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Novel imidazole-based histamine H_3 antagonists

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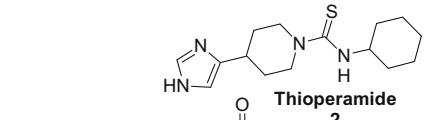
ABSTRACT

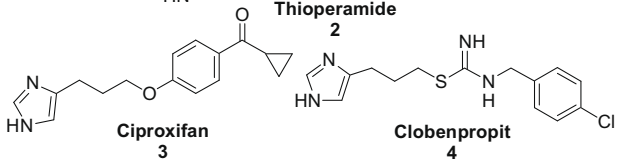
A novel series of imidazole containing histamine H_3 receptor ligands were investigated and found to be potent functional antagonists. After improving the stability of these molecules towards liver microsomes, these compounds were found to have no appreciable affinity for CYP P450s. Subsequent in vivo experiments showed significant brain uptake of (4-chloro-phenyl)-[2-(1-isopropyl-piperidin-4-ylmethoxy)-3-methyl-3H-imidazol-4-yl]-methanone **22**.

Biogenic amines accomplish a myriad of functions throughout the body, where their interdependent relationships and varying affinity for natural receptors and transporters allow these small molecules to elicit dramatic physiological responses. Histamine can affect conditions including allergic rhinitis through the histamine H_1 receptor[1] and gastric acid secretion through the histamine H_2 receptor.[2] The actions of histamine on the H_3 receptor[3] and the recently discovered H_4 receptor[4] are predominantly in the central nervous system (CNS) and immune systems, respectively. Following its characterization by Schwartz,[3] the function of the H_3 receptor was extensively evaluated. Later, cloning of the H_3 receptor allowed researchers to apply high throughput screening techniques to this target to identify novel structures.[5] Since this discovery a number of pharmaceutical companies have prepared small molecule H_3 antagonists, some of which have entered clinical trials for diseases such as ADHD, excessive daytime sleepiness and allergic rhinitis.[6]

The early development of therapeutic agents acting at the histamine H_3 receptor was particularly challenging. In order to maintain both affinity and efficacy, retention of the imidazole moiety of the endogenous ligand was thought to be necessary. Several of the first 1-*H*-4-substituted imidazole H_3 antagonists, thioperamide (**2**), ciproxifan (**3**) and clobenpropit (**4**), showed unfavorable interactions with cytochrome (CYP) P450s.[7,8] Initial



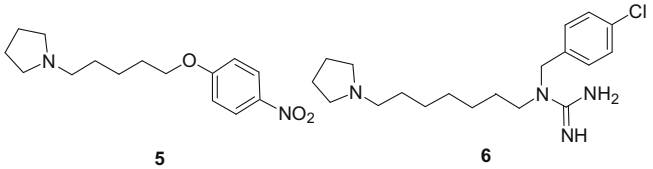
Thioperamide
2



Ciproxifan
3

Clobenpropit
4

approaches to replacing the imidazole included those from Ganellin and coworkers[9] and separately from the James Black Foundation[10] led to **5** and **6**.



5
UCL 1972
rat H_3 K_i = 39 nM

6
JB 98064
guinea pig H_3 K_i = 2.0 nM

High throughput screening of our corporate compound collection identified several series of lead compounds including the imidazopyridines (**7**), the indolizidines (**8**) and the *N*-methylimidazoles (**9**) some of which have been previously described.[11,12]

Of these templates, **9** represented a potent imidazole containing functional H_3 antagonist. In this structure the tri-substituted imidazole is presumably behaving in a different capacity to the imidazole present in compounds based on the endogenous ligand.[13] Thus

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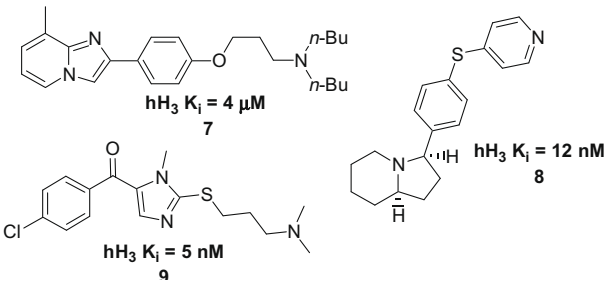


we set out to explore the structure activity relationship (SAR) around this lead and establish whether the structure was free of the aforementioned liabilities and therefore a viable drug template.

Results: Our investigations focused on optimizing the key fragments required for biological activity.[14] We found that the carbonyl could be converted to an oxime (**10**) without loss of affinity but that the corresponding alcohol **11** and methylene **12** exhibited reduced affinity, Table 1.

Replacement of the terminal nitrogen with a carbon (**13**) eliminated affinity, however replacing the dimethylamino group with a piperidinyl group (**14**), or introducing a conformationaly restricted linker (**15**) provided compounds with similar affinity for the receptor, a result that is consistent with that observed in our previously described efforts.[15] However, either shortening, compare **9** with **16**, or lengthening the distance, compare **14** with **17**, between the imidazole ring and the terminal amine led to a reduction in affinity (Table 2).

While many of the analogs we prepared, including the HTS hit (**9**), showed high affinity for the H_3 receptor, many were unstable when exposed to rat liver microsomes (RLM), as shown in Table 3. Interestingly these compounds proved to be much more stable in the presence of human liver microsomes (HLM). For example thiopropylpiperidine analog **14** was readily degraded in the presence of RLM with a $t_{1/2}$ = 7 min and displayed a HLM $t_{1/2}$ = 149 min. Since our in vivo models are rodent based, we hoped to increase the stability of these molecules to RLM by changing the atom linking the basic amine tail to the aromatic core of the molecule. Thus we prepared the oxygen (**18**), nitrogen (**19**) and carbon linked (**20**) analogs.

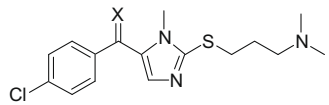
Of these analogues, the oxygen linked compound **18** offered the optimal combination of affinity and stability. Since replacing sulfur with oxygen reduced the distance between the terminal amine and the benzoylimidazole we prepared several compounds to explore this area, Table 4. For this study we focused our attention on modifications to the isopropylpiperidine **15**.

Replacing the sulfur linkage of **15** with oxygen afforded **21**, which did not significantly alter affinity. Insertion of one methylene into the linker of compound **21** provided analog **22** and these two compounds were found to be equipotent. Compound **23** bearing an additional methylene and replacing the Cl with a Br shows significantly reduced affinity with K_i = 70 nM. This result suggests that the longer chain length is responsible for the diminished binding affinity, assuming that the change from Br to Cl has little effect on binding affinity. This assumption is based on a study of the benzoyl substituents in the single methylene analogs (Table 5). In this study no significant changes in affinity were observed over a wide range of substituents including halogens, electron-withdrawing and electron donating groups, Table 5, with one exception.[16]

Synthesis: The H_3 ligands presented here were prepared via several routes as shown in Schemes 1–6.[17] Intermediate **34** was prepared in 66% yield by treatment of 2-thio-1-methylimidazole (**33**) with *t*-BuLi (2 equiv) followed by reaction with 4-chlorobenzaldehyde as described in Scheme 1.[18,19] Alkylation of **34** with 1-bromo-3-chloropropane followed by oxidation of the benzyl alcohol with MnO_2 provided alkyl chloride **35**, which was subsequently converted to analogs **9** and **14** by reaction with the appropriate amine. Along similar lines, intermediate **34** was also converted to compounds **13** and **16**. Benzyl ketone **9** was converted to its corresponding oxime **10** via treatment with NH_2OH/HCl and reduced with either $NaBH_4$ or under Wolff–Kischner conditions to provide analogs **11** and **12**, respectively. Intermediate **34** was also converted to sulfone **39** which led to compounds **18** and **22**.[20]

An alternative route to the sulfur and oxygen linked analogs is shown in Scheme 2.[21] Treatment of commercially available *N*-methylimidazole (**36**) with *n*-BuLi followed by diphenyldisulfide gave 1-methyl-2-phenylsulfanyl-imidazole. When this compound was subjected to LTMP (lithium 2,2,6,6-tetramethylpiperidine) in a mixture of THF and DME at −78 °C for 15 min followed by quenching with 4-chlorobenzaldehye, 2-thiophenylimidazole intermediate **37** was prepared. Stepwise oxidation of **37** with MnO_2 followed by MCPBA gave sulfone **39**. Both sulfur (**15** and **17**) and oxygen (**21**) linked analogs were prepared from this intermediate.

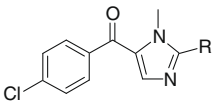
Table 1
Binding and functional antagonist data for the human histamine H_3 receptor for compounds **9**–**12**

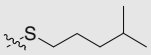
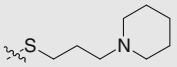
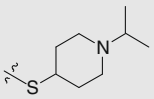
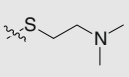
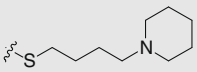


Compound	X	hH$_3$ K_i[a] (nM)	hpA$_2$[b]
9	O	5 (±0.8)	8.7[c]
10	N(OH)	2 (±0.05)	8.4
11	OH, H	18 (±5)	8.4[c]
12	H, H	20 (±1)	8.2

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Values are based on a single determination unless stated otherwise.
[c] Average of two runs.

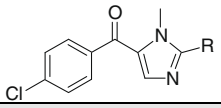
Table 2
Binding and functional antagonist data for the human histamine H_3 receptor for compounds **13**–**17**

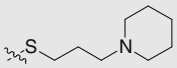
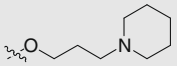
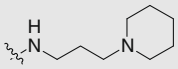
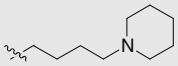


Compound	R	hH$_3$ K_i[a] (nM)	hpA$_2$[b]
13		>5000	5
14		6 (±2)	7.7[c]
15		2 (±0.3)	9.3
16		71 (±11)	7.3
17		50[d]	nd

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Values are based on a single determination unless stated otherwise.
[c] Average of two runs.
[d] Single determination.

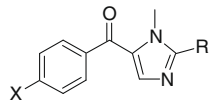
Table 3
Binding and functional data for the human histamine H_3 receptor and half-life ($t_{1/2}$) as predicted by liver microsomal assays for compounds **14**, **18**–**20**

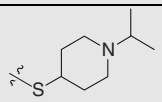
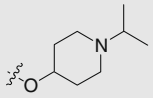
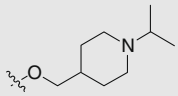
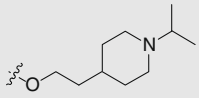


Compound	R	hH_3 K_i[a] (nM)	hpA_2[b]	RLM stability $t_{1/2}$ (min)	HLM stability $t_{1/2}$ (min)
14		6 (±2)	7.7[c]	7	149
18		14 (±1.5)	7.9[c]	55	>180
19		50 (±3.5)	7.4	4	>180
20		24 (±9)	8.0[c]	4	179

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Values are based on a single determination unless stated otherwise.
[c] Average of two runs.

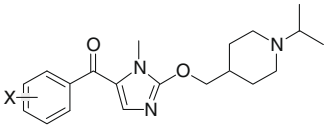
Table 4
Binding and functional antagonist data for the human histamine H_3 receptor for compounds **15**, **21**–**23**



Compound	X	R	hH_3 K_i[a] (nM)	hpA_2[b]
15	Cl		2 (±0.3)	9.3
21	Cl		10 (±5)	8.2[c]
22	Cl		3 (±1)	9.3[d]
23	Br		70 (±13)	7.1

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Values are based on a single determination unless stated otherwise.
[c] Average of three runs.

Table 5
Binding and functional data for the human histamine H_3 receptor for compounds **22**, **24**–**32**



Compound	X	hH_3 K_i[a] (nM)	hpA_2[b]
22	4-Cl	3 (±1)	9.2[c]
24	H	1 (±0.3)	9.5
25	2-Cl	1 (±0.1)	11.1[d]
26	3-Cl	5 (±0.6)	9.7
27	3,5-di Cl	4 (±0.3)	9.0
28	4-Br	3 (±0.9)	9.1
29	4-CF_3	4 (±0.6)	9.3[c]
30	4-NO_2	4 (±1)	9.0[d]
31	4-F	3 (±0.4)	9.5
32	4-*i*Pr	9 (±2)	8.9

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Values are based on a single determination unless stated otherwise.
[c] Average of four runs.
[d] Average of three runs.

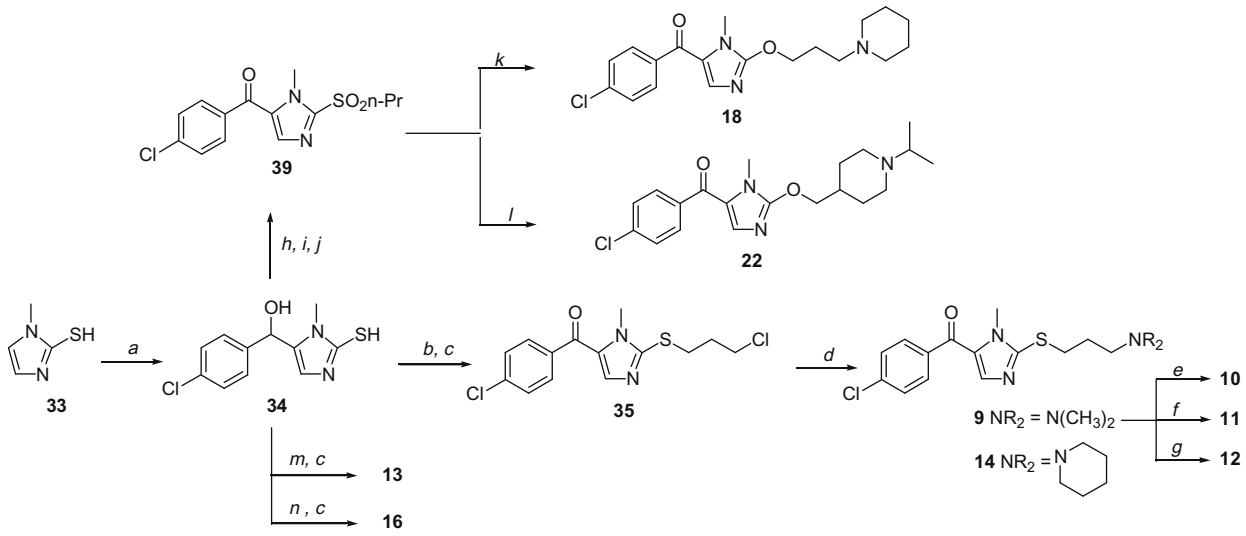
Compounds **23** and **28** were prepared using similar chemistry, from intermediate **40** as shown in Scheme 3. In addition, compound **28** was converted to **24** under hydrogenation conditions.

Deprotonation of *N*-methylimidazole (**36**) followed by quenching with 1-chloro-3-iodobutane and subsequent treatment of the alkyl chloride intermediate with piperidine provided compound **41**. The benzoyl moiety was then installed by deprotonation with LTMP at −78 °C, and subsequent reaction with 4-chlorobenzaldehyde. Oxidation with MnO_2 gave compound **20** as shown in Scheme 4.

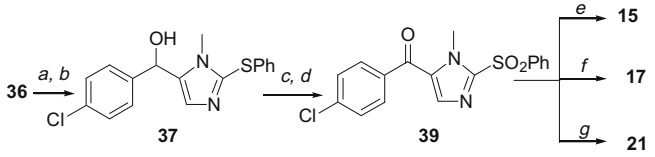
The nitrogen linked compound **19** was prepared using the previously described 2-Cl-imidazole intermediate (**42**) as shown in Scheme 5.[22]

In order to evaluate the effect of substitution on the benzoyl ring, we prepared intermediate **43** as shown in Scheme 6. This compound was then converted into analogs **25**–**27** and **29**–**32**. The low yields shown in Scheme 6 can be attributed to incomplete reaction in step d, as we recovered a significant amount of imidazole **43**.

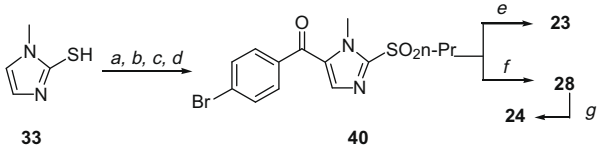
Biological results and discussion: Compound **22** was profiled in detail, in particular with respect to establishing whether the structure suffered from the aforementioned liabilities often associated with imidazoles. When exposed to RLM and HLM, compound **22** was found to be quite stable with $t_{1/2} > 180$ min in both RLM and



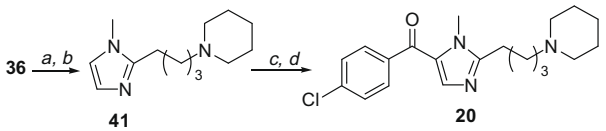
Scheme 1. Reagents and conditions: (a) i—*t*-BuLi (2 equiv), THF, −78 °C for 15 min then warm to 0 °C for 30 min; ii—4-Cl-PhCHO, THF, −78 °C, 66%; (b) K_2CO_3, Br-$(CH_2)_3$-Cl, DMF, acetone, 69%; (c) MnO_2, DCM, rt, 1 h, (81% for **35**), (86% for **13**), (87% for **16**); (d) HNR_2, K_2CO_3, acetone, 60 °C, 16 h, (94% for **14**), (6% for **9**); (e) NH_2OH-HCl, CH_3CH_2OH, pyridine, 80 °C, 16 h, 14%; (f) $NaBH_4$, CH_3OH, 16 h, 60%; (g) *n*-butanol, KO*t*Bu, NH_2NH_2, 120 °C, 16 h, 45%; (h) $Br(CH_2)_2CH_3$, K_2CO_3, DMF, 71%; (i) MnO_2, DCM, 16 h, 29%; (j) *m*-CPBA, DCM, rt, 93%; (k) 3-piperidin-1-yl-propan-1-ol, NaH, THF, 0 °C–rt, 16 h, 52%; (l) (1-isopropyl-piperidin-4-yl)-methanol, NaH, THF, 0 °C–rt, 16 h, 51%; (m) K_2CO_3, Cl-$(CH_2)_3CH(CH_3)_2$, DMF, acetone, 23%; (n) K_2CO_3, Cl-$(CH_2)_2N(CH_3)_2$, acetone, 69%.



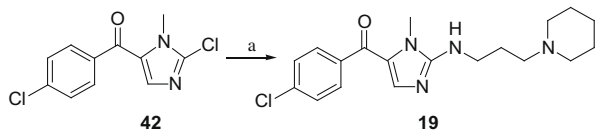
Scheme 2. Reagents and conditions: (a) i—*n*-BuLi, THF, 20 min, −78 °C; (ii) Ph_2S_2, −78 °C for 15 min then warm to rt over 45 min, 82%; (b) (i) 2,2,6,6-tetramethyl-piperidine (TMP), THF, DME, *n*-BuLi, −78 °C, 15 min; (ii) 4-Cl-PhCHO,THF, −78 °C–rt, 16 h, 69%; (c) MnO_2, DCM, rt, 1 h, 87%; (d) *m*-CPBA, diethyl ether, rt, quant.; (e) 1-isopropyl-piperidine-4-thiol, THF, NaH, 0 °C–rt, 16 h, 5%; (f) i—1,3-dioxolane-2-propanethiol, NaH, THF, 78%; ii—PPTS, acetone, H_2O, reflux, 18 h, quant.; iii—piperidine, $Na(OAc)_3BH$, HOAc, DCE, 97%; (g) 1-isopropyl-piperidin-4-ol, NaH, THF, 0 °C—rt, 16 h, 54%.



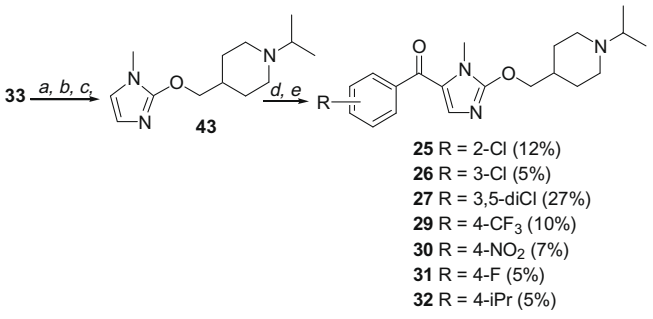
Scheme 3. Reagents and conditions: (a) i—*t*-BuLi (2 equiv), THF, −78 °C for 15 min then warm to 0 °C for 30 min; ii—4-Br-PhCHO, THF, −78 °C, 57%; (b) $Br(CH_2)_2CH_3$, K_2CO_3, DMF, 95%; (c) MnO_2, DCM, 16 h, 86%; (d) *m*-CPBA, DCM, rt, quant; (e) 2-(1-isopropyl-piperidin-4-yl)-ethanol, NaH, THF, 0 °C–rt, 16 h, 67%; (f) 2-(1-isopropyl-piperidin-4-yl)-methanol, NaH, THF, 0 °C–rt, 16 h, 51%; (g) H_2, Pd/C, ethanol, 90%.



Scheme 4. Reagents and conditions: (a) i—*n*-BuLi, THF, 30 min, −78 °C; ii—$Cl(CH_2)_4I$, THF, −78 °C for 3 h then warm to rt over 16 h, 38%; (b) piperidine, K_2CO_3, DMF, 53%; (c) i—2,2,6,6-tetramethylpiperidine, THF, *n*-BuLi, −78 °C, 3 h; ii—4-Cl-PhCHO, THF, −78 °C–rt, 8 h, 56%; (d) MnO_2, DCM, 16 h, 29%.



Scheme 5. Reagents and conditions: (a) 3-Piperidin-1-yl-propylamine, DIPEA, THF, reflux, 16 h, 16%.



Scheme 6. Reagents and conditions: (a) i—*n*-BuLi, THF, 20 min, −78 °C; ii—Ph_2S_2, −78 °C for 15 min then warm to rt over 45 min, 82%; (b) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 82%; (c) 2-(1-isopropyl-piperidin-4-yl)-methanol, NaH, THF, reflux, 36 h, 63%; (d) i—2,2,6,6-tetramethylpiperidine, THF, DME, *n*-BuLi, −78 °C; ii—then add substituted benzaldehyde) in THF and let warm to rt over 16 h; (e) MnO_2, CH_2Cl_2. Yield shown is the yield after steps d and e.

HLM assays. Additionally, analog **22** was evaluated as a substrate for the major cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6 and 3A4) and exhibited IC_{50}s > 10 μM in every case. In functional assays, **22** was approximately ten fold less potent at the rat receptor when compared to the human receptor (rat pA_2 = 8.0 vs human pA_2 = 9.2) and in broad selectivity screening (>50 receptors and/or ion channels) **22** only showed weak affinity for the sigma receptor (77% at 10 μM).

When **22** was administered to rats (10 mg/kg, ip) maximum brain and plasma concentrations of 17 and 2.6 μM, respectively, were ob-

served after 60 min. Significant amounts of **22** (3.8 μM) were also seen as long as 48 h after dosing. A rat pharmacokinetic study (10 mg/kg, po, iv) provided additional in vivo parameters such as an oral half-life (po $t_{1/2}$) = 9 h, oral bioavailability (%F) = 10%, clearance (CL) = 9.3 ml/min/kg and volume of distribution (Vd) = 5.2 L/kg. These observations indicate that **22** was free of the metabolic issues which have been observed of many imidazole-based ligands.

In summary we investigated a novel series of imidazole containing histamine H_3 antagonists. They were found to be potent functional antagonists and we were able to significantly improve their stability towards liver microsomes. Following in vivo administration compound **22** achieved high brain concentration.

References and notes

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