Novel Histamine H_3-Receptor Antagonists with Carbonyl-Substituted 4-(3-(Phenoxy)propyl)-1*H*-imidazole Structures like Ciproxifan and Related Compounds†

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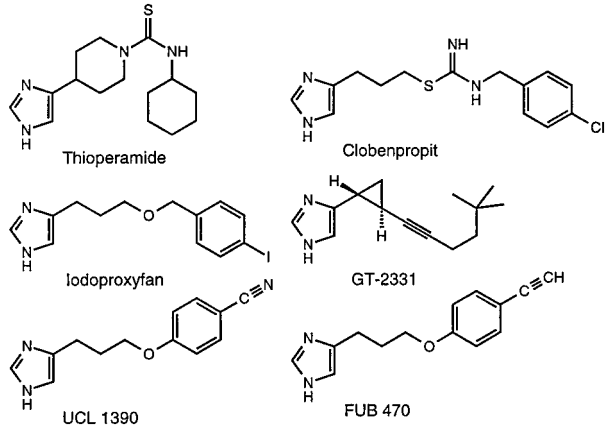
Novel histamine H_3-receptor antagonists possessing a 4-(3-(phenoxy)propyl)-1*H*-imidazole structure generally substituted in the *para*-position of the phenyl ring have been synthesized according to Mitsunobu or S_NAr reactions. With in vitro and in vivo screening for H_3-receptor antagonist potency, the carbonyl-substituted derivatives proved to be highly active compounds. A number of compounds showed in vitro affinities in the subnanomolar concentration range, and the 4-hexanoyl (**10**) and 4-acetyl-3-methyl (**29**) substituted derivatives showed in vivo antagonist potencies of about 0.1 mg/kg after po administration. Many proxifans were also tested for their affinities at other histamine receptor subtypes thereby demonstrating their pronounced H_3-receptor subtype selectivity. Since the cyclopropyl ketone derivative **14** (ciproxifan) had high affinity in vitro as well as high potency in vivo, it was selected for further studies in monkeys. It showed good oral absorption and long-lasting, dose-dependent plasma levels making it a promising compound for drug development.

Introduction

Histamine is a well-known messenger in various (patho)physiological conditions. Receptor-dependent effects are mediated by three different established proteins: H_1, H_2, and H_3 receptors.[3,4] Whereas the H_1 and H_2 receptors are located postsynaptically, the H_3 receptors can be located both pre- and postsynaptically. Discovery of the H_3 receptor helped to clarify the neurotransmitter function of histamine. On H_3-receptor activation, inhibition of histamine release[5] and inhibition of histamine synthesis[6] have been observed on histaminergic axon terminals. H_3-Receptor antagonists increase histaminergic neuron activity by inhibition of this feedback mechanism. H_3 Heteroreceptors on nonhistaminergic neurons in the brain as well as in the periphery influence a portfolio of different classical neurotransmitters and neuropeptides.[7] Therefore, numerous potential therapeutic targets for histamine H_3-receptor antagonists have been proposed, most of them derived from pharmacological in vitro or in vivo studies. Since the highest density of H_3 receptors is found in distinct areas of the central nervous system (CNS), the treatment of neurological and psychiatric diseases seems to be most promising, e.g., schizophrenia, attention-deficit hyperactivity disorder (ADHD), dementia, epilepsy, or narcolepsy.[8]

Chart 1. Histamine H_3-Receptor Antagonists



Developments in the medicinal chemistry field of histamine H_3-receptor antagonists have yielded numerous compounds that are highly active in vitro and some of them also in vivo. Although these compounds possess different functionalities, they all have more or less in common an imidazole heterocycle connected by a spacer with a polar group being optionally connected by another spacer to a lipophilic group.[8] With this modular construction pattern it seems that one element can be replaced by another structurally different moiety if the rest of the molecule displays enough receptor affinity. Classical antagonists are thioperamide and clobenpropit (Chart 1). Newer antagonists such as UCL 1390,[9] FUB 470,[10] or the (un)labeled iodoproxyfan,[11] which displays partial agonism in some test models, have been described which offer some potential benefit in affinity, selectivity, and/or toxicity. Most recently the chiral compound GT-2331[12] (Perceptin) has been described as

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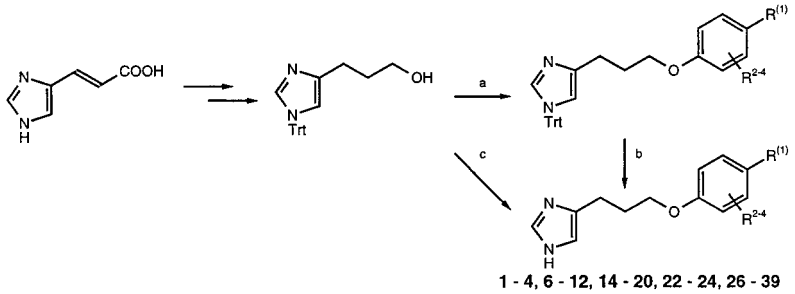
Scheme 1. General Procedures for Synthesis of Arylproxifans[a]



[a] Trt, trityl; (a) Ph_3P, DEAD, corresponding phenol, THF; (b) HCl, acetone; (c) (i) NaH, toluene, (ii) corresponding fluoroaromate, (iii) HCl, THF.

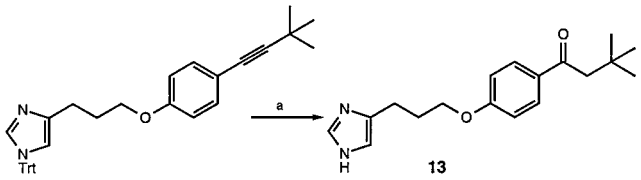
entering phase II in clinical trials for the treatment of ADHD.[13] The outcome of this first clinical trial of H_3-receptor antagonists and the recent cloning of human[14] and rodent[15] histamine H_3 receptors will highly influence further developments.

Since compounds such as UCL 1390 and FUB 470, which have an imidazolylpropoxy moiety in common, have high in vivo activity (cf. Table 1) we selected the *para*-substituted 4-(3-(phenoxy)propyl)-1*H*-imidazole as a pharmacophore for further elaboration. The triple bond of the cyano or alkynyl group should be replaced by other moieties, preferably by electron-withdrawing groups which are expected to be nontoxic. This study is focused on carbonyl-substituted derivatives since the antagonist potency of these compounds was found to be higher than that of compounds with other substituents. The influence of the acyl group in the *para*-position of the phenyl ring, the influence of the position of the carbonyl group in the *para*-substituents, and the effects of additional substituents in the phenyl ring were investigated. Synthesis and pharmacological H_3-receptor antagonist screening of the compounds are described to provide information for structure−activity relationships (SARs). Additional pharmacological screening for histamine receptor subtype selectivity, histamine-*N*-methyltransferase inhibitory activity, and in vivo kinetics was also performed for selected compounds.

Chemistry

The key intermediate for all the compounds was the trityl-protected 3-(1*H*-imidazol-4-yl)propanol which was conveniently prepared from commercially available urocanic acid.[11a] Ether formation was effected by a Mitsunobu type synthesis[16] with the corresponding phenol derivative as described before (Scheme 1).[9] Deprotection under acidic conditions resulted in the final products (**1**−**4**, **6**−**12**, **14**−**18**, **20**, **22**−**24**, **27**−**31**, **38**, **39**, and with modifications for **13** and **25**). The mild conditions using the Mitsunobu protocol were useful for almost all carbonyl-substituted phenol derivatives which tend to undergo unwanted side reactions under different reaction conditions. Alternative methods such as the Williamson synthesis with 4-(3-chloropropyl)-1*H*-imidazole[17] were not successful due to intramolecular cyclization and partial polymerization under basic conditions. The corresponding carbonyl-substituted phenol derivatives were prepared by Friedel−Crafts alkylation of phenol in nitrobenzene at ambient or slightly increased temperature using an excess of $AlCl_3$. Mixtures of isomeric *ortho*- and *para*-substituted phenol derivatives when obtained were readily separated by standard chromatographic procedures. The phenol for the synthesis of **24** was prepared by aldol reaction with 4-hydroxybenzaldehyde and acetone under standard conditions. In cases where the corresponding methoxy derivative was commercially available (**14**, **36**, **37**) the requisite phenol was obtained most conveniently by ether cleavage using BBr_3·etherate in dichloromethane at low temperature according to known methods.[10]

Scheme 2. Synthesis of **13**[a]

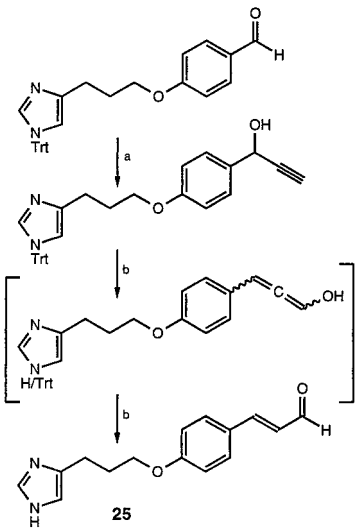


[a] Trt, trityl; (a) EtOH, HCl, acetone, reflux, 45 min or HCOOH (90%), ambient temperature, 24 h.

Another method for ether formation is a nucleophilic substitution (S_NAr) on fluoroaromatics containing additional electron-withdrawing substituents. This reaction was performed with the sodium salt of the synthon as nucleophile and corresponding fluorophenyl derivatives, followed by deprotection for compounds **19**, **26**, and **32**−**35** (Scheme 1). The yields vary to a large extent depending on the aryl substituents, but this is an expedient way to obtain the final compounds from commercially available starting materials.

The benzyl alcohol **5** was obtained by reduction of **4** with complex hydrides (e.g., $LiAlH_4$). The carboxylic acid **21** was prepared by acidic ester hydrolysis of **20**. As shown in Scheme 2 compound **13** was obtained from the corresponding alkynyl-substituted phenyl ether which was prepared by Heck reaction of (4-iodophenoxy)-methoxymethane (Mom-protected 4-iodophenol) with 3,3-dimethylbutyne, phenol deprotection with sodium ethanthiolate, and following Mitsunobu reaction with the key synthon, 3-(1-trityl-1*H*-imidazol-4-yl)propanol. The tritylated alkynyl precursor molecule obtained was prepared according to a method described before for related *tert*-butoxycarbonyl (Boc)-protected imidazole derivatives for the synthesis of alkynylphenyl derivatives.[10] Deprotection under acidic conditions led to an addition of water to the C−C triple bond and formation of the tautomeric carbonyl isomer **13** (Scheme 2). Taking corresponding trimethylsilyl- or alkyl-substituted alkynyl precursor molecules for the Heck reaction and performing the analogous reaction steps, compounds **6** or **7** and **8**, respectively, were also prepared by this

Scheme 3. Synthesis of **25**[a]



[a] Trt, trityl; (a) HC≡CMgBr, THF, reflux, 1 h; (b) EtOH, HCl, acetone, reflux, 45 min.

method, but total yields were lower as compared to the Mitsunobu protocol mentioned before (results not shown).

Another indirect way of preparation was applied for compound **25**. The tritylated precursor of the benzaldehyde compound **4** was isolated and subjected to a Grignard reaction with ethynylmagnesium bromide. This propargyl alcohol intermediate rearranged into the cinnamaldehyde derivative **25** in the course of acid-catalyzed detritylation (Scheme 3). This isomerization is known as Meyer−Schuster rearrangement and describes the acid catalyzed 1,3-rearrangement of secondary or tertiary alcohols with an ethynyl functionality leading to α,β-unsaturated carbonyl derivatives via the corresponding ketenol intermediate (Scheme 3).[18] By this rearrangement terminal alkynes result in corresponding aldehydes as shown with **25**. It should also be possible to get this compound directly by reacting 4-hydroxycinnamaldehyde with the key intermediate followed by deprotection. But the tritylated propargyl intermediate was available to us from previous studies for the design of histamine H_3-receptor antagonists,[10] and therefore, this was the most convenient route for the preparation of **25**.

Pharmacological Results and Discussion

In Vitro Assay on Synaptosomes of Rat Cerebral Cortex. The novel compounds were tested for their effect at histamine H_3 receptors in vitro on synaptosomes of rat cerebral cortex for the release of [^{3}H]-histamine (Tables 1 and 2).[19] All compounds had antagonist properties at H_3 receptors in vitro.

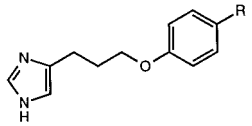
Most compounds displayed antagonist potencies in the nanomolar or even subnanomolar concentration range. It can be clearly seen that the electronic properties of the *para*-substituents do not influence affinity to a large extent because compounds possessing electron-donating substituents (**2**, **3**, **5**, **22**, **23**, **38**, **39**) showed comparable potency to those with electron-withdrawing substituents (e.g., **4**, **6**, **24**−**26**, **36**, **37**). The same is true for polysubstituted derivatives (e.g., **6** → **28** → **29**, **31** → **32**; Table 2). Nevertheless, it should be stated that most acyl derivatives possess a tendency for higher in vitro affinity compared to the rather low number of other substituents previously tested (F, CF_3, C≡C−R with R = CH_3, C_3H_7, $C(CH_3)_3$, $Si(CH_3)_3$)[9,10] and in this series. Moreover, steric factors seem to be more important than electronic properties. Larger alkyl substituents on the carbonyl moiety slightly decreased affinity (e.g., **6**, **7** → **8** → **9**, **10** → **11**; **12** → **13**; **14** → **15** → **16**). Compounds possessing moieties with additional binding properties distant to the carbonyl group, e.g., **18**−**21**, showed obviously decreased affinity. The steric factor is also important within the series of polysubstituted derivatives (Table 2). Two methyl groups in the neighborhood (*ortho*-related) of the acetyl group strongly decreased affinity, whereas the second methyl group in another position (*meta*-related) exhibited a less pronounced effect (**30** → **31**). Affinity was also decreased when other groups adjacent to the acetyl group could influence its orientation (**32**, **33**). In this series small lipophilic substituents on the carbonyl group seem to be optimal since the acetyl (**6**), propionyl (**7**), cyclopropylcarbonyl (**14**), and cyclobutylcarbonyl (**15**) derivatives displayed subnanomolar affinities.

In Vivo Screening in Mice CNS. The novel compounds were also screened for their effect at histamine H_3 receptors in vivo on mice brain cortex after po administration measuring the increase in N^τ-methylhistamine level, the main histamine metabolite.[19] All those compounds where potency could be detected in vivo had antagonist properties at H_3 receptors. Surprisingly, the simple phenoxy derivative **1** as well as the derivatives with hydroxy groups (**2**, **5**, **21**) did not show any in vivo potency. Compared to their relative high in vitro affinity, pharmacokinetic properties seem to be one of the most probable reasons for the in vivo failure of these compounds as well as of **4**, **18**−**25**, **27**, **30**, and **33**.

Our present data do not show direct correlation between the potencies of compounds as antagonists in vitro and in triggering histamine neuron activation in vivo. Very recently it has also been shown that not all histamine H_3-receptor antagonists influence the N^τ-methylhistamine CNS level to the same extent although they are reaching brain areas.[20] Therefore, it can be concluded that despite the direct antagonist effect on H_3 receptors other factors that influence the N^τ-methylhistamine level cannot be excluded. This complex topic needs further investigation because different G protein coupling, different pharmacology of somatodendritic vs presynaptic H_3 receptors, receptor cross-reactivity, influence on enzymes of histamine metabolism, etc., may be reasons for these apparent discrepancies.

The statement concerning the electronic and steric effect for the in vitro affinity also applies for the in vivo potency. Different "proxifans", which are compounds possessing a 3-(1*H*-imidazol-4-yl)propoxy moiety, showed strikingly high in vivo potency. Antagonists **3**, **6**−**11**, **13**−**17**, **28**, **29**, **31**, **32**, and **34** were active in a dose range below 1 mg/kg after peroral administration and compounds **10** and **29** even below 0.1 mg/kg. For the different *n*-alkyl chains on the carbonyl group (**6**−**21**) increasing chain length slightly increased potency reaching an optimum with the hexanoyl moiety (**10**). Its isomeric compound **13** was significantly less effective suggesting that in addition to the presumed benefit of

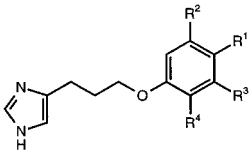
Table 1. Structures, Physical Data, and Pharmacological Screening Results of *Para*-Substituted 4-(3-(Phenoxy)propyl)-1*H*-imidazoles for Histamine H_3-Receptor Antagonist Potency in Vitro and in Vivo in Rodents



no.	R	formula	M_r	yield (%)	mp (°C)	K_i[a] (nM) $\bar{x} \pm s_{\bar{x}}$	ED_{50}[b] (mg/kg) $\bar{x} \pm s_{\bar{x}}$
1	H	$C_{12}H_{14}N_2O \cdot 0.95C_2H_2O_4$	278.8	35	163−165	55 ± 11	>10
2	OH	$C_{12}H_{14}N_2O_2 \cdot C_4H_4O_4$	334.3	30	138	18 ± 4	>10
3	OCH_3	$C_{13}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	352.9	85	120−121	2.2 ± 0.4	0.20 ± 0.08
4	CHO	$C_{13}H_{14}N_2O_2 \cdot C_4H_4O_4$	346.3	85	120	12 ± 3	∼30
5	CH_2OH	$C_{13}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	352.9	50	134	8.9 ± 1.5	>10
6	$CO-CH_3$	$C_{14}H_{16}N_2O_2 \cdot C_4H_4O_4$	360.4	80	118	0.80 ± 0.16	0.24 ± 0.06
7	$CO-C_2H_5$	$C_{15}H_{18}N_2O_2 \cdot C_4H_4O_4$	374.4	80	136	0.74 ± 0.07	0.27 ± 0.09
8	$CO-C_3H_7$	$C_{16}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$	406.4	75	87	1.9 ± 0.4	0.17 ± 0.05
9	$CO-C_4H_9$	$C_{17}H_{22}N_2O_2 \cdot C_4H_4O_4$	402.4	85	104−105	2.6 ± 0.7	0.15 ± 0.04
10	$CO-C_5H_{11}$	$C_{18}H_{24}N_2O_2 \cdot C_4H_4O_4$	416.5	75	113−115	2.5 ± 0.3	0.098 ± 0.029
11	$CO-C_6H_{13}$	$C_{19}H_{26}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	435.0	85	116−118	7.0 ± 1.3	0.15 ± 0.05
12	$CO-CH(CH_3)_2$	$C_{16}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	397.4	85	95	4.8 ± 0.6	3.9 ± 1.9
13	$CO-CH_2-C(CH_3)_3$	$C_{18}H_{24}N_2O_2 \cdot C_4H_4O_4$	416.5	70	139	27 ± 10	0.85 ± 0.14
14	CO−cyclopropyl	$C_{16}H_{18}N_2O_2 \cdot C_4H_4O_4$	386.4	55	118−120	0.49 ± 0.09[c]	0.14 ± 0.03[c]
15	CO−cyclobutyl	$C_{17}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	404.9	80	130	0.89 ± 0.18	0.19 ± 0.09
16	CO−cyclopentyl	$C_{18}H_{22}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	419.0	80	141	7.2 ± 1.1	0.85 ± 0.33
17	$CO-CH_2-Ph$	$C_{20}H_{20}N_2O_2 \cdot C_2H_2O_4 \cdot 0.75H_2O$	423.9	65	174−176	5.9 ± 2.4	0.46 ± 0.11
18	$CO-(CH_2)_3-$piperidino	$C_{21}H_{29}N_3O_2 \cdot 2C_2H_2O_4$	535.5	20	190−192	nd[d]	>10
19	$CO-(CH_2)_3-$pyridoindol[e]	$C_{30}H_{29}FN_4O_2 \cdot 2C_4H_4O_4 \cdot 3H_2O$	782.8	10	70	410 ± 139	>10
20	$CO-(CH_2)_3-COOC_2H_5$	$C_{19}H_{24}N_2O_4 \cdot C_4H_4O_4 \cdot H_2O$	478.5[f]	55	oil	122 ± 17	>10
21	$CO-(CH_2)_3-COOH$	$C_{17}H_{20}N_2O_4 \cdot HCl \cdot 2H_2O$	388.8	80	97	49 ± 10	>10
22	$CH_2-CO-CH_3$	$C_{15}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	383.4	75	89	53 ± 11	>10
23	$(CH_2)_2-CO-CH_3$	$C_{16}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	397.4	70	104	91 ± 20	>10
24	$(CH)_2-CO-CH_3$	$C_{16}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	395.4	45	123	20 ± 5	>10
25	$(CH)_2-CHO$	$C_{15}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$[g]	381.4	35	119−121	32 ± 7	∼30
26	SO_2-CH_3	$C_{13}H_{16}N_2O_3S \cdot C_4H_4O_4$	396.4	25	135	40 ± 10	8.8 ± 2.2
27	cyclopentyl	$C_{17}H_{22}N_2O \cdot 0.75C_2H_2O_4$	337.9	60	224−225	nd	∼30
UCL 1390	(R = C≡N)[h]					12 ± 3	0.54 ± 0.23
FUB 470	(R = C≡CH)[j]					2.3 ± 0.8	0.12 ± 0.07
thioperamide						4 ± 1[c]	1.0 ± 0.5[c]
clobenpropit						0.6 ± 0.1[c]	26 ± 7[c]

[a] Functional H_3-receptor assay in vitro on synaptosomes of rat cerebral cortex.[19] [b] Central H_3-receptor screening in vivo after oral administration to mice.[19] [c] Ref 21a and literature therein. [d] nd, not determined. [e] Pyridoindol, 8-fluoro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-yl. [f] Elemental analyses not performed. [g] C,H; N: calcd, 7.35; found, 8.02. [h] Ref 9. [j] Ref 10.

Table 2. Structures, Physical Data, and Pharmacological Screening Results of Polysubstituted 4-(3-(Phenoxy)propyl)-1*H*-imidazoles for Histamine H_3-Receptor Antagonist Potency in Vitro and in Vivo in Rodents



no.	R^1	R^2	R^3	R^4	formula	M_r	yield (%)	mp (°C)	K_i[a] (nM) $\bar{x} \pm s_{\bar{x}}$	ED_{50}[b] (mg/kg) $\bar{x} \pm s_{\bar{x}}$
28	$CO-CH_3$	F	H	H	$C_{14}H_{15}FN_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	382.9	80	114	1.1 ± 0.2	0.15 ± 0.06
29	$CO-CH_3$	CH_3	H	H	$C_{15}H_{18}N_2O_2 \cdot C_4H_4O_4$	374.4	80	109	1.2 ± 0.3	0.08 ± 0.02
30	$CO-CH_3$	CH_3	CH_3	H	$C_{16}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	397.4	85	92	90 ± 19	>10
31	$CO-CH_3$	H	H	CH_3	$C_{15}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	387.9	80	126	4.8 ± 0.8	0.39 ± 0.10
32	$CO-CH_3$	CF_3	H	H	$C_{15}H_{15}F_3N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	411.3	55	117	17 ± 5	0.64 ± 0.14
33	$CO-CH_3$	OCH_3	H	H	$C_{15}H_{18}N_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$	399.4	60	124	325 ± 164	>10
34	$CO-C_2H_5$	F	H	H	$C_{15}H_{17}FN_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	396.9	35	119−121	57 ± 11	0.9 ± 0.2
35	CO−cyclopropyl	H	H	NO_2	$C_{16}H_{17}N_3O_4 \cdot C_4H_4O_4$	431.4	60	151−152	nd[c]	5.5 ± 2.8
36	$-CO-CH_2-CH_2-$		H	H	$C_{15}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$	390.4	40	147	17± 4	1.5 ± 0.5
37	$-CO-CH_2-CH_2-CH_2-$		H	H	$C_{16}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	395.4	75	102	13 ± 3	7 ± 4
38	$-CH_2-CH_2-CH_2-$		H	H	$C_{15}H_{18}N_2O \cdot 0.8C_2H_2O_4$	314.3	40	188−190	38 ± 6	1.3 ± 0.2
39	$-CH_2-CH_2-CH_2-CH_2-$		H	H	$C_{16}H_{20}N_2O \cdot 0.85C_2H_2O_4$	332.9	20	171−173	45 ± 14	3.3 ± 1.3

[a] Functional H_3-receptor assay in vitro on synaptosomes of rat cerebral cortex.[19] [b] Central H_3-receptor screening in vivo after oral administration to mice.[19] [c] nd, not determined.

increased lipophilicity, steric factors have to be considered. The steric demands of this alkyl substituent were impressively shown by the isopropyl derivative **12** compared to its cyclized analogue **14**. In particular, the

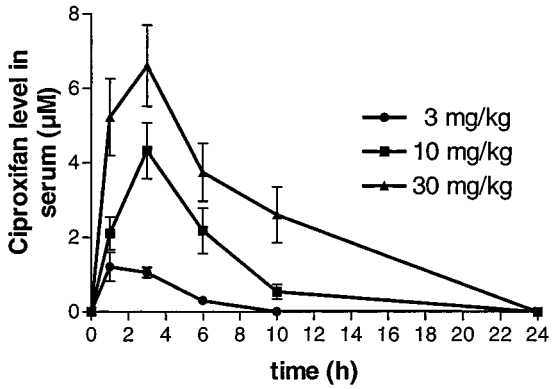


Figure 1. Kinetics of ciproxifan (**14**) in monkeys ($n = 6-11$) after single oral administration.

cyclopropyl derivative **14** is more than 25 times more potent than the isopropyl derivative **12**. Even the homologous cycloalkyl derivatives (**15**, **16**) are more potent than **12**. Shifting of the carbonyl moiety away from the phenyl ring (**22**−**25**), its exchange to sulfone (**26**), or its omission (**27**) led to strong decreases in potencies. The carboxylic acid **21** was synthesized for the preparation of antibodies for the development of a specific radioimmunoassay for the main compounds of this series (Ligneau et al., unpublished results).

Additional substitution of the phenyl ring was accepted when the substituents did not influence too much the little steric demands of the carbonyl moiety. One methoxy group (**33**) or two methyl groups (**30**) in the *ortho*-position relative to the carbonyl group led to inactive compounds, whereas a nitro group in the corresponding *meta*-position (**35**) only caused a decrease. Bicyclic compounds (**36**−**39**) gave no improvements. Additional substitution was tolerated with one fluoro (**28**, **34**), methyl (**29**, **31**), or trifluoromethyl (**32**) group since it led to retention of activity. Although compounds **28** and **29** showed an improvement in potency compared to **6**, this cannot be taken as a general rule (cf. **7** → **34**).

Compounds **10**, **14**, and **29** were the most active antagonists in vivo in this series and are also among the most active ones known so far to our knowledge. The potencies of these compounds were not statistically significantly different from each other. Compound **14**, named ciproxifan, was selected for further studies because it showed extremely high activity in vitro as well as in vivo. With these studies ciproxifan appears to be an orally bioavailable, extremely potent, and selective histamine H_3-receptor antagonist whose vigilance- and attention-promoting effects are promising for therapeutic applications in aging or degenerative disorders.[21] Oral bioavailability and detectable plasma levels for more than 6 h with different doses of ciproxifan are shown by the preclinical kinetic data in monkeys in Figure 1 although rapid formation of an active metabolite cannot be excluded by the method of determination. The areas under the curves (AUC) were 6.2, 26.6, and 61.6 μM/h for the 3, 10, and 30 mg/kg po doses, respectively. Furthermore, ciproxifan showed low inhibitory effect on the histamine-metabolizing enzyme, histamine-*N*-methyltransferase (E.C. 2.1.1.8) ($IC_{50} = 9.0 \pm 1.2$ μM), indicating that this enzyme is not influenced in therapeutic concentrations. Ciproxifan also showed low inhibitory affinity for the cytochrome P450 enzyme system ($-\log K_i = 5.6$, using a test system based on human placental microsomes) (Hartmann et al., unpublished results).

Table 3. Activity of Selected Compounds at Histamine Receptor Subtypes

no.	H_3 pK_i[a]	H_3 pK_b[b]	H_2 pK_b[c]	H_1 pK_b[d]
3	8.7	7.4	4.3	4.0
4	7.9	6.3		
5	8.1	6.7		
6	9.1	7.8	4.1[e]	4.2[e]
7	9.1	8.0	4.6	5.6
8	8.7	8.1	4.9	4.8
9	8.6	8.4	5.4	5.1
10	8.6	8.4	4.7	5.3
12	8.3	7.1	5.3	4.9
14[f]	9.3	8.4	4.9	4.6
15	9.1	8.5	5.4	<4.0
16	8.1	7.9	5.8	5.0
22	7.3	6.2		
23	7.1	6.9	4.3	3.9
28	8.9	7.9	4.5	4.1
29	8.9	7.9	5.0[e]	4.7[e]
32	7.8		4.8	4.8

[a] Functional H_3-receptor assay on synaptosomes of rat cerebral cortex.[19] [b] Functional H_3-receptor assay on guinea pig ileum.[22] [c] Functional H_2-receptor test on guinea pig atrium.[23] [d] Functional H_1-receptor test on guinea pig ileum.[23] [e] Ref 21b. [f] Ref 21a.

Screening of Selected Compounds at Functional Histamine Receptor Models on Guinea Pig Tissues. In addition to the extensive selectivity studies on ciproxifan,[21] selected compounds of this series were also tested on different functional models on isolated organs of guinea pigs for their histamine H_3-, H_2-, and/or H_1-receptor activities.[22,23] All compounds tested showed low activity at H_1 or H_2 receptors proving their selectivity (Table 3). For a number of compounds, the differences between the two functional H_3-receptor test systems were striking being sometimes more than 1.5 orders of magnitude (**4**). These differences are also observed in comparable assays even in the same species with compounds of other classes. However, the reason for this is not clarified to date.[24]

Conclusions

Compounds of the proxifan class possessing a *para*-substituted 4-(3-(phenoxy)propyl)-1*H*-imidazole moiety were prepared by different methods and screened for their histamine H_3-receptor potency in different assays. The hexanoyl derivative (**10**), cyclopropylcarbonyl derivative (**14**, ciproxifan), and the acetyl derivative with an additional methyl substituent (**29**) were extremely potent in the in vivo assay displaying ED_{50} values in the low 0.1 mg/kg dosage range on oral administration. The H_3-receptor selectivity for many compounds of this class was also proved by testing activity at other histamine receptor subtypes. Preclinical kinetic data of ciproxifan (**14**) in primates showed oral bioavailability and plasma levels lasting for 6 h or more, which makes this compound attractive for further development.

Experimental Section

Chemistry. General Procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus and are uncorrected. For all compounds ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^{1}H NMR data are reported

in the following order: multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; Im, imidazole; Mal, maleic acid), number of protons, and approximate coupling constants in hertz (Hz). Mass spectra were obtained on an EI-MS Finnigan MAT CH7A (170 °C, 70 eV) or a Finnagan MAT CH5DF ($FAB^{+/-}$; Xe, Me_2SO/glycerol). Elemental analyses (C, H, N) for the compounds were measured on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and were within ±0.4% of the theoretical values, unless otherwise stated. Preparative, centrifugally accelerated rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4-mm layers of silica gel 60 PF_{254} containing gypsum (Merck). Column chromatography was carried out using silica gel 63−200 μm (Macherey, Nagel & Co.). TLC was performed on silica gel PF_{254} plates (Merck); the spots were visualized with fast blue salt BB. Abbreviations for solvents are the following: Et_2O, diethyl ether; EtOH, ethanol; EtOAc, ethyl acetate; MeOH, methanol; THF, tetrahydrofuran. Synthesis procedures and spectral data are shown only for parent compounds (**5**, **6**, **13**, **21**, **25**, **26**) that were obtained by different reactions or methods and for the most active ones (**10**, **14**, **29**).

General Procedure A for Mitsunobu Type Ether Formation. Triphenylphosphine (6 mmol, 1.57 g) was dissolved in 15 mL of freshly distilled THF under Ar atmosphere together with 3-(1-triphenylmethyl-1*H*-imidazol-4-yl)propanol[11a] (5 mmol, 1.84 g) and 6 mmol of the phenol derivative and cooled in an ice bath. Then, diethyl azodicarboxylate (DEAD) (6 mmol, 0.95 mL) was slowly added followed by additional stirring for 12−72 h at ambient temperature. After removal of the solvent in vacuo purification was performed by column chromatography (eluent: EtOAc). The oil obtained was detritylated by heating for reflux in 20 mL of 2 N HCl and 20 mL of acetone (except for compound **20** in 30 mL of formic acid only) for 30−90 min. Acetone was removed under reduced pressure and the residue was extracted with Et_2O. The aqueous phase was neutralized with potassium carbonate and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by rotatory chromatography (eluent: CH_2Cl_2/MeOH (gradient from 99.5/0.5 to 90/10), ammonia atmosphere). The product obtained was crystallized as hydrogen maleate or hydrogen oxalate in EtOH/Et_2O.

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)ethanone (6): ^{1}H NMR (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.93 (d, J = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 7.43 (s, 1H, Im-5-H), 7.02 (d, J = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 6.05 (s, 2H, Mal), 4.11 (t, J = 6.2 Hz, 2H, CH_2-O), 2.80 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.50 (s, 3H, CH_3), 2.09 (m, 2H, Im-CH_2-CH_2); MS m/z 244 ([M$^{\bullet+}$], 2), 121 (10), 109 (87), 96 (51), 82 (100), 81 (74), 54 (12).

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)hexanone (10): ^{1}H NMR (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.92 (d, J = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 7.43 (s, 1H, Im-5-H), 7.01 (d, J = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 6.05 (s, 2H, Mal), 4.12 (t, J = 6.1 Hz, 2H, CH_2-O), 2.93 (m, 2H, CO-CH_2), 2.80 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.09 (m, 2H, Im-CH_2-CH_2), 1.59−1.28 (m, 6H, CO-CH_2-(CH_2)$_3$), 0.86 (m, 3H, CH_3); MS m/z 300 ([M$^{\bullet+}$], <1), 121 (15), 109 (100), 96 (201), 82 (64), 41 (12).

Cyclopropyl 4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl methanone (14): ^{1}H NMR (Me_2SO-d_6) δ 8.50 (s, 1H, Im-2-H), 8.03 (d, J = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 7.25 (s, 1H, Im-5-H), 7.05 (d, J = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 6.03 (s, 2H, Mal), 4.12 (t, J = 6.2 Hz, 2H, CH_2-O), 2.85 (m, 1H, CO-CH), 2.77 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2-CH_2), 0.98 (d, J = 6.1 Hz, 4H, cyclopropyl (CHH)$_2$); MS m/z 541 ([2M + H]$^+$, 1), 333 ([M + Cu]$^+$, 11), 271 ([M + H]$^+$, 70), 203 (2), 121 (8), 109 (100), 95 (13), 82 (44), 81 (34), 59 (14).

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)-2-methylphenyl)-ethanone (29): ^{1}H NMR (Me_2SO-d_6) δ 8.82 (s, 1H, Im-2-H), 7.82 (d, J = 8.6 Hz, 1H, Ph-6-H), 7.38 (s, 1H, Im-5-H), 6.83 (s, 1H, Ph-3-H), 6.81 (d, J = 8.6 Hz, 1H, Ph-5-H), 6.02 (s, 2H, Mal), 4.06 (t, J = 6.2 Hz, 2H, CH_2-O), 2.77 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.43 (s, 6H, 2CH_3), 2.06 (m, 2H, Im-CH_2-CH_2); MS m/z 258 ([M$^{\bullet+}$], 8), 149 (11), 109 (100), 96 (34), 82 (68), 43 (10).

4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenylmethanol (5). Compound **4** (free base, 2 mmol, 700 mg) in 20 mL of freshly distilled THF was slowly added to a suspension of $LiAlH_4$ (1 mmol, 40 mg) in 20 mL of freshly distilled THF. After heating for 2 h 5 mL of 2 N NaOH was added dropwise at ambient temperature. The organic phase was separated, washed with brine, dried (Na_2SO_4) and purified by column chromatography (eluent: CH_2Cl_2/MeOH (96/4), ammonia atmosphere). The colorless oil obtained was crystallized as hydrogen maleate in EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.87 (s, 1H, Im-2-H), 7.41 (s, 1H, Im-5-H), 7.22 (d, J = 8.5 Hz, 2H, Ph-2-H, Ph-6-H), 6.86 (d, J = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.04 (s, 2H, Mal), 5.00 (s, 1H, OH), 4.41 (m, 2H, CH_2-OH), 3.98 (t, J = 6.2 Hz, 2H, CH_2-O), 2.79 (t, J = 7.6 Hz, 2H, Im-CH_2), 2.06 (m, 2H, Im-CH_2-CH_2); MS m/z 232 ([M$^{\bullet+}$], 4), 109 (100), 96 (22), 82 (71), 81 (39), 72 (11).

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)-3,3-dimethylbutanone (13). 3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)propanol[11a] (3.7 mmol, 1.36 g) and 4-(3,3-dimethylbutynyl)-phenol[10] (3.7 mmol, 0.65 g) were reacted analogous to general procedure A. The trityl-protected intermediate was hydrolyzed either by heating in 5 mL of EtOH, 5 mL of acetone, and 30 mL of 2 N HCl for 45 min or by stirring in 20 mL of formic acid for 24 h at ambient temperature. After extraction with Et_2O, alkalization with NH_3, subsequent extraction with Et_2O and following rotatory chromatographic purification of the organic extracts (eluent: CH_2Cl_2/MeOH (gradient from 95/5 to 90/10), ammonia atmosphere) the colorless oil was crystallized as hydrogen maleate in EtOH/Et_2O to give the product in the same yield for both methods of hydrolysis: ^{1}H NMR (Me_2SO-d_6) δ 8.88 (s, 1H, Im-2-H), 7.93 (d, J = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 7.43 (s, 1H, Im-5-H), 6.99 (d, J = 8.8 Hz, 2H, Ph-3-H. Ph-5-H), 6.05 (s, 2H, Mal), 4.11 (t, J = 6.1 Hz, 2H, CH_2-O), 2.82 (m, 4H, Im-CH_2, CO-CH_2), 2.09 (m, 2H, Im-CH_2-CH_2), 0.99 (s, 9H, C(CH_3)$_3$); MS m/z 300 ([M$^{\bullet+}$], 2), 229 (7), 109 (100), 96 (36), 82 (54).

5-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)-5-oxovalerianic Acid (21). Compound **20** (~0.5 mmol, 200 mg) was dissolved in 1.6 mL of acetone, 0.48 mL of 6 N HCl, and 1.12 mL of water and stirred for 6 h at ambient temperature. Then 10 mL of acetone was added and carefully concentrated under reduced pressure. Compound **21** slowly crystallized in form of its hydrochloride salt on standing: ^{1}H NMR (Me_2SO-d_6) δ 8.84 (s, 1H, Im-2-H), 7.94 (d, J = 8.7 Hz, 2H, Ph-2-H, Ph-6-H), 7.39 (s, 1H, Im-5-H), 7.02 (d, J = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 4.11 (t, J = 6.0 Hz, 2H, CH_2-O), 2.99 (t, J = 7.2 Hz, 2H, CO-CH_2), 2.84 (t, J = 7.5 Hz, 2H, Im-CH_2), 3.32 (t, J = 7.3 Hz, 2H, CH_2-COO), 2.11 (m, 2H, Im-CH_2-CH_2), 1.83 (m, 2H, CO-CH_2-CH_2); MS m/z (FAB^-) 351 ([M + Cl], 25), 315 ([M − H]$^-$, 35), 207 (20).

***(E)*-3-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)propenal (25).** 3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)propanol[11a] (5 mmol, 1.84 g) and 4-hydroxybenzaldehyde (5 mmol, 0.61 g) were reacted according to general procedure A to result in the precursor for compound **4**. Ethynylmagnesium bromide (0.5 M solution in THF, 5 mmol, 10 mL) was added to the trityl-protected intermediate in 25 mL of freshly distilled THF and heated under reflux for 1 h. The mixture was evaporated, hydrolyzed in EtOH, acetone and 2 N HCl, and extracted as described before. The dried organic extracts were crystallized and recrystallized as hydrogen maleate in EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 9.62 (d, J = 7.8 Hz, 1H, CHO), 8.94 (s, 1H, Im-2-H), 7.70 (m, 3H, Ph-CH=CH, Ph-2-H, Ph-6-H), 7.46 (s, 1H, Im-5-H), 7.02 (d, J = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 6.74 (dd, $^3J_{H,H(E)}$ = 15.9 Hz, $^3J_{H,CHO}$ = 7.8 Hz, 1H, CH-CHO), 6.07 (s, 2H, Mal), 4.10 (t, J = 6.1 Hz, 2H, CH_2-O), 2.82 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2-CH_2); MS m/z 256 ([M$^{\bullet+}$], 5), 240 (1), 228 (3), 109 (100), 82 (30).

General Procedure B for Ether Formation by S_NAr Reaction. 3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)propanol[11a] (5 mmol, 1.84 g) was stirrred at 60 °C for 2 h with NaH (6 mmol, 240 mg of 60% in paraffin oil) under Ar in 20 mL of toluene. Then, the corresponding fluoroaromate (6 mmol) was added at ambient temperature in 5 mL of toluene, the mixture

warmed slowly to 70 °C and stirred for 2−8 h (TLC control). In some cases, yields could be increased by repeating the procedure by addition of NaH and fluoroaromate in 2 mmol amounts, but reaction conditions were not optimized. The mixture was evaporated, water was carefully added, and then it was heated to reflux in 35 mL of 2 N HCl and 20 mL of THF for 1.5 h. The organic solvent was removed under reduced pressure, and the residue extracted with Et_2O (3 × 20 mL). The aqueous solution was basified with K_2CO_3 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were evaporated and subjected to rotatory chromatography (eluent: CH_2Cl_2/MeOH (gradient from 99.5/0.5 to 90/10), ammonia atmosphere). The resulting product was converted into a salt (cf. Tables 1 and 2) and recrystallized from EtOH/Et_2O.

4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl methyl sulfone (26): ^{1}H NMR (Me_2SO-d_6) δ 8.83 (s, 1H, Im-2-H), 7.98 (d, J = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 7.39 (s, 1H, Im-5-H), 7.13 (d, J = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.03 (s, 2H, Mal), 4.09 (t, J = 6.0 Hz, 2H, CH_2-O), 3.13 (s, 3H, SO_2-CH_3), 2.79 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.09 (m, 2H, Im-CH_2-CH_2); MS *m*/*z* 288 ([M$^{\bullet+}$], 3), 109 (32), 96 (35), 81 (100), 41 (27).

Pharmacology. General Methods. Histamine H_3-Receptor Assay on Synaptosomes of Rat Cerebral Cortex. Compounds were tested for their H_3-receptor antagonist activity in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from rat synaptosomes according to Garbarg et al.[19] A synaptosomal fraction from rat cerebral cortex prepared according to the method of Whittaker[25] was preincubated for 30 min with L-[^{3}H]histidine (0.4 μM) at 37 °C in a modified Krebs-Ringer solution. The synaptosomes were washed extensively, resuspended in fresh 2 mM K^+ Krebs-Ringer's medium, and incubated for 2 min with 2 or 30 mM K^+ (final concentration). Drugs and 1 μM histamine were added 5 min before the depolarization stimulus. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels were determined after purification by liquid scintillation spectrometry. K_i values were determined according to the Cheng−Prusoff equation.[26] The data presented are given as mean values with standard error of the mean (SEM) for a minimum of three separate determinations each.

Histamine H_3-Receptor Antagonist Potency in Vivo in Mice. In vivo testing was performed after peroral administration to Swiss mice as described by Garbarg et al.[19] Brain histamine turnover was assessed by measuring the level of the main metabolite of histamine, N^τ-methylhistamine. Mice were fasted for 24 h before treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was prepared out. The cortex was homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^τ-methylhistamine level was measured by radioimmunoassay.[27] By treatment with 10 mg/kg of thioperamide the maximal N^τ-methylhistamine level was obtained and related to the level reached with the administered drug, and the ED_{50} value was calculated as mean values with SEM.[28]

Histamine-*N*-methyltransferase 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 (SAM) as a [^{3}H]methyl donor. HMT was purified from rat kidney according to the method of Bowsher et al.[29] with slight modifications.[30] Histamine (1 μM final concentration) was incubated with HMT and SAM (20 μM final concentration) alone or together with different concentrations of drugs for 20 min at 37 °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.[19] The IC_{50} value for each drug tested was calculated from the inhibition curve of the N^τ-methylhistamine formation obtained with increasing drug concentrations.

Kinetic Study with Ciproxifan (14) in Monkeys. Monkeys received single doses of drug orally in suspension with methylcellulose. At different times blood was collected, and the concentration of ciproxifan was determined after centrifugation (100*g*, 10 min, 4 °C) in the serum using a radioreceptor assay derived from the [^{3}H](*R*)-α-methylhistamine binding assay described before with mice.[19,21a] Values given represent the mean with SEM of an experiment with 6−11 monkeys for each dosage.

Histamine H_3-Receptor Antagonist Activity on Guinea Pig Ileum. For selected compounds H_3-receptor activity was measured by concentration-dependent inhibition of electrically evoked twitches of isolated guinea pig ileum segments induced by (*R*)-α-methylhistamine in the presence of the antagonist according to Ligneau et al.[22] In brief, longitudinal muscle strips were prepared from the small intestine, 20−50 cm proximal to the ileocecal valve. The muscle strips were mounted between two platinum electrodes (4 mm apart) in 20 mL of Krebs buffer, containing 1 μM of mepyramine, connected to an isometric transducer, continuously gassed with oxygen containing 5% CO_2 at 37 °C. After equilibration of the muscle segments for 1 h with washing every 10 min, they were stimulated continuously with rectangular pulses of 15 V and 0.5 ms at a frequence of 0.1 Hz. After 30 min of stimulation, a cumulative dose−response curve was recorded. Subsequently the preparations were washed three times every 10 min without stimulation. The antagonist was incubated 20−30 min before redetermination of the dose−response curve of (*R*)-α-methylhistamine.

In Vitro Screening at Other Histamine Receptors. Selected compounds were screened for histamine H_2-receptor activity on the isolated spontaneously beating guinea pig right atrium as well as for H_1-receptor activity on the isolated guinea pig ileum by standard methods described by Hirschfeld et al.[23] Each pharmacological test was performed at least in triplicate, but the exact type of interaction had not been determined in each case. The given values represent the mean.

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