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SHORT COMMUNICATION

In search of potent histamine-3 receptor antagonists

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KEYWORDS

Histamine-3;
Antagonist;
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Abstract Starting with modafinil, an alertness and wake-promoting agent but inactive in histamine 3 receptor (H_3R) binding assay, a series of potent H_3 receptor antagonists were developed.

1. Introduction

Due to the beneficial roles played by histamine 3 receptor (H_3R) in alertness, wake-promotion and cognition in central nervous system (CNS), the research in this field has become a subject of intense interest in recent years (Singh et al., 2013). Thus the development of potent H_3R antagonists has emerged as an attractive target for the treatment of various CNS disorders including narcolepsy, ADHD, and cognitive disorders either as a primary indication or associated with another disease state (Berlin et al., 2011; Vohora and Bhowmik, 2012; Celanire et al., 2005). Our interest in H_3R antagonists originated from modafinil (compound **1**, Fig. 1) a novel alertness and wake-promoting agent whose mechanism of action at the molecular level remains elusive to date (Saper and Scammell, 2004). Modafinil does not display any significant *in vitro* binding affinity for the H_3 receptor. However, it has been reported that in anesthetized rats, modafinil increased extracellular histamine concentrations (Ishizuka et al., 2003). Thus while designing a series of H_3R antagonists, we sought to incorporate some of modafinil's structural themes, especially its lipophilic bis-aryl moiety attached to a polar (i.e. sulfinyl) moiety. In a previous report, we disclosed results from our initial effort (Dunn et al., 2014). In this *Communication*, we offer a brief summary from our additional effort.

2. Chemistry

Scheme 1 depicts the synthesis of target compounds **9–10**. Pyridine derivative **2** was coupled with the boronic acid **3** under Suzuki condition to generate compound **4**. Separately, enantiomerically pure prolinols (compounds **5–6**) underwent reductive amination reactions with cyclobutanone to generate amino alcohols **7–8**. O-alkylation of compounds **7–8** with compound **4** generated compounds **9** and **10**, respectively.

In Scheme 2**,** the chloro group of compound **2** was displaced by the alkoxides generated from cyclic alkanols **11–13** to produce a series of compounds of general structure **14**. Separately, phenol derivative **15** underwent a Mitsunobu reaction with compound **13** to produce compound of general structure **16**. Compounds **14** and **16** underwent separate Suzuki reactions with 4-(methylsulfonyl)benzeneboronic acid to generate compounds of general structure **17** that were *N*-deprotected to produce free amines of general structure **18.** Reductive amination of compounds **18** with a set of cyclic ketones produced target compounds **19–25**.

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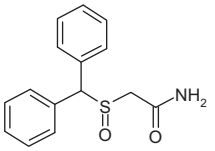

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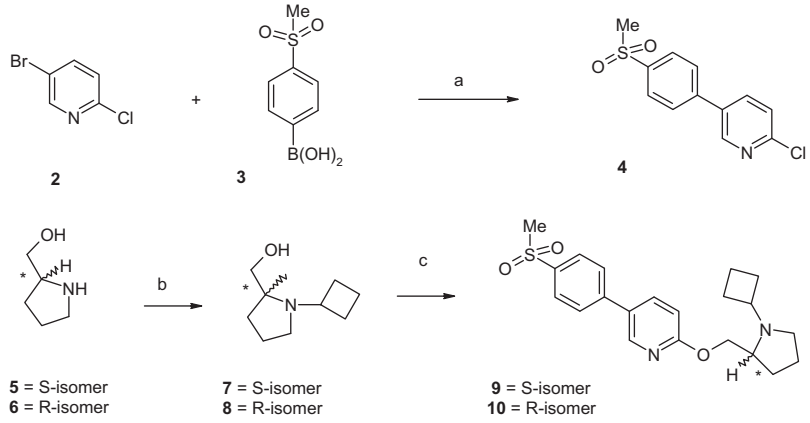
Figure 1 Chemical structure of compound **1**.

3. Biology

Following a literature procedure, binding properties of the target compounds were assessed against recombinant human H_3 (hH_3) and rat H_3 (rH_3) receptors by displacement of [^{3}H]-N-α-methylhistamine and reported as K_i values from an average of three experiments, done in duplicate (US Patent, 2012), while in triplicate for the potent analogs. The results are displayed in Table 1. The table also displays the result for a reference compound Pitolisant that entered into clinical trials (Schwartz, 2011).

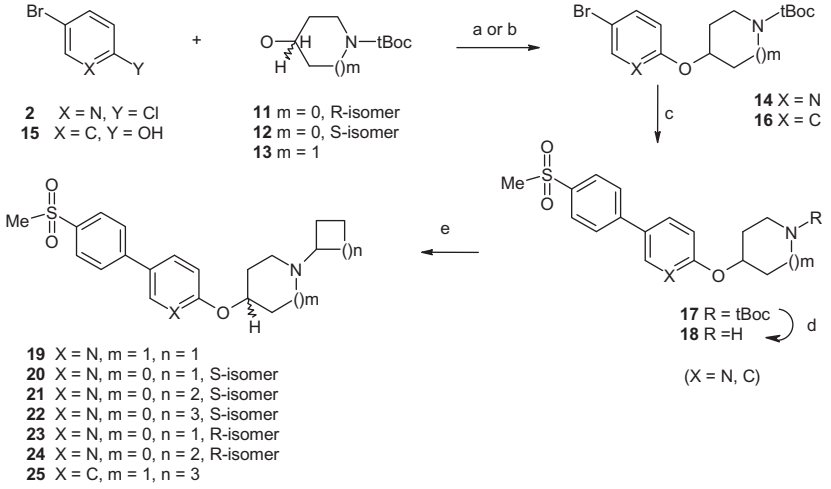
4. Discussion

As mentioned previously, compound **1** displayed no hint of any *in vitro* binding affinity (even at higher concentrations) for either H_3 receptor. Thus, our exploration began by re-orienting the aromatic region into a para-linked bi-aryl system, especially an aryl-heteroaryl system as the central lipophilic region. While a polar sulfonyl group was appended to the aryl ring, the heteroaryl moiety was attached via a methyleneoxy moiety, to a terminal cyclic amine moiety to impart some structural rigidity in that part of the molecule. Initially, structural fragments derived from (*S*)- and (*R*)- prolinol were



5 = S-isomer
6 = R-isomer
7 = S-isomer
8 = R-isomer
9 = S-isomer
10 = R-isomer

Scheme 1 Reagents and conditions: (a) 4-($Pd(PPh_3)_4$, 2 M aq. Na_2CO_3, toluene, EtOH, 95–100 °C, 3 h, 70%; (b) (i) cyclobutanone, gl. AcOH (catalytic), CH_2Cl_2, 0 °C, 20–30 min; (ii) sodium acetoxyborohydride, 0 °C to room temperature, 4–6 h, 60–65%; (c) (i) NaH, DMF, 0 °C to room temperature, 30 min; (ii) compound **4**, 100 °C, 2 h, 40–45%.



2 X = N, Y = Cl
15 X = C, Y = OH
11 m = 0, R-isomer
12 m = 0, S-isomer
13 m = 1
14 X = N
16 X = C
17 R = tBoc
18 R =H
(X = N, C)
19 X = N, m = 1, n = 1
20 X = N, m = 0, n = 1, S-isomer
21 X = N, m = 0, n = 2, S-isomer
22 X = N, m = 0, n = 3, S-isomer
23 X = N, m = 0, n = 1, R-isomer
24 X = N, m = 0, n = 2, R-isomer
25 X = C, m = 1, n = 3

Scheme 2 Reagents and conditions: for compound **14**: (a) (i) compounds **11**–**13**, 60%NaH, NMP, 0 °C to room temperature; (ii) compound **2**, 90 °C, overnight, 50–60%; for compound **16**: (b) PPh_3, 40% DEAD in toluene, THF, 0 °C to room temperature, overnight, 60%; (c) 4-(methylsulfonyl)benzeneboronic acid, 4-($Pd(PPh_3)_4$, 2 M aq. Na_2CO_3, toluene, EtOH, 95–100 °C, 6–8 h, 50–60% (d) 4 N HCl in dioxane, room temperature, 90–95%; (e) (i) cyclic ketone, gl. AcOH (catalytic), CH_2Cl_2, 0 °C, 30 min; (ii) sodium acetoxyborohydride, 0 °C to room temperature, 4–6 h, 50–60%.