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Discovery of a series of potent arylthiadiazole H_3 antagonists

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ABSTRACT

A series of 2-piperidinopiperidine-5-arylthiadiazoles was synthesized and subjected to a structure–activity relationship (SAR) investigation. The potency of this series was improved to the single digit nanomolar range. The key analogs were shown to be free of P450 issues, and they also maintained good ex vivo activity and brain penetration.

The biogenic amine histamine is a critical neurotransmitter which mediates a wide range of neurological responses. The effect of histamine is exerted through receptors that belong to the G protein-coupled receptors (GPCRs). There are four subtypes of the histamine receptor (HR): H_1, H_2, H_3 and H_4.[1] HR antagonists have historically provided medical benefits, along with pharmaceutical blockbusters, through modulation of the H_1 and H_2 receptors, in the treatment of allergic conditions and gastric disorders, respectively. Due to the success of H_1 and H_2 therapeutics, the potential of H_3 and H_4 antagonism has attracted considerable research efforts across the industry.[2]

Following the pharmacological identification of the H_3 receptor in 1983,[3] and its cloning in 1999,[4] significant strides were made to identify novel, selective H_3 receptor antagonists.[5] Although the exact therapeutic potential is unknown, H_3 antagonists lead to increased histamine levels at histaminergic neurons and subsequently may be useful in treating obesity and diabetes, as well as other CNS disorders such as cognitive disorders, Alzheimer's and Parkinson's disease, schizophrenia and sleep disorders.[6–8]

Among the earliest H_3 antagonists investigated were imidazole based compounds;[9] however cytochrome P450 (CYP) enzyme inhibition posed significant drug–drug interaction issues. This finding subsequently led to research in non-imidazole containing compounds.[10] In our effort to discover novel H_3 antagonists we identified a high throughput screen (HTS) lead with prototype structure **1** containing a piperidine thiadiazole core. This series showed modest in vitro potency, and it is likely that the pendent urea moiety would hinder entry into the brain due to its multiple H bond donor and acceptor characteristics. At the onset of lead optimization, based on literature precedents[11] and a H_3 pharmacophore model,[12] we envisioned the use of aryl groups to replace the urea, therefore increasing brain penetration[13](Scheme 1).

Introduction of an unsubstituted phenyl ring in place of the urea moiety afforded compound **2**. Compound **2** had comparable activity to **1** thus confirming our initial structural hypothesis. Furthermore, the caco2 permeability of **2** was improved to 104 nm/sec from 10.5 nm/sec for **1**, and the absorption was also improved to good from moderate. These results were consistent to the empirical rules that reduction of H bond donors and acceptors would improve CNS penetration.[13] Encouraged by these findings, we undertook a full optimization of the phenyl ring. Synthesis of this phenyl series was relatively straightforward. Commercial compound **3** was converted to the dibromo intermediate **4**, which was then displaced with piperidinopiperidine. The reaction can be controlled to afford **5** exclusively, since the amino substitution deactivated further addition. The bromothiadiazole **5** was subsequently coupled under Pd catalysis conditions with aryl boron or zinc species to afford the desired products (Scheme 2).

Since H_3 activity is centrally mediated, we focused on small substitutions on the aryl group to minimize molecular weight. Table 1 shows H_3 in vitro potency[14] for substitutions at the *ortho*-, *meta*- and *para*-positions. Polar substituents such as OMe, CN and acetyl groups afforded moderate improvement of potency (Table 1).

Considering these data, especially that of *meta*-substituted compounds, we speculated that an additional *meta*-substitution would provide a pseudo-symmetric interaction with the receptor,

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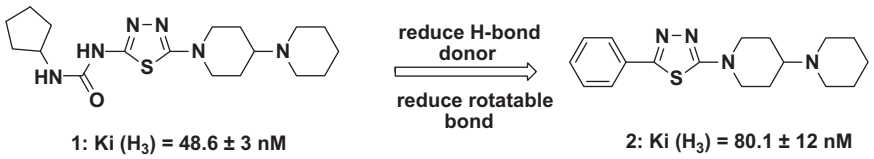
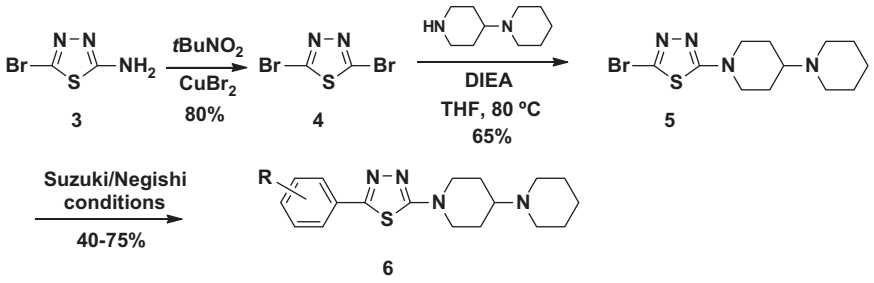
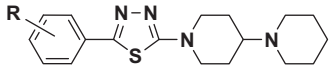


Scheme 1.



Scheme 2.

Table 1



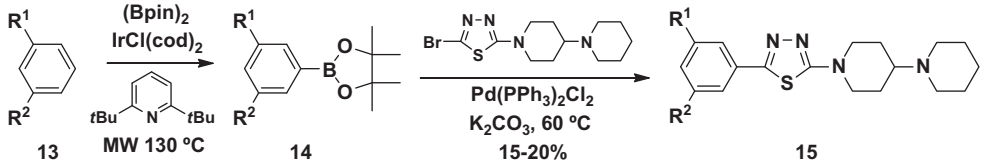
Entry	R	*ortho-*	K_i (H_3) (nM) *meta-*	*para-*
2	H	80.1 ± 12	80.1 ± 12	80.1 ± 12
7	OMe	40.0 ± 8	31.9 ± 6	40.1 ± 2
8	CN	N/A	42.6 ± 1	36.4 ± 7
9	F	36.0 ± 2	62.0 ± 11	39.0 ± 15
10	Cl	69.0 ± 1	49.0 ± 1	161 ± 69
11	Me	36.0 ± 4	60.0 ± 8	163 ± 23
12	$COCH_3$	8.4 ± 2	4.0 ± 0.2	65.0 ± 4

which could further increase the binding potency. This series of analogs was investigated and synthesized using commercially available boronic acids and esters. Custom synthesis of non-commercial 3,3′-disubstituted boronic esters **14** was also developed through microwave-accelerated Ir-catalyzed, direct borylation[15] of the corresponding aromatics, which were then coupled with bromothiadiazole **5**. (Scheme 3).

Notable in vitro binding data are shown below. Aside from the dichloro analog **15a**, bis-*m*,*m*′-substitution did increase potency compared to the corresponding mono-substituted analog. Further confirming our speculation, hetero-*m*,*m*′-disubstitutions afforded activity in the low double digit nanomolar range, as in entries Cl/OMe, CN/OMe, and F/OMe (Table 2).

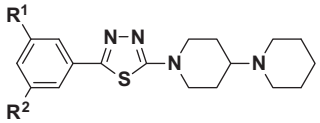
Additionally, following our initial heteroatom-containing lead, we sought to replace the phenyl group with heteroaromatic rings. Among the pyridyl substitutions, 2-pyridine showed the greatest increase in potency and was pursued further. Results are shown below (Table 3):

The 2-pyridyl analogs provided the most pronounced improvement in potency, compared to the less active pyrimidine and pyrazole analogs. Interestingly, the 3-methylpyridine and 3-methoxypyridine afforded the most potent analogs in this series, results consistent with the substituted phenyl series summarized above.



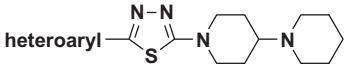
Scheme 3.

Table 2



Entry	**15a**	**15b**	**15c**	**15d**	**15e**	**15f**	**15g**
R^1/R^2	Cl/Cl	OMe/OMe	Cl/OMe	CN/OMe	F/OMe	F/F	CN/CN
K_i (H_3) (nM)	72.0 ± 9	15.0 ± 1	12.0 ± 1	12.0 ± 3	16.0 ± 2	50.0 ± 1	23.0 ± 1

Table 3



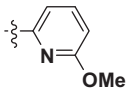
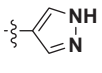
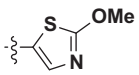
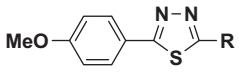
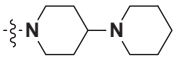
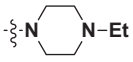
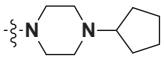
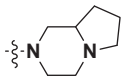
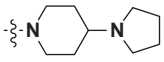
Entry	**16a**	**16b**	**16c**	**16d**	**16e**	**16f**
Heteroaryl						
K_i (H_3) (nM)	30.0 ± 0.1	3.5 ± 1	6.1 ± 2	103.0 ± 22	192.0 ± 27	28 ± 7

Table 4



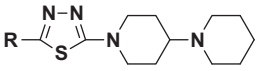
Entry	**17a**	**17b**	**17c**	**17d**	**17e**
R					
K_i (H_3) (nM)	40.1 ± 2	161.8 ± 2	182.3 ± 15	652.6 ± 79	600.9 ± 96

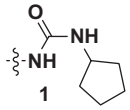
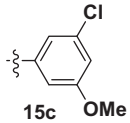
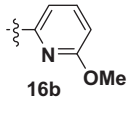
To complete the SAR study of this thiadiazole series, we also investigated the modifications at the piperidinopiperidine moiety. For example, the piperazine analogs **17b–17d** were aimed at modulating the basicity of the nitrogen. Additional analog such as **17e** was directed at reducing molecular weight. However, all these analogs showed drastic reduction of H_3 potency compared to the original analog **17a**. Indeed, only the piperidinopiperidine as the right hand side consistently afforded good potency (Table 4).

As mentioned previously, the earlier imidazole based H_3 compounds exhibited P450 inhibition issues. Therefore, in the current series, the most potent compounds **15c** and **16b** were screened against three CYP isoforms—3A4, 2D6 and 2C9. Fortunately, neither compound showed greater than 20 μM inhibition for 3A4, 2D6 and 2C9 under pre- or co-incubation conditions. Compound **15c** was particularly noteworthy due to its ex vivo potency.[16] This compound also showed high brain concentrations in mouse and a modest AUC in rat per oral dosing, a significant improvement from the original lead **1** (Table 5).

In conclusion, a series of 2-piperidinopiperidine-5-arylthiadiazoles as centrally active H_3 antagonists was designed and was subjected to a SAR investigation. First, we replaced the urea moiety in **1** with a phenyl group, which significantly improved the absorption and permeability. We then systematically investigated the effects of *ortho*-, *meta*- and *para*-substituted phenyl rings. The use of polar groups such as OMe, CN, and $COCH_3$ and particularly with the *m*,*m*′-disubstitutions afforded improvement of potency over phenyl analog. Aditionally, heteroaryl replacement of the phenyl ring was investigated. 2-Pyridyl substitutions increased potency significantly compared to the initial lead, while pyrimidine and pyrazole offered less activity. Further substitutions, 3-methylpyridine and 3-methoxypyridine offered potency in the single digit nanomolar range. The best compounds, **15c** and **16b**,

Table 5



Entry	K_i (H_3) (nM)	Rat AUC @10 mpk, po (ng h/ml 0–6 h)	Mouse brain level@10 mpk, po (ng/g @ 4 h)	Ex vivo @ 4 h	P450 inhib 3A4, 2D6, 2C9
 **1**	48.6 ± 3	0	ND	ND	>20 μM
 **15c**	12.0 ± 1	379	9027	90%	>20 μM
 **16b**	3.5 ± 1	0	1527	74%	>20 μM

were devoid of P450 inhibition issues, and showed good brain concentrations and ex vivo potency. Further optimization of the pharmacokinetic profile, as well as other biological parameters, led to an orally active H_3 antagonist in our mouse obesity model. These results will be disclosed in due course.

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14. *H_3 binding assay*: memberanes (P2 pellet) from rHu H_3–HEK cells (3 μg protein) were incubated in 200 μl 50 mM Tris–HCl, Ph 7.4, with 1 nM [^{3}H] *N*-α-methylhistamine (82 Ci/mmol) and compounds at concetrations equivalent to half orders of magnitude over a five-order of magnitude range. Nonspecific binding was determined in the presence of 10^{-5} M thioperamide. After 30 min at 30 °C, assay mixture were filtered through 0.3% polyethylenimine soaked GF/B glass fiber filters, which were rinsed thrice with buffer, dried, impregnated with Meltilex wax scintillant and counted. K_i values were determined from curves fit to the data using GraphPad Prism nonlinear, least-squares, curve-fitting program. H_3 binding K_i values were the average of at least two independent determinations. The assay-to-assay variation was generally ±2-fold.
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16. *H_3 ex vivo assay*: Individual Imprinting Control Region mice (Taconics, nomenclature IcrTacICR) cortexes were dissected and homogenized in ice cold assay buffer, 50 mM Na_2HPO_4–KH_2PO_4 buffer (pH 6.8). Samples were then frozen at −80 °C for at least 12 h. Protein concentration was determined by BCA Protein Assay. A 30 min room temperature incubation was performed, containing 140 μg/assay homogenized cortex sample, 0.1% BSA, 1 nM ^{3}H *N*-α-methylhistamine and 10 μM thioperamide for non-specific binding or assay buffer for total binding. Incubations were performed in quadruplet and stopped by rapid filtration on a Brandel Harvester using Unifilter-96, GF/B plates presoaked in 0.3% PEI for 30 min. The remining radioactivity was measured on a Packard TopCount-NTX. Specific binding was calculated by subtracting the non-specific binding from the total.