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TRANS-4-METHYL-3-IMIDAZOYL PYRROLIDINE AS A POTENT, HIGHLY SELECTIVE HISTAMINE H3 RECEPTOR AGONIST IN VIVO

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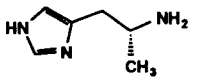
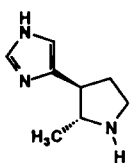
Abstract: Extensive structural modification of immepyr (+)-**2** led to the discovery of *trans*-4-methyl-3-imidazoyl pyrrolidine (±)-**3a** as a potent and highly selective H3 agonist. The pyrroline (±)-**3a** was resolved, and its (+) enantiomer, Sch 50971 [(+)-**3a**], showed a greater separation of H3 and H1 activities in vivo (H3/H1 ratio >> 330) than (R)-α-methylhistamine (+)-**1** (H3/H1 ratio = 17), the standard H3 agonist.

Introduction

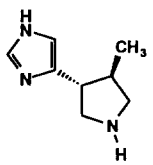
In 1983, Arrang and co-workers[1] suggested that inhibition of brain histamine release was mediated by a novel class of histamine receptor. Subsequent studies[2] showed this receptor (H3) to be pharmacologically distinct from the H1 and H2 receptors previously described.[3] The H3-receptor is located presynaptically on histaminergic neurons and modulates the release[4] as well as synthesis[5] of histamine (and other neurotransmitters such as serotonin,[6] noradrenaline,[7] and acetylcholine[8]) via a negative feedback mechanism. Early work in the area of H3-receptor agonists identified (*R*)-α-methylhistamine [(+)-**1**] (RAMHA)[2] as a potent and selective H3-agonist in vitro (H3/H1 ratio ~10,000). Although RAMHA [(+)-**1**] showed good selectivity in vitro, our own work showed substantial in vivo H1 activity.[9] In an effort directed towards the discovery of therapeutically useful H3 receptor agonists devoid of undesired H1 activity, we employed classical conformational analysis on RAMHA and identified a novel pyrrolidine (i.e., immepyr [(+)-**2**][10]) which showed a greater separation of H3 and H1 activity in vivo (H3/H1 >> 550) than RAMHA (H3/H1 = 17). Immepyr, (+)-**2**, was subsequently chosen for further SAR development. In this communication, we discuss the results of this SAR study which lead to the discovery of another novel, potent and highly selective H3 agonist (i.e., Sch 50971[(+)-**3a**]).



(+)-**1**



(+)-**2**



(+)-**3a**

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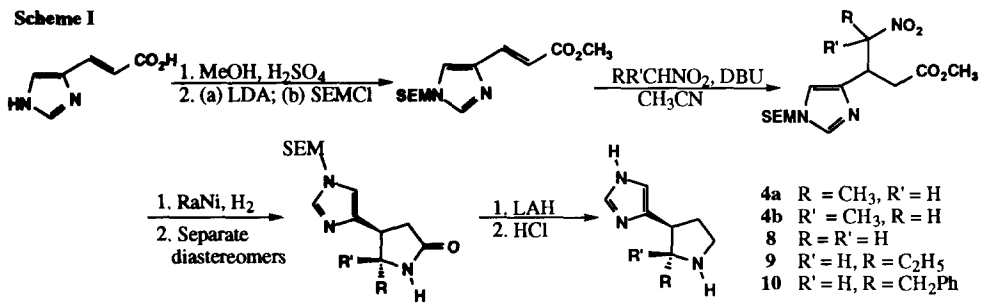
PII: S0960-894X(98)00020-1

Chemisty

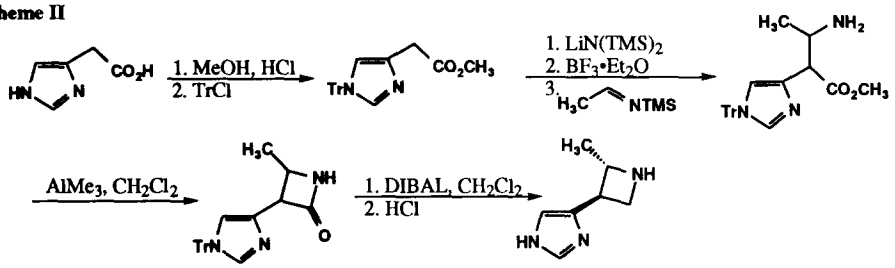
The compounds shown in charts I to III were synthesized as racemates by the protocols outlined in Schemes I to VI. For convenience, only one of the corresponding enantiomers is indicated in the Schemes.

Scheme I



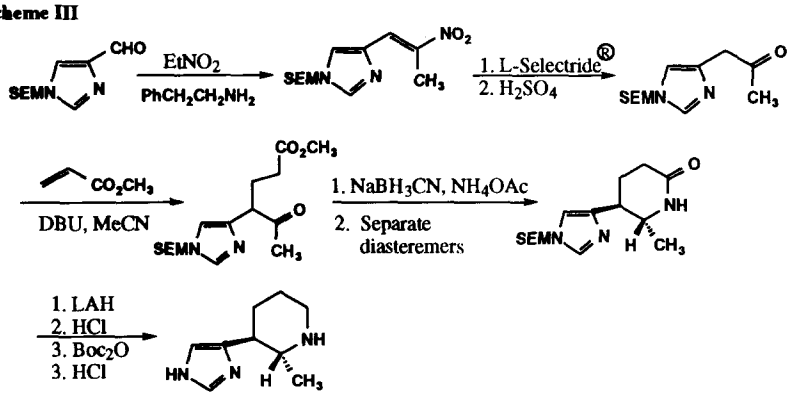
4a R = CH_3, R' = H
4b R' = CH_3, R = H
8 R = R' = H
9 R' = H, R = C_2H_5
10 R' = H, R = CH_2Ph

Scheme II



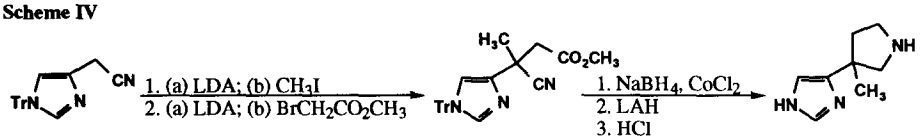
6

Scheme III



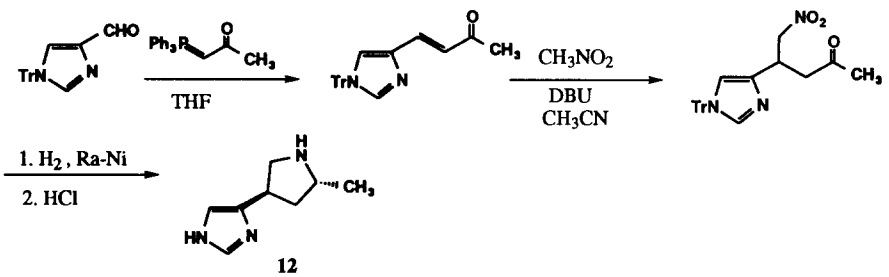
7

Scheme IV

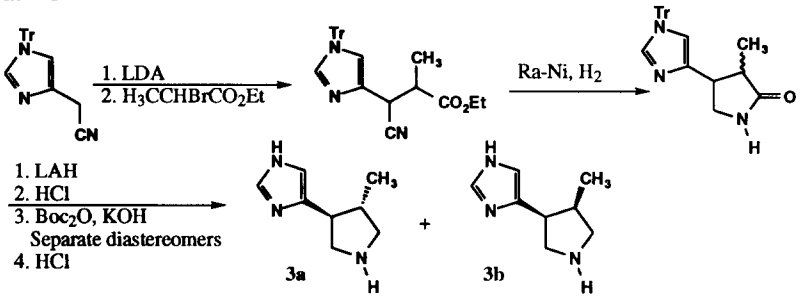


11

Scheme V



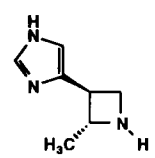
Scheme VI



Results and Discussion

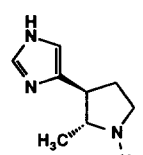
The structural modifications that were considered for the SAR investigation included (1) the ring size of the heterocyclic moiety of these compounds, (2) the size of the alkyl substitution at selected sites about the heterocyclic ring, and (3) the position of methyl substitution about the heterocyclic ring. Considering first the length of the methylene bridge from the β-carbon to the basic side chain nitrogen (heterocyclic ring size; see Chart I below), the 2-methyl substituted pyrrolidine **4a** (2-methylene bridge) was shown to be more than 500-fold more active in our H_3-binding assay[11] than the corresponding homologue, 2-methyl substituted piperidine **7** (3-methylene bridge). In addition, the pyrrolidine **4a** was very selective for the H_3-receptor; this compound showed no significant H_1 activity.[12a] While the corresponding 2-methyl substituted azetidine **6** (1-methylene bridge) was nearly equipotent to **4a** in the H_3-binding assay, it was not selective for this receptor as it possessed substantial H_1 activity.[12b]

Chart I



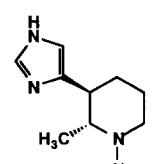
6

K_i (H_3-bind.) = 7.0 nM



4a

K_i (H_3-bind.) = 3.0 nM

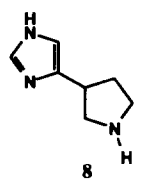


7

K_i (H_3-bind.) = >2000 nM

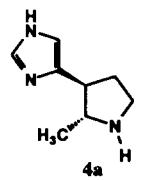
In light of the above described potency and selectivity associated with the 2-*trans*-methyl pyrrolidine moiety of **4a** (*trans*-relationship between the methyl and the imidazoyl moieties), we next considered the steric requirements of the substituent at the 2-position of the pyrrolidine ring (see Chart II below). With respect to substitution at this position, a marked decrease in H_3-binding activity was associated with an increase in size of the substituent from methyl [**4a**] to ethyl [**9**] to benzyl [**10**]. The nor-methyl pyrrolidine **8**, while quite active in the H_3-binding assay, showed substantial H_1-activity.[12b]

Chart II



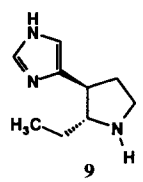
8

K_i (H_3-bind.) = 2.0 nM



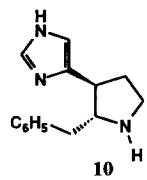
4a

K_i (H_3-bind.) = 3.0 nM



9

K_i (H_3-bind.) = 150 nM

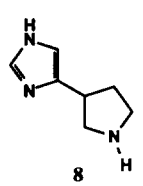


10

K_i (H_3-bind.) = >2000 nM

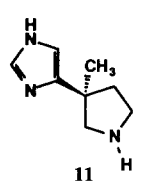
We next considered the position of methyl substitution about the pyrrolidine ring (see Chart III below). Methyl substitution at the 3-position [**11**] or the 5-position [**12**] resulted in compounds with significantly reduced H_3-binding activity compared to the nor-methyl pyrrolidine **8**. The 2-*cis*-methyl pyrrolidine **4b**, in contrast to **4a** (the corresponding *trans* diastereomer), showed much weaker H_3-binding activity. Methyl substitution at the 4-position, whether with a *cis*-relationship between the methyl and the imidazoyl moieties [**3b**] or a *trans*-relationship [**3a**], produced compounds nearly equipotent in the H_3-binding assay with the nor-methyl pyrrolidine **8**. While the 4-*trans*-methyl pyrrolidine **3a** was quite selective for the H_3-receptor, the 4-*cis*-methyl pyrrolidine **3b** showed indication of H_1-activity. The SAR analysis described above provided a novel potent H_3 receptor ligand **3a**.

Chart III



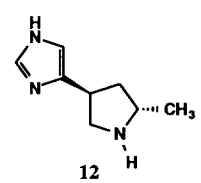
8

K_i (H_3-bind.) = 2 nM



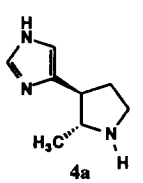
11

K_i (H_3-bind.) = 170 nM



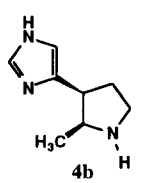
12

K_i (H_3-bind.) = 76 nM



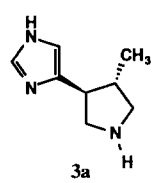
4a

K_i (H_3-bind.) = 3 nM



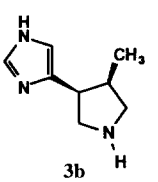
4b

K_i (H_3-bind.) = 59 nM



3a

K_i (H_3-bind.) = 5 nM

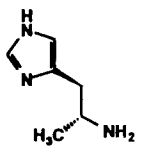


3b

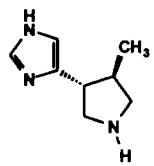
K_i (H_3-bind.) = 3 nM

In light of the known enantioselectivity of the H3-receptor [(*R*)-α-methylhistamine is ~100 fold more potent than the corresponding *S*-enantiomer in H3-binding studies[13]], we resolved (±)-**3a** and determined the absolute stereochemistry of the constituent enantiomers by single crystal X-ray analyses.[14] Further binding studies indicated that the dextrorotatory enantiomer (3*R*,4*R*)-(+)-**3a** was more than tenfold more active in the H3 binding assay than the levorotatory isomer (3*S*,4*S*)-(-)-**3a**. Further biological evaluation of (+)-**3a** (Sch 50971), in comparison with RAMHA, is summarized in the Table. In vitro, Sch 50971 [(+)-**3a**] was effective in inhibiting an electrically induced contraction of guinea pig ileum tissue.[15] Similarly, it was as effective as RAMHA in vivo (via intravenous administration) in the inhibition of an electrically induced CNS hypertensive response.[16] Most significantly, Sch 50971[(+)-**3a**] also exhibited a significantly enhanced in vivo selectivity for the H3-receptor compared to the biological profile of RAMHA [(+)-**1**](H_3/H_1 ratio >> 330 for [(+)-**3a**]). In fact, no evidence of H_1 activity was detected at doses of Sch 50971 [(+)-**3a**] as high as 100 mg/kg iv.

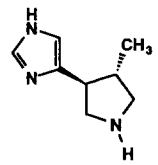
Table



RAMHA
[(+)-1]



Sch 50971
[(+)-3a]



[(-)-3a]

	H_3-Binding (K_i)		Guinea Pig Ileum (pD_2)		In Vivo (ED_{50}, mg/kg)[a]		H_3/H_1 ratio (in vivo)
	H_3	H_1	H_3	H_1	H_3[b]	H_1[c]	[$ED_{50}(H_1)/ED_{50}(H_3)$]
RAMHA	1.5	> 10,000	8.2	5.4	0.1	1.7	17
[(+)-**3a**]	2.3	> 10,000	7.5	< 4.0	0.3	> 100[d]	>>330

[a]Via intravenenous administration. [b]Determined in the CNS hypertension model (see ref 16). [c]Determined by an H_1-histamine mediated bronchospasm (see ref 9). [d]No evidence of any H_1 activity was detected at doses as high as 100 mg/kg.

In conclusion, structural modification of immepyr [(+)-**2**] led to the identification of another novel, potent and highly selective H3 agonist, pyrrolidine (±)-**3a**. The pyrrolidine (±)-**3a** was resolved and its (+) enantiomer, Sch 50971, showed a greater separation of H3 and H1 activities in vivo (H_3/H_1 ratio >> 330) than RAMHA [(+)-**1**] (H_3/H_1 ratio = 17), the standard H3 agonist.

Acknowledgement. The authors wish to thank Professor Andrew T. McPhail of Duke University who provided the single crystal X-ray analysis needed to determine the absolute stereochemistry of (3*R*,4*R*)-(+)-**3a**.

References and Notes

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11. All compounds were tested in a receptor binding assay, which was performed on guinea pig brain tissue using [H^3] N^{α}-methylhistamine as ligand; see Korte, A.; Myers, J.; Shih, N.-Y.; Egan, R. W.; Clark, M. A. *Biochem. and Biophy. Res. Comm.* **1990**, *168*, 979. The K_i value for H_3 receptor binding of each compound represents the mean of two independent experiments.
12. (a) H_1 agonist activity was determined by histamine H_1-mediated contraction of guinea pig ileum (in vitro) and histamine H_1-mediated bronchospasm (in vivo); see ref 9. (b) In the anesthetized guinea pig, compound **6** elicited H_1-mediated bronchoconstrictor effect at doses $\geq$ 0.3 mg/kg, iv. Compound **8** produced significant bronchoconstrictor effects at a dose of 0.3 mg/kg, iv.
13. Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. *Eur. J. Pharmacol.* **1985**, *117*, 109.
14. Resolutions ($\geq$ 99% ee) were accomplished via chiral stationary phase HPLC of the di-*t*-BOC derivatives of (±)-**3a**. Absolute stereochemistry of the enantiomers of **3a** were assigned based upon a single crystal X-ray analysis of the hydrocholide salt of (+)-**3a**.
15. An electrically-stimulated isolated guinea pig ileum preparation was used as the in vitro functional assay; an assay which differentiates H_3-agonists and H_3-antagonists. The assay used is based on studies described previously: Trzeciakowski; see Trzeciakowski, J. P. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 84.
16. H_3-agonist activity was determined in vivo using a model previously described: Hey, J. A.; del Prado, M.; Egan, R. W.; Kreutner, W.; Chapman, R. W. *Br. J. Pharmacol.* **1992**, *107*, 347.