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Azole derivatives as histamine H_3 receptor antagonists, Part 2: C–C and C–S coupled heterocycles

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ABSTRACT

With a small series of compounds we demonstrated the variability in the core region of the human histamine H_3 receptor (hH_3R) antagonist structural blueprint by introducing polar azole groups (oxazole, oxadiazole, thiazole and triazole). Additional variations achieved by coupling different residues to the heterocyclic core structure led to further optimisation of in vitro receptor binding of the novel azole derivatives.

The human histamine H_3 receptor (hH_3R) is responsible for histamine neurotransmission in the central nervous system (CNS) by activation of $G\alpha_{i/o}$-mediated signalling pathways. Due to the involvement in a multitude of neuronal functions pharmacological research mainly focuses on the treatment of CNS disorders (e.g., schizophrenia, Alzheimer's disease, epilepsy, narcolepsy) by modulation of the hH_3R by antagonists/inverse agonists.[1]

The identification of the hH_3R in 1983[2] and the cloning in 1999[3] led to an enormous interest in the discovery of novel H_3R ligands in both academia and industry. Compound development started with the preparation of agonists, which all closely resemble the endogenous ligand histamine by adopting the imidazole moiety, likewise the first antagonists. Due to potential drawbacks of the imidazole-based compounds like reduced brain penetration and interactions with hepatic cytochrome P_{450} enzyme systems, non-imidazole containing ligands were developed.[4]

Although the number of structural classes is continuously rising, almost all hH_3R antagonists/inverse agonists follow a general blueprint, which consists of a basic moiety, mostly a tertiary amine, linked by a spacer to a central core substituted by a variety of structural elements providing different physicochemical properties (Fig. 1).[5] The frequently used aromatic core structures[1,6] are not essential for potent binding to the hH_3R; even polar groups are accepted (Fig. 2).[7–11]

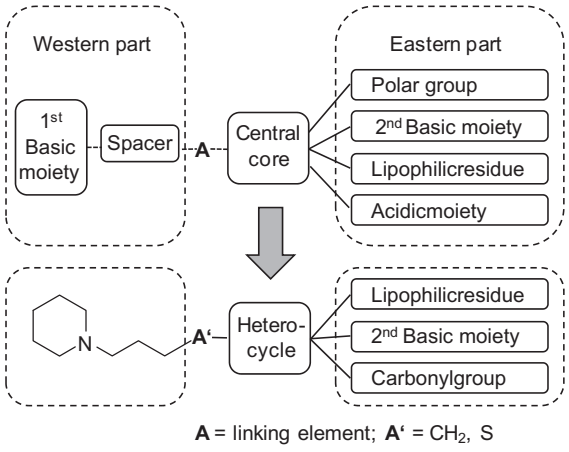

Figure 1. Expanded hH_3R antagonist structural blueprint[5] and general pharmacophore of presented H_3R ligands.

Recently, we successfully introduced polar thiazole groups into the core region of the structural blueprint.[11] The *S*,*N*-heterocycle had a lower impact on receptor binding than its substituents in the eastern part of the molecule. Enlargement of the molecule by lipophilic residues (e.g., ST-1025; cf. Fig. 2) and additional basic moieties were evaluated as major reason for high affine hH_3R ligands. Based on our previous work the aim of this study was the structural variation of the thiazol-2-yl ether derivatives by

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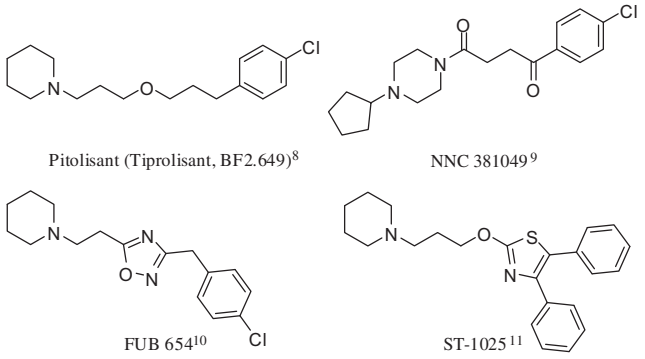


Figure 2. Representative hH$_3$R antagonists/inverse agonists.

modification of their linkage to the spacer. Additionally, we introduced new heterocycles containing one to three nitrogen atoms to extend the variation spectrum of the structural blueprint's core element. The eastern part of the molecule was modified by insertion of different lipophilic residues, carbonyl groups or additional basic moieties as substituents of the heterocycle to obtain further information on binding behaviour of the derivatives (cf. Fig. 1).

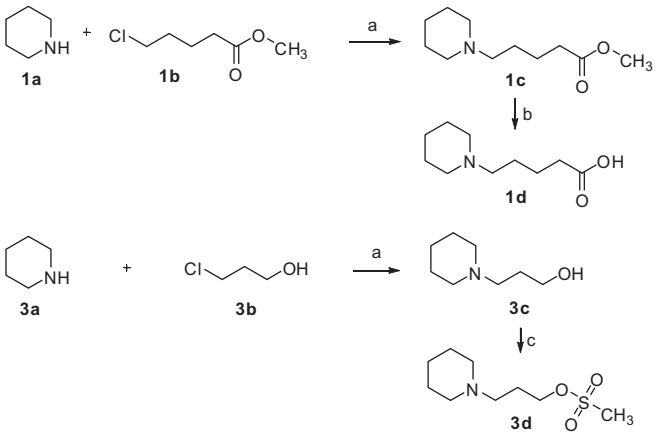
Compounds **1**–**7** were prepared as shown in Schemes 1–4.

The precursors 5-(piperidin-1-yl)pentanoic acid **1d** and 3-(piperidin-1-yl)propyl methanesulfonate **3d** were obtained by reaction of piperidine with methyl 5-chloropentanoate or 3-chloro-1-propanol, respectively, under Williamson-like conditions. The intermediates were further functionalized by alkaline hydrolysis of the methyl ester structure preparing precursor **1d** or by mesylation with methansulfonyl chloride yielding precursor **3d** (Scheme 1).[12]

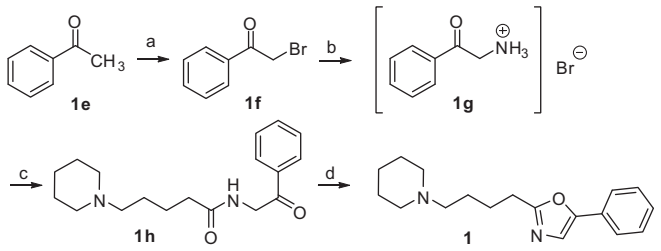
Preparation of compound **1** started with bromination of acetophenone **1e**, followed by Delépine-reaction[13] with hexamethylenetetramine to 2-oxo-2-phenylethanaminium bromide **1g**. By reaction with the acid chloride structure, obtained by activation of precursor **1d** with thionyl chloride, a β-ketonamide derivative was built. Dehydration of the β-ketonamide **1h** displayed the last step of the Robinson–Gabriel oxazole synthesis (Scheme 2).[14]

Oxadiazole ligand **2** was obtained by reaction of *N*′-hydroxynicotinamide **2b** with precursor **1d**, activated by CDI. Derivative **2b** was yielded from 3-cyanopyridine **2a** and hydroxylamine.[15] (Scheme 3).

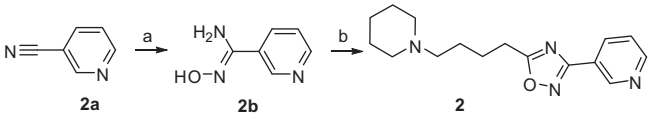
Nucleophilic substitution reactions led to the C–S-coupled heterocyclic compounds **3**–**7**. The 2-bromothiazole derivatives **3e**–**4e**



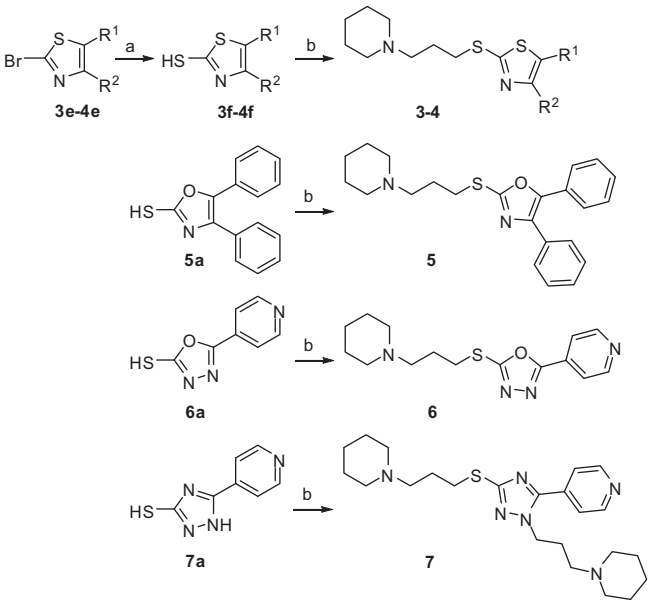
Scheme 1. Synthesis of precursors **1d** and **3d**. Reagents and conditions: (a) K_2CO_3, KI, acetone, 60 °C, 48–72 h, 70–79%; (b) 6 N KOH, THF/MeOH (3:2), MW, 70 °C, 15 min, 100%; (c) methanesulfonyl chloride, DCM, 0 °C → rt, 15 min, quantitative.



Scheme 2. Oxazole synthesis of ligand **1**. Reagents and conditions: (a) Br_2, chloroform, 0 °C → rt, 95%; (b) (i) hexamethylentetramin, chloroform, rt, 12 h; (ii) HBr, 50 °C, 12 h → reflux, 1.5 h, 100%; (c) (i) precursor **1d**, thionyl chloride, 0 °C → 60 °C, 2 h; (ii) triethylamine, 4-(dimethylamino)pyridine, 0 °C → rt, 48 h, 10%; (d) $POCl_3$, 0 °C → 70 °C, 1.5 h, 75%.



Scheme 3. Oxadiazole synthesis of ligand **2**. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, EtOH, reflux, 18 h, 3%; (b) (i) precursor **1d**, CDI, triethylamine, acetonitrile, rt, 30 min; (ii) MW, 130 °C, 30 min, 78%.



Scheme 4. Synthesis of thioether-linked heterocycles **3**–**7**. Reagents and conditions: (a) NaSH, ethanol, reflux, 12–24 h, 75–94%; (b) precursor **3d**, K_2CO_3, DMF, 60–80 °C, 2–12 h, 13–78%.

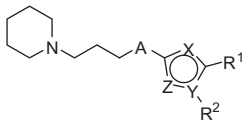
were converted into the mercapto analogues by sodium hydrogensulfide. The mercapto derivatives **3f**–**4f** reacted with mesylate precursor **3d** under basic conditions to compounds **3**–**4**. In the same way, reactions of the commercially available 2-mercaptoazoles **5a**–**7a** with precursor **3d** led to compounds **5**–**7** (Scheme 4).

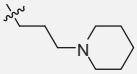
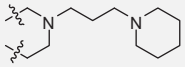
All final compounds **1**–**7** were tested with regard to their in vitro hH$_3$R binding affinity in a competitive binding assay (Table 1).[8,16]

The introduction of heteroaromatic ring systems containing one to three nitrogen atoms led to distinct differences in hH$_3$R binding. Affinities vary from the low nanomolar concentration range to the complete loss of receptor binding.

The C–C-coupled oxazol and oxadiazol ligands **1** and **2** showed moderate binding behaviour (K_i values of 63 nM and 110 nM,

Table 1
In vitro binding affinities of azole derivatives **1**–**7** to hH$_3$R



Compd	A	X	Y	Z	R^1	R^2	K_i hH$_3$R[a] (nM)
1	CH_2	O	C	N		H	63 ± 7
2	CH_2	N	N	O			110 ± 17
3	S	S	C	N			7.4 ± 1.1
4	S	S	C	N		CH_3	>1000
5	S	O	C	N			32 ± 5
6	S	O	N	N			187 ± 15
7	S	N	N	N			18 ± 3[b]
ST-1025	O	S	C	N			11.2 ± 2.1
ST-1093	O	S	C	N			20 ± 1
Pitolisant (Tiprolisant, BF2.649)[c]							2.7 ± 0.5

[a] [^{125}I]Iodoproxyfan competitive binding assay on HEK-293 cells stably expressing hH$_3$R; K_d = 44 pM; values are means ± SD of one experiment performed at least in triplicates.
[b] [^{3}H]Methylhistamine competitive binding assay on HEK-293 cells stably expressing hH$_3$R; K_d = 2.98 nM; mean value ± SD of two independent experiments performed in duplicates.
[c] Ref. 8.

respectively). Apparently, the substitution of the trimethylene-oxy spacer used in our previous work by a tetramethylene (buta-1,4-diyl) spacer do not lead to an enhancement in affinity. The C–C coupling of the heterocycle displayed a drawback compared to the most affine thiazol-2-yl ether derivatives.

Ganellin et al. investigated the bioisosterical replacement of oxy- and thioethers, which both showed similar receptor binding.[17] According to this finding we went on with C–S-coupled azole groups to obtain further information on the binding behaviour of the heterocyclic derivatives and determine the role of the ether function for hH$_3$R binding. Compound **3** with a K_i value of 7.4 nM showed comparable affinity to that of the oxyether analogue ST-1025 (K_i value of 11.2 nM)[11] in the low nanomolar concentration range. The promising substitution pattern of compound **3** was kept constant, whereas the thiazole group was bioisosterically replaced by an oxazole ring. This variation led to an impairment of receptor binding in compound **5** (K_i value of 32 nM). However, the advantage in receptor binding of the thiazole elements is restricted to their substituents. For instance, acylated thiazole derivative **4** showed clearly decreased affinity. According to our first series of thiazol-2-yl ether derivatives enlargement of the molecule by lipophilic moieties again led to enhancement in receptor binding (compounds **3** and **5** vs **4**). Additionally, the abolishment of potential π–π interactions or the change of electronic properties by substitution of the phenyl ring could have resulted in reduced affinity of compound **4**.

Compounds **2**, **6** and **7** contained pyridine as substituent of the heterocycle. The oxadiazoles **2** (C–C-coupled) and **6** (C–S-coupled) showed moderate receptor binding in the submicromolar concentration range (K_i values of 110 nM and 187 nM, respectively). The introduction of a central triazole ring in compound **7** resulted in a high affine ligand with a K_i value of 18 nM. Most probably, the incorporation of a further amino function had a higher impact on this improvement due to beneficial interactions with the receptor's binding pocket (Glu206).[18] Additionally, the steric enlargement of the molecule possibly allows positive effects in ligand–receptor binding.

We successfully introduced polar azole cycles containing one to three nitrogen atoms into the central core of the hH$_3$R antagonist structural blueprint. According to our previous work the presented small series of hH$_3$R ligands emphasised the importance of the azole substitution pattern and the lower impact of the type of heterocycle on receptor binding. Extending the variation spectrum of the incorporated azoles, the presented ligands enlarge the structure–activity relationships deduced from the former thiazole series and indicated again the enlargement of the molecule by lipophilic (**3**) and additional basic functions (**7**) as major reasons for high affine H$_3$R ligands. As linker between spacer and core element the thioether moiety resulted to be comparable to the oxyether of the thiazol-2-yl ether derivatives (compounds **3** and ST-1025). By introducing different C–C- and C–S-coupled heterocycles we confirmed the acceptance of polar moieties in the central core of the structural blueprint. Taken together the results of both series of azole derivatives we could establish a new structural class of hH$_3$R ligands containing polar heteroaromatic ring systems as core element.

Acknowledgements

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