Bioorganic & Medicinal Chemistry Letters 20 (2010) 6226–6230

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Indole- and benzothiophene-based histamine H_3 antagonists

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ARTICLE INFO

Article history:
Received 20 July 2010
Revised 19 August 2010
Accepted 20 August 2010
Available online 27 August 2010

Keywords:
Histamine
Indole
Benzothiophene
Mannich reaction
SAR

ABSTRACT

Previous research on histamine H_3 antagonists has led to the development of a pharmacophore model consisting of a central phenyl core flanked by two alkylamine groups. Recent investigation of the replacement of the central phenyl core with heteroaromatic fragments resulted in the preparation of novel 3,5-, 3,6- and 3,7-substituted indole and 3,5-substituted benzothiophene analogs that demonstrate good to excellent hH_3 affinities. Select analogs were profiled in a rat pharmacokinetic model.

The histamine H_3 receptor is a presynaptic autoreceptor in the central nervous system that controls the synthesis and release of histamine. Histamine H_3 antagonists have potential therapeutic utility in the treatment of sleeping, eating, attention and memory disorders.[1,2] The SAR of phenyl-based compounds related to **1**, **2**, **3** and **4**[1d,3–5] (Fig. 1) has been disclosed previously and has correlated to a proposed pharmacophore[4,6] consisting of a central core flanked by two alkylamine groups (Fig. 2). Phenyl ring replacement studies have shown that bicyclic ring systems are well tolerated including indole,[7] benzofuran,[8] benzazepine[9] and tetrahydro-isoquinoline[10] ring systems. The work presented in this paper further investigates the replacement of the central phenyl core (Fig. 1) with heteroaromatic fragments,[11] notably indole and benzothiophene ring systems.[12] Such replacement was undertaken in an effort to better understand central core SAR within our H_3 program.

For the 3,4- and 3,5-substituted indoles, two synthetic routes were utilized to enable ready diversification of both positions on the aromatic indole core. The first route (Scheme 1) favors the variation of the amide moiety late in the synthesis while the second route (Scheme 2) permits the introduction of different amines at the 3-position of the indole in the final step. Using Scheme 1, the synthesis of 5-amido substituted indoles was initiated by using the commercially available methyl carboxylate starting material **5**. Initial Mannich reaction of the indole with the desired amine in the presence of formaldehyde furnished the 3-amino methyl intermediate **6**. Subsequent hydrolysis gave the corresponding potassium salt **7** which was coupled to the cyclic diamine to provide the target compound **8**.

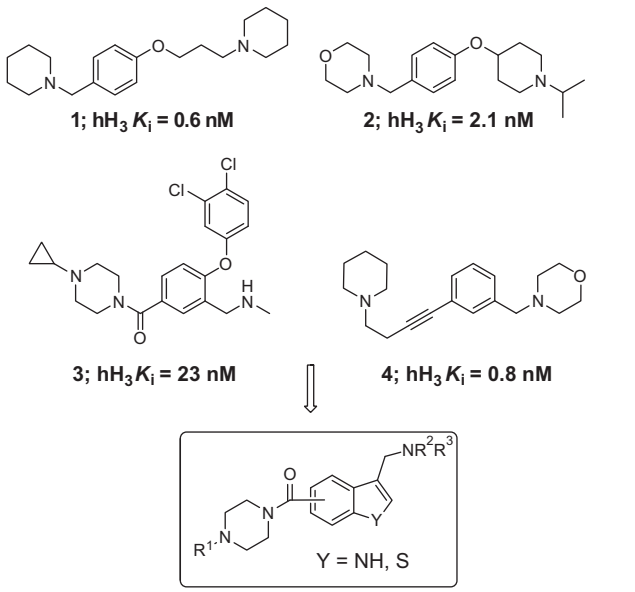

Figure 1. H_3 antagonists.[13]

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doi:10.1016/j.bmcl.2010.08.103

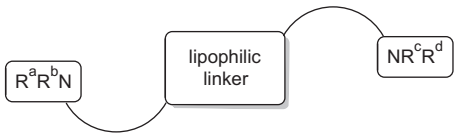
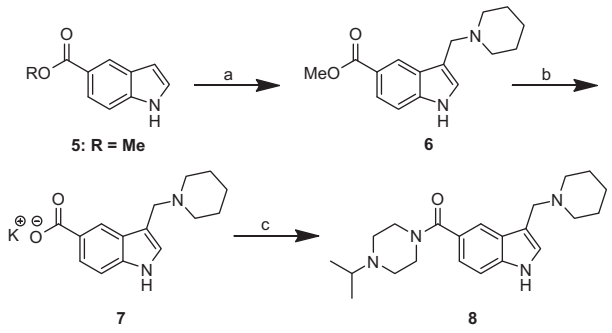
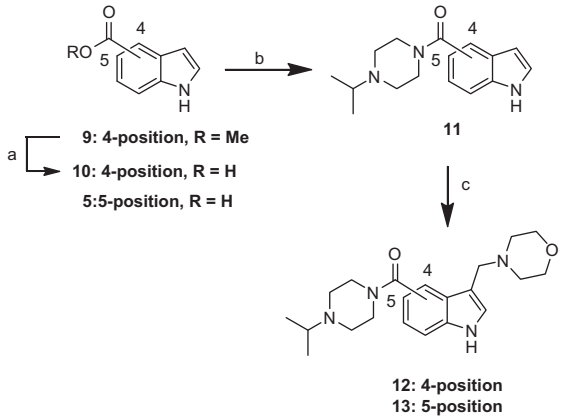


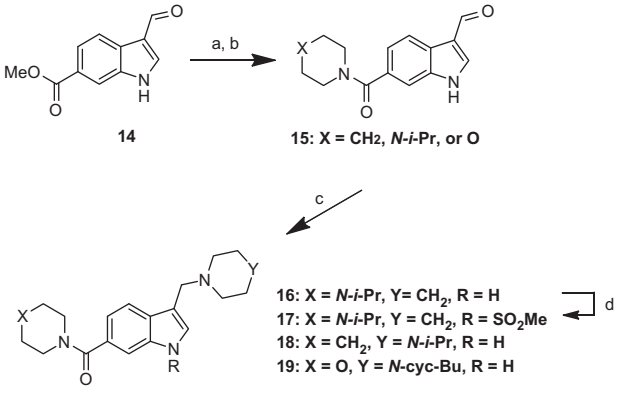
Figure 2. Pharmacophore model for H_3 antagonists.



Scheme 1. Reagents and conditions: (a) piperidine, CH_2O, dioxane:AcOH (1:1) (41%); (b) KOH, *i*-PrOH (quant.); (c) *N*-*i*-Pr-piperazine, EDCI, HOBt, DMF (15%).



Scheme 2. Reagents and conditions: (a) LiOH, THF/H_2O (quant.); (b) *N*-*i*-Pr-piperazine, EDCI, HOBt, K_2CO_3, DMF (61–62%); (c) morpholine, CH_2O, dioxane:AcOH (4:1) (8–21%).

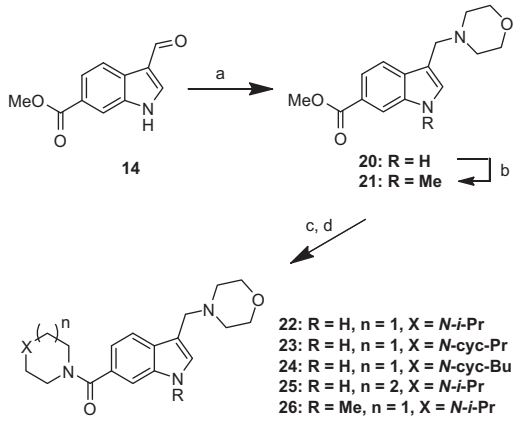


Scheme 3. Reagents and conditions: (a) LiOH, THF/H_2O (quant.); (b) *N*-*i*-Pr-piperazine or piperidine, EDCI, HOBt, DMF (36–43%); (c) *N*-*i*-Pr-piperazine, *N*-cyc-Bu-piperazine, or piperidine, $NaBH(OAc)_3$, dichloroethane or CH_2Cl_2 (65% quant.); (d) (i) NaH, DMF, 0 °C; (ii) $MeSO_2Cl$ (23%). For compound **19**: (b) morpholine, PyBOP, HOAt, Et_3N, DMF (37%); (c) MP-$BH(OAc)_3$ [solid-supported reagent, Biotage], DMF (30%).

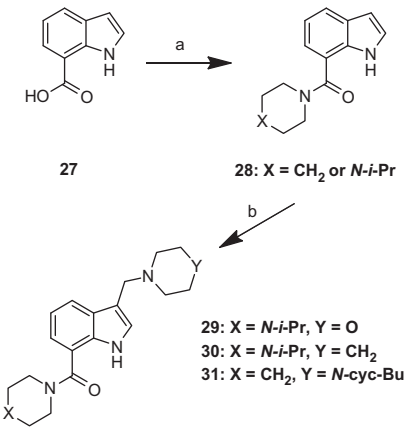
Alternatively, introduction of the 3-aminomethyl moiety late in the synthetic process commenced with starting materials **5** and **9** as shown in Scheme 2. Hydrolysis (as appropriate) of the ester followed by coupling of the acids with the cyclic diamine yielded intermediates related to structure **11**. Mannich reaction of these resulting indoles led to the desired target compounds **12** and **13**.

The synthesis of the 3,6-amido substituted indole analogs was achieved using the routes shown in Schemes 3 and 4. In Scheme 3, initial coupling of the acid (step b) with the appropriate amine furnished the desired 3-formyl indole intermediates **15**. The introduction of the aminomethyl at the 3-position was achieved under reductive amination conditions to furnish the target analogs **16**, **18**, and **19**. Further reaction of compound **16** with methanesulfonyl chloride led to the formation of **17**. In Scheme 4, additional target compounds were prepared using a modified route. Initial introduction of the 3-aminomethyl group using reductive amination conditions as above yielded **20**. Introduction of the methyl group under standard conditions yielded **21**. Subsequent hydrolysis and coupling led to the target compounds **22**–**26**.

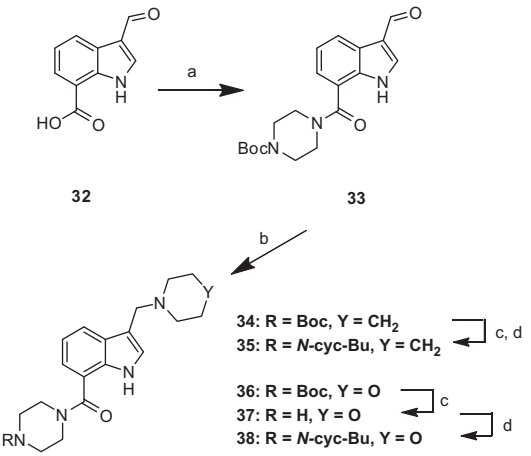
The 3,7-substituted analogs were prepared using the routes depicted in Schemes 5 and 6. Variation of the 3-aminomethyl group was facilitated by utilization of Scheme 5. Coupling of starting material **27** with the desired amines to yield intermediates **28** followed by Mannich reaction led to the desired compounds **29–31**.



Scheme 4. Reagents and conditions: (a) morpholine, $NaBH(OAc)_3$, dichloroethane (89%); (b) MeI, NaH, DMF, 0 °C to rt (92%); (c) KOH, *i*-PrOH; (d) *N*-*i*-Pr-piperazine, *N*-cyc-Pr-piperazine, *N*-cyc-Bu-piperazine, or *N*-*i*-Pr-homopiperazine, EDCI, HOBt, DMF, 60 °C or rt [Na_2CO_3 was added to prepare **22**–**24**] (27–54% over two steps).



Scheme 5. Reagents and conditions: (a) *N*-*i*-Pr-piperazine or piperidine, EDCI, HOBt, DMF, 60 °C or rt (62–82%); (b) *N*-*i*-Pr-piperazine, *N*-cyc-Bu-piperazine, or piperidine, CH_2O, dioxane:AcOH (1:1 or 4:1) (29–54%).



Scheme 6. Reagents and conditions: (a) *N*-Boc-piperazine, EDCI, HOBt, DMF (34%); (b) morpholine or piperidine, $NaBH(OAc)_3$, CH_2Cl_2 (79%); (c) (i) TFA, CH_2Cl_2; (ii) Dowex 550A OH anion-exchange resin, MeOH (94%-quant. over two steps); (d) cyclobutanone, $NaBH(OAc)_3$, CH_2Cl_2 (72%-quant.).

In Scheme 6, treatment of **32** with *N*-Boc-piperazine under standard coupling conditions resulted in the formation of intermediate **33**. Further reaction under reductive amination conditions allowed access to **34** and **36**. Removal of the Boc group of **36** gave the intermediate **37,** which could be further reacted to yield **38**. Compound **35** was prepared similarly from **34**.

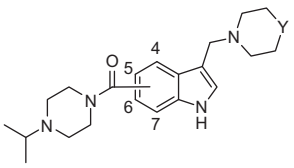
Analysis of the positional isomers within the indole series with respect to human H_3 (hH_3) binding affinity data[14] as illustrated in Table 1 shows a preference for the 3,6-substitution pattern. This trend is similar when the 3-amino moiety is morpholine (compounds **12, 13, 22**, and **29**) or piperidine (compounds **8, 16**, and **30**). Clearly, the 3,4-substitution pattern is the least preferred with compound **12** exhibiting little hH_3 activity (~5 μM). This data does indicate that the indole moiety is an acceptable phenyl core replacement.

The hH_3 binding affinity data of additional 3,6-substituted compounds (Table 2) provides greater SAR insight into the types of substitution on the indole that can maintain or adversely affect activity. Substitutions were made on the distal nitrogen of the amide and the amine at the 3-position (X and Y, Table 2). As seen by the data in Table 2, most of these modifications are well tolerated. The 3-methylpiperidinyl and 3-methylmorpholinyl substituted indoles (**16–17** and **22–26**, respectively) lead to compounds with excellent hH_3 affinities regardless of the substitution on the 7-amidopiperazine. Interestingly, if the piperidine and piperazine moieties are switched, a trend toward decreased hH_3 affinity is observed (compounds **16** vs **18** and compounds **19** vs **24**). The data also indicates that substitution on the indole nitrogen with small groups such as methyl and methylsulfonyl is well tolerated (compounds **26** and **17**). Several of the analogs in Table 2 were evaluated to assess functional activity and were found to be potent antagonists (hH_3 pA_2> 8.0).[14]

Referring back to Table 1, the 3,7-substituted indole analogs maintained reasonable potency. Additional analogs were prepared to better understand the SAR. Selected examples and the corresponding hH_3 affinities are summarized in Table 3. It appears that the *N*-cyclobutyl is favored over the *N*-isopropyl substitution on the distal nitrogen of the amide moiety (compounds **35** and **30**). Additionally, removal of the alkyl group at this site leads to a substantial loss in hH_3 activity (**37**). Finally, similar to the 3,6-isomers, removing the distal basic nitrogen on the amide with subsequent incorporation as part of the 3-aminomethyl moiety leads to a decrease in hH_3 activity (compare **29**, **30**, **35**, and **38** vs **31**).

Lastly, benzothiophene was explored as a phenyl ring replacement, but investigations were limited to the 3,5-substituted benzothiophenes due to the availability of starting material. The preparation of these analogs is summarized in Scheme 7. Initial reduction of 5-bromo-benzothiophene-3-carboxylic acid **39** was accomplished through the formation of a mixed anhydride. Amino carbonylation under microwave heating conditions[15] provided the key amide intermediate **41**. Oxidation followed by reductive amination with piperidine furnished the target compounds **43–44**.

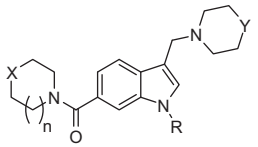
Table 1
Effect of indole substitution on hH_3 activity[a]



Compds	Substitution	Y	hH_3 K_i[a] (nM)
12	4	O	4900 ± 4490
8	5	CH_2	88 ± 58
13	5	O	180 ± 31
16	6	CH_2	2.8 ± 0.4
22	6	O	2.1 ± 0.6
30	7	CH_2	27 ± 16
29	7	O	12 ± 13

[a] hH_3 K_i values are the mean of at least three determinations unless otherwise stated.

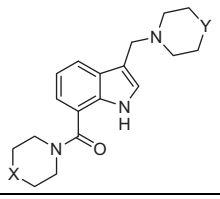
Table 2
SAR of 3,6-substituted indole analogs



Compds	X	Y	R	*n*	hH_3 K_i[a] (nM)	hH_3 pA_2[b]
16	*N*-*i*-Pr	CH_2	H	1	2.8 ± 0.4	9.3[c]
17	*N*-*i*-Pr	CH_2	SO_2CH_3	1	1.9 ± 1.8	8.5
18	CH_2	*N*-*i*-Pr	H	1	88 ± 31	—[d]
19	O	*N*-cyc-Bu	H	1	43[e]	—[d]
22	*N*-*i*-Pr	O	H	1	2.1 ± 0.6	9.6
23	*N*-cyc-Pr	O	H	1	2.0 ± 0.2	9.3
24	*N*-cyc-Bu	O	H	1	1.4 ± 0.2	9.8
25	*N*-*i*-Pr	O	H	2	0.9 ± 0.2	9.5
26	*N*-*i*-Pr	O	CH_3	1	15 ± 10	8.2

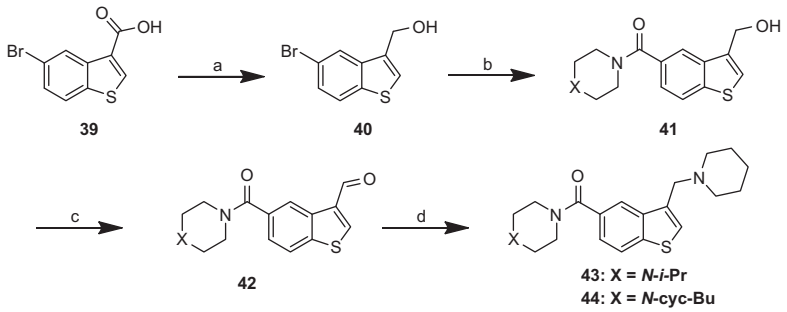
[a] See Table 1 for details.
[b] hH_3 pA_2 values are a result of a single point experiment unless otherwise noted.
[c] Result of two single point experiments.
[d] Samples were not tested.
[e] K_i value represents one determination.

Table 3
SAR of 3,7-substituted indole analogs



Compds	X	Y	hH_3 K_i[a] (nM)
29	*N*-*i*-Pr	O	12 ± 13
30	*N*-*i*-Pr	CH_2	27 ± 16
35	*N*-cyc-Bu	CH_2	1.6 ± 0.3
38	*N*-cyc-Bu	O	4.9 ± 2.6
37	NH	O	2130 ± 830
31	CH_2	*N*-cyc-Bu	240 ± 100

[a] See Table 1 for details.



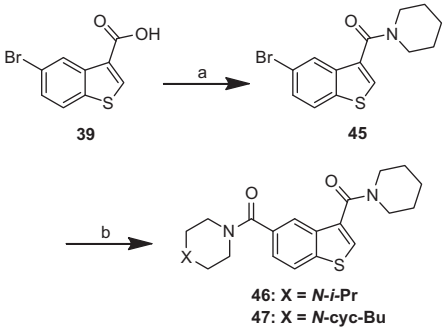
Scheme 7. Reagents and conditions: (a) (i) *i*-butyl chloroformate, Et_3N, THF, 0 °C; (ii) $NaBH_4$, THF:H_2O (1:1), 0 °C to rt (89% over two steps); (b) *N*-*i*-Pr-piperazine or *N*-cyc-Bu-piperazine, $Mo(CO)_6$, DBU, Hermann's catalyst, *t*-Bu_3PHBF_4, THF, 125 °C, microwave (18–24%); (c) MnO_2, $CHCl_3$, 70 °C (83–95%); (d) piperidine, $NaBH(OAc)_3$, CH_2Cl_2 (53–59%).

The corresponding amido analogs were prepared as seen in Scheme 8. Amide coupling of the acid **39** with piperidine provided the desired amide intermediate **45**. Amino carbonylation, with slightly modified conditions from the aforementioned examples, provided the desired amide analogs **46**–**47**.

The hH_3 binding affinity data for the 3,5-substituted benzothiophene analogs is summarized in Table 4. In agreement with the indole analogs, the benzothiophene core is seen as a viable phenyl core replacement. The hH_3 affinity of the 3-aminomethyl analogs is better (34- to 65-fold) than the corresponding 3-amide analogs (compounds **43**–**44** vs **46**–**47**) emphasizing the need for a basic amine at the 3-position and supporting the pharmacophore hypothesis.

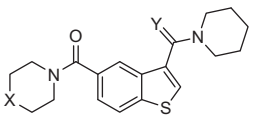
No cross-reactivity with the hERG channel was observed for select compounds in the indole and benzothiophene series using a high-throughput astemizole-binding assay.[16]

The encouraging in vitro potencies of the indole analogs prompted further exploration of the in vivo properties of compounds **22** and **23** in a rat pharmacokinetic model. The results of these studies are summarized in Figure 3. As seen from the data,



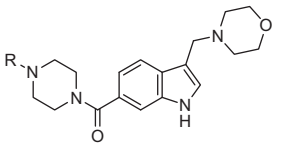
Scheme 8. Reagents and conditions: (a) piperidine, EDCI, HOBt, DMF (98%); (b) *N*-*i*-Pr-piperazine or *N*-cyc-Bu-piperazine, $Mo(CO)_6$, Na_2CO_3, Hermann's catalyst, H_2O, 130 °C, microwave (34–41%).

Table 4
SAR of 3,5-substituted benzothiophene analogs



Compds	X	Y	hH_3 K_i[a] (nM)
43	*N*-*i*-Pr	H_2	50 ± 8
44	*N*-cyc-Bu	H_2	15 ± 1
46	*N*-*i*-Pr	O	3280 ± 1890
47	*N*-cyc-Bu	O	520 ± 220

[a] See Table 1 for details.



22: R = *i*-Pr
hH_3 K_i = 2.1 nM
hH_3 pA_2 = 9.6
$t_{1/2}$ = 3.5 h
F = 100%
AUC = 3.9 μM*h (po, 10 mpk)
V_{ss} = 40 L/kg
CL = 160 mL/min/kg

23: R = *cyc*-Pr
hH_3 K_i = 2.0 nM
hH_3 pA_2 = 9.3
$t_{1/2}$ = 1.9 h
F = 38%
AUC = 7.4 μM*h (po, 10 mpk)
V_{ss} = 8.4 L/kg
CL = 77mL/min/kg

Figure 3. Rat PK profile of compounds **22** and **23**.

substitution on the piperazine amide can influence the PK profile. These two indoles display a range of bioavailabilities (F = 38–100%), volumes of distribution (V_{ss} = 8.4–40 L/kg) and clearance values (CL = 77–160 mL/min/kg). Possible phospholipidosis due to these compounds was not examined at this time.

In conclusion, our early efforts toward replacing the phenyl core with 6,5-bicyclic aromatic ring systems, represented by indole and benzothiophene, indicated that such changes were well tolerated. These analogs were efficiently generated and exhibited good to excellent hH_3 affinities. Moreover, the indole-based analogs showed promising rat PK properties and are suitable for further optimization. Such additional work will be necessary to better compare and contrast compounds with monocyclic versus bicyclic heteroaromatic cores.

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