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DIPHENYLMETHYL ETHERS: SYNTHESIS AND HISTAMINE H_3-RECEPTOR ANTAGONIST *IN VITRO* AND *IN VIVO* ACTIVITY

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Abstract: New potent histamine H_3-receptor antagonists containing an ether group were synthesized from 3-(1*H*-imidazole-4-yl)propanol and various substituted diphenylmethyl chlorides. Some of the designed ethers showed high activity at histamine H_3-receptors under *in vitro* as well as under *in vivo* conditions. Their activity at histamine H_1- and H_2-receptors was also investigated proving a pharmacological H_3-/H_1-antagonistic profile.

The research on antagonists of the histamine H_3-receptor has been stimulated by the discovery of numerous pharmacological properties of this receptor subtype first described in 1983 by Arrang et al.[1] Histamine H_3-receptor antagonists do not only stimulate histamine synthesis and release but also influence a number of neuronal functions by modulating the release of different neurotransmitters, e.g., serotonin,[2] acetylcholine,[3] noradrenaline,[4,5] and dopamine.[6] H_3-receptor antagonists may prove to be potential drugs for the treatment of different diseases or conditions in the central nervous system like epilepsy,[7] stress,[8] memory and learning deficits[9] as well as cognitive and sleep disorders.[10] The design of highly potent histamine H_3-receptor antagonists is necessary to gain further insight into the physiological and pharmacological regulation mechanisms of this receptor subtype.

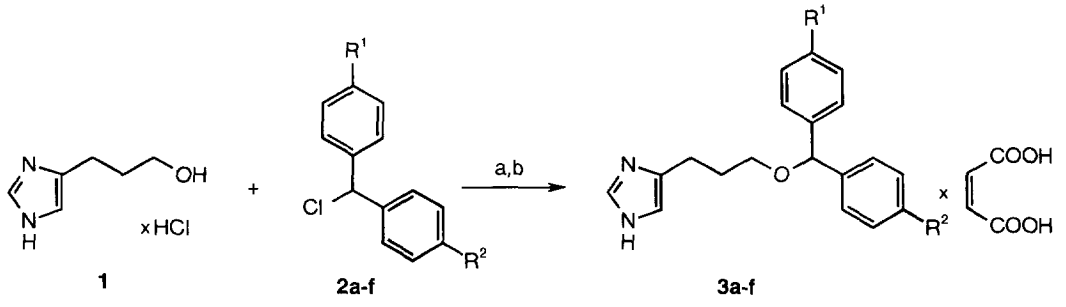
The reference antagonist thioperamide,[11] a thiourea derivative of 4-(1*H*-imidazol-4-yl)piperidine, shows (hepato)toxicity which prevents clinical trials. Therefore, in order to circumvent these toxic effects new compounds structurally different from thioperamide with various polar functionalities have been synthesized recently.[12-18] In particular compounds containing an ether group were promising new lead structures.[19,20] 3-(1*H*-Imidazol-4-yl)propyl phenylmethyl ether (FUB 186) and related compounds showed high *in vitro* activity in functional H_3-receptor assays on rat cerebral cortex and on guinea pig ileum. [20] Compounds with bulkier lipophilic residues, like 3-(1*H*-imidazol-4-yl)-propyl 1-naphthylmethyl ether (FUB 204), proved to be promising histamine H_3-receptor antagonists of high potency being active also under *in vivo* conditions after *p.o.* administration to mice (Table 2).[20] The aim of this study was to improve the *in vivo* activity of previously developed lead structures in order to obtain orally highly active histamine H_3-receptor antagonists as potential drugs. Therefore, 3-(1*H*-imidazol-4-yl)propyl ethers with diphenylmethyl structure (**3a**–

f) have been designed, and their activities *in vitro* ([^{3}H]histamine release assay on synaptosomes of rat cerebral cortex) and *in vivo* (N^{τ}-methylhistamine-level in mice brain after *p.o.* administration) have been determined. In addition, we have examined the activity of the title compounds at other histamine receptor subtypes in functional tests on isolated organs of the guinea pig[21] in order to investigate their selectivity.

Chemistry.

The central building block of the designed ether derivatives **3a–f** was 3-(1*H*-imidazol-4-yl)propanol hydrochloride (**1**).[22] Compound **1** was prepared from urocanic acid in a four step synthesis as described previously by Stark et al.[23] The ethers were obtained by refluxing diphenylmethyl chlorides **2a–f** with **1** in acetonitrile (Scheme 1). The required diphenylmethyl chlorides **2a–f** were prepared by reducing the corresponding benzophenone derivatives with complex hydrides and subsequent treatment with thionyl chloride according to standard methods. The nucleophilicity of the imidazole moiety was reduced by using the hydrochloride of **1**. Thus, the electrophilic attack was exclusively directed towards alcohol functionality.

Scheme 1. Synthesis of hydrogen maleates of the 3-(1*H*-imidazol-4-yl)propyl diphenylmethyl ethers **3a–f**.



(a) acetonitrile, 50 °C, 6–8 h; (b) chromatographic purification, maleic acid

Compounds **3a–f** were purified and characterized as hydrogen maleates by mp (cryst. solvent: Et_2O/EtOH), ^{1}H-NMR (not shown), EI-MS, and CHN analyses (all values were within ±0.4% of theoretical values, Table 1).

Table 1. Chemical data of hydrogen maleates of diphenylmethyl ethers **3a–f** (for general structure see Scheme 1).

Compound	R^1	R^2	mp [°C]	yield [%]	formula	molecular weight	mass peak $[M]^{+}$
3a	H	H	106	56	$C_{19}H_{20}N_2O \cdot C_4H_4O_4$	408.5	292
3b	F	H	90	65	$C_{19}H_{19}FN_2O \cdot C_4H_4O_4$	426.4	310
3c	F	F	108	42	$C_{19}H_{18}F_2N_2O \cdot C_4H_4O_4$	444.4	328
3d	Cl	H	107	50	$C_{19}H_{19}ClN_2O \cdot C_4H_4O_4 \cdot 0.25\ H_2O$	447.4	326
3e	Br	H	127	60	$C_{19}H_{19}BrN_2O \cdot C_4H_4O_4$	487.4	371
3f	CF_3	H	106	48	$C_{20}H_{19}F_3N_2O \cdot C_4H_4O_4$	476.5	360

Pharmacology. General Methods.

Histamine H_3-Receptor *in Vitro* Assay on Synaptosomes of Rat Cerebral Cortex. The presented compounds **3a–f** were tested for their H_3-receptor antagonist activity in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine of synaptosomes of rat cerebral cortex according to Garbarg et al.[24] (Table 2).

Histamine H_3-Receptor Antagonist *in Vivo* Activity in Mice. The increase in N^τ-methylhistamine levels in Swiss mice brain after *p.o.* application of the compound was selected to determine the histamine H_3-receptor antagonist *in vivo* activity[24] (Table 2). The ED_{50} values were calculated as mg free base kg^{-1}.

Histamine H_1- and H_2-Receptor Antagonist *in Vitro* Activity on Isolated Organs of Guinea Pigs. Functional tests on guinea pig ileum for H_1- and on guinea pig atrium for H_2-receptor antagonist *in vitro* activity were used to investigate the activity at these histamine receptor subtypes according to Hirschfeld et al.[21] (Table 2).

Table 2. Histamine H_1-, H_2-, and H_3-receptor activity of diphenylmethyl ethers **3a–f**.

Compound	H_1	H_2	H_3	
	$-\log K_b$ [a] *in vitro*	$-\log K$ [b,c] *in vitro*	$-\log K_i$ [d] *in vitro*	ED_{50} [mg kg^{-1}] [e] *in vivo* ($\bar{x} \pm s_{\bar{x}}$)
3a	6.3	5.5	7.6	2.4 ± 1.7
3b	6.9	5.3	7.6	1.2 ± 0.7
3c	6.7	5.6	7.6	1.1 ± 0.2
3d	7.1	5.2	7.1	3.9 ± 1.0
3e	7.1	5.4	6.9	3.6 ± 1.2
3f	n.d. [f]	n.d. [f]	6.7	> 10
Thioperamide	< 4 [g]	< 5 [g]	8.4 [g]	1.0 ± 0.5 [h]
Clobenpropit	< 6.0 [i]	< 6.0 [i]	9.2 [k]	26 ± 7 [h]
FUB 186 [l]	4.7	3.7	7.7	> 10
FUB 204 [m]	6.1	4.9	7.7	3.2 ± 1.9

(a) guinea pig ileum[21], except for thioperamide[11]; (b) different antagonistic behavior (competitive, non-competitive); (c) guinea pig atrium[21], except for thioperamide[11]; (d) synaptosomes of rat cerebral cortex[24]; (e) central activity after *p.o.* administration to mice[23]; (f) n.d. = not determined; (g) ref. 11; (h) ref. 25; (i) ref. 14; (k) ref. 26; (l) FUB 186 = 3-(1*H*-imidazol-4-yl)propyl phenylmethyl ether hydrogenmaleate, ref. 20; (m) FUB 204 = 3-(1*H*-imidazol-4-yl)propyl 1-naphthylmethyl ether hydrogenmaleate, ref. 20.

Pharmacological Results and Discussion.

Histamine H_3-Receptor *in Vitro* Testing on Synaptosomes of Rat Cerebral Cortex. In this *in vitro* test system all newly designed compounds with a diphenylmethyl ether structure showed pronounced histamine H_3-receptor antagonist potency (Table 2). The $-\log K_i$-values of the tested compounds are all in a similar range ($-\log K_i$ = 6.7–7.6). The difference was less than one order of magnitude indicating that in this class of antagonists electronegativity of the substituents did not play a dominant role in receptor–ligand interaction. The parent compound **3a**, the mono- (**3b**) and

difluorinated compounds (**3c**) presented the highest *in vitro* activities within this series. Compounds with chloro, bromo or trifluoromethyl substituents **3d–f** are less active so that the size of the substituents seemed to be a limitating factor for H_3-receptor antagonist *in vitro* activity. The new compounds **3a–f** showed lower activity under *in vitro* conditions compared to thioperamide, clobenprobit or previously developed compounds[20] (Table 2). However, the main advantage of this new class is their *in vivo* activity.

Histamine H_3-receptor *in Vivo* Testing in Mice Brain after *p.o.* Administration. Additional to the H_3-receptor *in vitro* activity we also determined the *in vivo* activity in mice brain after *p.o.* administration. The diphenylmethyl ethers **3a–c** presented high histamine H_3-receptor antagonist *in vivo* activity (ED_{50} < 2.5 mg/kg, Table 2). The unsubstituted compound **3a** and the fluorinated compounds **3b,c** showed the highest *in vivo* activities in this series, as also observed under *in vitro* conditions. However, while the *in vitro* activity of **3a–c** was identical, the introduction of fluorine atoms (**3b,c**) seemed to increase histamine H_3-receptor antagonist *in vivo* activity compared to the parent ether derivative **3a**. On the other hand, other halide substituents (**3d,e**) did not improve the *in vivo* activity indicating the same role of the substituent as claimed for *in vitro* activity. Introduction of a trifluoromethyl group (**3f**) led to a dramatic loss of activity under *in vivo* conditions (ED_{50} > 10 mg/kg, *p.o.*). Pharmacokinetic parameters like absorption, distribution, and metabolism must also be taken into account for those *in vivo* screening results. In general, lipophilicity of the ethers **3a–f** and steric parameters of the bulky diphenyl system seem to be favourable to high *in vivo* activity.

Summarizing the *in vivo* results, the activities of **3b,c** were in the same range as the activity of the reference antagonist thioperamide,[11] whereas compounds **3a–f** are less active under *in vitro* conditions compared to thioperamide and clobenpropit. It can be observed that within this series the ethers **3b,c** presented *in vivo* activities higher than the activities of clobenprobit and other previously designed compounds, e.g., FUB 186 and FUB 204 (Table 2). The advantage of these new diphenylmethyl ethers is their activity under *in vivo* conditions after *p.o.* administration containing structural distinction to other H_3-receptor antagonists, which is important for their potential use as drugs (Table 2).

Histamine H_1- and H_2-Receptor *in Vitro* Testing in Functional Tests on Isolated Organs of Guinea Pigs. Compounds with promising *in vivo* activities (**3a–e**) were screened for their activity at histamine non-H_3-receptors in functional tests on ileum (H_1) and atrium (H_2) of guinea pigs (Table 2). The diphenylmethyl ether derivatives **3a–f** show structural similarity with classical histamine H_1-receptor antagonists, e.g. diphenhydramine, containing also a lipophilic diphenylmethyl ether and a basic moiety as general construction pattern. Therefore, their relatively high activity at this histamine receptor subtype might be explained. The bromo derivative **3e** presented even higher activity at histamine H_1-receptors than at H_3-receptors, thus no H_3-/H_1-receptor selectivity was found. On the other hand, the activity of the title compounds at histamine H_2-receptors is at least 30 times lower than at H_3-receptors. Consequently, the designed diphenylmethyl ether derivatives **3a–f** present combined H_3-/H_1-receptor and low H_2-receptor antagonist activity.

Conclusions.

The described diphenylmethyl ether derivatives **3a–e** showed pronounced to good activity at histamine H_3-receptors under *in vitro* conditions. The high *in vivo* activity of some compounds (**3a–c**) was the most remarkable pharmacological property of this class of H_3-receptor antagonists. The most potent compound was the difluorinated ether **3c** ($-\log K_i$ = 7.6; ED_{50} = 1.1 mg/kg). Additionally, the tested compounds showed H_1-receptor antagonist activity, whereas their activity at H_2-receptors was more than 1.5 orders of magnitude lower than at H_3-receptors. Thus, the newly developed histamine H_3-receptor antagonists are characterized by a new activity profile.

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