(CYCLO)ALKYL 3-PIPERIDINOPROPYL ETHERS AS HISTAMINE H_3 RECEPTOR ANTAGONISTS

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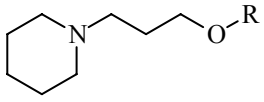
The histamine H_3 receptor belongs to the superfamily of G protein-coupled receptors. It has been described as a presynaptically located auto- and heteroreceptor in histaminergic and nonhistaminergic neurones mostly in the central, but also in the peripheral nervous system. Most of the histamine H_3 receptor antagonists consist of characteristic structural elements, such as a nitrogen-containig heterocyclic ring, connected with polar moiety by alkyl spacer, itself possibly connected by another spacer with hydrophobic residue [1]. This lipophilic part of compound is believed to be important for its biological activity as well as for pharmacokinetic and toxicological properties. Compounds are expected to act in CNS at logP ≈2 and cross the blood-brain barrier.

As a continuation of our previous works on piperidine derivatives [2, 3] possessing histamine H_3 receptor antagonist properties ethers were designed.



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The aim of this work was to synthesize (cyclo)alkyl 3-piperidinopropyl ethers (**1**) in order to study the influence of the lipophilic residue on histamine H_3 receptor activity. Compounds were obtained using *N*-piperidinopropan-1-ol as starting material via classical Williamson's synthesis. Microwave oven method was used too with good results.

The novel compounds were evaluated for the histamine H_3 receptor activity *in vitro* in a binding assay for the human histamine H_3 receptor stably expressed in CHO-K1 cells (or HEK 293) and for *in vivo* activity in the brain after oral administration to mice. The tested compounds possess good antagonist activities at the histamine H_3 receptor, some compounds have shown *in vivo* activities in a low mg/kg dosage range as ED_{50} value.

Lipophilicity of this series of compounds has been determined by means of logP values calculated using computer programs: Pallas 3.1, SciLogP, Alchemy, HyperChem. The influence of pH environment on lipophilicity was estimated by prediction of logD.

[1] H. Stark, M. Kathmann, E. Schlicker, W. Schunack, B. Schlegel, W. Sippl. *Mini Rev. Med. Chem.* **2004**, *4*, 965–977.
[2] D. Łażewska, K. Kieć-Kononowicz, H.H. Pertz, H. Stark, W. Schunack, S. Elz. *Pharmazie* **2001**, *56*, 927–932.
[3] Łażewska, D. Kieć-Kononowicz, K.; Pertz, H.H.; Elz, S.; Stark, H.; Schunack, W. *Pharmazie* **2002**, *57*, 791–795.