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Analogues and Derivatives of Ciproxifan, a Novel Prototype for Generating Potent Histamine H_3-Receptor Antagonists

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Abstract—Novel derivatives of the highly potent and selective histamine H_3-receptor antagonist ciproxifan (**3**) with different chain lengths as well as with structural variants of the cyclopropyl ketone moiety have been prepared and screened for their antagonist H_3-receptor potencies in vitro and in vivo. Some derivatives (**2**, **6**–**8**, **12**) containing other functionalities were effective in vitro in the same (sub)nanomolar concentration range and in vivo in a remarkably low oral dose. © 2000 Elsevier Science Ltd. All rights reserved.

It is widely recognized that histamine acts as neurotransmitter in the mammalian central nervous system by interacting with three different receptors.[1] Whereas antagonists for H_1 and H_2 receptors were introduced to therapy a long time ago, ligands for the histamine H_3 receptor are still missing in the repertoire for treatment of diseases. For H_3-receptor antagonists a number of different therapeutic indications have been proposed, e.g., 'cognitive enhancers' in Alzheimer's disease or attention deficit hyperactivity disorder (ADHD), as well as in schizophrenia, and epilepsy.[2–4] Various structural developments of H_3-receptor antagonists have been reported (thioperamide, clobenpropit, GT-2331 (Perceptin™) etc.)[1,3–6] in which the 'proxifan' class with a 3-(1*H*-imidazol-4-yl)propoxy structure ([^{125}I]iodoproxyfan,[7] FUB 470,[8] UCL 1390[9] etc.) seemed most promising for us having ciproxifan as a novel prototypic agent of high potency (Fig. 1).[10]

Structural variants of chain length between the imidazole and phenoxy moieties as well as of the cyclopropyl ketone moiety have been prepared and investigated for their influence on antagonist H_3-receptor potency in vitro and in vivo.

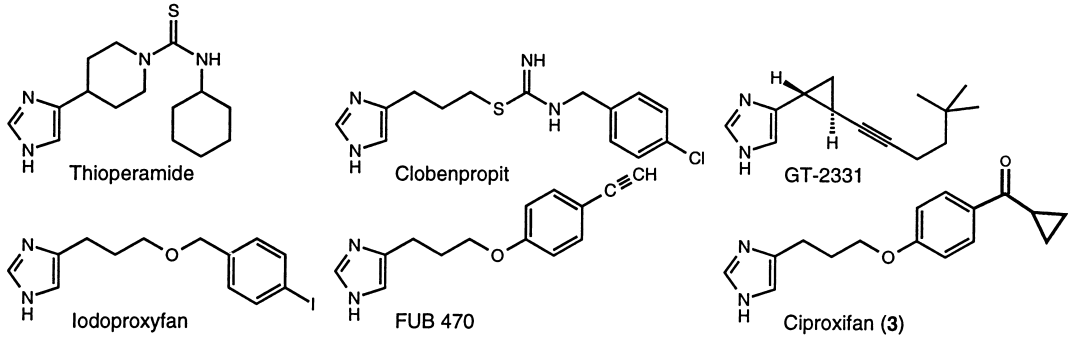

Figure 1. Histamine H_3-receptor antagonists.

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Chemistry

Alkyl aryl ethers were prepared from known sodium ω-(1*H*-1-(triphenylmethyl)imidazol-4-yl)alkanolates[7,9] and cyclopropyl 4-fluorophenyl ketone by an S_NAr reaction, under milder conditions by the Mitsunobu reaction of the corresponding alcohols (Scheme 1)[11] or by Williamson synthesis from the corresponding alkyl chloride.[12] Acidic deprotection of the intermediates resulted in compounds **1**–**4** with different alkyl chain lengths.[13]

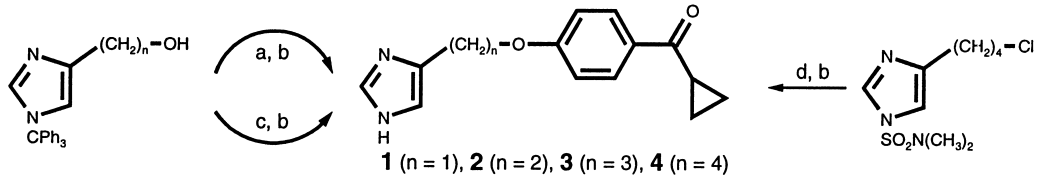
The trityl-protected intermediates for ciproxifan (**3**) were reduced under different conditions with complex hydrides and then deprotected to give **5** and **6**, respectively (Scheme 2). Ciproxifan was transformed into the corresponding oxime derivative **7** or catalytically reduced to the *n*-butyl derivative **8**. Treatment under strong acidic conditions at high temperature for 3–48 h led to ring opening (**9**, **10**, **12**). According to the conditions and reagents the 4-chlorobutyrophenone derivative (not shown) served as an intermediate for **9**, the ketal butanol derivative **10**, on the 4-hydroxybutyrophenone **11** via acidic hydrolysis of **10**. Compound **12** was obtained from **6** by C–C cleavage, elimination and simultaneous substitution (Scheme 2).

All compounds were purified chromatographically, characterized in the form of their hydrogen maleates (**2**, **3**, **5**–**7**, **10**, **11**) or hydrogen oxalates (**1**, **8**, **9**, **12**), and gave satisfactory analytical results. Compound **4** was free base and analysed for having retained some solvent (EtOH and H_2O).

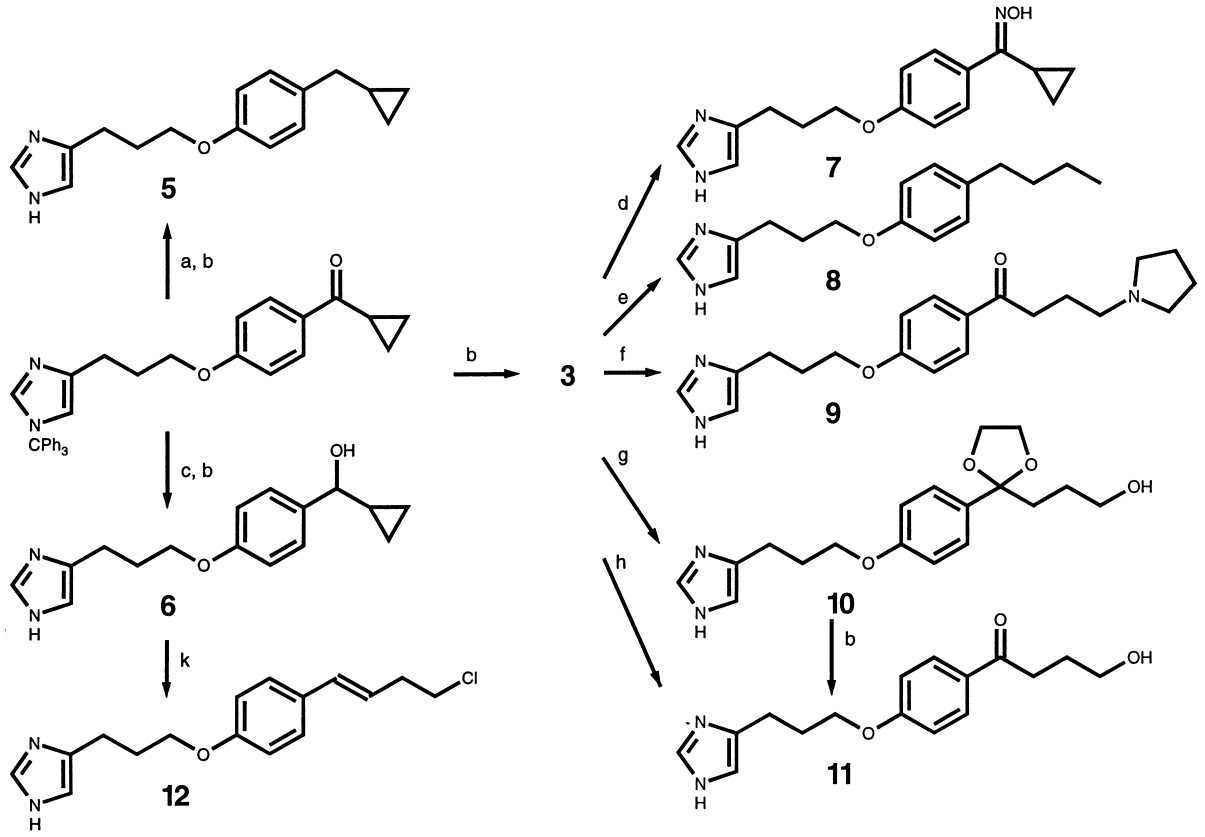
Pharmacology

Histamine H_3-receptor in vitro assay on synaptosomes of rat cerebral cortex

The compounds were tested for their H_3-receptor antagonist potencies in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from



Scheme 1. Synthesis of ciproxifan (**3**) and analogues thereof. (a) For $n = 1$–3: i: NaH, toluene; ii: 4-fluorophenyl cyclopropyl ketone, toluene, reflux; (b) 2 N HCl/THF, reflux; (c) for $n = 3$: Ph_3P, diethyl azodicarboxylate (DEAD), 4-hydroxyphenyl cyclopropyl ketone, THF; (d) for $n = 4$: NaH, 4-hydroxyphenyl cyclopropyl ketone, DMF, $(n\text{-}C_4H_9)_4NI$ (cat.).



Scheme 2. Synthesis of ciproxifan and derivatives thereof. (a) $LiAlH_4/AlCl_3$, THF, reflux; (b) 2 N HCl/THF, reflux; (c) $LiAlH_4$, THF/Et_2O, reflux; (d) $H_2NOH{\cdot}HCl$, K_2CO_3, EtOH, reflux; (e) H_2 (10 bar), Pd/C, MeOH; (f) i: MeOH, concd HCl, reflux; ii: pyrrolidine, NaI (cat.), reflux; (g) *p*-$H_3CC_6H_4SO_3H$, HOC_2H_4OH, reflux; (h) F_3CCOOH, reflux; (k) $SOCl_2$, *i*-PrOH/HCl, reflux.

synaptosomes of rat cerebral cortex according to Garbarg et al.[14] (Table 1).

Histamine H_3-receptor antagonist in vivo potency in mice

Increase in N^{τ}-methylhistamine levels in Swiss mice brain 90 min after p.o. administration of compounds was selected to screen histamine H_3-receptor antagonist in vivo potency[14] (Table 1). ED_{50} values were calculated as mg free base·kg^{-1}.

Results and Discussion

Depending on alkyl chain length, compounds with two (**2**) or three methylene (**3**) groups between the imidazole ring and phenoxy moiety were clearly more effective than those with shorter (**1**) or longer chains (**4**) in vitro, finding an optimum in the propyl derivative, but surprisingly not differing statistically significantly in in vivo potency. Since it had activity in both test systems and a good selectivity profile,[10,15] **3** was selected as a lead for further optimization. Reduction of the ketone functionality in **3** to a hydroxy group (**6**) maintained potencies in vitro as well as in vivo, whereas reduction to an alkane (compound **5**) showed no in vivo activity. Comparing this result of **5** with the analogous *n*-butyl derivative **8** shows that distinct steric parameters in vitro or pharmacokinetic effects in vivo could be the basis for these dramatic differences.

Transformation of a related acetyl derivative (FUB 372)[11,15] into an oxime functionality recently led to imoproxifan showing a strong increase in antagonist potency and being one of the most potent histamine H_3-receptor antagonists known so far.[13,16] The equivalent transformation of **3** into the oxime derivative **7** maintained potency, but did not give the improvement observed with imoproxifan.

Despite diverse or alike electronic properties, compounds were found which in some cases had almost equieffective (**3**→**6**; **8**→**10**→**11**) or also in other cases divergent receptor affinities (**3**→**7**; **3**→**8**; **3**→**10**; **3**→**11**) giving a hint for the importance of steric effects.

Introduction of additional binding sites with hydrogen bonding capabilities (**9**–**11**) or basic groups (**9**) on the phenyl side chain led to compounds with low if any in vivo potencies. The in vitro affinity in a nanomolar concentration range for the aliphatic primary alcohols **10** and **11** indicates that in these cases pharmacokinetic

Table 1. Antagonist histamine H_3-receptor in vitro and in vivo potencies[a]

Compound, formula, mp [°C]	In vitro K_i [nM] $(\bar{x} \pm s_{\bar{x}})$	In vivo p.o. ED_{50} [mg kg^{-1}] $(\bar{x} \pm s_{\bar{x}})$	Compound, formula, mp [°C]	In vitro K_i [nM] $(\bar{x} \pm s_{\bar{x}})$	In vivo p.o. ED_{50} [mg kg^{-1}] $(\bar{x} \pm s_{\bar{x}})$
1, $C_{14}H_{14}N_2O_2 \cdot C_2H_2O_4 \cdot \frac{1}{4}H_2O$ 177	>500	2.8±0.7	**7**, $C_{16}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot \frac{1}{4}H_2O$ 139–140	4.4±1.4	0.21±0.05
2, $C_{15}H_{16}N_2O_2 \cdot C_4H_4O_4$ 132–133	2.1±0.7	0.21±0.05	**8**, $C_{16}H_{21}N_2O \cdot \frac{3}{4}C_2H_2O_4$ 190	60±23	0.96±0.30
3[b,c], $C_{16}H_{18}N_2O_2 \cdot C_4H_4O_4$ 118–120	0.49±0.09[c]	0.14±0.03[c]	**9**, $C_{20}H_{27}N_3O_2 \cdot 2C_2H_2O_4 \cdot 1\frac{1}{2}H_2O$ 134–136	n.d.	>10
4, $C_{17}H_{20}N_2O_2 \cdot 1.7H_2O \cdot \frac{1}{4}C_2H_5OH$ 98–100	113±23	>10	**10**, $C_{18}H_{24}N_2O_4 \cdot C_4H_4O_4$ 104–105	40±8	>10
5, $C_{16}H_{20}N_2O \cdot C_4H_4O_4$ 113–114	n.d.	>10	**11**, $C_{16}H_{20}N_2O_3 \cdot C_4H_4O_4$ 107–108	30±8	>10
6[b], $C_{16}H_{20}N_2O_2 \cdot C_4H_4O_4$ 84–85	0.58±0.17	0.18±0.02	**12**, $C_{16}H_{19}ClN_2O \cdot C_2H_2O_4 \cdot \frac{1}{2}H_2O$ 159–161	n.d.	0.72±0.22
Thioperamide	4±1[c]	1.0±0.5[c]	FUB 470	2.3±0.8[d]	0.12±0.07[d]
Clobenpropit	0.6±0.2[c]	~ 25[c]	GT-2331	(0.12±0.04)[e]	(0.12)[f]

[a]Data in parentheses are obtained from different test systems. n.d., not determined.
[b]Ref. 15.
[c]Ref. 10.
[d]Ref. 8.
[e]Ref. 6.
[f]Ref. 17.

difficulties such as oral absorption, penetration of the blood–brain barrier or rapid metabolization seem likely explanations for the lack of in vivo activity.

The 4-chloro-1-butenyl derivative **12** was active in the same range as the butyl derivative **8** showing that steric effects are more important for receptor/ligand interaction than electronic properties of the substituents on the phenyl moiety (cf. **5**) or that pharmacokinetic reasons have been taken into account. The same is true for different cyclopropyl derivatives comparing compound **3** to compounds **6** or **7**. In this series the lack of in vivo activity of **5** was unexpected.

It can be concluded that structural variants of the ciproxifan lead result in some highly potent histamine H_3-receptor antagonists, regardless of different electronic effects of substituents in the phenyl ring. The ethyl derivative **2**, the cyclopropyl methanol derivative **6**, and the cyclopropyl ketone oxime derivative **7** show that various structural modifications can be performed with maintenance of potency, especially the high p.o. potency in vivo. Therefore, these compounds represent new leads for further improvements. Additional studies are currently in progress.

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