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Letter

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Discovery of a Potent Thiadiazole Class of Histamine H_3 Receptor Antagonist for the Treatment of Diabetes

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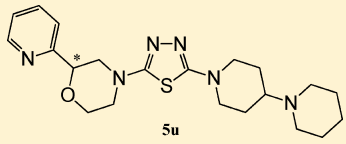
Supporting Information

ABSTRACT: A series of novel 2-piperidinopiperidine thiadiazoles were synthesized and evaluated as new leads of histamine H_3 receptor antagonists. The 4-(5-([1,4′-bipiperidin]-1′-yl)-1,3,4-thiadiazol-2-yl)-2-(pyridin-2-yl)morpholine (**5u**) displayed excellent potency and ex vivo receptor occupancy. Compound **5u** was also evaluated in vivo for antidiabetic efficacy in STZ diet-induced obesity type 2 diabetic mice for 2 or 12 days. Non-fasting glucose levels were significantly reduced as compared with vehicle-treated mice. In addition, **5u** dose dependently blocked the increase of HbA_{1c} after 12 days of treatment.



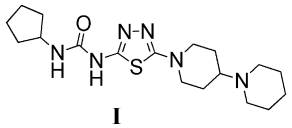
5u

KEYWORDS: *Histamine, H_3, antagonist, thiadiazole, type 2 diabetes, non-fasting glucose, HbA_{1c}*

Histamine receptors have been attractive drug targets, beginning with the development of classical antihistamines, which target the histamine H_1 receptor for the treatment of allergic reactions. Antagonists of the histamine H_2 receptor have been successful for the treatment of gastric acid-related disorders. Since the identification of a third subtype of histamine receptor, H_3, as a presynaptic autoreceptor that inhibits histamine release,[1] along with its subsequent recognition as a heteroreceptor that regulates the release of other important neurotransmitters,[2−4] there has been considerable effort by both industry and academia to develop a potent and selective H_3 receptor antagonist.[5,6] A fourth member of the histamine receptor family, H_4, has been identified that is expressed primarily in cells and tissues of the immune system, suggesting a novel therapeutic target for the regulation of immune function, particularly in allergy and asthma.[7]

The histamine H_3 receptor is a G-protein coupled receptor (GPCR) and one of four subtypes (H_1, H_2, H_3, and H_4) of the histamine receptor family.[8] By virtue of its unique central nervous system (CNS) localization (cerebral cortex, striatum, and hypothalamus),[9] antagonists of the H_3 receptor are sought for the potential treatment of a variety of disorders affecting cognition (attention deficit hyperactivity disorder, schizophrenia, and Alzheimer's disease),[10−15] sleep disorder,[16] as well as metabolic syndrome (MS, including obesity and diabetes).[17−21]

A number of investigational H_3 antagonists have been evaluated for anti-obesity effects in a variety of animal models.[22] Obesity is a worldwide health crisis that contributes to a number of pathophysiologic conditions including type 2 diabetes, a disorder characterized by abnormally high blood glucose levels caused by a dysregulation in leptin and insulin signaling in the hypothalamus. Leptin and insulin signaling in the hypothalamus are supplemented by the action of neurotransmitters, including H_3-mediated dopamine and serotonin, and directly influence glucose homeostasis.[23] The use of compounds that enhance histamine release from nerve terminals such as H_3 receptor antagonists may afford an effective therapeutic alternative. Indeed, several studies have shown that H_3 receptor antagonists increase histamine release from the hypothalamus and reduce energy intake in normal and leptin-resistant mice with diet-induced obesity (DIO).[24]



I

K_i (h) = 49 ± 3.0 nM
K_i (m) = 47 ± 15 nM
Rat $AUC_{0\text{-}6h}$ = 0 μM.h, 10 mg/kg, po

Figure 1. Target molecule of the study.

The initial development of H_3 receptor antagonists focused on imidazole-containing compounds (thioperamide, ciproxifan, and proxyfan) and has been reported effective.[25] However, imidazole derivatives are associated with inhibition of cytochrome P_{450} enzymes and poor CNS penetration.[26,27] More recently, several non-imidazole-based H_3 antagonists have also been developed. However, clinical efforts have not yet yielded a marketed entity despite the high level of interest in this area.[28−32]

We recently reported a non-imidazole-based series having antagonist activity at the H_3 receptor.[33] In our continuing efforts to identify structurally diverse H_3 antagonists, we identified a high-throughput screen (HTS) lead with a novel thiadiazole (**I**) pharmacophore (Figure 1).[34] This compound showed modest in vitro potency (hH_3 K_i = 49 nM and mH_3 K_i

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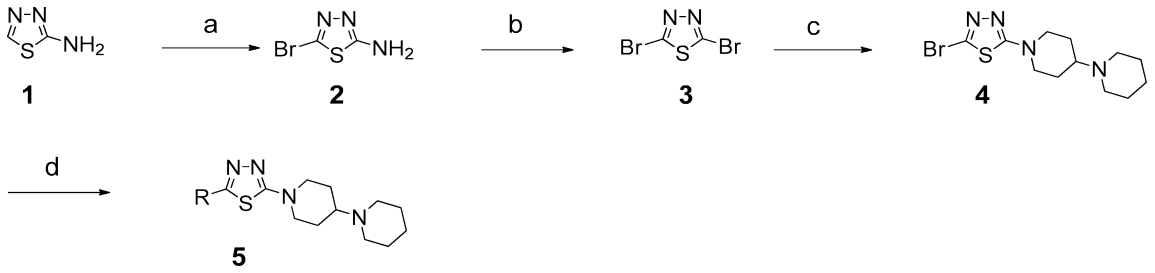
Scheme 1. [a]



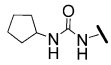
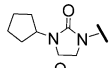
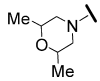
[a]Reagents and conditions: (a) Br_2, AcOH, NaOAc, room temperature, 12 h (91%). (b) $CuBr_2$, *t*-BuONO, MeCN, room temperature, 12 h (70%). (c) 4-Piperidinopiperidine, *N*,*N*-diisopropylethylamine, 1,4-dioxane, 120 °C, 2 h (63%). (d) Amines, *N*,*N*-diisopropylethylamine, $PhCF_3$-1,4-dioxane (2:1), microwave, 220 °C, 3 h (50−80%).

= 47 nM) in a [^{3}H]-*N*-α-methylhistamine human and mouse recombinant assay. In this paper, we report on the synthesis and structure−activity relationships (SAR) of this 2-piperidinopiperidine-5-substituted thiadiazole class of histamine H_3 receptor antagonists and its effect on glucose lowering in streptozotocin (STZ) DIO type 2 diabetic mice.

The 4-piperidinopiperidine thiadiazole moiety was constructed relatively straightforward by the bromination of commercially available 1,3,4-thiadiazol-2-amine **1** to afford **2**, which was then converted to intermediate **3**. The bromine of dibromo intermediate **3** was then easily displaced with 4-piperidinopiperidine under refluxing conditions. The reaction can be controlled to afford **4** exclusively, since the amino substitution deactivates further addition. The 2-piperidinopiperidine-5-bromothiadiazole **4** was subsequently coupled with both commercially available and custom synthesized amines under microwave conditions to afford the desired products **5** in 50−80% yields (Scheme 1).

In earlier studies, it was envisioned that the urea moiety would hinder entry into the brain due to its multiple H-bond donor and acceptor characteristics. Replacement of the urea with aryl groups improved brain penetration and absorption.[35] Encouraged by these findings, we used this lead compound as a starting point for modification of the urea moiety. Because H_3 activity is centrally mediated, we focused on removing the H-bond donors to improve CNS penetration and pharmacokinetic properties. Table 1 shows the binding affinities in a [^{3}H]-*N*-α-methylhistamine human and mouse recombinant assay. In compounds **5a** and **5b**, removal of the H-bond donors afforded moderate to no improvement in the binding affinities. Replacement of the urea moiety with piperidinone (**5c**) displayed a 2−3-fold drop in potency. The change of piperidinone to 3,3-difluoropyrrolidine (**5d**) showed improved H_3 binding affinity by 2-fold in both species when compared to **5c**. Interestingly, the 4,4-difluoropiperidine **5e** (hH_3 K_i = 15 nM, mH_3 K_i = 18 nM) displayed a 4-fold improvement in affinity as compared to **5d**. The effect of substitution on the piperidine ring was next investigated. Substitution at the 3-position of the piperidine ring with phenyl (**5f**) was over 5-fold weaker for both human and mouse H_3 receptor than **5e**. Attempts to replace the phenyl group with methoxy (**5g**), hydroxy (**5h**), or fluoro (**5i**) gave no improvement in human or mouse H_3 binding affinities. Replacement of the piperidine group with morpholine (**5j**) had weaker H_3 binding affinities in both species. However, basic compounds such as pyrrolidine (**5d**), piperidine (**5e**), and morpholine (**5j**) showed a promising interaction with the H_3 receptor and were deemed more appropriate for further optimization due to their better pharmacokinetic profile.[36]

Table 1. Binding Affinities of 2-Piperidinopiperidine Thiadiazole Derivatives

R	Compd	Human H_3[a] (K_i, nM)	Mouse H_3[a] (K_i, nM)
	**I**	49 ± 3.0	47 ± 15
	**5a**	34 ± 1.0	53 ± 5.0
	**5b**	30 ± 3.0	32 ± 1.0
	**5c**	120 ± 7.0	120 ± 3.0
	**5d**	61 ± 16	61 ± 4.0
	**5e**	15 ± 2.0	18 ± 1.0
	**5f**	75 ± 9.0	110 ± 15
	**5g**	37 ± 13	46 ± 3.0
	**5h**	46 ± 5.0	68 ± 3.0
	**5i**	66 ± 10	56 ± 16
	**5j**	53 ± 20	35 ± 13

[a]Binding affinity in a [^{3}H]-*N*-α-methylhistamine human and mouse recombinant assay. H_3 binding K_i values are the average of at least two independent determinations ± standard deviations.

Encouraged by these findings and on the basis of knowledge acquired from prior SAR studies, we then undertook a detailed study of the piperidine moiety by incorporating appropriate structural modifications (Table 2). Replacement of the phenyl ring with heterocycles such as pyridine (**5k**) and pyrimidine (**5l**) showed a 6-fold improvement in human and a 2−3-fold improvement in mouse H_3 affinity. A breakthrough in potency was achieved when pyridine (**5m**) (hH_3 K_i = 3 nM and mH_3 K_i = 5 nM) showed single digit nanomolar range in human and mouse H_3 receptor binding affinity. However, methoxy (**5n**) and hydroxy (**5o**) substitution at the 3-position of piperidine

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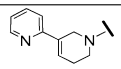
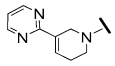
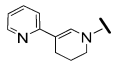
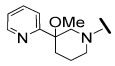
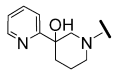
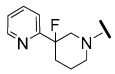
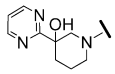
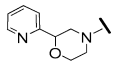
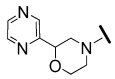
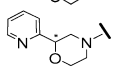
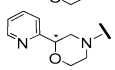
Table 2. Binding Affinities of 2-Piperidinopiperidine Thiadiazole Derivatives

R	Compd	Human H_3[a] (K_i, nM)	Mouse H_3[a] (K_i, nM)
	**5k**	12 ± 1.0	49 ± 3.0
	**5l**	14 ± 2.0	44 ± 3.0
	**5m**	3.0 ± 1.0	5.0 ± 1.0
	**5n**	11 ± 1.0	54 ± 35
	**5o**	53 ± 9.0	55 ± 7.0
	**5p**	4.0 ± 1.0	7.0 ± 1.0
	**5q**	67 ± 3.0	77 ± 17
	**5r**	5.0 ± 1.0	11 ± 1.0
	**5s**	8.0 ± 1.0	16 ± 2.0
	**5t**	34 ± 5.0	67 ± 1.0
	**5u**	3.0 ± 1.0	4.0 ± 2.0

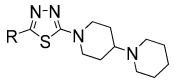
[a]Binding affinity in a [^{3}H]-*N*-α-methylhistamine human and mouse recombinant assay. H_3 binding K_i values are the average of at least two independent determinations ± standard deviations.

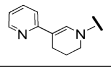
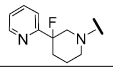
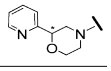
displayed an 18-fold drop in binding affinity in both species with the exception of **5n** (hH_3 K_i = 11 nM). Exchange of the hydroxy with a fluoro substituent (**5p**) (hH_3 K_i = 4.0 nM and mH_3 K_i = 7.0 nM) evoked high affinity at the human and mouse H_3 receptor. Replacement of the pyridine (**5o**) with pyrimidine (**5q**) displayed a decrease in potency. When the hydroxy pyridine (**5o**) was replaced with morpholine (**5r**), the binding affinity improved 11-fold with K_i = 5.0 nM in human and 5-fold with K_i = 11 nM in mouse. Replacement of the pyridine heterocycle with pyrazine (**5s**) resulted in no significant improvement in binding affinity.

To determine the importance of the stereogenic chiral center on affinity, the enantiomers of **5r** were separated by super critical fluid chromatography (SFC), and their single isomers (**5t** and **5u**) were tested individually.[37] The slower eluting enantiomer **5u** was found to have greater binding affinity at both human and mouse H_3 receptor as compared to the faster eluting enantiomer **5t**.

Table 3 summarizes the in vitro, ex vivo, and pharmacokinetic properties of compounds **5m**, **5p**, and **5u**. Compounds **5p** and **5u** exhibited significantly lower potential for human ether-à-go-go related gene (hERG) channel inhibition as measured using a high-throughput rubidium efflux assay.[38] These compounds showed no inhibition for 3A4, 2D6, and 2C9 under pre- or co-incubation conditions. Particularly noteworthy is that the compounds are potent in the ex vivo receptor occupancy study in imprinting control region (ICR) mouse. Four hours following oral administration of compounds at 30 mg/kg, the total brain concentrations were measured. Compounds **5m** and **5p** showed modest brain concentrations

Table 3. Pharmacokinetic Properties and ex Vivo and in Vitro Profiles of Representative Diamines



R / Compd	 **5m**	 **5p**	 **5u**
Human H_3 (K_i, nM)	3.0 ± 1.0	4.0 ± 1.0	3.0 ± 1.0
Mouse H_3 (K_i, nM)	5.0 ± 1.0	7.0 ± 1.0	4.0 ± 2.0
hERG inh. (% @ 10 μM)	54	16	26
P450 inh. 3A4, 2D6, 2C9	>20 μM	>20 μM	>20 μM
Ex vivo @ 30 mpk, po (% occupancy)	85	92	74
Mouse brain conc.@ 30 mpk, po (ng/g; 4 h)	1039	674	24
Plasma conc.(C_{max}) @ 30 mpk, po (ng/mL; 4 h)	1471	2967	1496

with good plasma exposure. The low brain concentration of compound **5u** may in part be due to their low lipophilicity (cLogP = 1.23).

For assessment of the antihyperglycaemic effect, STZ-induced (STZ at 80 mg/kg, ip) diabetic ICR mice (blood glucose; 250−500 mg/dL) were used to evaluate the capacity of **5p** and **5u** to lower blood glucose. The non-fasting glucose was monitored daily before quaque die (QD) dosing of **5p** and

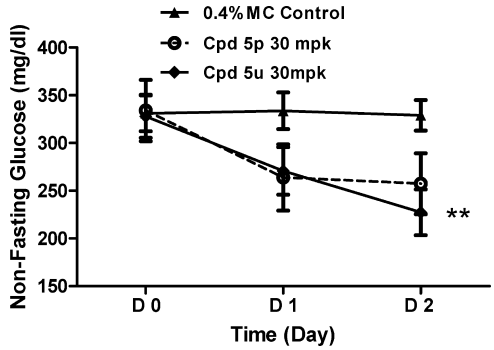


Figure 2. Antihyperglycemic effect of **5p** and **5u** in STZ-induced diabetic ICR mice. Data are expressed as the mean ± SEM (n = 12/group). **P < 0.01 as compared with the control (0) group.

5u (30 mg/kg). Figure 2 illustrates the change in blood glucose level. Compound **5u** (−104.5 mg/dL) significantly decreased non-fasting glucose on day 2 when compared to **5p** (−67.91 mg/dL). The pharmacokinetic profile of compounds **5p** and **5u** revealed that the brain/plasma ratios were not important to achieve efficacy in the diabetes model. For example, compound **5p** had a brain/plasma ratio of 0.227, demonstrating only moderate efficacy. On the other hand, compound **5u** with a brain/plasma ratio of just 0.016 was fully efficacious in the diabetes model. The link between exposure and efficacy is dependent on a number of factors in combination including the binding of the compound in blood and in the CNS, blood−brain barrier (BBB) permeability, the concentration−time (c-t) profile of the compound in blood, the distribution within the brain parenchyma, and the clearance out of the CNS. Indeed, there seem to be many CNS discovery programs that have

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identified compounds, which despite a very low brain/plasma ratio demonstrate the desired efficacy in animal models or human.[39]

Glycated hemoglobin (HbA_{1c}) is routinely used as a marker for long-term glycemic control. Elevated HbA_{1c} has been regarded as an independent risk factor for coronary heart disease (CHD) and stroke in subjects with diabetes. In view of this, it was rationalized to testify the potential of compound **5u** in a chronic study with the change of HbA_{1c} as the end point.

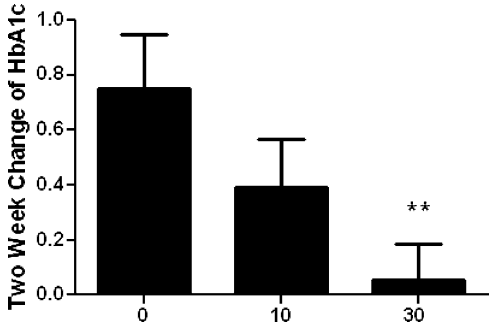

Figure 3. Dose–response effect of **5u** on HbA_{1c} levels in type 2 diabetic mice (10 and 30 mg/kg). $^{**}P < 0.01$ as compared with the control (0) group.

Compound **5u** dose dependently blocked the increase of HbA_{1c} following a 12 day treatment in STZ DIO mice (Figure 3).

In conclusion, we have synthesized and evaluated a new series of 2-piperidinopiperidine thiadiazole derivatives as H_3 receptor antagonists. Compound **5u** was identified as having excellent potency and ex vivo receptor occupancy. We also found that treatment with **5u** improves glycemic control in the STZ-induced diabetic mouse model. These findings indicate that **5u** may be a new therapeutic agent for the treatment of type 2 diabetes. The role of the H_3 receptor in type 2 diabetes needs to be further investigated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for assay protocols and synthesis and characterization of compounds **2**–**5a**–**u**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

GPCR, G-protein coupled receptor; CNS, central nervous system; MS, metabolic syndrome; HTS, high-throughput screen; SAR, structure–activity relationship; SFC, super critical fluid chromatography; hERG, human ether-à-go-go related gene; ICR, imprinting control region; STZ, streptozotocin; DIO, diet-induced obesity; QD, quaque die; BBB, blood–brain barrier; c-t, concentration–time; CHD, coronary heart disease; HbA_{1c}, glycated hemoglobin

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(36) Rat $AUC_{0-6\,h}$, 10 mg/kg, po: **5d** = 545 ng h/mL, **5e** = 2487 ng h/mL, and **5j** = 4321 ng h/mL.
(37) SFC conditions: Chiralpak ODH column, 50:50 liquid CO_2/1:1 MeOH/*i*-PrOH + 0.2% DIPA; flow, 210 g/min; pressure, 150 bar; UV detector, 278 nm. Retention time: enantiomer **5t**, 4.6 min; enantiomer **5u**, 5.2 min. Each enantiomer was determined to be ≥98% ee via analytical HPLC.
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