Medicinal Chemistry and Biological Properties of Non-Imidazole Histamine H_3 Antagonists

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Abstract: The H_3 receptor is prominently expressed in neuronal tissues, and H_3 antagonists have been proposed as drugs with benefits in disorders of cognition, attention, pain, allergic rhinitis, and obesity. The structure-activity relationships (SAR) of various classes of non-imidazole H_3 antagonists are reviewed, along with highlights of functional efficacy in tissue-based and animal disease models.

Keywords: Non-imidazole, histamine, H3, review, antagonist, inverse agonist.

INTRODUCTION

The histamine H_3 receptor has been the subject of much recent interest due to its central role in regulating neurotransmitter levels. Several excellent reviews have appeared which describe the general state of knowledge of H_3 receptor pharmacology, to which the reader is referred [1–6]. The importance of histamine H_1 and H_2 antagonists to improve human health is unquestioned, and the recent cloning [7] of the H_3 receptor has provided a new impetus to the development of drug-like ligands of this receptor as well. Pharmacological investigations have shown that the H_3 receptor is predominantly expressed in the CNS, where it plays a key role in negatively modulating the levels of neurotransmitters (NT) such as histamine (HA), acetylcholine (ACh), norepinephrine (NE), and others. The natural agonist HA reduces NT release and HA synthesis by acting at presynaptic H_3 autoreceptors and heteroreceptors, likely through $G_{\alpha i}$ or other G-protein mediated modulation of adenylate cyclase (AC) or other effector systems. H_3 antagonists have been shown to enhance the release of NT both *in vitro* and *in vivo*. Furthermore, the demonstrated constitutive activity [8,9] of the receptor suggests the possibility that the receptor exerts a tonic 'clamp' or 'brake' on NT release and neuronal activity in the absence of stimulation by histamine. Compounds acting as 'inverse agonists' at H_3 receptors may have special utility, by not only antagonizing the effects of HA, but also by further 'releasing the clamp' that intrinsically active H_3 receptors exert on NT levels. It should be noted that inverse agonists can be considered as a special class of antagonists, so the more generally used term antagonist will be used throughout this review, except in cases where compounds were specifically shown to be inverse agonists, or where the property is important for interpreting pharmacological data. It is expected that many compounds described as antagonists may be able to demonstrate inverse agonism in certain assays designed specifically to test for this property.

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The substantial pharmacological evidence that H_3 antagonists can regulate NT levels has generated and supported hypotheses that agents of this class may have utility as medicines to improve cognition, enhance attention and wakefulness, and to treat obesity, pain, and allergic rhinitis. H_3 antagonists have demonstrated beneficial effects in animal disease models (vide infra). However, to assure that beneficial results in preclinical animal models can be translated into clinical success in humans, a compound should ideally have similar H_3 potency and properties at both animal H_3 and human H_3 receptors. Importantly, there are reports that different compounds may have substantially different binding affinities at H_3 receptors from different species [10,11]. Even though there is substantial homology in H_3 receptors across species, changes of only two key amino acid residues have been shown to control compound potency [12,13]. Therefore, the reader should recognize that the comparisons of the SAR of a series is most valid for the species from which the data were generated, and be mindful that both absolute and relative potencies of compounds might vary substantially if compounds were tested in all possible species and functional assays.

IMIDAZOLE-BASED H_3 ANTAGONISTS

There is an extensive history of potent H_3 antagonists [1,3] with structures containing imidazoles, designed by extensive modification of the natural ligand histamine (**1**), as seen in (Fig. **1**). This structural class, as seen in (Fig. **1**), has produced established reference compounds, such as (**2**-**5**). One potential liability of imidazole-based drug candidates is the possibility for mechanism-based inhibition of hepatic CYPs (cytochromes P_{450}), caused by imidazole nitrogen complexation to heme iron in the active site of the enzyme [14]. Since these enzymes are a major route of clearance for most medicines, drugs that are cytochrome P_{450} inhibitors perpetrate drug-drug interactions by reducing or preventing the clearance of co-administered medicines. The dangers of such interactions are illustrated by the ability of ketoconazole (**6**) to increase blood concentrations of co-administered terfenadine to dangerous levels [15]. Additionally, the inhibition of CYPs by imidazole-based H_3 antagonists can interfere with adrenal [16] steroid synthesis

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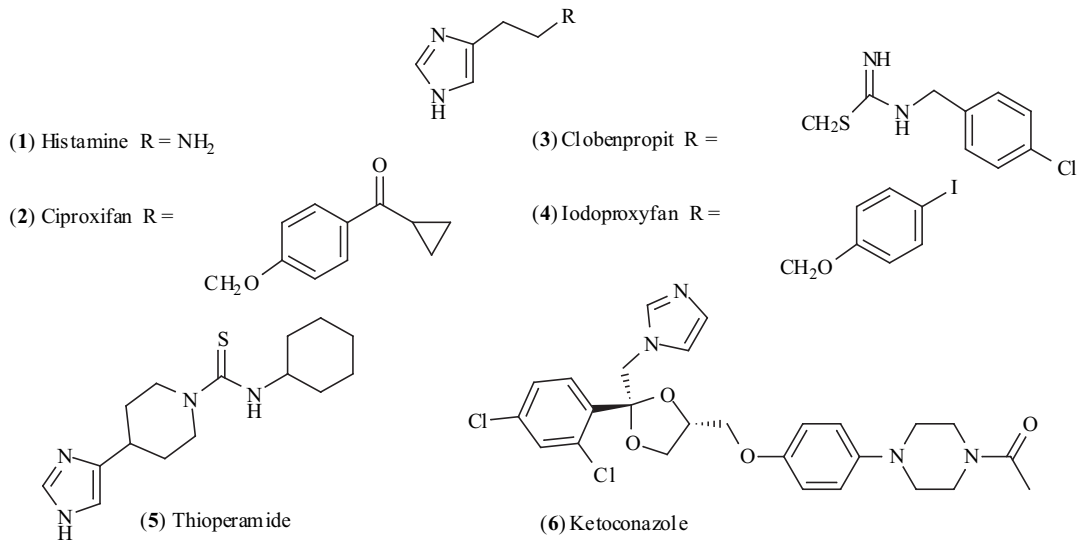


Fig. (1). Structures of some important H_3 antagonists containing imidazoles.

via inhibition of heme containing enzymes. For these reasons, workers in the field have sought to produce H_3 antagonist drug candidates that do not contain an imidazole moiety, now generically called 'non-imidazole' H_3 antagonists.

EARLY EXAMPLES OF NON-IMIDAZOLE H_3 ANTAGONISTS

Early in the field of investigation into H_3 antagonists, several non-imidazole compounds were reported to have very weak affinity for the H_3R, for example, clozapine [17], sabeluzole [18], betahistine [19], dimaprit [20], and phencyclidine [21], as seen in (Fig. **2**). While the structural features of some of these have been used as starting points for the design of new classes of non-imidazole H_3 antagonists, there is a larger family of structures loosely based on a different structural motif. Compounds with a basic dialkylamine-alkylene group-oxygen-lipophilic structure have been discovered by many different laboratories to possess potent H_3 receptor affinity, and therefore this class of compounds merits a summary as a separate group. This pharmacophore has been discovered, and rediscovered, several times and from different starting points: by modification of known imidazole-based structures, by high throughput screening (HTS) of large compound libraries, and in one case, from a natural product. In retrospect, this pharmacophore appears to represent a sort of "privileged structure" richly populated with potent and selective H_3 antagonists. Indeed, recently a similar general pharmacophore for homologous imidazole-containing H_3 antagonists has been proposed [22,23].

NON-IMIDAZOLE H_3 ANTAGONISTS BASED ON THE DIALKYLAMINE-ALKYLENE GROUP-OXYGEN-LIPOPHILIC GROUP PHARMACOPHORE

The marine natural product aplysamine-1 (**7**) (Fig. **3**) was reported to be a weak H_3 antagonist with an IC_{50} of 0.834 μM, and shown to be an antagonist in a guinea pig ileum

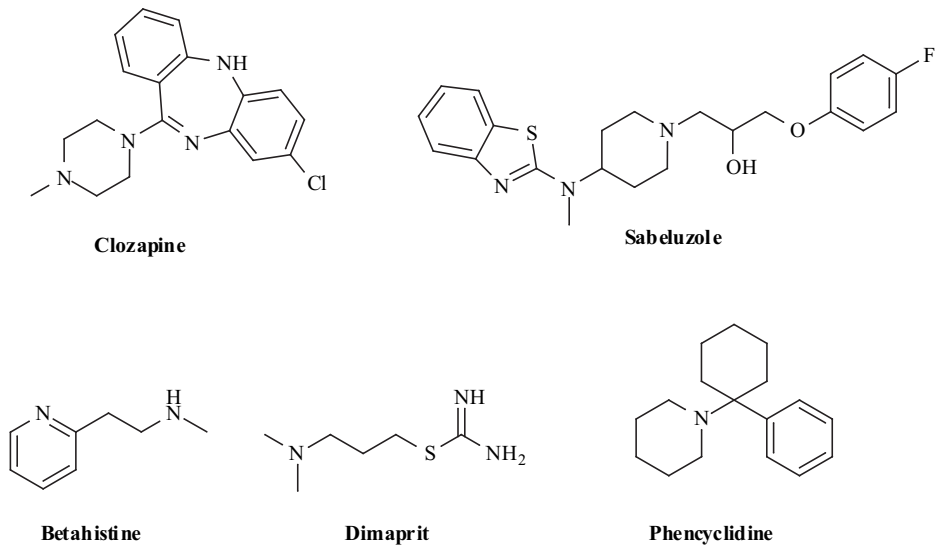
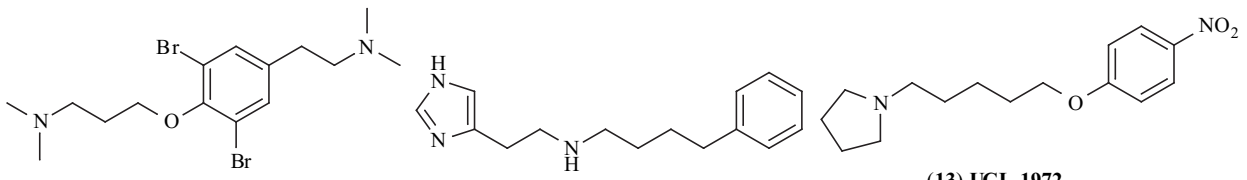


Fig. (2). Structures of non-imidazole compounds reported to have weak H_3 antagonistic activity.



(**7**) Aplysamine I (**8**) (**13**) **UCL 1972**

$R_1\,R_2N\text{-}(CH_2)_n\text{-}X\text{-}R_3$
(**9**)

Fig. (3). Structures of some early non-imidazole H_3 antagonists.

assay (GPi) at 2.4 μM [24]. The GPi assay is a tissue-based assay that indirectly measures the H_3 blockade and modulation of neurotransmitter release. This interesting non-imidazole was mentioned in an early patent application, but appears not to have influenced research in the field. Instead it stands as an interesting island of activity without connection to the large body of later work in the field.

An early description of a systematic design of non-imidazoles and their SAR was reported by Ganellin [25],

Table 1. SAR of Non-Imidazole H_3 Antagonists of Structure (9) $R_1R_2N\text{-}(CH_2)_n\text{-}X\text{-}R_3$

	R_1	R_2	n	X	R_3	pK_i	ΔpK_i (imid)	pA_2 GPi	ΔpA_2 (imid)	ED_{50} mg/kg
8			3	CH_2	Ph	6.15				
10	Et	H	3	CH_2	Ph	5.88				>10
11	Et	Et	3	S	Ph	6.74				>10
12	$-(CH_2)_4-$		5	O	Ph(4-CN)	7.72				1.9
13 UCL 1972	$-(CH_2)_4-$		5	O	Ph(4-NO_2)	7.41				1.1
14 UCL 2190	$-(CH_2)_5-$		3	O	Ph(4-COcyclopropyl)	8.4	-0.9	7.9	-0.5	0.18
15 FUB 637	$-(CH_2)_5-$		3	O	$(CH_2)_3$Ph	7.8	0	8.1	0.8	3.7
16 FUB 649	$-(CH_2)_5-$		3	O	$(CH_2)_3$Ph(4-Cl)	7.8	-0.1	8.3	0.1	1.6
17	$-(CH_2)_5-$		3	S	C(=NH)NHCH_2Ph(4-Cl)	6.3	-2.9	7.4	-2.5	>10
18	$-(CH_2)_5-$		3	O	CONHPh	6.6	-1.3	6.2	-0.6	>10
19	$-(CH_2)_5-$		1	CH_2	3-(4-Cl-benzyl)-[1,2,4]-oxadiazol-5-yl	6.9	-1.3	7.2	-0.9	~20
20 FUB 407	$-(CH_2)_5-$		3	O	CH_2CH_2 (t-Bu)			6.5	-0.9	~30
21	$-(CH_2)_5-$		3	CH_2	CH_2 CH_2Ph	6.7	-0.4	6.5	-1.2	>10
22 UCL 2138	$-(CH_2)_5-$		3	O	Ph(4-CN)	7.96*				0.2
23 UCL 2173	$-(CH_2)_5-$ (trans-3,5-dimethyl)		3	O	Ph(4-$COCH_3$)	8.74*				0.12
24	$-(CH_2)_5-$ (trans-3,5-dimethyl)		3	O	Ph(4-COcyclopropyl)	8.60*				

Table details: pK_i is the –log (Ki) at H_3, in this case, at the rat H_3 receptor; Δ_{imid} is the change in pK_i of the non-imidazole analog versus the imidazole analog, while ΔpA_2 is the difference in activity in the GPi (guinea pig ileum assay); ED_{50} mg/kg p.o. assesses the ability of compounds to induce an increase in the brain histamine metabolite tele-methylhistamine (N^{t}-MeHA) following oral administration to mice; *pK_i histamine release from rat cortical synaptosomes.

starting from N-phenylbutylhistamine (**8**), shown in (Fig. **3**). A systematic exploration of the SAR of a series of non-imidazole dialkylamine analogs of general structure (**9**) was conducted. It was discovered that some activity was retained upon replacement of the imidazole moiety with a basic amine group, as in compounds **10** and **11**. Potency of analogs in the series was increased when cyclic amines were selected as the preferred group, by optimizing the chain length, by replacing a chain methylene with oxygen or sulfur, and by attaching a nitro group to the phenyl ring. This process led to enhanced potency and *in vivo* activity, with UCL 1972 (**13**) being highlighted as particularly interesting (Table **1**).

The successful replacement of the imidazole moiety with piperidine and other basic amines was demonstrated with a variety of analogs (Table **1**). The results of this body of work were described in publications by Meier [26], Schwartz [27], and Liedtke [28]. It was found that the effect of replacement of the imidazole by basic tertiary amines affected H_3 inhibitory potency to widely different degrees, depending on the chemical series. Many compounds such as **17**, **18**, and **19** showed large losses in potency upon replacement of imidazole with piperidine, as seen in Table **1**. However, a subset of compounds such as **15** and **16** retained potency comparable to their imidazole homologs. The ciproxifan analog (**14**) retained high potency, although not as much as for the parent imidazole, ciproxifan (**2**). Other piperidine analogs (**17**-**20**) were found to be substantially weaker [28, 29] than their imidazole homologs, indicating SAR differences between the series. From these results, it can be concluded that imidazole replacement by piperidine is more likely to be successful in ethereal analogs (O at position X in **9**) than in the other series, especially in compounds where the oxygen is directly connected to an aromatic group (**15**, **16**). This finding supports the cautionary statement that even within the common pharmacophore of basic amine-alkylene-oxygen-lipophilic group, only a small subset of possible non-imidazole compounds in the class may have potent H_3 antagonistic activity, and that substantial optimization effort may be required to increase potency with this pharmacophore. For instance, in subsequent work exploring the effects of adding

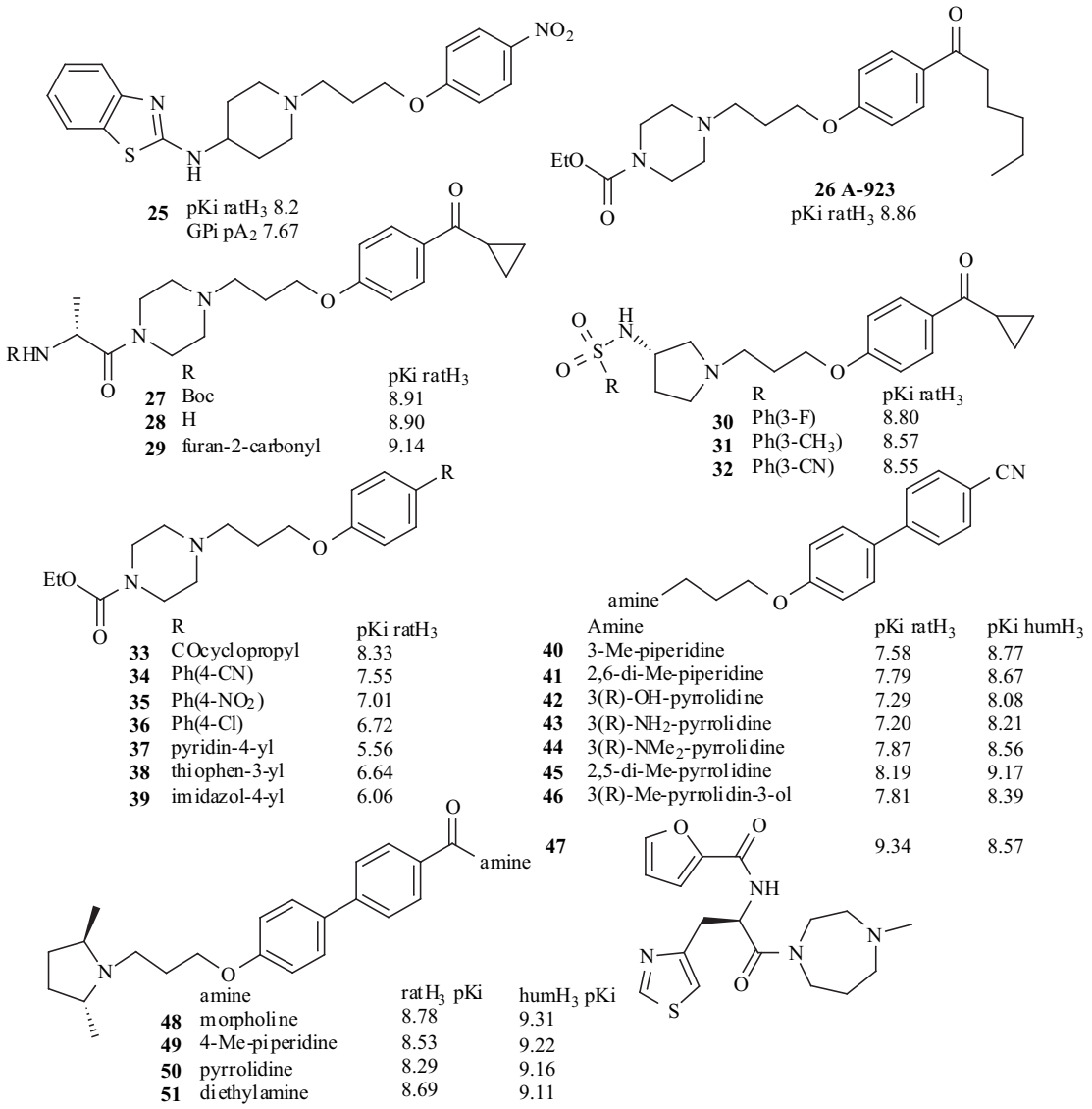


Fig. (4). Structures of non-imidazole H_3 antagonists **25**-**51**.

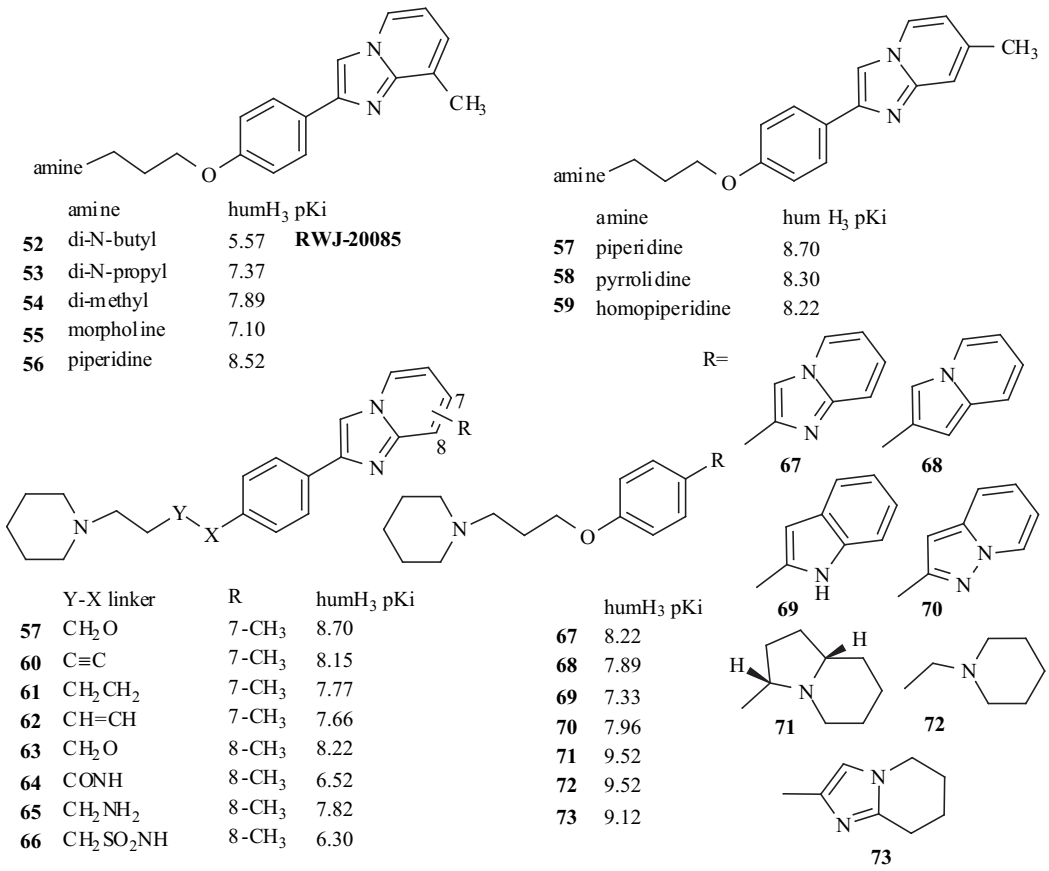


Fig. (5). Structures of non-imidazole H_3 antagonists **52**-**73**.

substituents to the piperidine in analogs of **14**, improvements in potency were seen with 3-methyl piperidine and in particular, with the trans-3,5-dimethylpiperidine analogs **23** and **24** [30].

Another potent early example in this pharmacophore class is compound **25**, reported by Menge [31], seen in (Fig. **4**). This compound was produced by an optimization of a series of analogs of sabeluzole, seen in (Fig. **2**), by removal of a hydroxyl at the 2-position of the propyl linker, removal of the methyl group on the nitrogen, and replacement of fluorine with a nitro group.

Using high throughput screening of a large compound library, the Abbott group found that the 923rd compound in the corporate collection, A-923 (**26**) shown in (Fig. **4**), was a potent H_3 antagonist, with a rat H_3 pK_i of 8.86, but without oral bioavailability in rat [32]. Improving on the already high potency of this compound proved initially difficult, though many analogs of comparable potency, and better oral bioavailability were discovered. Of 38 different carbamoyl, amide, and sulfonamide replacements of the ethyl carbamate group of **26**, no improvement in potency could be obtained. Likewise, no gain in potency was obtained when the n-pentyl group of A-923 was replaced with 19 other alkyl and aryl groups. More extensive modification of the structure eventually led to improvements in potency, with the D-alanine analogs (**27**-**29**) giving compounds that retained the potency of A-923 at the rat receptor, but also demonstrated acceptable oral bioavailability in the rat [32]. For example, **28** (A-304121) had especially high (F = 83%) oral bioavailability, and was also potent in the GPi (pA_2 6.98) and rat synaptosomal histamine release (pK_b 8.75) assays.

The disappointingly low potency of **28** and **29** and analogs [33] at the human H_3 receptor ($pK_i < 6$) forced the investigation of alternative structures. Altering the piperazine moiety of **28** to a 3(S)-amino substituted pyrrolidine reduced the potency, but functionalization of the amine group to give sulfonamides (**30**-**32**) gave compounds of high potency [34]. Replacement of the hexanoyl moiety of **A-923** with a cyclopropyl carbonyl (**33**) or a nitrile (**34**) led to a slight reduction in potency, with more pronounced reductions in potency noted with substituted phenyl analogs (**35**, **36**), and especially with the heteroaromatic analogs (**37**-**39**) [35a]. However, when the piperazine carbamate of **34** was replaced with selected amines (**40**-**46**), a dramatic recovery of potency was seen, and for the first time in the series, good potency was produced at the human H_3 receptor. Compound **44** (A-331440) proved to have the most interesting overall profile of the series. Curtis [35a] described similar structures that combined the 4-cyanophenyl moiety found in compounds (**40**-**46**) with a homopiperazine homolog of **29**, to produce compound **47,** which was found to have balanced high H_3 potency at both human and rat receptors.

In an investigation of the SAR of a broad series of 46 benzamides (**48**-**51**), a good balance of potency at the rat and human H_3 receptors was achieved, with **48** having the best overall profile [36]. This compound demonstrated functional antagonism in the GPi assay (pA_2 9.47), and a rat synaptosomal histamine release assay (pK_b 9.23). It

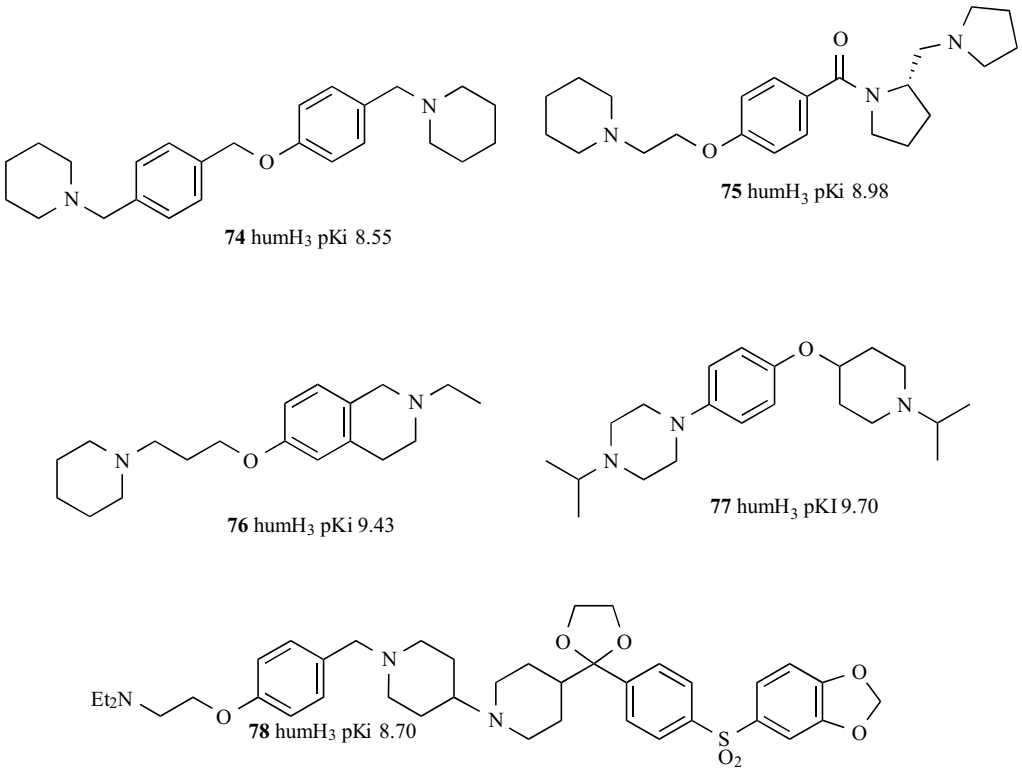


Fig. (6). Structures of non-imidazole H_3 antagonists **74**-**78**.

antagonized the H_3 agonist (R)-α-methylhistamine (RAMH) induced inhibition of forskolin-stimulated adenylate cyclase (rat H_3 pA_2 8.67, human H_3 pA_2 8.71). The compound also antagonized the agonist-induced (RAMH) increase in water drinking in rats at doses of 0.001-10 mg/kg, i.p.

The JNJ group found RWJ-20085 (**52**), seen in (Fig. **5**) by high throughput screening as a weak non-imidazole lead [37], and in the course of SAR investigations determined that the optimal amine was piperidine (**57**). This compound was found to have good CNS penetration, and was 57% orally bioavailable in rats, with a $t_{1/2}$ of 5.2 hours. Its potency at rat H_3 (pK_i 7.7–8.0) was weaker than at human H_3 receptors (pK_i 8.70). In a series of analogs (**57, 60**-**66**) in which the linker was varied, the propyloxy chain was again found to be slightly better than other close homologs, consistent with earlier findings by other groups in other series. Of the heterocyclic analogs (**67**-**70**), all had comparable potency, but a trend toward greater potency was proposed for the more basic heterocycles [38]. Accordingly, when saturated heterocycles of greater basicity were introduced at this position, as in analogs **71** [39], **72** [40], and **73** [41], binding to H_3 receptors was increased still further. Such structures as **71** and **72** are reminiscent of the dibasic structure of the marine natural product aplysamine I (**7**), and illustrate a general principle that a second basic moiety at a homologous position (from 10 to 20 Angstroms separation between the amines) imparts additional binding potency. This has been discovered and demonstrated several times by groups working in different structural series, seen in (Fig. **6**). For example, the compound **74** [42] is a further example of a compound demonstrating the boost in potency obtainable by incorporation of a second basic group. Compound **74** was also demonstrated to be active *in vivo* in elevating brain N^{t}-MeHA levels, an index of histamine release induced by the compound. Compounds such as **75** and **76** [43], **77** [44], **78** [45], and others [46], provide additional examples demonstrating the potent H_3 antagonism that can be achieved with dibasic compounds.

An additional example of a series of H_3 antagonists bearing the amine-alkyl-oxy pharmacophore has been reported [47], based on the HTS hit **79** (pK_i 7.40) seen in (Fig. **7**). None of the compounds described in the series substantially exceed the potency of the lead. In a patent application, Goldstein [48] claimed **80** as an H_3 antagonist. While the binding potency was not given, in mice the compound was found capable of inducing a 252% elevation N^{t}-MeHA levels at 10 mg/kg i.p., supporting an elevation of HA *in vivo*. A series of antagonists with large hydrophobic groups has been described [49], where compounds such as **81** had good potency at the human H_3 receptor.

As a product of efforts to design compounds combining H_3 antagonism with inhibition of the HA metabolizing enzyme, histamine N-methyltransferase (HMT), Apelt [50,51] produced the extremely potent H_3 antagonists **82** (FUB 701, pK_i 10.07) and **83** (FUB 836, pK_i 10.04) seen in (Fig. **7**). Here, new compounds were designed that combined structural features found in some H_3 antagonists (piperidine-alkyl-oxygen-phenyl) with the tacrine-like 4-aminoquinoline moiety, which is capable of inducing inhibition of histamine N-methyl transferase. The potency found in these analogs may be partly a product of the basicity of the aminoquinoline moiety, but more importantly they demonstrate that the H_3 receptor can not only tolerate very large groups such as in compounds **78** or **84**, but certain select large hydrophobic groups can induce substantial potency at H_3 receptors. The same report [50] also describes

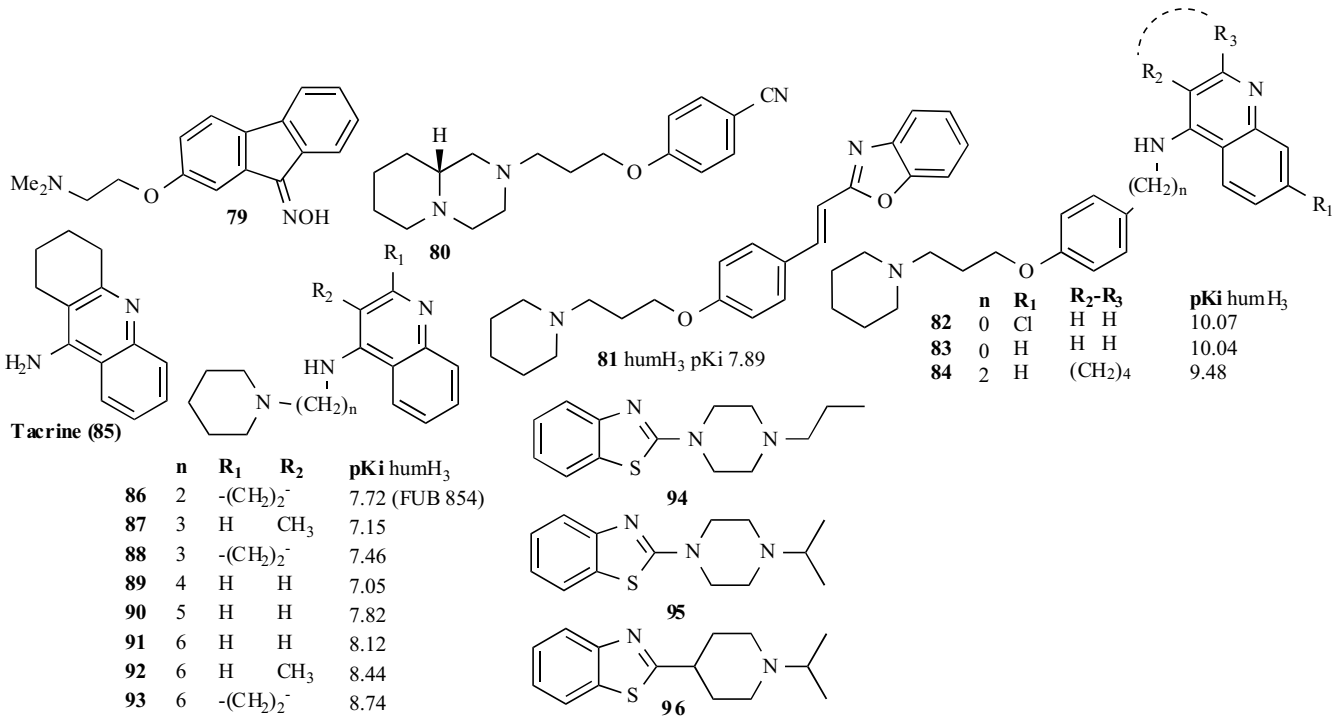


Fig. (7). Structures of non-imidazole H_3 antagonists **79-96**.

a different series of compounds departing from the piperidine-alkyl-oxygen-phenyl pharmacophore, but still possessing the bulky 4-aminoquinoline moiety. Since these can be viewed as belonging to a different structural class, these compounds (**86-93**), as seen in (Fig. **7**) will be discussed below, but they serve to illustrate the H_3 receptor's tolerance of antagonists with certain large groups.

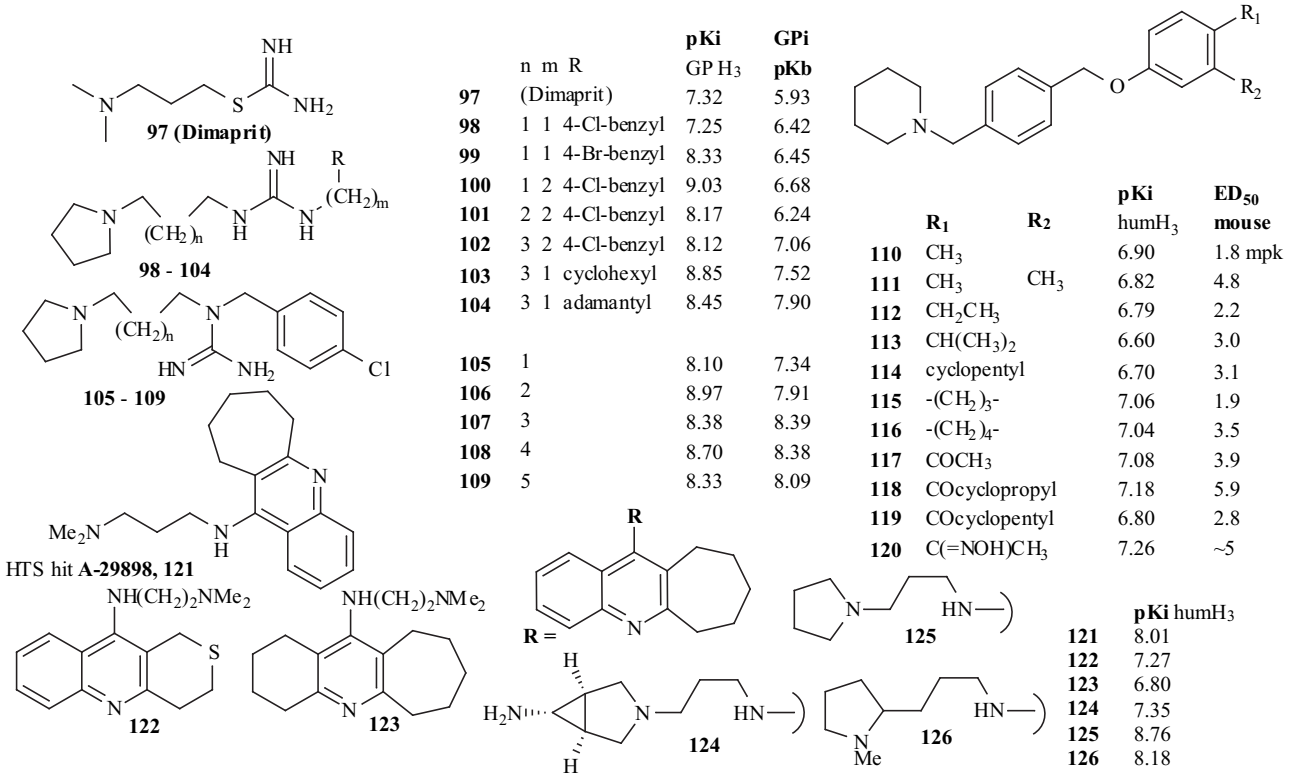


Fig. (8). Structures of non-imidazole H_3 antagonists (**97-126**). Data from competitive binding experiments are given as pK_i values in guinea pig (GP) or human H_3 receptors; $pK_i = -\log(K_i)$. Data representing potency in the guinea pig ileum assay are given as GPi pKb values. Potencies to elevate N^{t}-MeHA histamine *in vivo* in mice are given as ED_{50} values.

NON-IMIDAZOLE H_3 ANTAGONISTS-BASED OTHER PHARMACOPHORES

As a continuation of the search for dual H_3 antagonist/histamine methyl transferase (HMT) inhibitors that led to compounds **82**-**84**, Apelt [50] designed a different structural class of compounds (**86**-**93**). Building onto the structure of tacrine (**85**), itself a potent inhibitor of HMT, piperidine was selected as the basic amine moiety, and a study was performed evaluating the effects of alkylene chain length and the structure of the heterocyclic moiety on potency. Compounds with long alkylene chains seemed to confer optimal H_3 antagonist potency, with the six methylene linker analogs **91**-**93** having pK_i at hH_3 of 8.12-8.74, with either the tetrahydroacridine or quinoline as base. Compound **86** combined the best overall balance of H_3 antagonism (pK_i 7.72) and histamine methyl transferase inhibition (pIC_{50} 7.47).

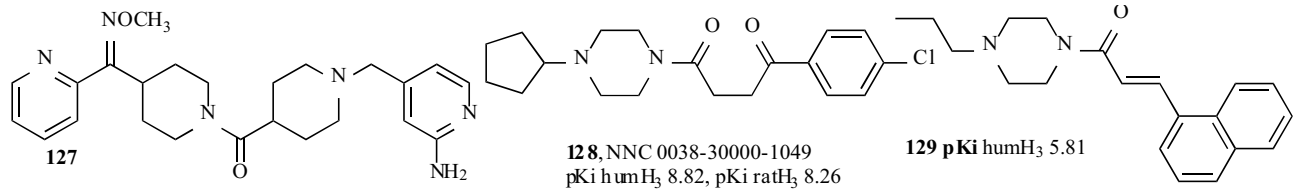
Many other classes of potent non-imidazole H_3 antagonists have been discovered that seem to fall outside of the aforementioned class of cyclic amine-alkyl-oxygen-lipophilic group pharmacophore. For example, in extending the SAR investigation of one of the earliest non-imidazole H_3 antagonist series [52], it was found that the propyloxyphenyl moiety in compounds such as **25** was not necessary, as seen in (Fig. **8**). Low molecular weight analogs (**94**, **95**, **96**) [53,54] with small alkyl groups were found to have an activity in functional (GPi) assays, with pA_2 values of 7.03, 7.21, and 7.03, respectively.

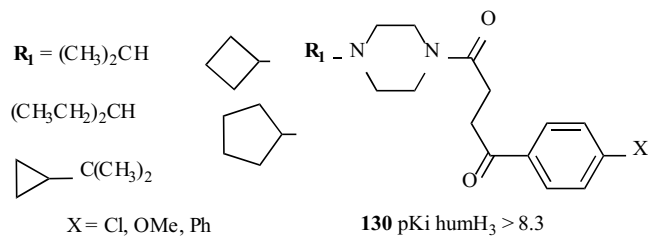
Linney [55] used the H_2 antagonist dimaprit (**97**) as a lead structure to generate non-imidazole H_3 antagonists, as seen in (Fig. **8**). Dimaprit is itself a weak antagonist at H_3 receptors, but by varying the length of the alkylene chain, and by replacing the isothiourea of **97** with a guanidine, and then subsequently attaching lipophilic groups, H_3 binding potency was increased as seen in compounds **98**-**104**. It was found that analogs of **98**, where the guanidine group was replaced with a sulfonamide, amide, thiourea, or sulfamide group (not shown), were all less potent than the guanidine analog. These compounds are non-imidazole homologs of the imidazole isothiourea clobenpropit seen in (Fig. **1**). However, the guanidine isomers **105**-**109**, in which the lipophilic chlorobenzyl moiety is attached to the same nitrogen as the alkylpyrrolidine, were consistently potent antagonists in GP cortex H_3 binding, and **107** and **108** were especially potent in the GPi assay.

Miko [42] made a series of benzylpiperidines seen in (Fig. **8**) where the propyloxy methylene groups present in compounds like UCL 2190 (**14**) were replaced with a para-phenylene moiety. Of the resulting analogs, compounds **110**-**120** were weak H_3 antagonists at the human H_3 with pK_i values of 6.6-7.3, but demonstrated *in vivo* activity in mice at 2-6 mg/kg following oral administration (elevation of cortical N^t-MeHA).

A series of analogs was described by Turner [56], who started from the high-throughput screening hit **121** (pK_i 8.01), which bears a seven-membered ring heterocyclic moiety. The six-membered ring mercaptan **122** is a bioisostere of the seven-membered ring analog **121**, but suffered a loss of potency, as did a tetrahydro analog (**123**). By holding the tetrahydro-cyclohepta[b]quinolin-11-yl constant, the effects on compound potency were studied by varying both the amine moiety and the linker chain (**124**-**126**). In this case, the trimethylene pyrrolidine **125** (pK_i 8.76) was optimal. The effects on HMT were not determined for any compounds of the series. There are interesting structural similarities between two members (**125** c.f. **88**) of the heterocyclic series of **121**-**126** and **86**-**93**, which suggests that these compounds may bind the H_3 receptor in a similar manner.

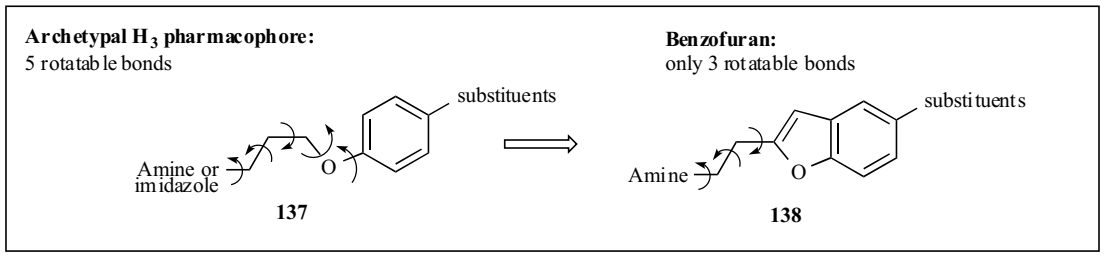
Some newer structural classes are disclosed only in published patent applications, and have not yet been fully described in the scientific literature. Often specific potencies are not given for compounds, and are sometimes only described as being within a certain range. In one application, Aslanian [57] specifically describes the potency of one compound (**127**, guinea pig H_3 pK_i 9.08). Likewise, the

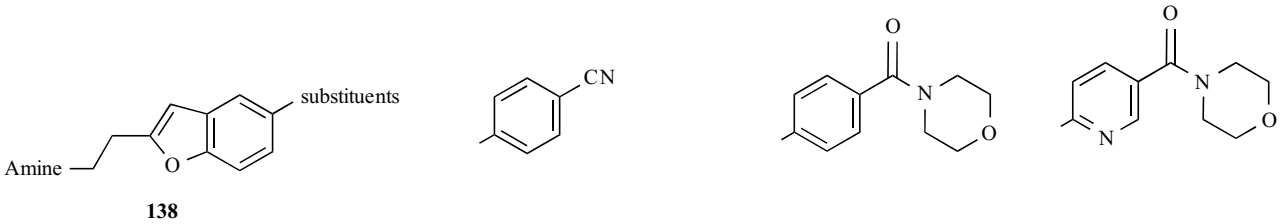




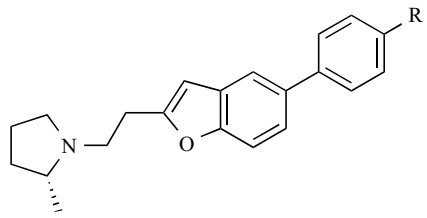
	n	X	R	GPi pKb	ED_{50} *in vivo* (mpk p.o.) mouse
15	3	O	$(CH_2)_3Ph$	8.1	3.7
131	4	$-CH_2-$	Ph	6.38	≥30
132	2	—	$(CH_2)_3Ph$	7.21	>10
133	3	—	$(CH_2)_2Ph$	6.91	15
134	2	—	H	5.69	1.3
135	3	—	H	6.16	1.4
136	3	-OCONHPh(4-OMe)		6.76	

Fig. (9). Structures of non-imidazole H_3 antagonists **127**-**136**.





Amines	humH3/ratH3	humH3/ratH3	humH3/ratH3
piperidine	8.05/7.23 (**139**)	8.30/7.92 (**148**)	7.92/7.31 (**155**)
2,6-dimethylpiperidine (cis)	8.62/7.66 (**140**)	8.66/8.01 (**149**)	8.25/7.35 (**156**)
4-methylpiperidine	7.70/7.60 (**141**)	7.39/7.13 (**150**)	6.69/6.53 (**157**)
hexamethyleneimine	8.00/7.11 (**142**)	8.22/7.85 (**151**)	7.80/7.48 (**158**)
2-methylpyrrolidine (R)	9.35/8.87 (**143**, **ABT-239**)	9.15/8.70 (**152**)	9.26/8.80 (**159**)
3-hydroxypyrroldine (R)	8.05/7.02 (**144**)	8.30/7.26 (**153**)	7.92/7.17 (**160**)
2,5-dimethylpyrrolidne (R,R)	9.05/8.00 (**145**)	8.40/8.05 (**154**)	8.22/7.59 (**161**)
2-methylpyrrolidine (S)	9.82/8.80 (**146**)		
2-hydroxymethylpyrrolidine (S)	8.66/7.59 (**147**)		



R	humH3/ratH3
F	8.40/7.11 (**162**)
CH_3	8.24/6.95 (**163**)
OCH_3	8.00/7.24 (**164**)
COcyclopropyl	9.59/8.19 (**165**)
CH_2OH	9.06/8.48 (**166**)

Fig. (10). Structures of non-imidazole H_3 antagonists based on 2-aminoethylbenzofurans **137**-**166**.

Novo Nordisk/Boehringer Ingelheim group has described H_3 antagonists in several applications, but compound potencies were not listed [58]. However, one compound (NNC 0038-0000-1049) (**128**) was later described [59,60] as a potent H_3 antagonist (pK_i 8.82 hH_3, 8.26 $ratH_3$) with oral bioavailability, and activity to reduce food consumption and body weight in obese rats. This compound and several other potent analogs of general structure **130** were discovered by using a parallel synthesis strategy to optimize the high throughput-screening hit **129**.

In a systematic exploration [61] of the SAR of analogs of FUB 637 (**15**, GPi pA_2 = 8.1), it was found that replacement of the oxygen at position X gave much weaker compounds in the GPi assay, as illustrated by **131** (GPi pA_2 = 6.38). Furthermore, analogs with additional methylenes in the chain had high activity at muscarinic M_3 receptors that interfered with the assessment of H_3 mediated activity in the GPi assay. It was found that when an acetylene moiety replaced the oxygen at position X, active H_3 antagonists (**132**, **133**) were produced, though activity was reduced for these compounds compared to **15** in the GPi assay and *in vivo*. It was interesting that two very low molecular weight compounds **134** and **135** had potent *in vivo* activity, in spite of their relatively weak activity in the GPi assay. Other linkers such as the carbamoyl moiety in **136** have been used in the chain to replace oxygen at X, but these modifications have so far resulted in compounds with lower H_3 affinities compared to **15** [62].

NON-IMIDAZOLE H_3 ANTAGONISTS BASED ON 2-AMINOETHYLBENZOFURANS

A class of 2-aminoethylbenzofurans (**138**) has been described [63] as high affinity H_3 antagonists with activity in functional and *in vivo* models [64]. The motivation for the design of the benzofuran class was the belief that improvements in overall drug-like properties and H_3 selectivity would be obtained by rigidification of the flexible propyloxy side chain found in the pharmacophore (**137**)

common to many non-imidazole H_3 antagonists (vide supra). These compounds may be viewed as highly modified variations of the amine-alkyl-oxy-phenyl pharmacophore. In this analogy, one of the alkyl methylenes is transformed into an sp^2 carbon and joined to a second newly incorporated sp^2 carbon on the phenyl ring to produce the benzofuran moiety. Many of the compounds (**139**-**166**) were highly potent in binding assays and had balanced affinity for the human and rat H_3 receptors. An SAR study of the amine substituents suggested that compounds that possess a 2-alkyl substitution (**146**, **143**), a 2,5-dialkyl substitution (**145**, **140**), or 2-hydroxymethyl substitution (**147**) all have high potency at both human and rat H_3 receptors. The same trend for the SAR of the basic amine was observed in three related series, the 4-cyanophenyl series (**139**-**147**), the morpholine-4-benzamide series (**148**-**154**), and the pyridinyl morpholine-4-benzamide series (**155**-**161**). Of the series described, compound **143** (also known as ABT-239) exhibited the best overall combination of balanced potency at the H_3 receptor from different species, good PK properties and CNS penetration, as well as potent activity in behavioral models. The 4-cyano moiety present in **143** was replaced with other substituents, (compounds **152**, **159**, and **162**-**166**), where it was found that the 4-cyano group was more potent than other small groups like F (**162**), alkyl (**163**), or methoxy (**164**). However, all of the compounds bearing a carbonyl group in the place of the nitrile (compounds **152**, **159**, **165**) had comparable potency to **143**.

THE THERAPEUTIC UTILITY OF NON-IMIDAZOLE H_3 ANTAGONISTS

H_3 antagonists have been proposed [1-6] to have therapeutic potential in humans, most prominently for diseases and disorders such Alzheimer's disease, allergic rhinitis, attention deficit hyperactivity disorder (ADHD), cognitive deficits, dementia, narcolepsy, and obesity. However, no member of this new class of compounds has yet reached the status of an approved drug. Therefore, the best indicators of the therapeutic potential of the class are to be found in animal models of disease. Very few results have been published describing the *in vivo* profile of non-imidazole H_3 antagonists in such models, but various imidazole-based H_3 antagonists have been profiled. However, to the extent that comparisons can be made, both classes of compounds show equivalent efficacy in behavioral models.

The key difference in these two classes of H_3 antagonists is the presence of an imidazole, and the most relevant clinical distinction between the two classes is the likely freedom of the non-imidazoles from inhibiting CYP enzymes and related heme-based enzymes [14,15]. This is a very important difference that should enhance the likelihood that non-imidazole H_3 antagonists will be free of the side effects of interference with hepatic metabolism of co-administered drugs, and consequently from perpetrating drug-drug interactions. They also should not interfere with adrenal corticosteroid synthesis, which has been reported for some imidazole-based H_3 antagonists [16]. Other possible distinguishing advantages for non-imidazole H_3 antagonists over imidazole-containing H_3 antagonists are more speculative, but merit consideration. Some imidazole-based potent H_3 ligands have been reported to bind potently to the H_4 receptor [65,33]. Of the H_3 non-imidazoles described above that have been tested for H_4 binding at Abbott [33], none of the benzofurans, including ABT-239, or **28** and **29** interacted potently with the H_4 receptor ($pK_i < 5$). There have also been reports that some imidazole-based compounds found to be antagonists in some assays (such as GT-2331, iodoproxyfan, proxyfan, and GR175737) can actually show H_3 agonist-like activity in other assay systems [11,66]. Esbenshade [33] found that two representative non-imidazole H_3 antagonists, A-304121 (**28**), and its furoyl amide derivative A-317920 (**29**), were inverse agonists at H_3 receptors. The same trend held for other non-imidazoles tested in the same paradigm. For example, A-331440 (**44**) [67] and especially ABT-239 (**143**) [64] were more efficacious inverse agonists than three reference imidazole based H_3 antagonists (ciproxifan, thioperamide, and clobenpropit). If non-imidazole H_3 antagonists are less likely to have residual partial H_3 agonism in tissues *in vivo*, or if they are more likely to be more efficacious inverse agonists than imidazole-based H_3 antagonists, then this could lead to enhanced clinical efficacy. Aside from such speculative differences, compounds with comparable potency, tissue exposure, and degree of inverse agonism should be able to induce comparable H_3-mechanism-based beneficial effects in both animal models and in humans, regardless of whether they are imidazoles or non-imidazole H_3 antagonists. Therefore, although non-imidazoles have been tested in fewer animal models, the positive results of the imidazole-based H_3 antagonist reference compounds indicate the potential for efficacy of the non-imidazoles.

There is substantial pharmacological evidence that H_3 antagonists can regulate NT levels and elicit pharmacological effects in animal disease models, where their efficacy suggests a therapeutic role to improve cognition, enhance attention and wakefulness [68], and treat obesity, pain, and allergic rhinitis. H_3 receptor antagonists have been demonstrated to induce beneficial effects in animal models of neuropathology, including epilepsy [69,70]. There have been reports of anti-nociceptive activity for some H_3 antagonists [71] like thioperamide. On the other hand, H_3 agonists have shown anti-nociceptive effects via peripheral actions in mechanical pain models [72]. The potential of H_3 antagonists as anti-depressants is supported by reports that ciproxifan [73], clobenpropit and thioperamide [74] are effective in the mouse forced swim test.

H_3 antagonists have been proposed to have benefits in vestibular disorders. In animal models of vertigo, H_3 antagonists have demonstrated efficacy [75, 76]. The efficacy of betahistine (methyl-(2-pyridin-2-yl-ethyl)-amine) for treatment of Meniere's disease is interesting [77], and since this non-imidazole compound has weak H_3 antagonism [78] among it's other pharmacological properties, it provides support for the potential of H_3 antagonists in the treatment of vertigo. Another important utility for H_3 antagonists has been pursued by the Schering group, where it has been found that H_3 antagonists, in combination with H_1 antagonists, demonstrated decongestive [79-81] activity in animal models of allergy without the liability of adrenergics to induce hypertension.

There is evidence that histamine is involved in modulating appetite, food consumption and even rate of eating behaviors. It has been reported that intracerebroventricular dosing with the H_3 antagonist, thioperamide, reduced food consumption [82-84], while another imidazole based compound, ciproxifan [85], has been shown to decrease feeding. Yates [86,87] has reported that imidazole-based compounds were able to reduce food intake and body weight gain, and that inverse agonists have enhanced efficacy over neutral antagonists. Several studies have shown that the H_3 antagonists, such as thioperamide, are able to reduce food consumption in several rat models [88-90]. However, recent studies of H_3 receptor knockout mice have produced interesting results, with some findings supportive of the H_3/obesity link, and other data inconsistent with such a connection. In the first published study, H_3 knockout animals had slightly, but not statistically significantly, lower body weight than heterozygotes or normal mice [91]. In contrast to this finding, knockout animals of both sexes developed a time-dependent elevation of body weight compared to wildtype mice [92]. In this report, the authors measured hypothalamic histamine and found high levels in the knockout animals, which led them to hypothesize that if histamine levels were sufficiently elevated, and then this might desensitize the postsynaptic H_1 receptors, which may be needed for feeding inhibition. Importantly, thioperamide failed to block acute feeding responses in the knockout animals, compared to wild-type mice [92].

Hancock [67] has reported the robust efficacy of the non-imidazole H_3 antagonist **44** (A-331440) in a mouse diet-induced obesity (DIO) model. In a 28-day trial in mice fed a high fat diet, the compound was well-tolerated, and reduced body weight by ~12% (at 5 mg/kg/b.i.d., p.o.) and ~20% (at 15 mg/kg/b.i.d., p.o.) over the course of the trial. At the high dose, mice showed improved insulin sensitivity and reduced leptin levels. Body fat was decreased at both doses.

The Novo-Nordisk group has reported that NNC 0038-0000-1049 (**128**) [59,60] is a potent non-imidazole H_3 antagonist with high selectivity for H_3 versus H_1, H_2, H_4, serotonin, and other receptors, with oral bioavailability in rats. The compound was able to inhibit food intake in adult obese rats at 20 mg/kg i.p. without overt side effects. The compound was also shown to elevate hypothalamic histamine levels ~50% at 5 mg/kg, and >600% at 20 mg/kg.

Histaminergic neurons have long been recognized [93] to play an important role in regulating arousal, attention, wakefulness, cognition, and memory. The ability of H_3 antagonists such as thioperamide [94,95] to promote wakefulness has been reported by several groups, and H_3 antagonists have also demonstrated positive effects in different aspects of memory [96-98] in the rat, such as in spatial learning, avoidance acquisition, and social memory. For example, thioperamide [99-101] was able to improve spatial memory. Other H_3 antagonists with demonstrated benefits in different models of learning and memory include FUB 181 (3-(4-chlorophenyl)propyl-3-(1H-imidazol-4-yl)propyl ether) [102], and GT-2016 (5-cyclohexyl-1-[4-(1H-imidazol-4-yl)-piperidin-1-yl]-pentan-1-one) [103]. Fox [104] has described a variation of the 5-trial inhibitory avoidance acquisition test using spontaneously hypertensive (SHR) rat pups as a particularly sensitive model for demonstration of impulsive behavior and memory. It was shown that the reference imidazole-based H_3 antagonist ciproxifan (3 mg/kg s.c.) was particularly potent and efficacious in its ability to enhance learning, while the imidazole-based compound GT-2331 (4-[2-(5,5-dimethyl-hex-1-ynyl)-(1R, 2R)-cyclopropyl]-1H-imidazole) was less effective, with statistical significance noted at only one dose (1 mg/kg, s.c.). The Abbott group has reported non-imidazole H_3 antagonists that are potent and as efficacious as the standard ciproxifan in this paradigm [105]. In a 5-trial inhibitory avoidance test, A-304121 (**28**) at 10 mg/kg s.c., its 2-furoyl derivative A-317920 (**29**) at 3-10 mg/kg s.c., and A-349821 (**48**) [106,107] at 10 mg/kg s.c., were all able to enhance learning with a magnitude of effect equivalent to ciproxifan at 3 mg/kg. In the same paradigm, the non-imidazole ABT-239 (**143**) showed equivalent efficacy (64, 108) to the other compounds at the even lower dose of 0.1 mg/kg s.c.

In a model of short-term social memory in adult rats, the reference compound ciproxifan reached the maximal learning enhancement at a dose of 0.3-3 mg/kg i.p., In the same paradigm, the non-imidazole antagonist A-304121 (**28**) reached this level of efficacy at 3-10 mg/kg, while ABT-239 (**143**) was much more potent, and reached the same level of efficacy at 0.01 mg/kg i.p. The therapeutic window for the production of these effects was very high for the non-imidazoles when comparing maximally efficacious doses in the 5-trial inhibitory avoidance with doses capable of inducing CNS side effects like hypothermia or locomotor effects. The therapeutic window was 30x for compound A-304121 (**28**), 42x for A-317920 (**29**), and was >350x for ABT-239 (**143**).

CONCLUSION

In summary, H_3 antagonists/inverse agonists show efficacy in diverse animal disease models, and this supports the belief that this class of compounds has broad therapeutic potential for treating human neurological, neuropsychiatric, allergic, and metabolic diseases. The acceptability of drug candidates depends on more than just efficacy against disease, but also on the lack of side effects such as toxicity or interactions with co-administered drugs. To that end, a variety of potent and selective non-imidazole compounds have been described that are highly potent antagonists/inverse agonists at H_3 receptors and active in animal models. Furthermore, they are often more H_3 selective than their non-imidazole counterparts, and less likely to perpetrate interactions with other drugs due to their freedom from imidazole-based inhibition of cytochrome P_{450} enzymes. These findings suggest a bright future for non-imidazole H_3 antagonists for treating a broad spectrum of human diseases.

ABBREVIATIONS

SAR = Structure-activity relationships

NT = Neurotransmitters

HA = Histamine

ACh = Acetylcholine

NE = Norepinephrine

HA = Histamine

AC = Adenylate cyclase

CYP = Cytochrome P_{450}

GP = Guinea pig

GPi = Guinea pig ileum assay

pK_i = The –log (K_i) at H_3 in a competition binding assay

N^t-MeHA = Brain histamine metabolite tele-methyl-histamine

RAMH = (R)-α-methylhistamine, an H_3 agonist

HMT = Histamine methyl transferase

ADHD = Attention deficit hyperactivity disorder

DIO = Diet-induced obesity

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