HISTAMINE H3 RECEPTOR LIGANDS: STRUCTURE ACTIVITY RELATIONSHIPS

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ABSTRACT

***Background**: The H3R is an attractive and potential drug target as it relates to various diseases of the central nervous system (CNS). So far, several H3R compounds are or have been in clinical trials and some have been rejected as well. Therefore, it is necessary to develop new H3R ligands. **Objects**: This review surveys around 46 accessible articles about H3R antagonists/inverse agonists from the last six years, investigates recent structure activity relationships for H3R antagonists/inverse agonists and agonists and examine which properties of H3R ligands are required for high binding affinity and functional activity on H3R. **Results**: The review revealed the variety of H3R ligand structure as well as some certain basic amine moieties that contribute much more toward the affinity than others. **Conclusion**: In order to make progress in H3R development, SAR investigation is not only important for high binding affinity but also for the best pharmacokinetic and pharmacodynamics properties. Therefore, additional SAR efforts on this receptor, as outlined in this review, may bring a wider future for the development of H3R ligands for the mentioned diseases.*

***Keywords**: Histamine H3 receptor, structure activity relationship, SAR, ligands.*

I. INTRODUCTION

The histamine H3 receptor (H3R) is a G-protein-coupled receptor (GPCR) and the third receptor in four histamine receptors that were discovered sequentially. The identification of H3R in 1983 and the cloning of its cDNA in 1999 have facilitated further research into H3R. The H3R is an attractive and potential drug target as it relates to various diseases of the central nervous system (CNS) including Alzheimer's disease (AD), attention-deficit/hyperactivity disorders (ADHD), schizophrenia, narcolepsy, epilepsy, pain, stroke and tremor. So far, several H3R compounds are or have been in clinical trials. Especially Pitolisant is noteworthy, as it was filed for approval at the EMA in May 2014. Nevertheless, it is still necessary to develop new H3R ligands. Therefore, it is necessary to examine which properties of H3R ligands are required for high binding affinity and functional activity on H3R.

This review investigates the recent structure activity relationships in the search for H3R antagonists/inverse agonists and agonists. The investigated data is collected from accessible articles using Pubmed in the duration of 2010 to 2014 for H3R antagonists/inverse agonists and from 2008 to 2014 for H3R agonists. In order to have a clear setup for the diversity of the claimed compounds, these ligands have been classified into some main groups based on the differences in pharmacology (agonist, antagonist/inverse antagonist) and/or the core of the structure.

i) Non-imidazole antagonists and inverse agonists with different cores:

Monoaromatic

Bicyclic ring

Urea

ii) Miscellaneous antagonist and inverse agonist chemotypes including spirocycle compounds, conessine-derived compounds, ergoline-derived compounds, and

antiarrhythmic drugs Amiodarone and Lorcainide.

iii) Histamine H3R agonists

Because of the limitation, this review shows only the structure activity relationship of non-imidazole based histamine H3R antagonists/inverse agonists with monoaromatic core and miscellaneous antagonist/inverse agonist chemotypes. In the accompanying pictures, a **bold** text indicates preferable while an *italic* text means unfavorable.

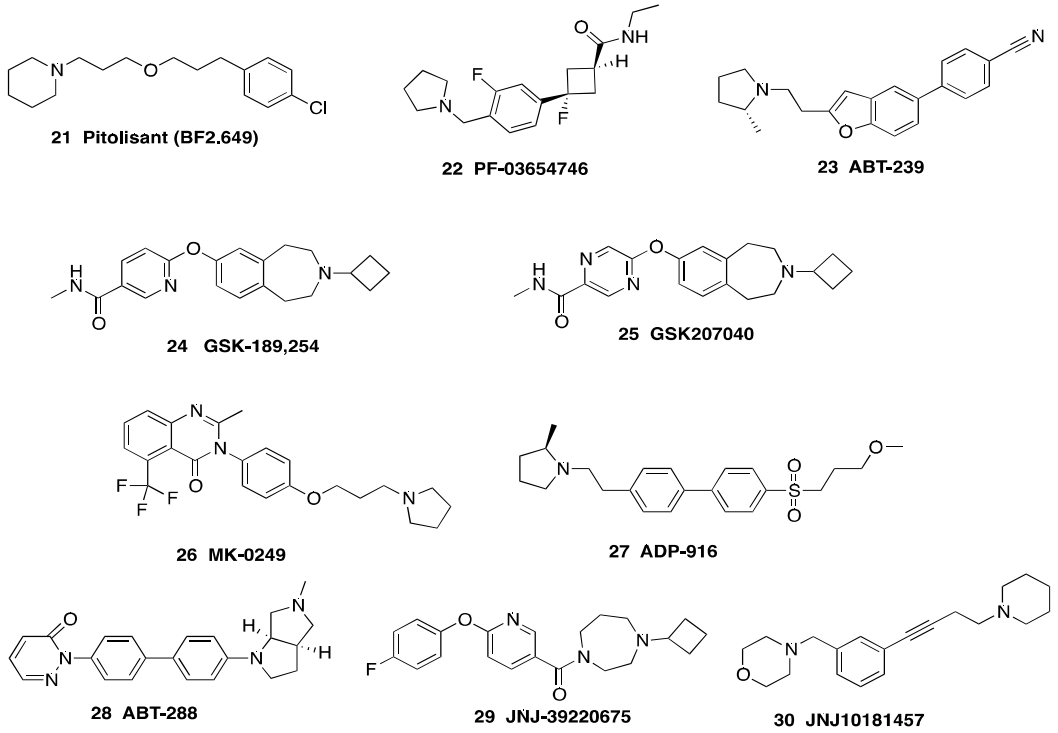

Figure 1: Some clinically tested ligands of H3R

II. HISTAMINE H3 RECEPTOR

2.1. Histamine H3 receptor and its biological role

The H3R was first described in 1983 by Arrang and co-workers as an additional histamine receptor, which mediates a negative feedback on the release of histamine from rat cerebral cortex slices [1]. Afterwards, the cDNA of hH3R was cloned in 1999 facilitating further research into H3R [2]. The H3R plays an important role in mediation of functional effects of histamine in different tissues. H3R functions as presynaptic autoreceptor and also occurs as heteroreceptor on nonhistaminergic neurons, therefore regulating neurotransmission not only of histamine, but also of other biogenic amines such as glutamate, acetylcholine, norepinephrine, dopamine, GABA and serotonin in the CNS and periphery [3].

2.2. General H3R pharmacophore

In the beginning of H3R antagonist/inverse agonist discovery, the imidazole moiety was supposed to be critical for H3R binding and activity. Therefore, scientists focused mostly on variations of the histamine scaffold. The H3R pharmacophore model at that time consisted of an imidazole moiety, a spacer, a polar moiety and a hydrophobic part, which covered most of the known H3R antagonists/inverse agonists structures. However, further development of H3R antagonists/inverse agonists has revealed one more

new modification in the Eastern part of the pharmacophore model, which is the presence of an acidic moiety (figure 2).

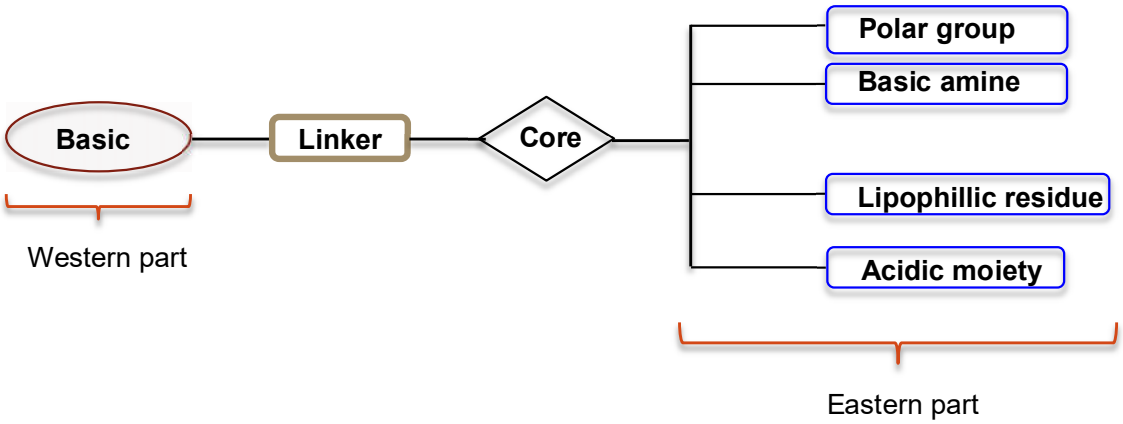

Figure 2: Pharmacophore of non-imidazole H3R antagonists/ inverse agonists with 4 parts: the Western part, linker, core and the Eastern part.

III. MONOAROMATIC CORE

So far, several research groups have attempted to optimize the phenoxypropylamine pharmacophore part. A design strategy is to rigidify the skeleton of the phenoxy core with the modulation of the other parts including the Western (1st basic amine), Eastern part, and linker. Some main modifications are introduced: pyridazine-3-one, morpholine- and piperazine-ketone, cyclobutoxy linker.

3.1 Pyridazine-3-one

Recently, by using pyridazine-3-one as the Eastern part with the presence of the phenoxy core, Hudkins and colleagues discovered CEP-26401 (irdabisant) as a potent H3R clinical candidate, which has been in Phase IIa for cognition-enhancing and wake-promoting activities [4]. The SAR results are collectively demonstrated in figure 3. Besides, the position of attachment of pyridazinone ring to the phenoxy core was also explored at carbon C-5 (**1**) and N-2 (**2**) of the ring demonstrating the unfavorable outcome of attachment on N-2 with over 40-fold weaker affinity compared to **1**.

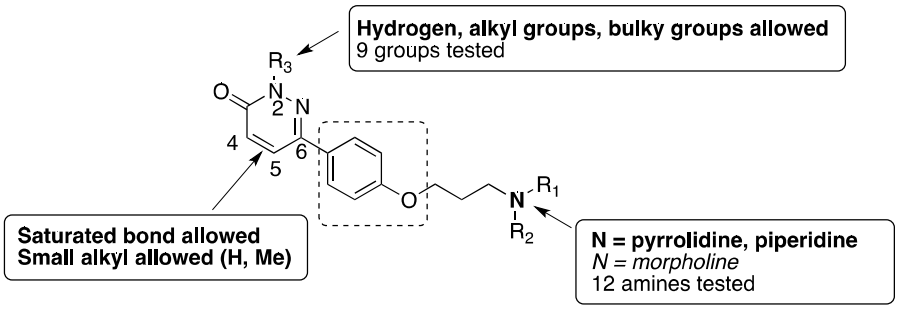

Figure 3: SAR for a series of phenoxy-amine pyridazin-3-one H3R antagonists/inverse agonists. An assay of [3H]-NAMH binding to membranes prepared from cells transfected with human H3R was used.

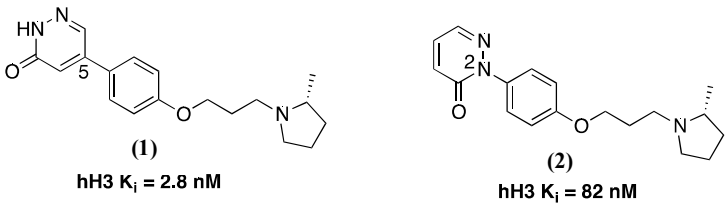

Figure 4: Some SAR results in a series of phenoxy amine pyridazin-3-one H3R antagonists/inverse agonists: C-regiomer (1) and the N-regiomer (2)

3.2. Morpholine- and Piperazine-ketone

The SAR on a novel ketone class of H3R antagonists/inverse agonists, including the modulations of the Western part, was disclosed by groups of Sundar and Zulli in 2012 [5], [6]. The general SAR results are shown in Figure 5.

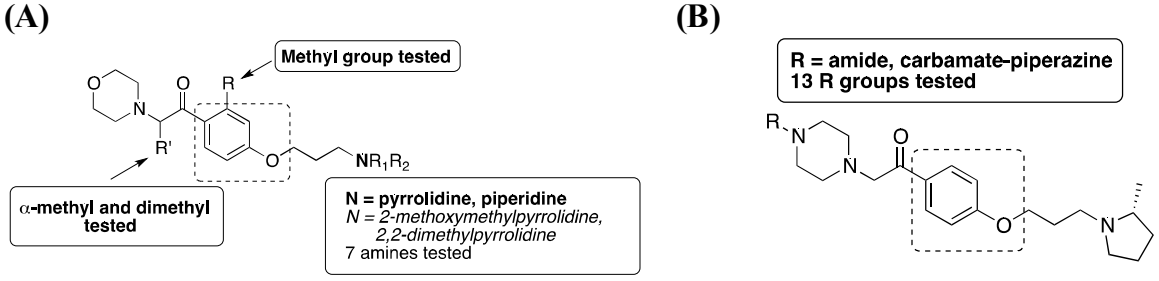

Figure 5: SAR for a series of (A) Morpholine ketone analogs and (B) Piperazine ketone analogs. An assay of [3H]-NAMH binding to membranes prepared from cells transfected with human H3R was used.

The H3R binding affinity of the morpholine ketone series (figure 5A) was significantly improved when modifying the basic amine NR1R2 linked to the phenoxy core. Incorporation of 2,2-dimethylpyrrolidine (K_i >1000 nM) or either (R)- and (S)-enantiomers of 2-methoxymethylpyrrolidine (K_i >3000 nM) led to big drop in binding affinity compared to methylpyrrolidine (K_i = 5.4 nM).

The replacement of morpholine by a piperazine with the terminal nitrogen substituted by R groups (such as amide or carbamate) was examined while the basic amine moiety (R)-2-methylpyrrolidine was fixed. The binding results indicated that bulky substituents were tolerated as R since each compound in the analog series showed high binding affinity for hH3R (K_i from 0.9 to 4.6 nM). Therefore, compared to morpholine ketones, piperazine ketones would be more promising in further investigation of ligands for wake-promoting activity.

3.3. Cyclobutoxy linker

Aside from the modification on Western or Eastern part, the linker between the core and the Western part has also been examined by several groups, notably the group of Wijtmans in 2010 and the group of Provins in 2012, leading to the introduction of a 3-cyclobutoxy linker as a key spacer for H3R antagonists/inverse agonists (figure 6) [7], [8]. Both groups conducted a comparison between compounds containing an unconstrained propoxy and constrained cyclobutoxy linker revealing the better affinity of the latter.

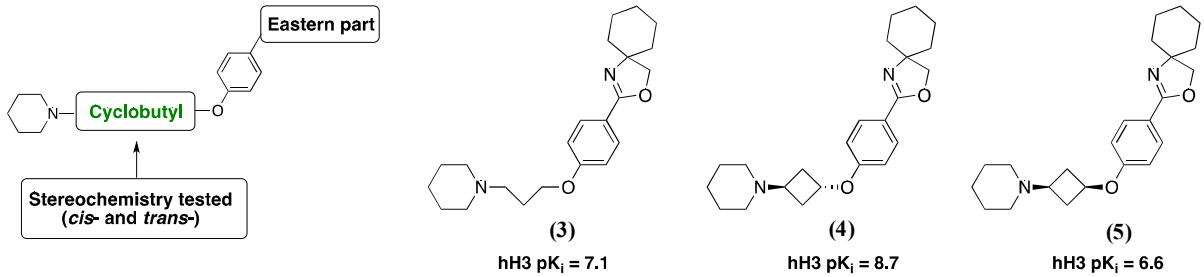

Figure 6: Modification on linker between the core and Western part and representive compounds of the classical linker (3) and constrained linker: trans- (4) and cis- (5)

IV. ATYPICAL ANTAGONIST/INEVERSE AGONIST CHEMOTYPES

4.1. Spirocycle compounds

The SAR for cyclobutyl spirobenzopyran piperidine system was mostly evaluated at the nitrogen atom in piperidine ring (figure 7).

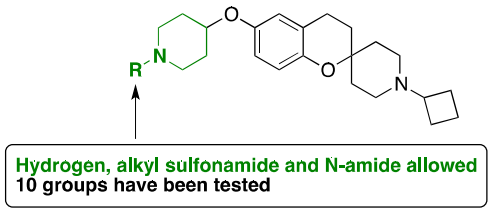

Figure 7: SAR for a series of the cyclobutyl spirobenzopyran piperidine H3R antagonists/inverse agonists. An assay of [3H]-NAMH binding in membranes prepared from cells transfected with human H3R was used.

The introduction of a (substituted) piperidine ring on the simple spirobenzopyran piperidine phenol led to a significant improvement from 50-fold to more than 500-fold in H3R binding affinity. The modification was conducted by the introduction of various substituents R such as sulfonamide and amide derivatives. The result from amide analogs such as an acetamide, isobutylamide and cyclopropylamide showed high affinity for H3R. On the other hand, SAR exploration of alternative spirocycle compounds was recently investigated by the group of Brown giving the results described in figure 8 [9].

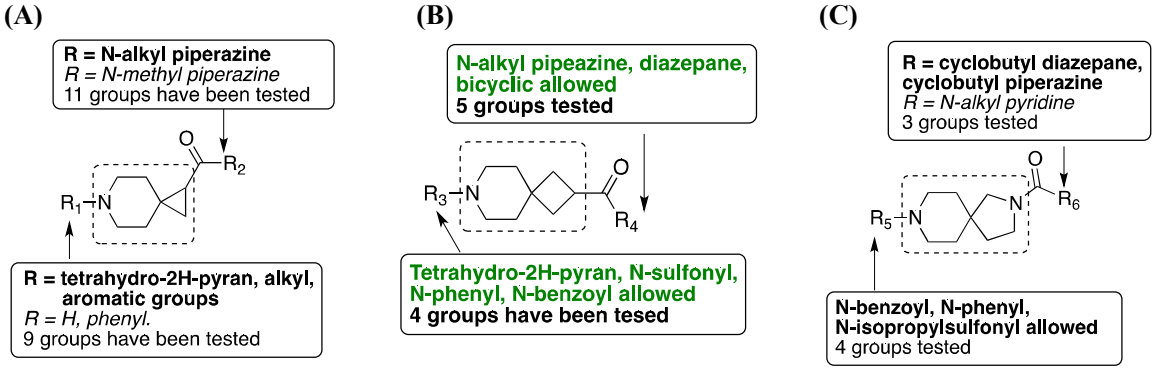

Figure 8: SAR for a series of azaspiro[2.5]octane (A), azaspiro[3.5]nonane (B) and Spirofused pyrrolidine-piperidine (C) H3R antagonists/inverse agonists. A functional GTPγS assay and [3H]-NAMH binding assay.

4.2. Conessine-derived compounds

Conessine is one of the natural compounds that were discovered to have affinity for H3R. The group of Zhao reported research on Conessine analogs as potent histamine H3R antagonists in 2008 [10]. Their initial work aimed to figure out which nitrogen atom in Conessine structure is more crucial leading to the identification of the critical role of the nitrogen in pyrrolidine ring. Therefore, in order to maintain high binding affinity, SAR evaluation was conducted at the basic nitrogen at the position 3 of the steroid skeleton when the nitrogen in pyrrolidine ring was kept constant (figure 9).

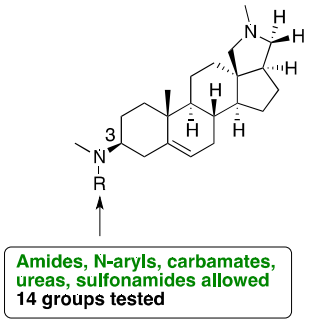

Figure 9: SAR for a series of Conessine analogs. An assay of [^{3}H]-NAMH binding in membranes prepared from cells transfected with human H3R.

Modification at the basic nitrogen was introduced with various substituents such as amides (**6**), N-aryls (**7**), carbamates, ureas and sulfonamides leading to a series of equivalent potency. Among those analogs, the most tolerated substituent was an amide (figure 10).

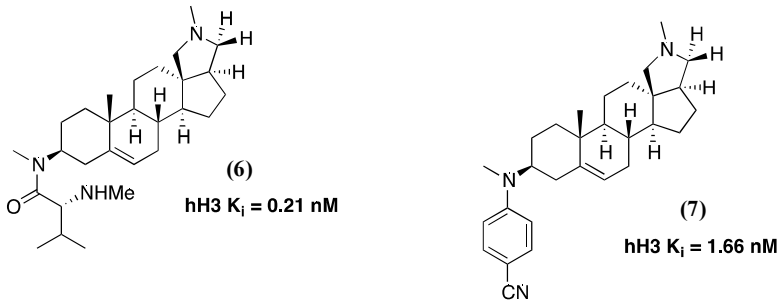

Figure 10: Representive compounds of Conessine analogs

4.3. Ergoline-derived compounds

An ergoline derivative, which is a chemokine receptor CXCR3 antagonist, was considered as a novel H3R inverse agonist chemotype in research of Auberson [11]. From this lead compound, the optimization was explored at the positions 1, 6 and 8 on the ergoline core (figure 11).

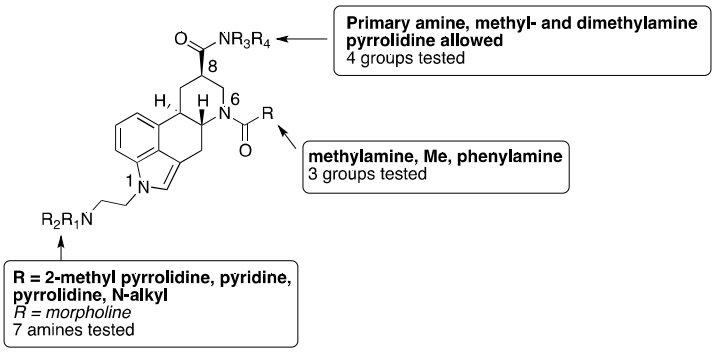

Figure 11: SAR for a series of ergoline derivatives H3R inverse agonits. A functional GTPγS assay using recombinant expressed in human H3 receptors was used

The SAR at positions 6 and 1 were explored with various substituents. The final modification was aimed at position 8. After the previous investigations on the other two points, Auberson et al. kept the most potent group at each position for further modification at position 8, which led to the most optimal substituent being dimethylamine. However, the optimization of ergoline derivatives is still ongoing to finally achieve a suitable candidate for further development.

4.4. Anticrrhythmic drugs Amiodarone and Lorcainide

Amiodarone (90) and Lorcainide (91) - two of a collection of antiarrhythmic drugs - were reported as potent and selective antagonists/inverse agonist of H3R by the group of Del Tredici in 2014 [12] (figure 12).

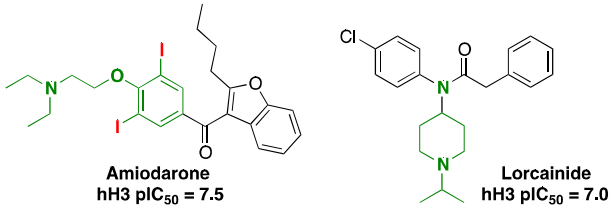

Figure 12: Two antiarrhythmic drugs Amiodarone, Lorcainide

The work was done by using a cellular proliferation assay R-SAT to screen a collection of more than 200,000 compounds including more than 2000 clinically used drug and other products from medicinal chemistry efforts. Amiodarone and Lorcainide then were tested in radioligand binding assay using [3H]-NAMH on both human and rat H3Rs showing that both amiodarone and lorcainide were slightly more potent at hH3R than at rH3R. This discovery might contribute to the structural diversity of H3R antagonists/inverse agonists pharmacophore.

V. H3R PHARMACOPHORE INSPECTION

The comparison between H3R ligands and the known pharmacophore model (2.2) has been inspected revealing high consistency of many H3R antagonists/inverse agonists with the pharmacophore model. However, conessine and ergoline analogs showed complex and bulky structures, which do not really obey the general pharmacophore model. This suggests that maybe there is the presence of an allosteric pocket for H3R

antagonists/inverse agonists.

VI. CONCLUSIONS

Since the discovery of thioperamide, the H3R field has been developed significantly with several drugs which are currently in clinical trials (phase I and II), notably Pitolisant (21) that was already filed for approval at the EMA in May 2014. In order to have an overview about H3R ligands disclosed in the last four to six years for antagonists/inverse agonists/agonists, this review has focused on the analysis of structure activity relationships disclosed in around 46 published articles. In all, reported diseases related to H3R so far have been suggesting a promising role of H3R in drug discovery. In order to make progress in H3R development, SAR investigation is not only important for high binding affinity but also for the best pharmacokinetic and pharmacodynamics properties. Therefore, additional SAR efforts on this receptor may bring a wider future for the development of H3R ligands for the mentioned diseases.

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