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Synthesis and Biological Evaluation of Novel 2-(1*H*-imidazol-4-yl)cyclopropane Carboxylic Acids: Key Intermediates for H_3 Histamine Receptor Ligands

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Abstract—A new synthetic methodology to provide *cis*-2-(1H-imidazol-4-yl)-cyclopropane carboxylic acids is described. These cyclopropanes are useful for the preparation of novel H_3 receptor agents.

The different pharmacological actions of histamine are mediated via the activation of four distinct receptor subtypes, namely H_1, H_2, H_3[1] and H_4 receptors.[2] The histamine H_3 receptor is responsible for controlling neuronal synthesis of histamine and regulates its release into the synaptical cleft.[3] Furthermore, this receptor has been shown to modulate the release of other neurotransmitters, such as acethylcoline, dopamine, serotonin and noradrenaline, in both the central and peripheral nervous systems.[4] Therefore, the H_3 receptor can be considered a potential target for several diseases and neurological disorders, for example, epilepsy, schizophrenia, eating and drinking behaviour, arousal and sleep disorders, memory and learning deficits, and Alzheimer's disease.[5]

It has been demonstrated that potent and selective histamine receptor ligands possess distinct stereochemical characteristics.[6] The development of rigid histamine analogues will contribute to the determination of the H_3 receptor pharmacophore. Due to its structural features, the cyclopropane ring has been used to improve histamine H_3 receptor affinity. The activity of some cyclopropanic derivatives like the agonist cyclopropylhistamine[7] or the antagonist GT-2331[8] has been reported (Fig. 1). Therefore, as part of our medicinal chemistry studies directed towards the preparation of new H_3 receptor ligands, we have initiated the synthesis of new precursors of cyclopropylhistamine derivatives. We have synthesised a series of novel 2-(1*H*-imidazol-4-yl)-cyclopropane carboxylic acids **I** (Fig. 2), as key synthetic intermediates, on which an alkyl or an aryl moiety was attached to the

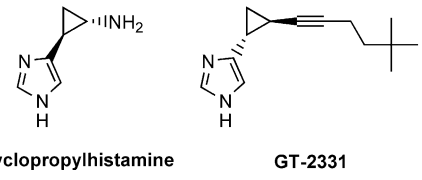

Figure 1.

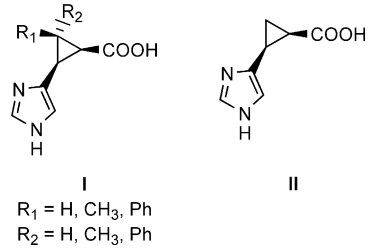

Figure 2.

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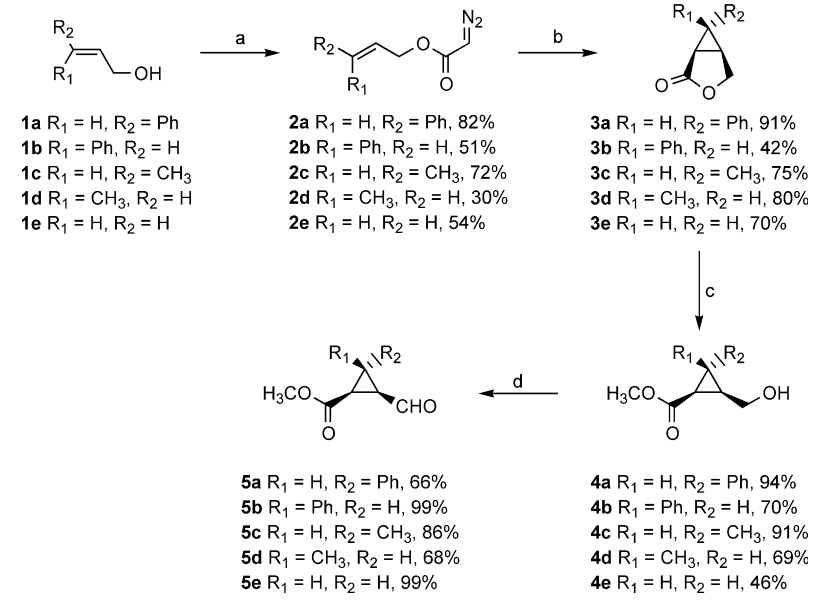
C3 position of the cyclopropane ring. We have explored the *cis* stereochemical relation between C1 and C2 positions of the cyclopropane ring, as a first approach to the synthesis of the *cis*-cyclopropylhistamine precursor **II** (Fig. 2).

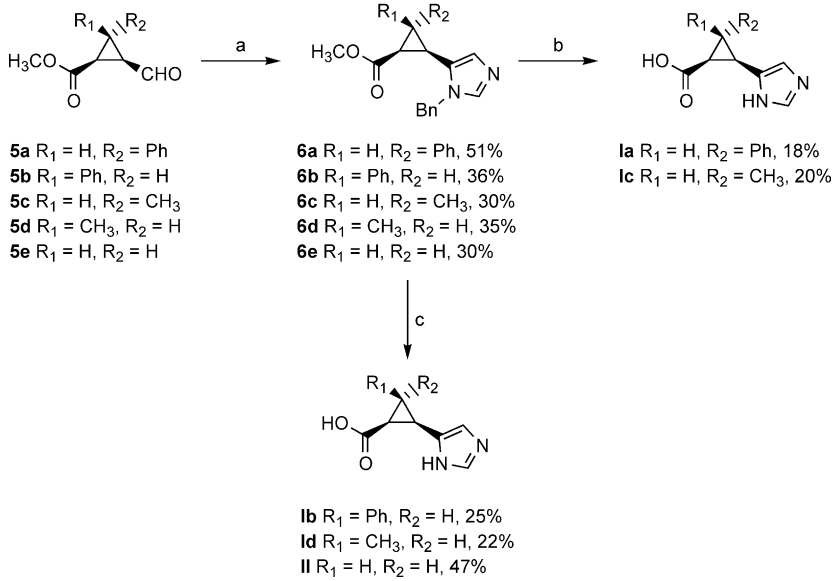
Chemistry

The general pathway outlined in Schemes 1 and 2 yielded the desired compounds **I** and **II**. The alcohols **1a**–**e**[9] were transformed into their corresponding allylic diazocetates **2a**–**e**, by reaction with diketene (or the diketene equivalent 2,2,6-trimethyl-4*H*-3-dioxin-4-one)[10] and subsequent diazo transfer, followed by base-induced deacylation.[11] The unsaturated diazo esters **2a**–**e** underwent cyclopropanation to give lactones **3a**–**e** upon slow addition to a refluxing solution of bis-(*N*-*tert*-butyl-salicyladiminato) copper (II) catalyst.[12] The lactones **3a**–**e** were opened with LiOH and converted into their methyl esters **4a**–**e** by reaction with diazomethane. Thus, oxidation of the primary alcohol function in **4a**–**e** rendered the aldehydes **5a**–**e** (Scheme 1).

The imidazole ring moiety was obtained from **5a**–**e** by reaction with benzylamine and TosMIC in a single pot.[13] The esters **6a**,**c** were hydrolysed under basic conditions and subsequent transfer hydrogenation,[14] with cyclohexene and the Pd-C (10%) catalyst, providing **Ia**,**c**. The hydrogenation of the *N*-benzyl group in esters **6b**,**d**,**e**, followed by acidic hydrolysis, furnished **Ib**,**d** and **II**, respectively (Scheme 2).



Scheme 1. (a) (i) diketene, THF, Δ; (ii) 4-acetamidobenzene-sulfonyl azide, CH_3CN, rt; (iii) LiOH, H_2O; (b) $Cu(TBS)_2$, toluene; (c) (i) LiOH, H_2O; (ii) CH_2N_2, Et_2O; (d) PCC, CH_2Cl_2, rt.



Scheme 2. (a) (i) $BnNH_2$, DMF; (ii) TosMIC; (iii) K_2CO_3; (b) (i) LiOH, H_2O; (ii) cyclohexene, Pd-C (10%), absolute EtOH, Δ; (c) (i) cyclohexene, Pd-C (10%), absolute EtOH, Δ; (ii) HCl 6N, Δ.

Table 1. Histamine H_3 receptor-binding affinities for compounds **Ia–d** and **II**

Compd	% Inhibition[a]	n[b]
RMHA (1×10^{-8} M)	30.8 (±3.4)	6
Ia (1×10^{-5} M)	33.5 (±6.0)	6
Ib (1×10^{-5} M)	4.3 (±1.8)	6
Ic (1×10^{-5} M)	10.0 (±3.1)	6
Id (1×10^{-5} M)	3.7 (±2.7)	6
II (1×10^{-5} M)	11.6 (±5.5)	6

[a]Mean values given, standard error is given in parentheses.
[b]n is the number of assays.

Biological Evaluation

The affinity of new compounds for the histamine H_3 receptor was assessed by the study of the inhibition of the specific binding of [^{3}H] (*R*)-α-methylhistamine ([^{3}H] RMHA) in rat brain membranes. (*R*)-α-methylhistamine (RMHA) was used as the reference compound. The procedure used for the [^{3}H] RMHA binding assay was that described by Arrang et al.,[15] with some modifications in centrifugation methodology: 12000 rpm, 30 min, 4 °C, buffer Tris–HCl 0.05 M, pH 7.4.

The results of histamine H_3 receptor binding affinities for **Ia–d** and **II** are summarized in Table 1. All the compounds showed less affinity than RMHA. Although these molecules are just key intermediates in the synthesis of new *cis*-cyclopropylhistamine derivatives, the slight affinity of **Ia** to the H_3 receptor should be noticed. The carboxylic group of compounds **I** and **II** could be transformed into an amine group or into an apolar group in order to study their activity as H_3 agonists or antagonists.

In conclusion, we have developed a new synthetic methodology to provide *cis*-2-(1H-imidazol-4-yl)-cyclopropane carboxilic acids that could be useful for preparing conformationally restricted novel histamine H_3 receptor agents.

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