**) in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) in freshly distilled THF as required for a Mitsunobu type coupling.[21] The resulting product was collected, treated with hydrochloric acid to remove the triphenylmethyl (trityl) protecting group, isolated, and then converted into the hydrogen oxalate salt. The latter was triturated with diethyl ether to remove excess oxalic acid or crystallized from methanol, ethanol, or 2-propanol/diethyl ether.

Compounds **18** and **20** were prepared (Scheme 2) by a Williamson synthesis[22] from 4-(2-chloroethyl)-1*H*-imidazole[14] and sodium 3-(trifluoromethyl)(thio)phenate (generated from sodium hydride and the substituted phenol or thiophenol) in DMF. Compound **19** was made (Scheme 3) from the doubly protected imidazole 1-(*N*,*N*-dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-(4-chlorobutyl)imidazole[23] and sodium 3-(trifluoromethyl)phenolate (generated with sodium hydride and tetrabutylammonium iodide) in DMF, followed by deprotection with hydrochloric acid. Initial attempts to synthesize compound **22** were unsuccessful. The first synthesis investigated required as key intermediate a protected 3-(1*H*-imidazol-4-yl)propionaldehyde that could then be coupled with an *m*-(trifluoromethyl)benzylphosphonium reagent in a Wittig reaction. Trityl was selected as the protecting group, but oxidation of 1-(triphenylmethyl)-4-(3-hydroxypropyl)imidazole to the corresponding aldehyde using pyridinium chlorochromate or dichromate did not go cleanly. In an alternative approach, activated manganese(IV) oxide was selected as the oxidizing agent, but since this requires an allylic carbinol as starting material, the sequence outlined in Scheme 4 using 1-(triphenylmethyl)-4-(3-hydroxyprop-2-enyl)imidazole was identified. The latter was prepared by tritylation of ethyl urocanate[24] followed by reduction with LAH ($LiAlH_4$). This sequence was successful, but two of the stages were low-yielding. Esterification of urocanic acid gave a low yield probably because of the low solubility of urocanic acid in ethanol; the reduction of the ester also gave a low yield because LAH produced a small amount of the

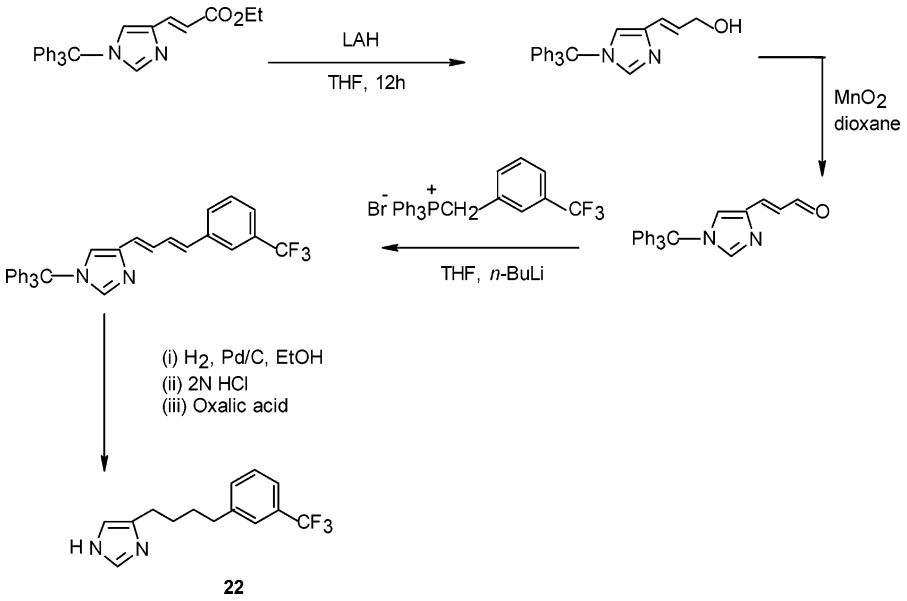
Scheme 2



Scheme 3



Scheme 4



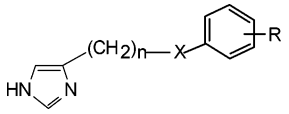
fully saturated carbinol that had to be separated chromatographically. The propenyl alcohol was oxidized with MnO_2 to the corresponding propenal, and the latter was treated with [3-(trifluoromethyl)benzyl]triphenylphosphonium bromide and *n*-BuLi in a Wittig reaction. The resulting mixture of butadienes was reduced by hydrogenation and deprotected with hydrochloric acid to give the product, isolated as hydrogen oxalate. The compounds synthesized for testing as hydrogen oxalate salts are listed in Table 2 along with their molecular formulas, melting points, solvent used for isolation (or crystallization), percentage purity as indicated by UV detection following HPLC, and overall percentage yields (for **6**−**17**, **21**) based on the quantity of 1-triphenylmethyl-4-(3-hydroxypropyl)imidazole taken. All compounds had satisfactory mass spectra and ^{1}H NMR spectra.

Pharmacology

In Vitro. The compounds were tested in vitro as agonist or antagonist for their activity at histamine H_3 receptors in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from synaptosomes. The synaptosomal fraction from rat cerebral cortex was preincubated for 30 min with L-[^{3}H]histidine at 37 °C, and the assay was conducted according to the method previously described.[8a] The intrinsic activity of the agonists was determined by comparing the maximal inhibition elicited by the test substance with that produced by histamine (1 μM).

In Vivo. The compounds were tested in vivo for activity at histamine H_3 receptors by administration of the oxalate salt as a solution or suspension in 1% methylcellulose per os to groups of 6−12 male Swiss mice (weighing 18−22 g) as previously described.[8a] After

Table 2. Aryloxy(thio)alkyl-1*H*-imidazoles, Their Molecular Formulas, Physical Data, and Percentage Yields



compd	*n*	X	R	molecular formula[a]	mp (°C)[b]	solvent[c]	HPLC[d] purity (%)	yield[e] (%)
6	3	O	*m*-CN	$C_{13}H_{13}N_3O$, $C_2H_2O_4$	181−183	A	97.0	40
7	3	O	*m*-CF_3	$C_{13}H_{13}F_3N_2O$, $C_2H_2O_4$	204−206	D	97.9	45
8	3	O	*o*-CF_3	$C_{13}H_{13}F_3N_2O$, $0.85C_2H_2O_4$	188−191	A	99.4	34
9	3	O	3,5-$(CF_3)_2$	$C_{14}H_{12}F_6N_2O$, $1.2C_2H_2O_4$	206−207	A	98.8	27
10	3	O	H	$C_{12}H_{14}N_2O$, $0.95C_2H_2O_4$	163−165	A	99.6	35
11	3	O	*m*-Me	$C_{13}H_{16}N_2O$, $1.1C_2H_2O_4$	156−158	A	100	28
12	3	O	*m*-Et	$C_{14}H_{18}N_2O$, $0.85C_2H_2O_4$	173−175	B	98.4	22
13	3	O	*m*-*i*-Pr	$C_{15}H_{20}N_2O$, $0.8C_2H_2O_4$	180−182	A	100	32
14	3	O	*m*-*t*-Bu	$C_{16}H_{22}N_2O$, $0.8C_2H_2O_4$	183−185	A	99.3	28
15	3	O	*m*-Br	$C_{12}H_{13}BrN_2O$, $0.8C_2H_2O_4$	175−178	A	98.2	36
16	3	O	*m*-$COCH_3$	$C_{14}H_{16}N_2O_2$, $0.8C_2H_2O_4$	156−158	A	99.2	35
17	3	O	*m*-NO_2	$C_{12}H_{13}N_3O_3$, $0.9C_2H_2O_4$	189−191	A	100	48
18	2	O	*m*-CF_3	$C_{12}H_{11}F_3N_2O$, $C_2H_2O_4$	160−163	A	99.1	5
19	4	O	*m*-CF_3	$C_{14}H_{15}F_3N_2O$, $0.8C_2H_2O_4$	175−176	C	98.3	36
20	2	S	*m*-CF_3	$C_{12}H_{11}F_3N_2S$, $0.85C_2H_2O_4$	158−160	A	99.0	38
21	3	S	*m*-CF_3	$C_{13}H_{13}F_3N_2S$, $C_2H_2O_4$	166−168	A	99.0	18
22	3	CH_2	*m*-CF_3	$C_{14}H_{15}F_3N$, $0.85C_2H_2O_4$	181−183	A	98.3	20

[a] All compounds had C, H, and N analyses within ±0.4%. [b] Melting points determined in open capillaries using an Electrothermal electrically heated Cu block apparatus and are uncorrected. [c] A = triturated with Et_2O; B = crystallized from MeOH; C = crystallized from EtOH; D = crystallized from *i*-PrOH/Et_2O mixture. [d] HPLC on a Gilson binary gradient apparatus with UV detection at 215 nm and a 250 mm × 4.6 mm Kromasil C_{18} 1 μm column with a flow rate of 1 mL/min. [e] Overall yield for compounds **6**−**17** and **21** based on the amount of 1-trityl-4-(3-hydroxypropyl)imidazole taken.

treatment, animals were sacrificed by decapitation and the cerebral cortex was dissected out and homogenized in 10 volumes (w/v) of ice-cold perchloric acid (0.4 N). The brain histamine turnover was determined by measuring the level of the main metabolite of histamine, N^{τ}-methylhistamine, by radioimmunoassay as described.[8a] Treatment with 10 mg/kg of imetit furnished the maximal decrease in N^{τ}-methylhistamine level for comparison with the level reached after the administration of the maximal dose of the drug as agonist. For antagonists, 10 mg/kg of thioperamide was used to provide the maximal increase in N^{τ}-methylhistamine level for comparison with the administered test drug.

Determination of HMT Activity. Histamine-*N*-methyltransferase (HMT) activity was quantified by measuring the conversion of histamine into [^{3}H]-N^{τ}-methylhistamine by using *S*-[^{3}H]adenosylmethionine as a [^{3}H]methyl donor.[8a] In brief, histamine in increasing concentrations was incubated with HMT purified from rat kidney and a mixture of unlabeled compound and *S*-[^{3}H]adenosylmethionine (5 μM final concentration) for 1 h at 25 °C. The reaction was stopped by addition of perchloric acid (0.4 N final concentration) followed by sodium hydroxide (1 N final concentration). [^{3}H]-N^{τ}-methylhistamine was extracted into toluene/isoamyl alcohol (3:2) and quantified by liquid scintillation spectrometry.[8a]

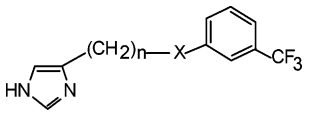
Results and Discussion

As already mentioned, the position of the CF_3 substituent appears to determine the nature of the activity. Compound **5b** (*p*-CF_3, $n = 3$) is a potent antagonist in vivo and **7** (*m*-CF_3, $n = 3$) is a potent agonist in vivo; hence, the corresponding ortho-substituted isomer **8** (*o*-CF_3, $n = 3$) was also investigated. Compound **8** was found to be a weak antagonist. The possibility that two substituents might be better than one was explored with the 3,5-ditrifluoromethyl analogue (**9**); however, it was not a partial agonist but an antagonist. A series of meta-substituted phenoxy compounds was constructed in which R is an alkyl group or a selection of electron-withdrawing groups (Table 1). The results of testing the compounds as H_3 receptor agonists and/or antagonists in vitro and in vivo are presented in Table 1.

For comparison, the compound without any substituent in the phenyl ring (**10**) was examined and found to present no detectable agonism and to be active as an antagonist in vitro ($K_i = 55 \pm 11$ nM) but not active in vivo at the dose tested (up to 30 mg/kg). The *m*-methyl-substituted compound (**11**) was similarly not active in vivo and was an antagonist in vitro. Increasing the size of the alkyl substituent, however, as with **12**, **13**, and **14** (R = Et, *i*-Pr, and *t*-Bu, respectively) afforded compounds that showed partial agonist behavior. These compounds were weakly active in vitro (intrinsic activities (ia) approximately 20−30% of the maximal effect of histamine) but, surprisingly, were nearly full agonists in vivo (ia = 0.78−0.85) having ED_{50} values of 0.5−1.0 mg/kg.

As indicated above, compound **7** (R = CF_3) was a full agonist in vivo but only a partial agonist in vitro. Other substituents such as R = CN and Br only provided compounds (**6**, **15**) that were antagonists in vitro but not active in vivo. Two strongly electron-withdrawing groups, R = $COCH_3$ and NO_2, furnished compounds (**16** and **17** respectively) that, however, were potent partial agonists in vivo (ia of 0.9 and 0.6, respectively), having ED_{50} values of 0.4 and 1.1 mg/kg, respectively. These results are remarkable. First, there is a considerable influence from the position of substitution, and second, there is a considerable sensitivity to the nature of the substituent. On one hand, mildly electron-releasing alkyl substituents provide partial agonists if they have a size larger than methyl. Clearly it will be of interest in future to explore the extent to which an alkyl group larger than *tert*-butyl may be accommodated as a partial

Table 3. *m*-(Trifluoromethyl)phenyl(oxy/thio)alkylimidazoles and Their Potencies as H_3 Receptor Histamine Antagonists or Partial Agonists (K_i and EC_{50} in Vitro for [^{3}H]Histamine Release from Rat Cerebral Cortex Synaptosomes and ED_{50} per Os and Intrinsic Activities in Vivo in Mice for Modulation of Brain N^τ-Methylhistamine Formation)



			in vitro			in vivo	
compd	*n*	X	$EC_{50} \pm$ SEM (nM)	ia [a]	$K_i \pm$ SEM (nM)	$ED_{50} \pm$ SEM po (mg/kg)[b]	ia [a]
7	3	O	98 ± 32	0.40	8.4 ± 2.5	0.6 ± 0.3	1.0
18	2	O			18 ± 7	<10[c]	0[d]
19	4	O				~1.0	0.7
20	2	S	318 ± 73	0.40	23 ± 4	0.94 ± 0.05	0.7
21	3	S			38 ± 8	>10	
22	3	CH_2			38 ±10	6.5	0[d]

[a] Intrinsic activity = maximal effect relative to the maximal effect of histamine (ia = 1.0) in vitro and imetit in vivo. [b] Calculated as the base. [c] ED_{50} not determined more precisely. [d] Antagonist.

agonist. On the other hand, powerful electron-withdrawing substituents that are larger than a methyl group also furnish partial agonists. The situation is very complex, however, since *m*-CF_3 substitution gives a partial agonist but *m*-CN does not.

The influence of chain length $n = 2-4$ was also investigated (Table 3) for structure **4** (X = O, R = CF_3). The lowest homologue **18** ($n = 2$) was an antagonist, and the highest homologue **19** ($n = 4$) was a partial agonist in vivo and slightly less active than the lead compound **7** ($n = 3$). Of great interest was the finding (Table 3) that sulfur can replace oxygen in this type of structure to give a partial agonist but that the dependence of activity on chain length is different. The lower homologue **20** (i.e., structure **4**, $n = 2$, X = S, R = CF_3) was a partial agonist in contrast to the oxygen analogue **18**, whereas the higher homologue directly comparable with **7**, i.e., **21** (structure **4**, $n = 3$, X = S, R = CF_3), was a rather weak antagonist in vivo. The methylene isostere **22** (structure **4**, $n = 3$, X = CH_2, R = CF_3) was also an antagonist. These results might suggest that the distance between the imidazole ring and the aryl group is critical for the agonist effect. For the oxygen ethers, $n = 2$ is too short. For the thioethers, the H_2C-S (1.81 Å) and Ph−S (1.73 Å) bonds are longer than the H_2C-O (1.43 Å) and Ph−O (1.36 Å) bonds.[25] Thus, $n = 2$ for the S compound is more comparable with $n = 3$ for the O compound, and $n = 3$ for the S compound (**21**) is then too long. This is unlikely to be the sole reason; otherwise, the highest ether homologue **19** (structure **4**, $n = 4$, X = O, R = CF_3) should not be active as a partial agonist. The methylene compound **22** (C−C bond is 1.54 Å)[25] would fit between the oxygen homologues **7** and **19** and should therefore be a partial agonist. That it is only an antagonist suggests that other factors are contributing to the partial agonist activity, for example, the O or S atom may act as polarizable groups or as hydrogen-bond acceptors, whereas the equivalent CH_2 group in **22** cannot.

In the assay in vivo, agonism or partial agonism is revealed by a decrease in the N^τ-methylhistamine level because histamine released from neurons is catabolized to N^τ-methylhistamine.[26] Such an effect could also occur if the compound inhibited the enzyme histamine-*N*-methyltransferase (HMT) (EC 2.1.1.8) responsible for methylating the imidazole ring of histamine. Therefore, compound **7**, as a representative member of this group of compounds, was tested for interaction with HMT (at concentrations up to 10 μM). It was not found to be a substrate for HMT and neither was it an activator nor an inhibitor of this enzyme. As already indicated above, *p*-CF_3 substitution provides a compound (**5b**, $n = 3$) that is a potent antagonist in vivo.[20] Likewise, it has been found[20b,27] that compounds with *p*-$COCH_3$ or *p*-Et substituents and $n = 3$ are also potent antagonists in vivo (ED_{50} values of 0.20 and 0.24 mg/kg, respectively), whereas the corresponding meta isomers (**12**, **16**) are partial agonists in vivo. It is noteworthy that for the whole series of meta-substituted compounds (excepting **6**) the K_i values fall within a narrow affinity range of 8−38 nM and that among these compounds it is only the partial agonists that are active in vivo (ED_{50} values of 0.4 to 1.1 mg/kg). The most potent partial agonist from this series is **7**; it has the lowest EC_{50} value in vitro for [^{3}H]histamine release from rat cerebral synaptosomes and an intrinsic activity of 0.40. In accord with an action at H_3 receptors the agonistic effect of **7** at increasing concentrations (from 10^{-8} to 10^{-5} M) was totally reversed by 3×10^{-6} M thioperamide, the reference H_3 receptor antagonist. It also has the highest affinity when tested as an antagonist on this preparation, $K_i = 8.4$ nM. On the guinea pig isolated and electrically stimulated ileum, only an antagonist effect of **7** could be determined,[28a,b] $K_B = 17$ nM. This measure of affinity at H_3 receptors is in the same range as that determined from binding studies using [^{3}H]-*R*-α-methylhistamine on guinea pig cerebral cortex ($pK_i = 8.45$, 8.67; $n_H = 1.07 \pm 0.09$, 1.24 ± 0.14).[28b] Compound **7** also has a high affinity for the recombinant human histamine H_3 receptor showing $K_i = 1.1 \pm 0.2$ nM in a binding assay versus [^{125}I]iodoproxyfan in transfected CHO-K1 cells.[29] In vivo, it is the only compound of this series to show a full agonist effect (ia = 1.0) and it has one of the lowest ED_{50} values, namely, 0.6 ± 0.3 mg/kg (i.e., 2.2 μmol/kg) when given per os to mice.

A dose−response curve for **7** in vivo is shown in Figure 1 in the dose range 0.15−30 mg/kg. The reduction in the N^τ-methylhistamine level is the same as that produced by 10 mg/kg of the reference H_3 receptor agonist imetit, indicating ia = 1.0. The dose−response curve for the nitro-substituted analogue **17** in the same dose range is also given, indicating that it acts as a partial agonist reaching only 61% of the reduction in N^τ-methylhistamine level produced by imetit, i.e., ia = 0.61. By contrast, the unsubstituted compound **10**, at 10 mg/kg, has no effect; i.e., at this dose it is neither an agonist nor an antagonist.

Compound **7** (UCL 1470), which we have named trifluproxim, is 2−3 times more potent than imetit as an agonist when given per os to mice in vivo. Imetit is one of the most potent H_3 receptor agonists known[8] and, under similar test conditions, has $ED_{50} = 1.0 \pm 0.3$ mg/kg (i.e., 5.8 μmol/kg). Trifluproxim is also over 10 times more potent than the selective agonist (*R*)-α-methylhistamine in vivo, which has $ED_{50} = 3.7 \pm 2.6$ mg/kg, i.e., 30 μmol/kg.[8a] Although **7** is less active than imetit or (*R*)-α-methylhistamine in vitro, the high potency in

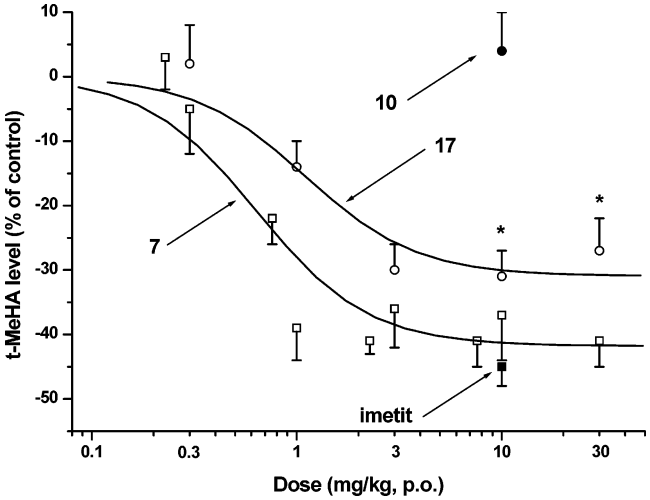


Figure 1. Agonist dose−responses (measured as a reduction in N^{τ}-methylhistamine (*t*-MeHA) levels in mouse cerebral cortex 90 min after oral dosing) for compounds **7** (**4**, X = O, R = CF_3), □; **10** (**4**, X = O, R = H), ●; **17** (**4**, X = O, R = NO_2), ○; and imetit (Chart 1), ■. *t*-MeHA levels are expressed in percentages (mean ± SEM of 12 values) of the *t*-MeHA level in control mice (140 ± 5 ng/g tissue): (*) $p < 0.01$ compared to imetit.

vivo is probably due to an enhanced ability to penetrate the central nervous system (CNS). Having a side chain that is noncationic and contains no NH hydrogen-bond donor group should greatly assist penetration of the blood−brain barrier. Furthermore, the compound is much more lipophilic; the l-octanol/water log *P* is estimated to be 3.26 by CLOGP;[30] (*R*)-α-methylhistamine and imetit in comparison have estimated log *P* values of −0.81 and −0.23, respectively, for the free bases.

The intrinsic activities in vivo are higher than those seen in vitro, suggesting that there is a greater receptor reserve involved in the in vivo situation. Indeed, for most of the compounds the maximal agonist responses in vitro were too low (low intrinsic activities) to allow EC_{50} values to be calculated. A similar situation exists for the carbamate (**1**) and alkyl ether (**2**) partial agonists;[14,16] that is, in general, the intrinsic activities are much lower in the in vitro test on rat synaptosomes than in vivo in the mouse evaluated from modulation of the N^{τ}-methylhistamine levels in the brain. Again, because of the low intrinsic activities, the EC_{50} values for most of the compounds could not be determined. Although both tests evaluate the influence of H_3 autoreceptor stimulation upon endogenous histamine release, this apparent difference in receptor reserve may be due to the involvement of both presynaptic and somatodendritic H_3 autoreceptors[31] in the inhibition of histamine neuron activity, i.e., in the decrease of N^{τ}-methylhistamine levels in vivo, whereas only presynaptic receptors are involved in the inhibition of histamine release in vitro.[31a] To relate to previous work in this area, the term antagonist is used because the compounds are seen to antagonize the effect of histamine in the in vitro assays under consideration. However, H_3 receptors display a high level of constitutive activity[32] and most antagonists are, in fact, acting as inverse agonists abrogating this constitutive activity not only at recombinant rat and human H_3 receptors but also at native H_3 receptors present in rodent brain.[32a,b] Moreover, constitutive activity of H_3 autoreceptors inhibits histamine neuron activity in vivo and inverse agonists such as thioperamide and ciproxifan enhance N^{τ}-methylhistamine levels in vivo.[32a] It is therefore likely that compounds behaving as antagonists in vitro and increasing N^{τ}-methylhistamine levels, such as para-substituted compounds **5a** and **5b**, behave in fact as inverse agonists in vivo. The apparent lack of in vivo activity of compounds acting as antagonists in vitro, such as meta-substituted compounds **10**, **11**, and **15**, could be a pharmacokinetic problem, e.g., poor oral absorption, differences in distribution, inadequate brain penetration, or very rapid metabolism. However, the similarity in chemical structures, e.g., **11** and **12** (R = Me vs Et), **15** and **7** (R = Br vs CF_3), suggests that this is an unlikely explanation. It is also unlikely that the difference in behavior is due to a species difference because the amino acid sequence of the seven transmembrane domains of the mouse and rat H_3 receptors is reported to be nearly identical (amino acid sequence of 98% homology).[17g] The pharmacological profile of these compounds is more likely reminiscent of the neutral antagonism previously reported with proxyfan.[32a,b] Proxyfan potently antagonized both the increases and decreases in N^{τ}-methylhistamine levels induced by inverse agonists and agonists, respectively, but administered alone failed to affect N^{τ}-methylhistamine levels, indicating that it was behaving as a neutral antagonist in vivo at H_3 autoreceptors displaying constitutive activity.[32a] Very recently, neutral antagonism was attributed to a partial agonism promoting an active state of the receptor with the same level of efficacy, i.e., intrinsic activity, as that of the constitutively active state of the receptor.[17a] This would suggest that compounds **10**, **11**, and **15** were already intrinsically acting as partial agonists in vivo but that this partial agonism could not be observed because it was of similar efficacy as the constitutive activity of H_3 autoreceptors. The agonism observed with the other meta-substituted compounds, such as compounds **7** and **17**, indicates that these compounds promote an active state of the receptor with a level of efficacy higher than that of constitutive activity.[17a]

Conclusion

Certain meta-substituted phenyloxy(thio)alkyl-1*H*-imidazoles have been shown to activate the histamine H_3 receptor both in vitro and in vivo as partial agonists. Compound **7** (trifluproxim) in particular is a very potent full agonist in vivo. These partial agonists do not contain a nitrogen atom in the side chain attached to the imidazole ring, and the side chain is not cationic at physiologic pH. It is conceivable that the (thio) ether (sulfur)oxygen atom of these aryloxy(thio) compounds could act as a hydrogen-bond acceptor, although aryl ethers have rather low basicities, and that the meta substituent assists binding by interacting with a suitable receptor pocket to produce the conformational change in the receptor protein required to activate a response. Most probably, these meta-substituted phenoxy groups interact at a site other than at an aspartic acid residue. It has been shown that the H_3 receptor in the brain is constitutively active,[31] and it is therefore likely that these compounds stabilize an active state of the receptor with a level of efficacy higher than that of

constitutive activity, thereby appearing to produce an agonist response.

Experimental Section

Chemistry. General Methods. Melting points (mp) were taken in open capillaries on an Electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-400 (400 MHz) spectrometer unless otherwise indicated, 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; d, doublet; t, triplet; q, quadruplet; quint, quintet; m, multiplet. Mass spectra were recorded on a VG 7070H double-focusing spectrometer with a Finnigan Incos data system. 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 215 nm and a Kromasil C_{18} 1 μm (250 mm × 4.6 mm) column using a mobile phase of A = water and B = MeOH (ratio A/B = 40:60 or 50:50) containing 0.1% trifluoroacetic acid with a flow rate of 1 mL/min. Column chromatography was conducted using Merck silica gel 60 (particle size 0.063−0.200 mm).

4-[3-(3-(Trifluoromethyl)phenoxy)propyl]-1*H*-imidazole Hydrogen Oxalate, UCL 1470 (7). 1-(Triphenylmethyl)-4-(3-hydroxypropyl)imidazole[20] (300 mg, 0.81 mmol) was dissolved in freshly distilled THF (8 mL). Triphenylphosphine (277 mg,1.06 mmol) and 3-(trifluoromethyl)phenol (145 mg, 0.89 mmol) were added, and the resulting mixture was cooled and stirred for 5 min under nitrogen. Diethyl azodicarboxylate (184 mg, 1.06 mmol), dissolved in freshly distilled THF (4 mL), was added slowly to the reaction mixture, and stirring continued at room temperature for 12 h. After removal of the solvent in vacuo, column chromatography (SiO_2; first eluent, petroleum spirit; second eluent, petroleum spirit/Et_2O (1:1)) of the crude reaction mixture gave a white powder that was triturated in petroleum spirit to give 1-(triphenylmethyl)-4-[3-(3-(trifluoromethyl)phenoxy)propyl]imidazole as an oil (210 mg, 50%). ^{1}H NMR ($CDCl_3$): δ 7.37 (s, 1H, Im-2*H*), 7.32−6.99 (m, 19H, trityl-*H* + Ph-*H*), 6.54 (s, 1H, Im-5*H*), 3.97 (t, 2H, CH_2−O), 2.72 (t, 2H, Im-CH_2), 2.12 (quint, 2H, CH_2−CH_2−CH_2). MS FAB(+): *m*/*z* 513 (M + H), 243 (CPh_3).

A solution of the above product (210 mg, 0.41 mmol) in THF (5 mL) and 2 N HCl (12 mL) was heated at 70 °C for 4 h. The THF was evaporated under reduced pressure, and Ph_3COH was extracted into Et_2O. The aqueous layer was neutralized (K_2CO_3), and the product was extracted into Et_2O. The Et_2O solution was dried and evaporated to give an oil that was dissolved in *i*-PrOH and treated with oxalic acid (1.5 equiv) to give a precipitate of the hydrogen oxalate (0.086 g, 58%). Crystallization from *i*-PrOH/Et_2O gave the product having mp 204−206 °C. ^{1}H NMR (D_2O): δ 8.60 (s, 1H, Im-2*H*), 7.53 (t, 1H, Ph-5*H*), 7.38 (d, 1H, Ph-4*H*), 7.24 (m, 3H, Im-4*H*, Ph-2*H*, and Ph-6*H*), 4.21 (t, 2H, CH_2−O), 2.97 (t, 2H, Im-CH_2), 2.22 (quint, 2H, CH_2−CH_2−CH_2). MS FAB(+): *m*/*z* 271 (M + H). HPLC: 97.9% at 6.4 min, A (water)/B (MeOH) = 40:60 with 0.1% CF_3CO_2H.

4-[2-(3-(Trifluoromethyl)phenoxy)ethyl]-1*H*-imidazole Hydrogen Oxalate (18). To a cold solution of 3-(trifluoromethyl)phenol (1.9 g, 12 mmol), in dry DMF (10 mL), was added slowly sodium hydride (60% dispersion in mineral oil, 0.24 g, 6 mmol). The mixture was stirred, under nitrogen, at room temperature for 2 h. 4-(2-Chloroethyl)-1*H*-imidazole (0.2 g, 1.2 mmol) and tetrabutylammonium iodide (15 g) were added, and the mixture was stirred at 80 °C for 72 h. The mixture was then cooled to room temperature, and Et_2O (150 mL) was added to give a precipitate that was filtered off. The filtrate was evaporated and the resulting oil was submitted to column chromatography (SiO_2; first eluent, chloroform; second eluent, chloroform/methanol (97:3)) to give a small amount (0.018 g) of the pure compound that was converted into the hydrogen oxalate, mp 160−163 °C, and 0.2 g of a mixture of the desired compound and of a product of elimination. ^{1}H NMR (D_2O): δ 8.60 (s, 1H, Im-2*H*), 7.53 (t, 1H, Ph-5*H*), 7.38 (d, 1H, Ph-4*H*), 7.24 (m, 3H, Im-5*H*, Ph-2*H*, and Ph-6*H*), 4.21 (t, 2H, CH_2−O), 2.97 (t, 2H, Im-CH_2), 2.22 (q, 2H, CH_2−CH_2−CH_2). MS FAB(+): *m*/*z* 257 (M + H).

4-[4-(3-(Trifluoromethyl)phenoxy)butyl]-1*H*-imidazole Hydrogen Oxalate (19). 3-(Trifluoromethyl)phenol (1.92 mL, 2.56 g, 15.8 mmol) was dissolved in dry DMF (30 mL) under an atmosphere of nitrogen and cooled to 0 °C, and sodium hydride (60% dispersion in mineral oil, 0.316 g, 7.9 mmol) was added. The resulting mixture was stirred at 0 °C for 10 min, then at room temperature for a further 2 h. Then 1-(*N*,*N*-dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-(4-chlorobutyl)imidazole[23] (0.60 g, 1.58 mmol) and tetrabutylammonium iodide (50 mg) were added. The mixture was stirred at 80 °C for 72 h, then cooled to 20 °C and diluted with Et_2O (50 mL) and filtered. The filtrate was evaporated in vacuo to give an oil that was purified by column chromatography on silica gel using $CHCl_3$/MeOH (9:1) as eluant to yield 1-(*N*,*N*-dimethylsulfamoyl)-5-[4-(3-(trifluoromethyl)phenoxy)butyl]imidazole as a yellow oil (0.247 g, 40% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (s, 1H, Im-2*H*), 7.40−6.98 (m, 4H, Ph-*H*), 6.82 (s, 1H, Im-4*H*), 4.00 (t, 2H, CH_2O), 2.82 [s, 6H, N−(CH_3)$_2$], 2.80 (t, 2H, Im-CH_2), 1.98−1.74 [m, 4H, CH_2(CH_2)$_2$CH_2]. MS FAB(+): *m*/*z* 392 (M + H), 230 (M − $OC_6H_4CF_3$), 108 (SO_2N-(CH_3)$_2$).

A solution of 1-(*N*,*N*-dimethylsulfamoyl)-5-[4-(3-(trifluoromethyl)phenoxy)butyl]imidazole (0.2 g, 0.5 mmol) in 2 N HCl (50 mL) was heated under reflux for 12 h. After the reaction mixture (which contained the crude amine hydrochloride salt) was cooled to room temperature, it was basified (anhydrous K_2CO_3) and subsequently extracted with $CHCl_3$ (4 × 30 mL). The combined chloroform extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give the crude base as a yellow oil (16 mg, 73% overall yield). The yellow oil was converted to the oxalate salt in EtOH by adding 1.5 molar equiv of oxalic acid. Upon evaporation of the solvent and trituration of the resulting residue several times with Et_2O, the crude hydrogen oxalate was obtained (0.145 g). This was recrystallized from EtOH to give the product (0.117 g, 80% yield) as a white crystalline solid, mp 175−176 °C. ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H, Im-2*H*), 7.51 (t, *J* = 8.0 Hz, 2H, Ph-5*H*), 7.28−7.21 (m, 3H, Ph-2*H*, Ph-4*H*, Ph-6*H*), 7.15 (s, 1H, Im-4*H*), 4.07 (t, *J* = 5.46 Hz, 2H, *C*H_2O), 2.65 (t, *J* = 6.40 Hz, 2H, Im-CH_2), 1.77−1.74 (m, 4H, CH_2(CH_2)$_2$CH_2). MS FAB(+): *m*/*z* 285 (M + H), 139 [Im − $(CH_2)_4$ − O], 123 [Im − $(CH_2)_4$], 109 [Im − $(CH_2)_3$], 95 (Im − CH_2CH_2), 81 (Im − CH_2), 67 (Im).

4-[2-(3-(Trifluoromethyl)phenyl)thioethyl]-1*H*-imidazole Hydrogen Oxalate (20). To a cold solution of 3-(trifluoromethyl)thiophenol (1.6 g, 8.9 mmol), in dry DMF, was added slowly 0.18 g (4.5 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred, under nitrogen, at room temperature for 1 h. 4-(2-Chloroethyl)-1*H*-imidazole (0.15 g, 0.89 mmol) and tetrabutylammonium iodide (10 mg) were added, and the mixture was stirred at 80 °C for 24 h. The solvent was evaporated, and the oily residue was triturated with Et_2O. The mixture was filtered, and the product was extracted from the filtrate with dilute HCl. The aqueous layer was washed again with Et_2O and then basified (K_2CO_3). The product was extracted into $CHCl_3$ as an impure oil that was submitted to column chromatography (SiO_2; first eluant, $CHCl_3$; second eluant, $CHCl_3$/MeOH (97:3)) and then converted into the hydrogen oxalate (0.12 g, 38%), mp 158−160 °C. ^{1}H NMR: (D_2O) δ 8.41 (s, 1H, Im-2*H*), 7.65−7.45 (m, 4H, Ph-*H*), 7.18 (s, 1H, Im-5*H*), 3.37 (t, 2H, CH_2−S), 3.10 (t, 2H, Im CH_2). MS FAB(+): *m*/*z* 273 (M + H).

4-[4-(3-(Trifluoromethyl)phenyl)but-1-y1]-1*H*-imidazole Hydrogen Oxalate (22). Urocanic acid (4 g, 29 mmol)

was dissolved in absolute ethanol (140 mL), and a catalytic quantity of concentrated sulfuric acid (1.5 mL) was added. The resulting mixture was heated under reflux for 16 h. The solvent was evaporated to give an oily residue that was dissolved in water (30 mL), the solution was neutralized ($NaHCO_3$), and the resulting ethyl urocanate was extracted into EtOAc and isolated as an oil (2 g, 42% yield). The oil (0.77 g, 4.64 mmol) in dry DMF (11.5 mL) was treated with triethylamine (0.74 mL, 5.1 mmol) and triphenylmethyl chloride (1.43 g, 5.1 mmol) at room temperature, under nitrogen, for 6 h. The mixture was poured onto crushed ice (160 g) to give a cream precipitate that was collected and crystallized (Et_2O) to afford ethyl 3-[1-(triphenylmethyl)imidazol-4-yl]-propenate, mp 164−166 °C (yield 96%), reported[24] mp 160−161 °C. The propenate (1 g, 2.45 mmol), dissolved in freshly distilled THF (75 mL), was added dropwise with stirring and cooling to LAH (0.107 g, 0.28 mmol) in THF (6 mL), and stirring was continued at room temperature for 12 h. The mixture was decomposed by the dropwise addition of saturated aqueous Na_2SO_4. The resulting complex was filtered off, and the THF filtrate was dried ($MgSO_4$) and evaporated to give an oil that was submitted to column chromatography (first eluent, EtO_2; second eluent, Et_2O/EtOAc (50:50); third eluent, EtOAc) to furnish 1-(triphenylmethyl)-4-(3-hydroxypropenyl)-imidazole, mp 209−211 °C (yield 38%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40 (s, 1H, Im-2*H*), 7.37−7.08 (m, 16H, trityl-*H* and C_1−*H*), 6.72 (s, 1H, Im-5*H*), 6.42 (m, 1H, C_2−*H*), 4.25 (d, 2H, CH_2). MS FAB(+): *m*/*z* 367 (M + H), 243 (CPh_3).

1-(Triphenylmethyl)-4-(3-hydroxypropenyl)imidazole (0.355 g, 0.96 mmol) was dissolved in dioxane (10 mL), and activated MnO_2 (0.843 g, 9.6 mmol) was added. The resulting mixture was heated under reflux for 4 h. The hot reaction mixture was filtered through a Celite pad, and the dioxane was evaporated in vacuo. The product was recrystallized from Et_2O and petroleum spirit (1:3) to afford 1-(triphenylmethyl)-4-(2-carboxaldehydoethenyl)imidazole in 70% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.58 (d, 1H, C*H*O, $J_{2,3}$ = 8 Hz), 7.50 (s, 1H, Im-2*H*), 7.48−7.04 (m, 17H, trityl-*H*, C_1−*H*, and Im-5*H*), 6.76 (dd, 1H, C_2−*H*, $J_{1,2}$ = 16 Hz and $J_{2,3}$ = 8 Hz). MS FAB(+): *m*/*z* 365 (M + H), 243 (CPh_3).

To a stirred solution of 3-(trifluoromethyl)benzyltriphenylphosphonium bromide (0.49 g, 0.98 mmol) in freshly distilled THF (6 mL) at −78 °C under nitrogen was added dropwise *n*-butyllithium (0.49 mL of 1.6 M solution in hexane). The resulting yellow mixture was allowed to reach room temperature very slowly during 2 h. The solution was cooled again to −78 °C, and a solution of 1-(triphenylmethyl)-4-(2-carboxaldehydoethenyl)imidazole (0.18 g, 0.49 mmol) in 4 mL of freshly distilled THF was added dropwise over 10 min. After the mixture was stirred at −78 °C for 30 min, the reaction was continued at room temperature overnight. The THF was evaporated, and the resulting oil was submitted to column chromatography (first eluent, Et_2O/petroleum spirit (25:75); second eluent, Et_2O/petroleum spirit (50:50)). The first fraction contained 0.09 g (0.18 mmol) of the isomer *EE* and the second fraction contained 0.06 g (0.12 mmol) of a mixture of isomers *EE* and *EZ* of the product 1-triphenylmethyl-4-[4-(3-(trifluoromethyl)phenyl)buta-1,3-dienyl]imidazole. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62 (t, 1H, Ph-5*H*), 7.52 (s, 1H, Im-2*H*), 7.44−7.09 (m, 19H, trityl-*H*, Ph-4*H*, C_1−*H*, C_2−*H*, and C_3−*H*), 6.81 (s, 1H, Im-5*H*), 6.56 (d, 1H, C_4−*H*), 6.39−6.36 (m, 2H, Ph-2*H* and Ph-6*H*). MS FAB(+): *m*/*z* 507 (M + H), 264 (M − CPh_3 + H), 243 (CPh_3).

The mixture of 1-triphenylmethyl-4-[4-(3-(trifluoromethyl)-phenyl)buta-1,3-dienyl]imidazoles (0.133 g, 0.26 mmol) was dissolved in EtOH (10 mL) and hydrogenated with 10% palladium on charcoal (30 mg) at 50 °C for 7 h. The catalyst was filtered off and the EtOH was evaporated to give the reduced compound partially deprotected as an oil. This oil was dissolved in THF (1 mL) and heated with HCl (2 N, 4.5 mL) at 70 °C for 4 h. The THF was evaporated under reduced pressure, and Ph_3COH was extracted with Et_2O. The aqueous layer was neutralized (K_2CO_3), and the product was extracted into $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to give an oil that was dissolved in *i*-PrOH. Oxalic acid (1.2 equiv) was added, and the product precipitated as a hydrogen oxalate (0.028 g, 32%) by addition of Et_2O, mp 181−183 °C. ^{1}H NMR (DMSO− d_6): δ 8.27 (s, 1H, Im-2*H*), 7.50 (m, 4H, Ph-*H*), 7.07 (s, 1H, Im-5*H*), 2.66 (m, 2H, Im-CH_2), 2.59 (t, 2H, Ph-CH_2), 1.60 (m, 4H, CH_2−(CH_2)$_2$−CH_2). MS FAB(+): *m*/*z* 269 (M + H^+), 201 (M − imidazole).

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References

(1) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-inhibition of Brain Histamine Release Mediated by a Novel Class (H_3) of Histamine Receptor. *Nature (London)* **1983**, *302*, 832−837.

(2) 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.

(3) 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.

(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) (a) Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J.-C.; Shankley, N. P.; Young, J.-M.; Schunack, W.; Levi, R.; Haas, H. L. International Union of Pharmacology. XIII. Classification of Histamine Receptors. *Pharmacol. Rev.* **1997**, *49*, 253−278. (b) Hough, L. B. Genomics Meets Histamine Receptors: New Subtypes, New Receptors. *Mol. Pharmacol.* **2001**, *59*, 415−419.

(6) (a) Stark, H.; Arrang, J.-M.; Ligneau, X.; Garbarg, M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W. The histamine H_3 receptor and its ligands. *Prog. Med. Chem.* **2001**, *38*, 279−308. (b) Phillips, J. G.; Ali, S. M.; Yates, S. L.; Tedford, C. E. Recent Advances in Histamine H_3 Receptor Agents. *Annu. Rep. Med. Chem.* **1998**, *33*, 31−40. (c) Stark, H. Recent Advances in Histamine H_3/H_4 Receptor Ligands. *Expert Opin. Ther. Pat.* **2003**, *13*, 851−865. (d) Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. Therapeutic Potential of Histamine H_3-Receptor Agonists and Antagonists. *Trends Pharmacol. Sci.* **1998**, *19*, 177−183.

(7) (a) Stark, H.; Krause, M.; Rouleau, A.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. Enzyme-Catalyzed Prodrug Approaches for the Histamine H_3 Receptor Agonist (*R*)-α-Methylhistamine. *Bioorg. Med. Chem.* **2001**, *9*, 191−198. (b) Rouleau, A.; Stark, H.; Schunack, W.; Schwartz, J.-C. Anti-inflammatory and Antinociceptive Properties of BP 2-94, a Histamine H_3-Receptor Agonist Prodrug. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 219−225. (c) Rouleau, A.; Garbarg, M.; Ligneau, X.; Mantion, C.; Lavie, P.; Advenier, C.; Lecomte, J.-M.; Krause, M.; Stark, H.; Schunack, W.; Schwartz, J.-C. Bioavailability, Antinociceptive and Anti-inflammatory Properties of BP 2-94, a Histamine H_3 Receptor Agonist Prodrug. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1085−1094.

(8) (a) 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. (b) Ganellin, C. R.; Bang-Andersen, 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. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1231−1234. (c) 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. (d) Howson, W.; Parsons, M. E.; Raval, P.; Swayne, G. T. G. Two Novel, Potent and Selective Histamine H_3 Antagonists. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 77−78.

(9) (a) Vollinga, R. C.; de Koning, J. P.; Jansen, F. P.; Leurs, R.; Menge, W. M. P. B.; Timmerman, H. A New Potent and Selective Histamine H_3 Receptor Agonist, 4-(1*H*-Imidazol-4-ylmethyl)-

piperidine. *J. Med. Chem.* **1994**, *37*, 332−333. (b) Shih, N. Y.; Lupo, A. T.; Aslanian, R.; Orlando, S.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Clark, M. A.; Tozzi, S.; Kreutner, W.; Hey, J. A. A Novel Pyrrolidine Analog of Histamine as a Potent, Highly Selective Histamine H_3 Receptor Agonist. *J. Med Chem.* **1995**, *38*, 1593−1599.

(10) (a) Harusawa, S.; Imazu, T.; Takashima, S.; Araki, L.; Ohishi, H.; Kurihara, T.; Yamamoto, Y.; Yamatodani, A. Synthesis of Imifuramine and Its Stereoisomers Exhibiting Histamine H_3-Agonist Activity. *Tetrahedron Lett.* **1999**, *40*, 2561−2564. (b) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. Cyclopropane-Based Conformational Restriction of Histamine. (1*S*,2*S*)-2-(2-Aminoethyl)-1-(1*H*-imidazol-4-yl)cyclopropane, a Highly Selective Agonist for the Histamine H_3 Receptor, Having a *cis*-Cyclopropane Structure. *J. Med. Chem.* **2003**, *46*, 1980−1988.

(11) (a) Vollinga, R. C.; Menge, W. M. P. B.; Leurs, R.; Timmerman, H. Homologs of Histamine H_3 Receptor Antagonists. A New Potent and Selective H_3 Antagonist, 4(5)-(5-Aminopentyl)-1*H*-imidazole *J. Med. Chem.* **1995**, *38*, 266−271. (b) Leurs, R.; Kathmann, M.; Vollinga, R. C.; Menge, W. M. P. B.; Schlicker, E.; Timmerman, H. Histamine Homologues Discriminating between Two Functional H_3 Receptor Assays. Evidence for H_3 Receptor Heterogeneity? *J. Pharmacol. Exp. Ther* **1996**, *276*, 1009−1015.

(12) (a) Gros, J.; Manning, B. S.; Pietri-Rouxel, F.; Guillaume, J.-L.; Drumare, M.-F.; Strosberg, A. D. Site-Directed Mutagenesis of the Human β_3-Adrenoceptor. Transmembrane Residues Involved in Ligand Binding and Signal Transduction. *Eur. J. Biochem.* **1988**, *251*, 590−596. (b) Fraser, C. M.; Wang, C.-D.; Robinson, D. A.; Gocayne, J. D.; Venter, J. C. Site-Directed Mutagenesis of the m_1 Muscarinic Receptor; Conserved Aspartic Acids Play Important Roles in Receptor Function. *Mol. Pharmacol.* **1989**, *36*, 840−847. (c) Jackson, T. Structure and Function of G Protein Coupled Receptors. *Pharmacol. Ther.* **1991**, *50*, 425−442. (d) Beck-Sickinger, A. G. Structural Characterization and Binding Sites of G-Protein Coupled Receptors. *Drug Discovery Today* **1996**, *1*, 502−513.

(13) (a) Ohta, K.; Hayashi, H.; Mizuguchi, H.; Kagamiyama, H.; Fujimoto, K.; Fukui, H. Site-Directed Mutagenesis of the Histamine H_1 Receptor: Roles of Aspartic Acid[107], Asparagine[198] and Threonine[194]. *Biochem. Biophys. Res. Commun.* **1994**, *203*, 1096−1101. (b) Wieland, K.; Laak, A. M. T.; Smit, M. J.; Kuhne, R.; Timmerman, H.; Leurs, R. Mutational Analysis of the Antagonist-Binding of the Histamine H_1 Receptor. *J. Biol. Chem.* **1999**, *274*, 29994−30000. (c) Gantz, I.; DelValle, J.; Wang, L.-D.; Tashiro, T.; Munzert, G.; Guo, Y.-J.; Konda, Y.; Yamada, T. Molecular Basis for the Interaction of Histamine with the Histamine H_2 Receptor. *J. Biol. Chem.* **1992**, *267*, 20840−20843. (d) Shin, N.; Coates, E.; Murgolo, N. J.; Morse, K. L.; Bayne, M.; Strader, C. D.; Monsma, F. J. Molecular Modeling and Site-Specific Mutagenesis of the Histamine-Binding Site of the Histamine H_4 Receptor. *Mol. Pharmacol.* **2002**, *62*, 38−47. (e) Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. Cloning and Functional Expression of the Human Histamine H_3 Receptor. *Mol. Pharmacol.* **1999**, *55*, 1101−1107.

(14) (a) Sasse, A.; Stark, H.; Reidemeister, S.; Hüls, A.; Elz, S.; Ganellin, C. R.; Ligneau, X.; Schwartz, J.-C.; Schunack, W. Novel Partial Agonists for the Histamine H_3 Receptor with High in Vitro and in Vivo Activity. *J. Med. Chem.* **1999**, *42*, 4269−4274. (b) Sasse, A.; Stark, H; Ligneau, X.; Elz, S.; Reidemeister, S.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W. (Partial) Agonist/Antagonist Properties of Novel Diarylalkyl Carbamates on Histamine H_3 Receptors. *Bioorg. Med. Chem.* **2000**, *8*, 1139−1149. (c) Sasse, A.; Ligneau, X.; Rouleau, A.; Elz, S.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. Influence of Bulky Substituents on Histamine H_3 Receptor Agonist/Antagonist Properties. *J. Med. Chem.* **2002**, *45*, 4000−4010.

(15) Schunack, W.; Sasse, A.; Stark, H.; Elz, S.; Ligneau, X.; Ganellin, C. R.; Schwartz, J.-C. Partial Agonists for the Histamine H_3 Receptor with High in Vivo Activity. In *Histamine Reasearch in the New Millenium*; Watanabe, T., Timmerman, H., Yanai, K., Eds.; Elsevier Science B.V.: Amsterdam, 2001; pp 77−82.

(16) (a) Van der Vliet, A.; Van der Werf, J. F.; Bast, A.; Timmerman, H. Frequency-Dependent Autoinhibition of Histamine Release from Rat Cortical Slices: A Possible Role for H_3 Receptor Reserve. *J. Pharm. Pharmacol.* **1988**, *40*, 577−579. (b) Leurs, R.; Smit, M. J.; Timmerman, H. Molecular Pharmacological Aspects of Histamine Receptors. *Pharmacol. Ther.* **1995**, *66*, 413−463.

(17) (a) Gbahou, F.; Rouleau, A.; Morisset, S.; Parmentier, R.; Crochet, S.; Lin, J.-S.; Ligneau, X.; Tardivel-Lacombe, J.; Stark, H.; Schunack, W.; Ganellin, C. R.; Schwartz, J.-C.; Arrang, J.-M. Protean Agonism at Histamine H_3 Receptors in Vitro and in Vivo. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 11086−11091. (b) Schlicker, E.; Kathmann, M.; Bitschnau, H.; Marr, I.; Reidemeister, S.; Stark, H.; Schunack, W. Potencies of Antagonists Chemically Related to Iodoproxyfan at Histamine H_3 Receptors in Mouse Brain Cortex and Guinea-Pig Ileum: Evidence for H_3 Receptor Heterogeneity? *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1996** *353*, 482−488. (c) Wulff, B. S.; Hastrup, S.; Rimvall, K. Characteristics of recombinantly expressed rat and human histamine H_3 receptors. *Eur. J. Pharmacol.* **2002**, *453*, 33−41. (d) Low, C. M. R.; Vinter, J. G.; Kalindjian, S. B.; Pether, M. J. The Molecular Origins of Agonism at Histamine H_3-Receptors: An Investigation of Agonist Behaviour in Halogenated Derivatives of Proxyfan, 3-(1*H*-Imidazol-4-yl)propylphenylmethyl ether. Presented at the British Pharmacological Society Autumn Meeting, Edinburgh, September 1−4, 1997; Poster P151; *Br. J. Pharmacol.* **1997**, *122* (Suppl.), 433P. (e) Watt, G. F.; Sykes, D. A.; Roberts, S. P.; Shankley, N. P.; Black, J. W. Estimation of Agonist Affinity and Efficacy Parameters of Histamine H_3-Receptor Ligands in Guinea-Pig Ileum. *Br. J. Pharmacol.* **1997**, *122* (Suppl.), 435. (f) Lovenberg, T. W.; Pyati, J.; Chang, H.; Wilson, S. J.; Erlander, M. G. Cloning of Rat Histamine H_3 Receptor Reveals Distinct Species Pharmacological Profiles. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 771−778. (g) Chen, J.; Liu, C.; Lovenberg, T. W. Molecular and Pharmacological Characterization of the Mouse Histamine H_3 Receptor. *Eur. J. Pharmacol.* **2003**, *467*, 57−65.

(18) Vollinga, R. C.; Zuiderveld, O. P.; Scheerens, H.; Bast, A.; Timmerman, H. A Simple and Rapid in Vitro Test System for the Screening of Histamine H_3 Ligands. *Methods Find. Exp. Clin. Pharmacol.* **1992**, *14*, 747−751.

(19) (a) 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. (b) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. [^{125}I] Iodoproxyfan and Related Compounds: A Reversible Radioligand and Novel Classes of Antagonists with High Affinity and Selectivity for the Histamine H_3 Receptor. *J. Med. Chem.* **1996**, *39*, 1220−1226.

(20) (a) Ganellin, C. R.; Fkyerat, A.; Bang-Andersen, B.; Athmani, S.; Tertiuk, W.; Garbarg, M.; Ligneau, X.; Schwartz, J.-C. A Novel Series of (Phenoxyalkyl)imidazoles as Potent H_3-Receptor Histamine Antagonists. *J. Med. Chem.* **1996**, *39*, 3806−3813. (b) Ligneau, X.; Lin, J.-S.; Vanni-Mercier, G.; Jouvet, M.; Muir, J. L.; Ganellin, C. R.; Stark, H.; Elz, S.; Schunack, W.; Schwartz, J.-C. Neurochemical and Behavioral Effects of Ciproxifan, a Potent Histamine H_3 Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 658−666. (c) Stark, H.; Sadek, B.; Krause, M.; Hüls, A.; Ligneau, X.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. Novel Histamine H_3-Receptor Antagonists with Carbonyl-Substituted 4-(3-(Phenoxypropyl)-I*H*-imidazole Structures Like Ciproxifan and Related Compounds. *J. Med. Chem.* **2000**, *43*, 3987−3994. (d) Sasse, A.; Sadek, B.; Ligneau, X.; Elz, S.; Pertz, H. H.; Luger, P.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. New Histamine H_3-Receptor Ligands of the Proxifan Series: Imoproxifan and Other Selective Antagonists with High Oral in Vivo Potency. *J. Med. Chem.* **2000**, *43*, 3335−3343.

(21) (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.

(22) Williamson, A. About the Theory of the Formation of Ethers. *Ann. Chem.* **1851**, *77*, 37−49.

(23) Vollinga, R. C.; Menge, W. M. P. B.; Timmerman, H. A New Convenient Route for the Synthesis of 4(5)-(ω-Aminoalkyl)-1-*H*-imidazoles. *Recl. Trav. Chim. Pays-Bas.* **1993**, *112*, 123−125.

(24) Griffith, R. K.; DiPietro, R. A. Improved Synthesis of Vinylimidazoles. *Synth. Commun.* **1986**, *16*, 1761−1770.

(25) Pauling, L. *The Nature of the Chemical Bond*; Cornell University: Ithaca, NY, 1960; pp 224−229.

(26) Schwartz, J.-C.; Pollard, H.; Bischoff, S.; Rehault, M. C.; Verdiere, M. Catabolism of ^{3}H-Histamine in the Rat Brain after Intracisternal Administration. *Eur. J. Pharmacol.* **1971**, *16*, 326−335.

(27) Jensen, T. S. Synthesis of Imidazole Derivatives Acting at Histamine H_3 Receptors. M.Sc. Thesis, University College, London, 1995; pp 73−75.

(28) (a) Watt, G. F.; Hamilton, L. C.; Shankley, N. P.; Black, J. W. Analysis of H_1-, H_2- and H_3-Receptor-Mediated Components of the Response to Histamine in Guinea-Pig Isolated Ileum. *Br. J. Pharmacol.* **1997**, *122* (Suppl.), 435. (b) Result provided by Dr. Gillian F. Watt, James Black Foundation, London, U.K.

(29) (a) Ligneau, X.; Morisset, S.; Tardivel-Lacombe, J.; Gbahou, F.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J.-C.; Arrang, J.-M. Distinct Pharmacology of Rat and Human Histamine H_3

Receptors: Role of Two Amino Acids in the Third Transmembrane Domain. *Br. J. Pharmacol.* **2000**, *131*, 1247−1250. (b) Apelt, J.; Ligneau, X.; Pertz, H. H.; Arrang, J.-M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. Development of a New Class of Nonimidazole Histamine H_3 Receptor Ligands with Combined Inhibitory Histamine *N*-Methyltransferase Activity. *J. Med. Chem.* **2002**, *45*, 1128−1141.

(30) *CLOG P for Windows*, version 2.0.0.b; BioByte Corp.: Claremont, CA.

(31) (a)Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Autoregulation of histamine release in brain by presynaptic H_3-receptors. *Neuroscience* **1985**, *15*, 553−562. (b) *The Histamine Receptor*; Schwartz, J.-C., Haas, H. L., Eds.; Wiley-Liss: New York, 1992; pp 161−177. (c) Takeshita, Y.; Watanabe, T.; Sakata, T.; Munakata, M.; Ishibashi, H.; Akaike, N. Histamine modulates high-voltage-activated calcium channels in neurons dissociated from the rat tuberomammillary nucleus. *Neuroscience* **1998**, *87*, 797−805.

(32) (a) Morisset, S.; Rouleau, A.; Ligneau, X.; Gbahou, F.; Tardivel-Lacombe, J.; Stark, H.; Schunack, W.; Ganellin, C. R.; Schwartz, J.-C.; Arrang, J.-M. High Constitutive Activity of Native H_3 Receptors Regulates Histamine Neurons in Brain. *Nature* **2000**, *408*, 860−864. (b) Rouleau, A.; Ligneau, X.; Tardivel-Lacombe, J.; Morisset, S.; Gbahou, F.; Schwartz, J.-C.; Arrang, J.-M. Histamine H_3-Receptor-Mediated [^{35}S]GTPγ[S] Binding: Evidence for Constitutive Activity of the Recombinant and Native Rat and Human H_3 Receptors. *Br. J. Pharmacol.* **2002**, *135*, 383−392. (c) Wieland, K.; Bongers, G.; Yamamoto, Y.; Hashimoto, T.; Yamatodani, A.; Menge, W. M. B. P.; Timmerman, H.; Lovenberg, T. W.; Leurs, R. Constitutive Activity of Histamine H_3 Receptors Stably Expressed in SK-N-MC Cells: Display of Agonism and Inverse Agonism by H_3 Antagonists. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 908−914.

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