

## 5-Lipoxygenase inhibition by *N*-hydroxycarbamates in dual-function compounds

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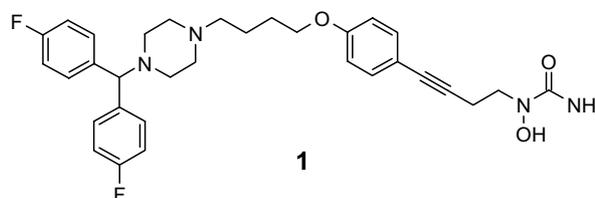
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**Abstract**—A series of *N*-hydroxycarbamates containing a histaminergic H<sub>1</sub> receptor antagonist pharmacophore was synthesized. In vitro assays determined the compounds had both histaminergic binding and 5-lipoxygenase inhibiting activities comparable to the corresponding *N*-hydroxyurea analog. Animal models demonstrated antihistaminergic and the 5-lipoxygenase inhibitory activity, with the *N*-hydroxyurea analog having a better overall profile.

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Histamine plays a role in the pathophysiology of asthma alongside its key role in allergic response. Clinical studies have demonstrated that asthmatics treated simultaneously with an H<sub>1</sub> receptor antagonist and a LTD<sub>4</sub> receptor antagonist experienced less airway obstruction than those patients treated with either drug alone.<sup>1</sup> A similar combination proved to be as efficacious as a corticosteroid in treating the airway symptoms of allergic rhinitis and asthma.<sup>2</sup> Inhibition of 5-lipoxygenase (5-LO) is potentially a more efficacious treatment than antagonism of leukotriene receptors, as biosynthesis of all the pro-inflammatory leukotrienes would be diminished.

Our work has focused on dual-function antihistaminergic/5-LO inhibiting compounds such as the *N*-hydroxyurea UCB 62045 (**1**), which demonstrates both activities in vitro and in vivo.<sup>3</sup> UCB 62045 is effective in reducing ovalbumin-induced bronchoconstriction in the guinea pig bronchoconstriction model with oral dosing, and has been investigated as a treatment for asthma and allergic rhinitis. Reports on the 5-LO inhibitory effect of *N*-hydroxycarbamates<sup>4</sup> supported investigating this moiety in similar dual-function molecules.



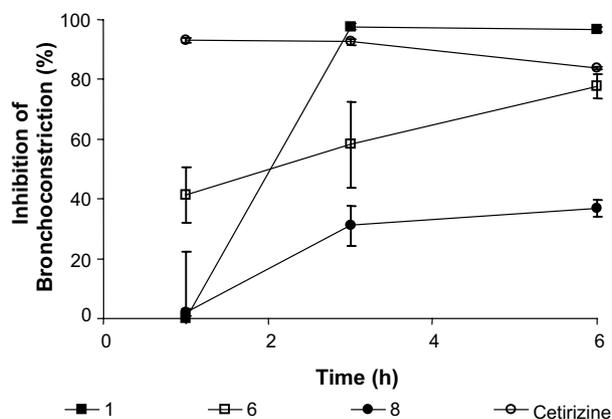
Synthesis of **1** began by reacting 4-iodophenol with 1,4-dibromobutane to give **2** (Scheme 1). Palladium catalyzed coupling of **2** with 3-butyn-1-ol gave **3**. *N*-Alkylation of 1-bis-(4-fluorophenyl)methyl piperazine with **3** gave alcohol **4**, which was converted to *N*-hydroxyurea **1** using a literature procedure.<sup>5</sup> Synthesis of the carbamate analogs began with alcohol **4**, which was converted into hydroxylamine **5** via mesylation and displacement with aqueous hydroxylamine. Treatment of **5** with ethyl chloroformate gave the desired *N*-hydroxycarbamate **6**. However, treatment of **5** with isopropyl chloroformate gave predominately the undesired *N,O*-bis-acylated product **7** in 43% yield. Treatment of **7** with KOH/*i*-PrOH hydrolyzed only the carbonate group to afford *N*-hydroxycarbamate **8**. This two step procedure, alkyl chloroformate addition to **5** making the diacyl product followed by basic hydrolysis, also proved more convenient for the preparation of the methyl, isobutyl, and benzyl *N*-hydroxycarbamates **9–11**.<sup>6</sup>

Human H<sub>1</sub> receptor binding was performed using CHO-K1 cells expressing the recombinant H<sub>1</sub> receptor<sup>7</sup> (Table

**Keywords:** 5-LO inhibitor; *N*-Hydroxycarbamate; Antihistamine.

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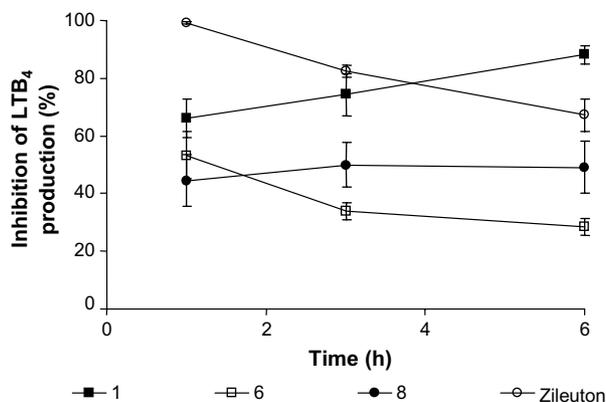


**Figure 1.** The effect of dual-function compounds on histamine-induced bronchoconstriction in guinea pigs (**1**, **6**, and **8**, 2 mg/kg, po; cetirizine, 0.5 mg/kg, po,  $n = 3$  animals/timepoint).

dual-function compounds are as active as cetirizine, which displayed nearly complete inhibition of histamine-induced bronchoconstriction at all time points with a lower dose (0.5 mg/kg).

The ex vivo 5-LO assay monitors the inhibition of LTB<sub>4</sub> production after calcium ionophore-induced stimulation<sup>12</sup> (Fig. 2). Zileuton was tested alongside the dual-function compounds as a reference. Inhibition of 5-LO activity by the three dual-function molecules was detected up to six hours after challenge. *N*-Hydroxyurea **1** has better activity than the two *N*-hydroxycarbamates tested, and the activity increases with time. The *N*-hydroxycarbamate activities are fairly constant in this assay, or decrease with time.

In conclusion, in a dual-function antihistaminergic system, *N*-hydroxycarbamates demonstrate 5-LO inhibitory activity, both in vitro and in vivo with oral dosing. However, the ex vivo 5-LO activities of the *N*-hydroxycarbamates are lower at 1, 3, and 6 h than the analogous *N*-hydroxyurea. Further work is required to



**Figure 2.** The effect of dual-function compounds and of zileuton on the inhibition of A-23187-stimulated LTB<sub>4</sub> production in guinea pigs (for **1**, **6**, **8**, 2 mg/kg, po; zileuton, 5 mg/kg, po,  $n = 3$  animal/timepoint).

fully determine the therapeutic potential of *N*-hydroxycarbamates.<sup>13</sup>

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.12.023.

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- Experimental procedures for the synthesis of all intermediates and final compounds, plus the biological experimental procedures can be found in the [Supplementary material](#).