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Original paper

Histamine analogues. 32nd communication: synthesis and pharmacology of sopromidine*, a potent and stereoselective isomer of the achiral H_2-agonist impromidine

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Summary — Synthesis and pharmacology of sopromidine ((*R*)-**7**) and (*S*)-**7**, 2 position isomers of impromidine derived from the enantiomeric α-methylhistamines, are reported. The enantiomers of **7** show high stereoselectivity at the atrial H_2-receptor of the guinea-pig. (*R*)-**7** is revealed to be a full H_2-agonist with 7.4-fold potency relative to histamine, while (*S*)-**7** is a competitive H_2-antagonist.

Résumé — Analogues de l'histamine. 32e communication: synthèse et pharmacologie de la sopromidine, un isomère puissant et stéréosélectif de l'impromidine agoniste-H_2 achiral. *La synthèse et la pharmacologie de la sopromidine ((R)-**7**) et de (S)-**7**, dérivés des antipodes de l'histamine α-méthylée et des isomères de l'impromidine, sont décrites. Les énantiomères de **7** possèdent un degré de stéréosélectivité prononcé vis-à-vis du récepteur H_2 de l'atrium du cobaye. ((R)-**7** est un agoniste-H_2 total avec 7,4 fois l'activité de l'histamine, tandis que (S)-**7** est un antagoniste-H_2 compétitif.*

chiral H_2-agonists / histamine H_2-receptor / impromidine analogues / α-methylhistamine

Introduction

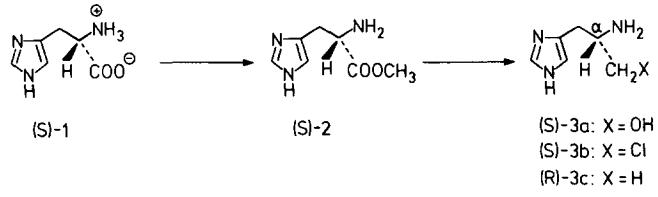
The existence of 2 subtypes of histamine receptors, proposed in 1966 by Ash and Schild [2], was established by the introduction of H_2-selective antagonists [3] in the early seventies. Since that time attempts have been made to develop chiral agonists of histamine which would be valuable tools to elucidate structure–activity relationships of H_1- and H_2-agonists, especially concerning receptor selectivity and stereoselectivity of the interaction between the active center of the receptor and the agonist molecule [4–11].

The enantiomers of α-methylhistamine (for nomenclature see [12]) and several closely related amines [5–9] show significant stereoselectivity towards the H_2-receptor of the guinea-pig atrium while they are equipotent at the H_1-receptor of the guinea-pig ileum. The observed affinity ratios (1.7–7.2) are rather low in accordance with Pfeiffer's rule [13], modified by Porthoghese [14], as the compounds – with the exception of the α-chloromethyl derivatives of histamine [8] – show only 0.3 up to 8.7% of the affinity of histamine. Chiral agonists, at least equipotent to histamine, would possibly show a higher degree of stereoselectivity at the H_2-receptor, provided the center of chirality is close to the active site of the molecule. Following the structural features of impromidine [15] the weak H_2-agonist α-methylhistamine was chosen to be integrated into a guanidine structure, bearing the affinity contributing cimetidine-like 2-[(5-methyl-4-imidazolyl)methylthio]ethyl substituent.

Results

Chemistry

(*R*)- and (*S*)-α-methylhistamine (**3c**) were synthesized



Scheme 1. Synthesis of (*R*)-(−)-α-methylhistamine ((*R*)-**3c**) from L-histidine ((*S*)-**1**) [6].

*Proposed I.N.N. for (−)-3-[(*R*)-2-(4-imidazolyl)-1-methylethyl]-1-{2-[(5-methyl-4-imidazolyl)methyl]thioethyl}guanidine (I.U.P.A.C.).
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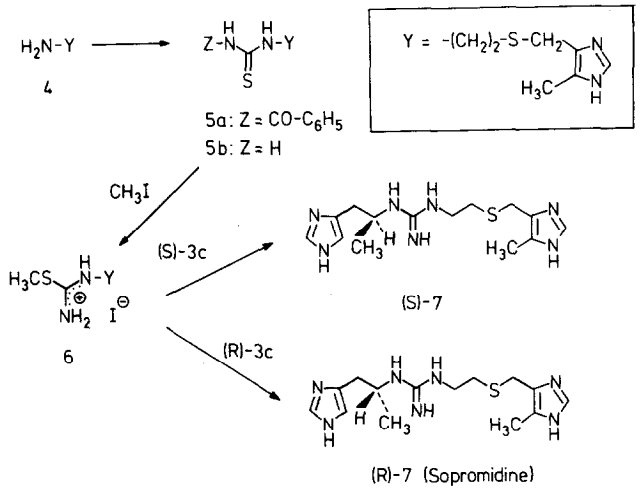
according to Scheme 1 [6], outgoing from (*S*)- and (*R*)-histidinol (**3a**) which were chlorinated ($SOCl_2$), followed by reduction of the chloromethyl substituent with H_2/Pd-C. The change of the *R,S*-nomenclature [16] from (*S*)-**3b** to (*R*)-**3c**, *e.g.*, is due to the alteration of the priority of substituents at the α-carbon atom, while the absolute configuration is retained. The route illustrated in Scheme 2 leads to sopromidine ((*R*)-**7**) and its (*S*) enantiomer, respectively. Acylation of the primary amine **4** [17] with benzoyl isothiocyanate provided the benzoyl thiourea **5a** which by alkaline hydrolysis and alkylation of the intermediate thiourea **5b** afforded the isothiouronium iodide **6** [18].



Scheme 2. Synthesis of sopromidine and its enantiomer, outgoing from 2-[(5-methyl-4-imidazolyl)methylthio]ethylamine (**4**) and the stereoisomeric α-methylhistamines **3c**.

Compound **6** was condensed with (*R*)- and (*S*)-**3c** respectively, to give the title guanidines (*R*)- and (*S*)-**7**, which were characterized as *meso*-tartrates.

Pharmacology

(*R*)- and (*S*)-**7** were assayed for histaminergic activity on the isolated guinea-pig ileum (H_1) and atrium (H_2), respectively. The results are listed in Table I. The enantiomers of **7** reveal poor H_1-activity. Sopromidine shows only 20% of the maximal response produced by histamine, while (*S*)-**7** is an H_1-antagonist even weaker than impromidine itself.

At the H_2-receptor, however, sopromidine turns out to be a full agonist with 7.4-fold affinity relative histamine. The effect is due to H_2-receptor stimulation, since the presence of 0.3 μM propranolol does not impair the concentration response curve, while cimetidine antagonizes chronotropic stimulation competitively. Surprisingly the heart rate does not increase when (*S*)-**7** is administered in concentrations up to 0.1 mM. On the other hand, competitive H_2-antagonism can be observed for (*S*)-**7** towards histamine ($pA_2 = 5.6$) and sopromidine ((*R*)-**7**) ($pA_2 = 5.4 \pm 0.2$; $N = 4$). The pharmacological properties of the racemate *rac*-**7** hint at the revealed divergency of the enantiomers, as the affinity ratio (*R*)-**7**/*rac*-**7** = 2.55 indicates an antagonistic contribution of (*S*)-**7**, while a totally inactive (*S*) enantiomer would induce an affinity ratio (*R*)/*rac* = 2.0. The enantiomers of **7** show a high degree of stereoselectivity towards the H_2-receptor ((*R*)/(*S*) > 1000). Furthermore, sopromidine reveals pronounced H_2-selectivity, expressed as the ratio of potencies relative to histamine at both H_2- and H_1-receptors (H_2/H_1) = 7.4/0.017 = 435/1.

Table I. Activity of **7** and related compounds at both H_1- and H_2-receptors.

Compound	H_1-activity guinea-pig ileum				H_2-activity guinea-pig atrium			
	i.a.	pD_2	potency rel. to histamine	pA_2	*i.a.*	pD_2	potency rel. to histamine	pA_2
Histamine	1.0	6.85	1	–	1.0	6.00	1	–
Impromidine [15]	0	–	–	5.5	0.99	7.68	48.1	–
(*R*)-7 (sopromidine)	0.2	–	0.017	–	1.0	6.87 (6.65–7.03)	7.4 (4.5–10.7)	–
(*S*)-**7**	0	–	–	4.8[a]	0	–	–	5.6[b]
rac-**7**[c]	not determined				0.8	6.46 (6.11–6.71)	2.9 (1.3–5.1)	–
8a [10]	0.4	–	0.02	–	0.8	5.10	0.13	–

For intrinsic activity (*i.a.*), pA_2, pD_2, see [19, 20]. Potency of (*R*)-**7** and racemic **7** with 95% confidence limits in parentheses. $N = 8$ experiments for (*R*)-(*S*)- and *rac*-**7**, respectively. For structures see Scheme 2 and Table II.

[a] 0.05% relative to diphenhydramine (pA_2=8.15).

[b] 16% relative to cimetidine (pA_2=6.4).

[c] Obtained by mixing equimolar amounts of (*R*)-**7** and (*S*)-**7**.

Discussion

Methyl branching of the histamine molecule at the α-carbon atom provides weak partial H_2-agonists that show a low affinity ratio (1.7:1) in favour of the (*S*) enantiomer, while the maximal effect is identical (80%) [6]. Additional N^{α}-methylation halves affinity of both enantiomers, while a significant differentiation of the intrinsic activities occurs, in favour of the more active (*S*)-α,N^{α}-dimethylhistamine (90% *versus* 60%) [7]. Linking the enantiomeric α-methylhistamines with **4**, an affinity contributing moiety of many H_2-antagonists, by a guanidine group leads to the enantiomers of **7** which reveal completely opposite pharmacological properties. The dualistic character of the guanidine moiety [21] is emphasized by the fact that (*S*)-**7** which is derived from (*S*)-**3c**, is a pure H_2-antagonist with lower affinity than histamine, while sopromidine ((*R*)-**7**) behaves as a full H_2-agonist and surmounts the potency of histamine by nearly one order of magnitude.

The equivalent derivatisation of the achiral histamine leads to **8a** [10]. Though **8a** shows increased affinity compared with the weak partial agonist N^{α}-guanylhistamine [22], it still achieves only submaximal response (80%). However, the derivatisation of homohistamine, a homologue with weak atrial contraction rate increasing properties, partially due to β_1-stimulation ($-\log EC_{50}$ = 3.94 [23]), yields N^{α}-guanylhomohistamine [24], a weak partial H_2-agonist. Combination of the latter with **4** leads to impromidine and generates a 1000-fold increase of affinity and full agonist properties in most preparations [15]. Though impromidine reveals a better fit and 6.5-fold affinity towards the H_2-receptor than sopromidine does, the latter and its (*S*) antipode are so far the most stereoselective tools at the H_2-receptor. Obviously the steric requirements for guanidine-like H_2-agonists differ from those observed for α-branched histamine analogues, since in the latter series compounds derived from (*S*)-α-methylhistamine reveal greater affinity [5–9, 11], while sopromidine is (*R*) configurated. Nevertheless, a tautomeric process at the imidazole nucleus [25] seems to be involved, too.

The center of chirality close to the guanidine group indicates that the N^{α}-guanyl-α-methylhistamine moiety is the agonist acitivity determinating structure while the thioether substituent related to cimetidine contributes receptor affinity [26]. This hypothesis is supported by the rather low affinity ratios observed in potent chiral impromidine analogues bearing lower alkyl substituents at the chain linking guanidine and 5-methylimidazole moiety (compounds **9b–d**, Table II) [27]. α-Methylimpromidine (**9e**, Table II, pD_2 = 7.16) [27], the racemic homologue of sopromidine, is significantly more potent than *rac*-**7**. The enantiomers of **9e** seem to be promising compounds for further studies on stereoselectivity in the field of chiral impromidine analogous H_2-agonists.

It is noteworthy that at the recently described central histamine H_3-autoreceptor [28] impromidine, sopromidine and (*S*)-**7** turned out to be competitive antagonists of histamine with K_i-values of 40–60 nM [29]. On the other hand, the weak H_1- and H_2-agonist (*R*)-α-methylhistamine

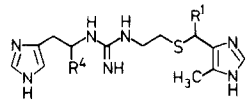
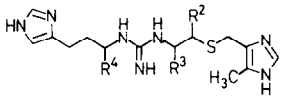
structure	compound	substituents	(R)/(S)
		R^1 R^4	
	(R)-7	H CH_3	>1000
	(S)-7		
	8a	H H	
	(R)-8b	CH_3 H	0.6
	(S)-8b		
		R^2 R^3 R^4	
	9a	H H H	
	(R)-9b	CH_3 H H	4.4
	(S)-9b		
	(R)-9c	H CH_3 H	7.2
	(S)-9c		
	(R)-9d	H C_2H_5 H	3.1
	(S)-9d		
	rac-9e	H H CH_3	

Table II. Structures of impromidine (**9a**), **8a** and related chiral guanidines (**8b**, **9b–e**). (*R*)/(*S*): affinity ratio of **7–9** at the H_2-receptor of the guinea-pig atrium [10, 27].

((*R*)-**3c**) is so far the most potent and stereoselective H_3-agonist with 15-fold and 120-fold activity compared with histamine and (*S*)-**3c**, respectively. Apparently the high degree of stereoselectivity towards impromidine-like chiral guanidines revealed by the atrial H_2-receptor is not observed for the H_3-receptor, since the slight difference between sopromidine and (*S*)-**7** is not statistically significant [29].

Experimental protocols

Chemistry

Melting points (uncorrected) were determined on a Büchi melting point apparatus according to Dr. Tottoli. ^{1}H NMR spectra were recorded on a Bruker WM 250; chemical shifts (δ [ppm]) are relative to TMS. Optical rotations were measured using a Perkin–Elmer 241 MC. Analyses indicated by elemental symbols were within ± 0.4% of the theoretical values and were done by the microanalytical laboratory of the Institute of Organic Chemistry, Johannes Gutenberg-Universität, Mainz.

S-Methyl-N-{2-[(5-methyl-4-imidazolyl)methylthio]ethyl}isothiouronium iodide **6**

a) N-Benzoyl-N'-{2-[(5-methyl-4-imidazolyl)methylthio]ethyl}thiourea **5a**. To a solution of 0.2 mol **4**, prepared from the dihydrochloride [17], in 500 ml of $CHCl_3$ a solution of 0.2 mol benzoyl isothiocyanate in 100 ml of $CHCl_3$ is added. After 30 min of stirring at room temperature the mixture is refluxed for 30 min, followed by removal of the solvent *in vacuo*. The oily residue is dissolved in *i*-PrOH and poured into water. The crude precipitate is recrystallized from MeOH. Yield 83%, mp: 160–163°C (165–166 [17]). Anal. $C_{15}H_{18}N_4OS_2$ (C,H,N).

b) N-{2-[(5-Methyl-4-imidazolyl)methylthio]ethyl}thiourea **5b**. 0.15 mol **5a**, dissolved in 100 ml of MeOH, is added to an aqueous solution of 0.2 mol K_2CO_3 and stirred for 1 h at 60°C. The resulting solution is acidified (pH = 1) with aqueous HCl, benzoic acid removed with ether, the aqueous pase adjusted to pH = 9, evaporated to dryness *in vacuo* and the oily residue crystallized from EtOH. Yield 70%, mp: 111–114°C (110–112 [17]). Anal. $C_8H_{14}N_4S_2$ (C,H,N).

c) S-Methyl-N-{2-[(5-methyl-4-imidazolyl)methylthio]ethyl}isothiouronium iodide **6**. 0.11 mol MeI is added to 0.1 mol **5b** in 100 ml of EtOH and stirred for 12 h at room temperature. The crystallization of **6** starts spontaneously and is completed after 12 h at 4°C. Yield 75%, mp: 150–151°C (128–131 [18]). Anal. $C_9H_{16}N_4S_2 \cdot HI$ (C,H,N,S).

(R)-(−)- and (S)-(+)-3-[2-(4-Imidazolyl)-1-methylethyl]-1-{2-[(5-methyl-4-imidazolyl)methylthio]ethyl}guanidine meso*-tartrate (sopromidine = (R)-**7**, and (S)-**7**)*

A solution of 0.015 mol **6** and 0.015 mol (*R*)-(−)-**3c** (free base) in 30 ml of DMF and 30 ml of ether is stirred for 3 days under reduced pressure. The resulting mixture is finally heated under reflux for 2 h and evaporated to dryness *in vacuo*. The free guanidine base is obtained by ion exchange (Amberlite IRA 401). The eluate is concentrated to ≈ 50 ml and extracted continuously for 48 h ($CHCl_3$). The aqueous phase is evaporated to dryness, the residue is dissolved in absolute EtOH and (*R*)-**7** precipitated by slow addition of a solution of *meso*-tartaric acid in absolute EtOH. Yield 30%, mp: 86–95°C, $[\alpha]_D^{20} = -14.0°$ (β = 1.0 g/100 ml; H_2O). Anal. $C_{14}H_{23}N_7S \cdot 2\,C_4H_6O_6 \cdot 0.75\,C_2H_5OH \cdot H_2O$ (C,H,N).

(*S*)-**7** *meso*-tartrate is prepared by the same procedure. Yield 30%. mp: 87–98°C, $[\alpha]_D^{20} = +13.0°$ (β = 1.0 g/100 ml; H_2O). Free base of (*S*)-**7**: mp: 67–69°C, $[\alpha]_D^{20} = +26.0°$ (β = 1.0 g/100 ml; H_2O). Anal. $C_{14}H_{23}N_7S \cdot 2\,C_4H_6O_6 \cdot 0.75\,C_2H_5OH$ (C,H,N).

The presence of 2 mol *meso*-tartaric acid and 0.75 mol ethanol per mol guanidine base is confirmed by ^1H NMR (D_2O): δ = 8.62 (s; 2-H; 1.0 H), 8.5 (s; 2-H, 1.0 H), 7.31 (s; 5-H; 1.0 H), 4.36 (s; CH of *meso*-tartrate; 4.0 H), 3.95–3.80 (m; 4-CH_2-C*H*-N; 1.0 H), 3.84 (s; 4-CH_2-S; 2.0 H), 3.65 (quart; ^3J = 7 Hz; CH_3-CH_2-OH; 1.5 H), 3.35 (t; ^3J = 6 Hz; S-CH_2CH_2-N; 2.0 H), 3.09–2.89 (m; ABX-system, δ_A = 2.94, δ_B = 3.04 ppm, $\Delta\nu_{AB}$ = 23.8 Hz, J_{AB} = 15.7 Hz, J_{AX} = 8.0 Hz, J_{BX} = 5.0 Hz; 4-CH_2-CH-N; 2.0 H), 2.68 (t; ^3J = 6 Hz; S-CH_2CH$_2$-N; 2.0 H), 2.29 (s; 5-CH_3; 3.0 H), 1.29 (d; ^3J = 6.5 Hz; α-CH_3; 3.0 H), 1.18 (t; ^3J = 7 Hz; CH_3-CH$_2$-OH; 2.2 H).

Pharmacology

H_1-activity on the isolated guinea-pig ileum

Ileum strips of ≈ 3 cm from guinea-pigs (300–500 g) of either sex were placed in a 10 ml organ bath and loaded with 0.5 g (Tyrode solution gassed with carbogen, 37°C). Concentration–response curves were recorded isotonically (cumulative technique as described by [19, 20]. pD_2, pA_2 and intrinsic activity [19, 20] were calculated by adaptation to the sigmoid function $y = a \cdot (1 + e^{(-bx+c)})^{-1}$ [30]; *a,b,c* were determined by non linear regression. Calculations were performed on an HP 9845 B (programmes: Dr. K. Wegner). The effects of H_1-agonists could be antagonized by 0.1 μM diphenhydramine and were not sensitive to the presence of atropine.

H_2-activity on the spontaneously beating guinea-pig atrium

Atria from guinea-pig (300–500 g) of either sex were attached to a tissue holder, loaded with 1.0 g and placed in a 60 ml organ bath (McEwen solution [3] gassed with carbogen, 32.5°C). After 30–40 min of equilibration concentration–response curves were recorded isometrically (cumulative technique) as described by [19, 20]. pD_2, pA_2 and intrinsic activity [19, 20] were calculated as described above. The effect of H_2-agonists could be antagonized by 1 μM cimetidine and was not sensitive to the presence of 0.3 μM propranolol. For H_2-blockers competitive antagonism was observed. Schild plot slopes were not significantly different from unity.

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