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Azole derivatives as histamine H_3 receptor antagonists, Part I: Thiazol-2-yl ethers

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ABSTRACT

Most human histamine H_3 receptor (hH_3R) antagonists follow a general structural blueprint, containing a basic moiety linked by a spacer to a substituted core element. In this investigation the acceptance of thiazol-2-yl ether moieties in the core region is proved with some ether derivatives showing hH_3R binding affinities in the nanomolar concentration range. A diversity of structural motifs is used as substituents to enhance the in vitro hH_3R binding affinity.

The human histamine H_3 receptor (hH_3R) is one of four known G protein-coupled histamine receptors (hH_1R–hH_4R).[1] hH_3R is acting as autoreceptor on synthesis and liberation of histamine. As heteroreceptor it modulates the release of several other neurotransmitters.[2] Due to a distinct expression pattern in the central nervous system (CNS) and the resulting involvement in several neuronal functions the hH_3R is an attractive target for the treatment of CNS disorders.[3]

Since the identification of the H_3R in 1983[4] and its cloning in 1999[5] many H_3R ligands were developed by academia and industry, which led to extensive knowledge of antagonist/inverse agonist pharmacophores and ligand–receptor interactions. Among the diversity of structural classes, almost all compounds follow a general hH_3R antagonist blueprint, which contains a basic moiety, mostly a tertiary amine, linked by a spacer to a central core, that is, substituted by a variety of structural elements providing different physicochemical properties (Fig. 1).[6] Several pharmacophore models[7] indicated the usefulness of an aromatic, lipophilic element as central core moiety. Hence, a phenyl ring is used in numerous potent hH_3R ligands.[8]

The identification of new lead structures required differentiation from these frequently approached scaffolds. Here, we focused on the central core element. In earlier studies, the benzthiazol-2-yl ether derivative **FUB-658** and others were identified as moderately acting H_3R inverse agonist (ED_{50} value of 18 ± 7 mg/kg p.o.).[9,10] We used this lead compound as a starting point for modification of the thiazole ring aiming at the evaluation of the variability of the central core group. The acceptance of polar heterocycles replacing the

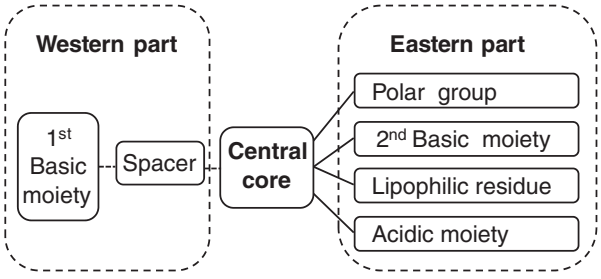

Figure 1. Expanded hH_3R antagonist blueprint.[6]

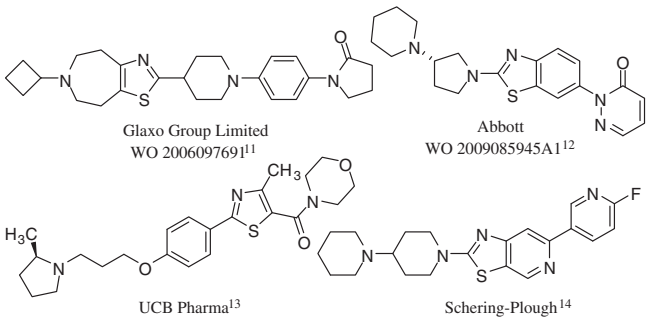

Figure 2. Representative thiazole-containing hH_3R antagonists.

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commonly used phenyl residue should be proven. Several other thiazole-containing series published in patents and original literature were regarded as proof of concept (Fig. 2).[11–14] However, H_3R binding properties still had to be improved.

Enlargement of the thiazole motif in the eastern part of the molecule by different substituents such as lipophilic residues, basic moieties and/or carbonyl groups should enhance the knowledge about structure–activity relationships (SAR) of thiazole-containing ligands, leading to new affine hH$_3$R antagonists/inverse agonists. The western part of the molecule, represented by an 1-(3-oxypropyl)amine element, was kept constant (Fig. 3).

Synthesis of the thiazole ligands **1**–**15** is shown in Scheme 1. The varying substitution pattern on positions 4 and 5 of the heterocycle required different ways of preparation. The 2-aminothiazole intermediates were obtained by Hantzsch-thiazole synthesis, a reaction of α-bromoketones with thiourea.[15] 1-(3-(Piperidine-1-yl)propyl)piperidine-4-one **8a** was prepared by N-alkylation of piperidone with 1-(3-chloropropyl)piperidine under basic conditions. The commercially available ketones **1a**–**7a** and **9a**–**15a** as well as precursor **8a** were brominated either in chloroform or in glacial acetic acid under addition of hydrobromide.[16] By adding thiourea the ring closure took place in ethanol. 2-Aminothiazoles **1b**–**15b** were further functionalized in 2-position to enable the coupling of piperidine- or the (dimethylamino)propyl building block. They were converted into 2-bromothiazole derivatives **1c**–**15c** by generating a diazonium salt and subsequent reaction with hydrobromide.[17] Alternatively, the substitutive de-amination with copper(II)bromide and *tert*-butyl nitrite was performed.[18]

An ether synthesis displayed the last step of the reaction. First the precursor alcohols 3-(piperidine-1-yl)- (**A**) and 3-dimethylaminopropan-1-ol (**B**), prepared according to literature methods,[19] were converted into the respective alcoholates by reaction with sodium hydride. The formation of compounds **1**–**15** occurred by adding the appropriate 2-bromothiazole derivatives **1c**–**15c**.

The final compounds **1**–**15** were tested with regard to their in vitro hH$_3$R binding affinity in an [^{125}I]iodoproxyfan binding assay (Table 1).[20]

Introduction of the thiazol-2-yl ethers as core element with a diversity of substituents in 4- and 5-positions of the heterocycle

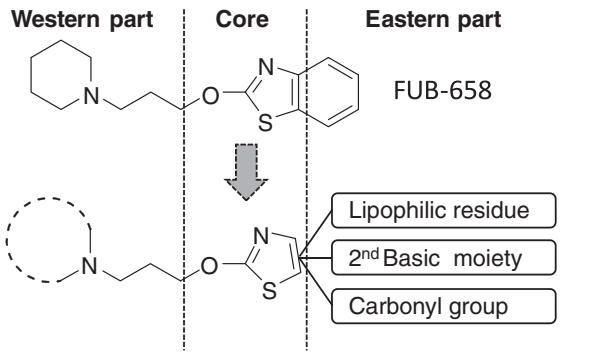
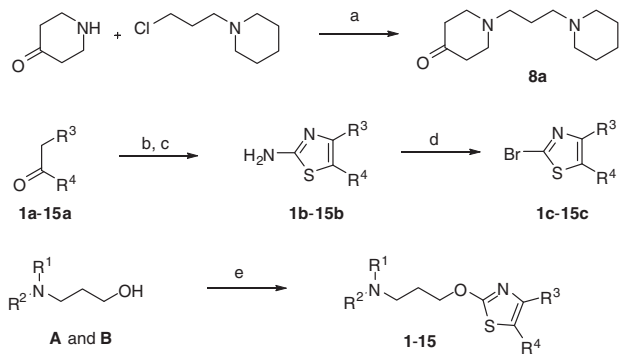
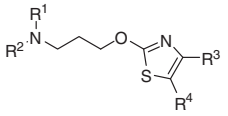


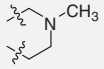
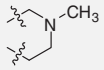
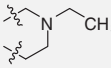
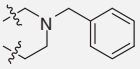
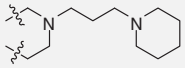
Figure 3. Lead structure modification and scaffold development.



Scheme 1. Synthesis of thiazole ligands **1**–**15**. For definition of R^{1-4}, see Table 1. Reagents and conditions: (a) K_2CO_3, KI, acetone, reflux, 72 h, 79%. (b) For compounds **2**–**4**, **8**–**15**: Br_2, chloroform, 0 °C → rt/50 °C, respectively, 1–3 h, 66–100%; for compounds **1**, **5**–**7**: Br_2, HBr, glacial acetic acid, 0 °C → rt, 15 min, 100%. (c) Thiourea, ethanol, 90 °C, 1.5–3 h, 8–92%. (d) For compounds **2**–**4**, **8**–**15**: $CuBr_2$, *tert*-butyl nitrite, acetonitrile, 0 °C → rt, 4–18 h, 29–75%; compounds **1**, **5**–**7**: $NaNO_2$, HBr, −30 °C, 1 h → 4 °C, 18 h, 29–37%. (e) (i) NaH, THF, 40 °C, 30 min–3 h; (ii) 2-bromothiazole derivatives **1c**–**15c**, 40–90 °C, 3–18 h, 5–66%.

Table 1
In vitro binding affinities of azole derivatives **1**–**15** at hH$_3$R



Compd	R^1R^2N	R^3	R^4	K_i hH$_3$R[a] (nM)
1				257 ± 76
2				>1000
3				>1000
4				153 ± 48
5				24 ± 3
6				14 ± 2
7				261 ± 62
8				20 ± 1
9				357 ± 54
10				344 ± 15
11		Br		93 ± 16
12		CH_3		41 ± 6
13				11.2 ± 2.1
14			CH_3	155 ± 34
15				>1000
Pitolisant (Tiprolisant, BF2.649)[b]				2.7 ± 0.5

[a] [^{125}I]Iodoproxyfan (K_d = 44 ± 6 pM) competitive binding assay on HEK-293 cells stably expressing hH$_3$R; values as means ± SD of one experiment performed at least in triplicates

[b] Ref. 20c.

led to pronounced differences in hH$_3$R binding. Affinities vary from the low nanomolar concentration range to the complete loss of receptor binding.

In compounds **1**–**4** the first basic moiety in the western part of the structural blueprint is represented by a dimethylamino function. These derivatives showed only weak binding behaviour with K_i values ranging from 150 to >1000 nM. Hence, we replaced the (dimethylamino)alkyl group by an alkylated piperidine.

Introduction of an additional basic moiety often leads to improved receptor binding caused by an additional beneficial interaction with the receptor's binding pocket (Glu206).[7] This effect can be noticed in compounds **5** and **6**, which both showed a comparable affinity in the nanomolar concentration range (K_i values of 24 nM and 14 nM, respectively). The analogue compound of ligands **5** and **6**, the benzyl amine **7**, showed decreased receptor binding (K_i value of 261 nM). Possibly, the phenyl ring sterically hindered the interaction of the second basic moiety with the ligand binding site. The incorporation of a third basic moiety (ligand **8**) offered no further enhancement of affinity compared to that of compounds **5** and **6**. Receptor binding remained in the low nanomolar concentration range (K_i value of 20 nM). Dibasic compounds show a certain potential to accumulate centrally. As a consequence they might induce unwanted side effects,[21] on which one must pay attention in further developments.

The exchange of the amino group in the fused thiazole structure either by non-polar methylene (compound **9**) or polar ether functions (compound **10**) revealed the importance of additional basic moieties for receptor binding. Both modifications led to decreased affinities (**9** and **10** vs **5**) with K_i values of about 350 nM.

The 5-bromo-4-phenyl derivative **11** offered a moderate binding behaviour (K_i value of 93 nM). Exchange of bromo to methyl substituent in compound **12** led to a slight improvement in receptor binding (K_i value of 41 nM), whereas the addition of a second phenyl residue in compound **13** evoked high affinity at the hH$_3$R (K_i value of 11.2 nM). Obviously, affinity is influenced by lipophilicity, steric as well as electronic effects. Whereas electron-withdrawing properties showed detrimental effects on binding behaviour (**11** vs **12** and **13**), increased lipophilicity is advantageous (**12** < **13**). Positive effects on hH$_3$R affinity of bulky/lipophilic residues as substituents in the eastern part of the molecule have previously been reported in other classes.[22]

Incorporation of a carbonyl function next to the heterocycle led to reduced receptor binding. Compound **14** showed an affinity in the submicromolar concentration range (K_i value of 155 nM). The conformationally constrained derivative **15** completely lost hH$_3$R affinity. Due to the sterically modified constitution of the carbonyl moiety as hydrogen bond acceptor, electronic properties were largely modified (**14** vs **15**), which may cause impairment of affinity.

In comparison to the dimethylamino motif the 1-(3-oxypropyl)piperidine element in the western part of the molecule, which was kept constant in compounds **5**–**15**, offered higher receptor binding. Only hH$_3$R affinity of compound **4** with a K_i value of 153 nM was increased in contrast to the inactive piperidine analogue **15**. The affinity of compound **4** was even comparable to the non-constrained carbonyl analogue **14**. These opposing effects of the dimethylamino compounds (**1**–**3** vs **4**) clearly demonstrated the limitations of SAR within our series of thiazole-containing compounds.

We successfully introduced polar thiazo-2-yl ether moieties in the central core of the hH$_3$R antagonist structural blueprint. The different substituents on positions 4 and 5 of the heterocycle led to a great variation in hH$_3$R affinity ranging from nanomolar binding strength to completely loss of affinity. Obviously, in our series of thiazoles the heterocycle seemed to have a lower impact on receptor binding than its substituents. SAR of the presented ligands indicated additional basic moieties (compounds **5**, **6**, **8**) and enlargement of the molecule by lipophilic residues (compound **13**, ST-1025) as major reason for high affine hH$_3$R antagonists. We proved the acceptance of polar moieties and therefore the variability in the core region of the hH$_3$R antagonist/inverse agonist blueprint. Research concerning this variability by further optimisation of the thiazole derivatives and the incorporation of other heterocycles are awaited for following investigations.

Acknowledgments

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Supplementary data

Supplementary data (analytical data of parent compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.098.

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