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New lead elements for histamine H_3 receptor ligands in the pyrrolo[2,3-*d*] pyrimidine class

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ABSTRACT

This work describes the microwave assisted synthesis of twelve novel histamine H_3 receptor ligands. They display pyrrolo[2,3-*d*]pyrimidine derivatives with rigidized aliphatic amines as warheads. The compounds were screened for H_3R and H_4R binding affinities in radioligand displacement assays and the most potent compounds were evaluated for H_3R binding properties *in vitro* and in docking studies. The combination of a rigidized H_3R warhead and the pyrrolo[2,3-*d*]pyrimidine scaffold resulted in selective activity at the H_3 receptor with a pK_i value of 6.90 for the most potent compound. A bipiperidine warhead displayed higher affinity than a piperazine or morpholine motif, while a naphthyl moiety in the arbitrary region increased affinity compared to a phenyl derivative. The compounds can be starting points for novel, simply synthesized histamine H_3 receptor ligands.

The physiological effects of histamine are facilitated by four G protein coupled receptors (GPCRs). [1] H_1, H_2, H_3, and H_4 receptors belong to the same family but differ in their structure, signalling mechanisms, function, tissue distribution and ligand binding. Histamine H_3 receptors (H_3Rs) are spread mainly in sympathetic and parasympathetic neurons of the CNS, regulating the release of various neurotransmitters such as histamine, dopamine, serotonin, acetylcholine and noradrenaline.[1] As ligands at the receptor are known for modulating memory functions and arousal, the human H_3R gained interest of the pharmaceutical industry due to its involvement in pathologies such as schizophrenia, Alzheimer's disease and sleep disorders.[2]

A general pharmacophore for ligands at the H_3R contains a basic moiety connected by a linker (mostly an alkyl) to a central core, which can be further substituted by an arbitrary region.[3] The basic moiety and the linker display the functional framework, essential for receptor binding, while the arbitrary region is mainly responsible for potency and pharmacokinetic properties.[4] The first generation H_3R ligands usually contained imidazole-based scaffolds, with regard to histamines structure.[4] Although they displayed high potency, the nucleus resulted in lack of selectivity and pharmacokinetic issues (e.g. interaction with cytochrome P450 enzymes).[5] Hence, several non-imidazolic ligands have been synthesized and successful replacement was accomplished with piperidine moieties. This led to pitolisant (Fig. 1),[6] which was approved by the EMA for the treatment of narcolepsy in 2016. With JNJ 7737782 (Fig. 1), the alkylspacer was rigidized and a morpholine structure was added in the arbitrary region. The structure displayed beneficial pharmacokinetic properties (e.g. short half-life), affinity remained high and the compound increased wakefulness in rats.[7] Compound **I** (Fig. 1) was developed as centrally acting antagonist with a bipiperidine structure. It displayed high activity *in vitro* as well as *in vivo* with optimized pharmacokinetic properties.[8]

On the other hand, pyrrolo[2,3-*d*]pyrimidine scaffolds are present in many anti-inflammatory,[9] antitumor[10] and anti-infective compounds.[11,12] Though the combination of the H_3R pharmacophore and 2,4,7-trisubstituted pyrrolo[2,3-*d*]pyrimidine as central core could be promising for developing H_3R ligands with additional pharmacological properties. As the pyrrolo[2,3-*d*]pyrimidine scaffold exhibits low micromolar affinity at the H_4 receptor,[13] all compounds were screened for their H_4 receptor binding properties as well.

Thus, we synthesized rigidized modifications of piperidine moieties in this work, as those are reported to deliver high affinities at the H_3R and provide beneficial pharmacokinetic properties.

In this work, we show the microwave-assisted synthesis of twelve new pyrrolo[2,3-*d*]pyrimidine derivatives with several rigidized aliphatic amines as warheads and different hydrophobic arbitrary

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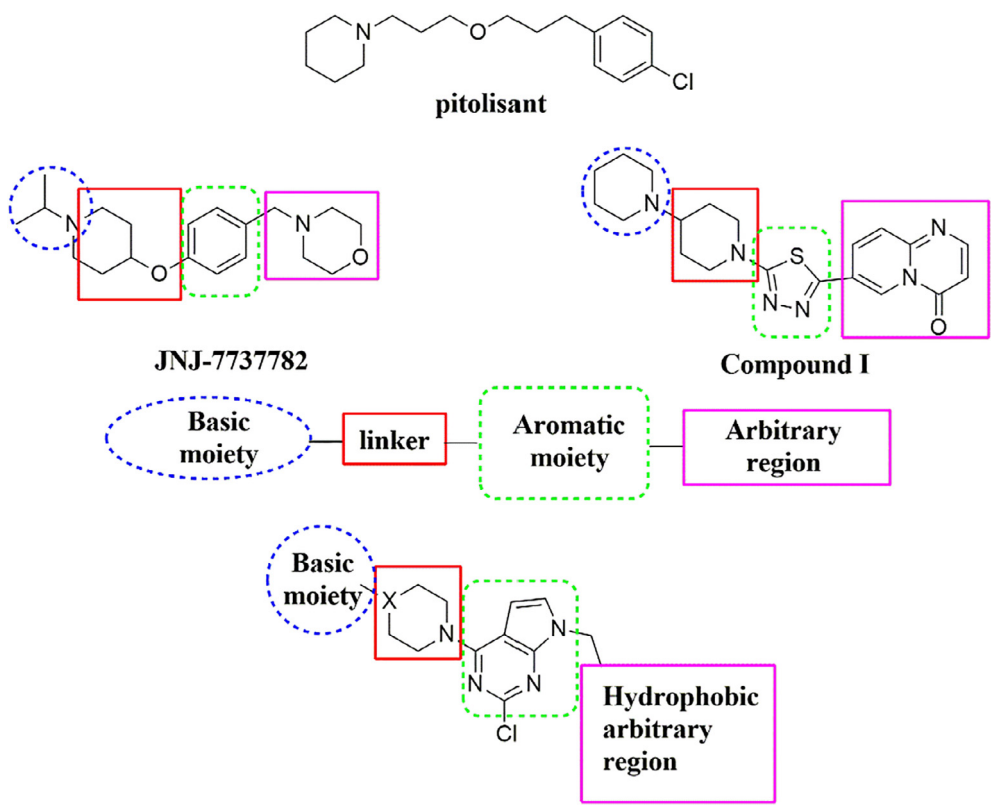
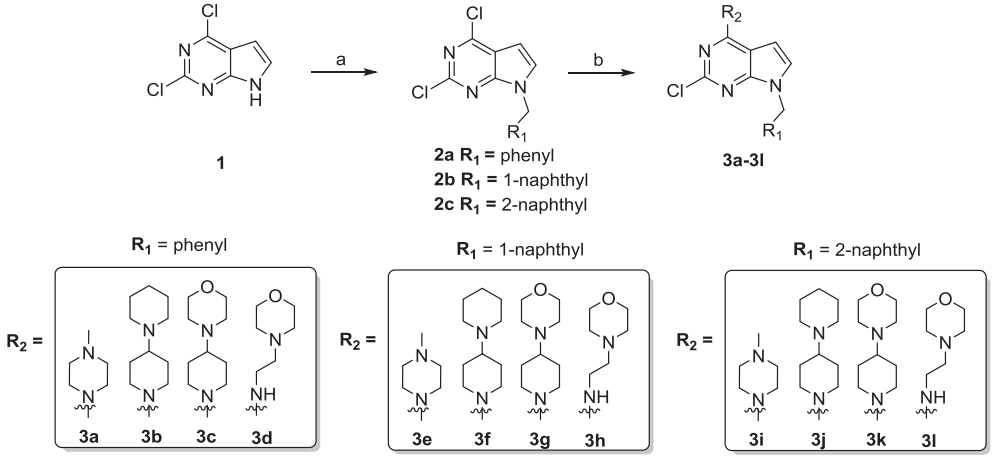


Fig. 1. Chemical structures of H_3 receptor ligands, pharmacophore and proposed structures in this work.



Scheme 1. Reagents and conditions a) Alkyl halides, K_2CO_3, DMF, r.t. 6 h, 50–89% b) Amines, NEt_3, EtOH, 80 °C, MW, 15 min, 62–99%.

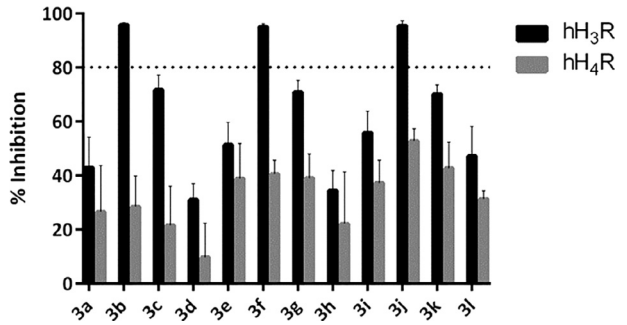


Fig. 2. Inhibition of radioligand binding at the hH_3R and hH_4R. Compounds were tested at 1 μM in two independent experiments, each as triplicate. Values are calculated relative to specific binding (mean% ± range).

Table 1
pK_i values of compounds **3b**, **3c**, **3f** and **3j** at the hH_3R determined in radioligand displacement assays. Binding energy determined by molecular modelling approaches.

Compounds	hH_3R pK_i $\bar{x}$ ± SEM	Energy (kcal/mol)
I	7.89[a]	−6.68
3b	6.31 ± 0.19	−6.22
3c	5.97 ± 0.15	−6.18
3f	6.83 ± 0.23	−8.63
3j	6.90 ± 0.27	−8.1

Data show mean ± standard error of mean (SEM) of five to six independent experiments in duplicates.
[a] Published in8.