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N^{α} -ALKYLATED DERIVATIVES OF 2-PHENYLHISTAMINES: SYNTHESIS AND IN VITRO ACTIVITY OF POTENT HISTAMINE H₁-RECEPTOR AGONISTS

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Abstract. New potent N^{α} -alkylated histamine H₁-receptor agonists have been prepared and functionally evaluated for partial agonist potency and selectivity. N^{α} -Methyl-2-(3-trifluoromethylphenyl)histamine contracts ileal segments and aortic rings of guinea-pig with a relative potency of 174% (95% confid. lim. 161 - 188%) and 217% (164 - 287%), respectively (histamine: 100%) and is the most potent H₁ receptor agonist described so far. © 1998 Elsevier Science Ltd. All rights reserved.

During the last two decades numerous histamine H₁-receptor mediated effects have been described¹ which emphasize the important physiological and pathophysiological role of histamine. For example, histamine acting through H1-receptors is effective as an endogenous anticonvulsant,² increases wakefulness,³ inhibits appetite,⁴ modulates pain,^{5,6} and regulates intestinal transit.⁷ Additionally, H₁-receptor stimulatory properties of histamine are responsible for cardiovascular parameters such as blood pressure,⁸ inotropic effects,⁹ and occurrence of coronary spasms.¹⁰ Research in the above-mentioned fields has always been hampered by the lack of highly potent and subtype-selective H₁-receptor agonists. Since the discovery of the class of 2-substituted histamines¹¹ by *Dziuron* and *Schunack* in 1975,¹² several derivatives with improved potency and selectivity, predominantly meta-substituted 2-phenylhistamine derivatives have been synthesized.^{13,14} The most prominent members of this series, 2-(3-chlorophenyl)histamine, 2-(3-trifluoromethylphenyl)histamine (6) and 2-(3bromophenyl)histamine (7) are full agonists and at least equipotent with histamine in the guinea-pig ileum assay (96%, 128%, and 112% relative potency vs. 100% for histamine)¹⁴ whereas they display partial agonist activity in the isolated guinea-pig aorta and other preparations.¹³⁻¹⁶ Guided by the finding of *Hepp* and *Schunack*¹⁷ that in a series of N^{α} -substituted 2-methylhistamines, di- and mono-methylated congeners maintained H₁-receptor agonist potency or even possessed threefold activity compared with the primary amine, we intended to synthesize a new series of secondary and tertiary amines derived from 6 and 7. The aim of the present study was to develop more potent analogues in order to acquire additional information about structure-activity relationships of histamine-type H₁-receptor agonists.

Scheme 1 outlines the general synthetic approach used to prepare N^{α} -substituted 2-phenylhistamines. Cyclization of benzimidates 1 and 2 with 2-oxobutane-1,4-diol (3) in liquid ammonia afforded imidazole ethanols 4 and 5. Imidates 1 and 2 were obtained by acid-catalyzed addition of methanol to the respective benzonitriles.¹⁸ Diol 3 was prepared by mercury(II)-catalyzed addition of water to butine-1,4-diol.¹⁹ Imidazole ethanols 4 and 5 were converted to chloroethanes which yielded N^{α} -substituted 2-phenylhistamines 8 - 13 upon treatment with excess amine. The target compounds were characterized as dihydrogen oxalates (Table 1). The synthesis of primary amines 6 and 7 has been reported elsewhere.¹⁴

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Experimental conditions: (a) liq. NH₃ (6 - 8 bar, ambient temp., 12 h; then 25 - 27 bar, 60 °C, 6 h), column chromatography (silica gel, CH₂Cl₂/MeOH/triethylamine 90+9+1), yield 77% ($R^3 = CF_3$), 16% ($R^3 = Br$); (b) SOCl₂, Δ , 4 h, column chromatography (silica gel, CH₂Cl₂/MeOH 9+1), yield 36% ($R^3 = CF_3$), 74% ($R^3 = Br$); (c) excess NHR¹R², aqu. EtOH (90/10), KI, K₂CO₃, Δ , 4 - 6 h, rotatory chromatography (silica gel containing gypsum, CH₂Cl₂/MeOH 9+1, NH₃-saturated), excess oxalic acid (crystallization from EtOH/Et₂O). For yields and mp see Table 1.

Table 1. Physico-chemical data of dihydrogen oxalates of substituted histamine derivatives 8 - 13.^a

| compound | I R ¹ | R ² | R ³ | mp [°C] (decomp.) | yield [%] | formula | mol. mass | m/z [M+H ⁺] |
|----------|--|-----------------|-----------------|----------------------|--------------|--|--------------|-------------------------|
| 8 | CH ₃ | Н | CF ₃ | 202 - 204 | 50 | $C_{13}H_{14}F_{3}N_{3} \cdot 2 C_{2}H_{2}O_{4}$ | 449.3 | 270 |
| 9 | CH ₃ | CH_3 | CF ₃ | 204 - 206 | 47 | $C_{14}H_{16}F_3N_3 \cdot 2 C_2H_2O_4$ | 451.4 | 284 |
| 10 | C_2H_5 | Н | CF ₃ | 223 - 225 | 52 | $C_{14}H_{16}F_3N_3 \bullet 2\ C_2H_2O_4$ | 451.4 | 284 |
| 11 | c-C ₃ H ₅ ^b | Н | CF ₃ | 200 - 201 | 50 | $C_{15}H_{16}F_3N_3 \cdot 2 C_2H_2O_4$ | 475.4 | 296 |
| 12 | CH ₃ | н | Br | 206 - 207 | 19 | $C_{12}H_{14}BrN_3 \cdot 2 C_2H_2O_4$ | 460.2 | 280, 282 |
| 13 | CH ₃ | CH ₃ | Br | 200 - 204 | 16 | $C_{13}H_{16}BrN_3 \cdot 2 C_2H_2O_4$ | 474.3 | 294, 296 |

^a For structure see Scheme 1. All compounds gave satisfactory elemental analyses (C, H, N within $\pm 0.4\%$ of theoretical values), IR (KBr), ⁺FAB (Xe, DMSO/glycerol) and ¹H-NMR spectra (see note 21 for 8 and 12). ^b Cyclopropyl.

Phenylhistamines 6 - 13 were studied functionally for interaction with H_1 -receptors of guinea-pig ileum and aorta (Table 2 and 3), and with H_2 -, H_3 - and cholinergic M_3 -receptors of guinea-pig, respectively (Table 3). The most potent derivative (8) was also examined with regard to selectivity vs. other neurotransmitter receptors in functional assays (Figure 1). All histamine analogues exhibited partial H_1 -receptor agonism in the guinea-pig ileum preparation. Vasoconstrictory properties were observed when the more potent compounds (6 - 9, 12, 13) were studied on the endothelium denuded guinea-pig aorta (Figure 2). All contractile effects were antagonized by nanomolar concentrations of mepyramine, a selective and competitive H₁-receptor antagonist. The fact that for all agonists studied, pA₂ values for mepyramine close to 9.0 were calculated in both assays, conclusively shows that a pure H₁-receptor-mediated mechanism is involved. Furthermore, the concentration-effect curve of histamine was shifted to the right in a concentration-dependent manner, when partial agonists were incubated as competitors for histamine at the H_1 -receptor site (Figure 3). This dextral shift allowed the calculation of micromolar affinity values (pKp) for 6 - 13 in the ileum assay due to the existence of a high amount of spare receptors in this preparation.²⁰ In radioligand binding studies, similar pK_i values for 6 and 7 have been determined in guinea-pig cerebellar membranes (5.92 and 6.10).¹⁴ The lower pEC₅₀ value for the full agonist histamine (5.92 vs. 6.70) as well as the diminished relative maximum effects of partial agonists in the aorta preparation compared with the ileum model reflect the less efficient coupling of the aortic H1-receptor to intracellular signal transduction.

| | | | | agonism ^b | | | affinityc | mepyramine antagonism ^d | |
|------------|-----------------------------------|--------|-----------------|----------------------|-----------------------|--------------------------|----------------------------|------------------------------------|------------------------------------|
| no | \mathbf{R}^1 | R^2 | R ³ | $E_{\max} \pm SE$ | rel. pot. (95% c. l.) | | 95% c. l.) $pK_P \pm SE^e$ | | $E_{\text{max}} \pm SE^{\text{f}}$ |
| his | tamine | _ | | 100 | 100 | - | - | 9.07 ± 0.03^{g} | 100 |
| 6 h | н | Н | CF_3 | 100 | 128 | (120 - 136) ⁱ | 6.23 ± 0.07 | 9.05 ± 0.05^{g} | 97/80/65j |
| 7 h | Н | Н | Br | 100 | 112 | (95 - 133) | 5.97 ± 0.07 | 9.13 ± 0.03^{g} | 97 - 61 ^k |
| 8 | CH ₃ | Н | CF ₃ | 97 ± 1 | 174 | (161 - 188) ⁱ | 6.47 ± 0.04 | 9.04 ± 0.06 | 77 ± 2 |
| 9 | CH ₃ | CH_3 | CF ₃ | 88 ± 2 | 95 | (80 - 111) | 6.39 ± 0.05 | 8.92 ± 0.08 | 67 ± 3 |
| 10 | C_2H_5 | Н | CF ₃ | 63 ± 3 | 30 | (26 - 35) | 5.68 ± 0.05 | 8.98 ± 0.11 | 40 ± 7 |
| 11 | c-C ₃ H ₅ l | Н | CF_3 | 36 ± 2 | 28 | (22 - 35) | 6.12 ± 0.03 | 9.13 ± 0.11 | 20 ± 2 |
| 12 | CH ₃ | Н | Br | 95 ± 1 | 109 | (92 - 128) | 6.17 ± 0.08 | 9.13 ± 0.09 | 71 ± 6 |
| 13 | CH ₃ | CH_3 | Br | 81 ± 3 | 87 | (60 - 126) | 6.20 ± 0.07 | 9.15 ± 0.18 | 58 ± 4 |

Table 2. Interaction of compounds 6 - 13 with histamine H₁-receptors of guinea-pig ileum.^a

^a Experimental conditions: whole segments (1.5 cm), preload 5 mN, isotonic registration, *Tyrode* solution with 0.1 μ M atropine (37 °C), 3 priming doses of histamine (1 + 10 μ M), first cumulative curve for histamine (0.01 - 30 μ M), 10 min after washout second curve for partial agonist, finally third curve for histamine in the presence of partial agonist (determination of pK_P value). ^b n = 7 - 21. ^c n = 6 - 9 (for 8 see Figure 3). Partial agonist conc. was 30 μ M (6, 7, 11) or 100 μ M (9, 10, 12, 13). Incubation time 10 min except for 10 (2 min) and 11 (1 min) to avoid a complete breakdown of the contractility of the preparations. ^d Incubation time 10 min. Mepyramine conc. 1 (10, 11, n = 4), 3 (9, 12, 13, n = 4), 10 (8, n = 5), 0.3 - 100 (histamine , n = 29), 1 - 100 (6, n = 21), and 1 - 300 nM (7, n = 24). ^e Negative logarithm of the dissociation constant of the receptor/partial agonist complex. ²⁰ ^f E_{max} of (partial) agonist in the presence of mepyramine. ^g pA₂ from *Schild* plot²² constrained to unity. ^h Data for agonism from ref. 14. ⁱ More potent than histamine (P < 0.001). ^j For 1, 10, and 100 nM mepyramine. ^k For 1 - 300 nM mepyramine. ¹ Cyclopropyl.

Table 3. Interaction of compounds 6 - 13 with histamine (H1-H3) and M3-acetylcholine receptors of guinea-pig.

| | | | H ₁ (aorta) ^a | H_2^b | H ₃ c | \mathbf{M}_{3}^{d} | | |
|------------|-------------------|---|-------------------------------------|------------------------------------|-----------------------|-------------------------------|----------------------------|----------------------------|
| - | a | lgonism ^e | | mepyramine antagonism ^f | | (atrium) pD'2 ^h | (ileum) pA ₂ | (ileum) pA ₂ |
| no. | $E_{\max} \pm SE$ | $E_{\text{max}} \pm SE$ rel. pot. (95% c. l.) | | $pA_2 \pm SE$ | $E_{\max} \pm SE^{g}$ | | | |
| hist. | 100 | 100 | - | 9.11 ± 0.02^{i} | 100 | - | - | n. d. |
| 6 i | 80 ± 3 | 94 | (77 - 114) | 9.01 ± 0.04^{i} | | 3.48 | 5.21 | 3.97 |
| 7 j | 64 ± 1 | 48 | (41 - 56) | 8.90 ± 0.04 | | 3.37 | 5.20 | 3.81 |
| 8 | 59 ± 4 | 217 | (164 - 287) ^k | 9.08 ± 0.14 | 66 ± 3 | 4.04 | 5.36 | 3.94 |
| 9 | 54 ± 5 | 169 | (130 - 221) ^k | 8.85 ± 0.04 | 64 ± 4 | 4.56 | 5.95 | 4.57 |
| 10 | n. d. | n. d. | | n. d. | n. d. | 4.55 | 5.63 | 4.16 |
| 11 | n. d. | n. d. | | n. d. | n. d. | 4.36 | n. d. | n. d. |
| 12 | 76 ± 2 | 43 | (26 - 70) | 9.01 ± 0.03 | 75 ± 6 | 3.86 ¹ | 4.93 | 3.95 |
| 13 | 58 ± 4 | 31 | (23 - 43) | 8.94 ± 0.16 | 49 ± 6 | 4.74 | 5.84 | 4.19 |

n. d. not determined. ^a Conditions:¹⁴ Endothelium-denuded aortic segments (3 - 4 mm), initial tension 10 mN, isometric registration, modified *Krebs* solution (37 °C), 3 priming doses of histamine (10 μ M), first cumulative curve for histamine (0.1 - 300 μ M), 30 min after washout second curve for partial agonist in the absence or presence of mepyramine. ^b See ref. 23 (n = 2 - 3, range ±0.05 - ±0.23, 20 - 300 μ M in the presence of 0.3 μ M mepyramine). ^c See ref. 24 (n = 5 - 6, SE 0.04 - 0.12, 15.8 - 50 μ M in the presence of 2 μ M mepyramine). ^d See ref. 25 (n = 4 - 8, SE 0.05 - 0.15, 30 - 100 μ M in the presence of 1 μ M mepyramine). ^e n = 7 - 19. ^f Incubation time 30 min. Mepyramine conc. 1 - 1000 (histamine, n = 34), 2 - 50 (6, n = 12), 3 (7, n = 8), and 5 nM (8, 9, 12, 13, n = 4). ^g E_{max} of (partial) agonist in the presence of mepyramine. For 6, 7 see ref. 14. ^h For pD'₂ see ref. 26. ⁱ pA_2 from Schild plot²² constrained to unity. ^j Data for H₁, H₂, and M₃ activity from ref. 14. ^k More potent than histamine (P < 0.001 (8) and P < 0.01 (9)). ¹ Transient positive ino-tropic and chronotropic effect ($EC_{50} ca$. 10 μ M, $E_{max} = 27 - 39\%$ of histamine) but not sensitive to cimetidine (30 μ M).

Figure 1. Functional *in-vitro* selectivity of 8 was determined on guinea-pig right atrium (H₂, β_1), 23 ileum (H₃, 24 M₃, 25 5-HT₃²⁷), and iliac artery (5-HT_{1B}), 28 and on rat aorta (α_{1D}), 25 tail artery (5-HT_{2A}), 25 and oesophagus (5-HT₄), 27 respectively. Compound 8 displayed no agonist effects at all except on histamine H₁-receptors. Similar antagonist activity patterns have been obtained for 6 and 7.¹⁴







Figure 2. Partial H₁-receptor agonist activity of 8 (\oplus , n = 7, $E_{max} = 62 \pm 4$ % of first histamine curve) and 9 (Δ , n = 8, 58 \pm 5 %) on the endothelium-denuded guinea-pig aorta, compared with histamine controls (\Box , n = 8, 105 \pm 1 %). Only second curves are shown. The contractile effect of 8 was antagonized by 5 nM mepyramine (\bigcirc , n = 4, 69 \pm 4 %) yielding a pA₂ of 9.08 \pm 0.14. For further data see Table 3. Error bars indicate *SE* of the arithmetic mean.

Figure 3. Determination of H₁-receptor affinity of **8** on the guinea-pig ileum. Contractions elicited by 1, 3, 10, 30, and 100 μ M **8** (84 ± 3, 92 ± 1, 95 ± 2, 98 ± 1, 96 ± 1 %, open symbols) faded to 44 ± 2, 48 ± 3, 42 ± 6, 49 ± 2, 46 ± 4 % (closed symbols) within 10 min. Afterwards, without washing, histamine concentration-effect curves in the presence of 1 (\bullet , n = 5), 3 (\blacksquare , n = 4), 10 (\blacktriangle , n = 5), 30 (\blacktriangledown , n = 10), and 100 μ M **8** (\bullet , n = 5) were shifted to the right compared with the first histamine curve (open hexagons). All curves were normalized to 100% histamine response. *Inset: Kaumann-Marano* plot for the calculation of partial agonist affinity (pK_P).²⁹ Data were approximated by a straight line of unity slope ($m = 0.94 \pm 0.06$, not significantly different from 1 (P > 0.20)) and yielded pK_P = 6.47 ± 0.04 (95% confidence limits 6.39 - 6.55, n = 29).

Considering the results of both H₁-receptor assays allows to conclude that the *meta*-trifluoromethyl substitution is more favourable for agonist potency than *meta*-bromo (Table 2 and 3). This fact is also reflected by the higher affinity values measured on the ileum ($pK_P 6.23 - 6.47 vs. 5.97 - 6.20$, Table 2). While brominated

phenylhistamines 7, 12, and 13 are equipotent with histamine on the ileum, their counterparts in the trifluoromethyl series exceed histamine in potency, except 9 on the ileum, and 6 on the aorta preparation, respectively. With regard to the degree of amine nitrogen substitution, the rank order of potency is *secondary* > *tertiary* > *primary* amine in either assay for trifluoromethyl derivatives 6, 8, and 9 while brominated agonists 7, 12, and 13 are equipotent in both *in-vitro* systems. Potency and intrinsic activity of the secondary amine 8 are attenuated when the methyl substituent is replaced by more space-demanding groups such as ethyl (10) or cyclopropyl (11), indicating that the fit of bulkier side-chain residues may be sterically hindered. This trend is in agreement with data for N^{α} -substituted histamines.¹⁷ As far as intrinsic activity (E_{max}) is concerned, CF₃- and Br-substituted derivatives display the same rank order (*primary* > *secondary* > *tertiary* amine) on the ileal preparation while their rank orders differ in the vascular system.

The search for potent and selective histamine H₁-receptor agonists has been a quite fruitless task for several decades. With the advent of 2-phenylhistamines¹²⁻¹⁴ compounds have been devised that are nearly *as potent as* or at least *equipotent with* the biogenic amine, *vic.* 6.¹⁴ The present *in-vitro* study conclusively demonstrates that the secondary amine 8 (N^{α} -methyl-2-(3-trifluoromethylphenyl)histamine) is the most potent histamine H₁-receptor agonist reported so far in the literature. The H₁-receptor agonist potency of 8 is about 200% compared with histamine while the compound is devoid of agonist properties on several neurotransmitter receptor subtypes including histamine H₂- and H₃-receptors. The antagonist activity at these sites is negligible, or moderate in some cases (Figure 1). Therefore, 8 may become an attractive tool for research into physiology and pathophysiology of histamine H₁-receptor-mediated functions.

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- 21. ¹H-NMR (DMSO- d_6) for compound **8** (salt): δ [ppm] 8.79 (broad, exchangeable with D₂O, 2 H, NH₂⁺), 8.26 (s, 1 H, ph-2-H), 8.22 (dd, ³J = 4 Hz, 1 H, ph-5-H), 7.69 (2 d, ³J = 4 Hz, 2 H, ph-4-H, ph-6-H), 7.14 (s, 1 H, imi-5-H), 3.21 (t, ³J = 7.5 Hz, 2 H, CH₂CH₂NH₂⁺CH₃), 2.91 (t, ³J = 7.5 Hz, 2 H, CH₂CH₂NH₂⁺CH₃), 2.62 (s, 3 H, CH₃); for compound **12** (salt): δ [ppm] 8.81 (broad, exchangeable with D₂O, 2 H, NH₂⁺), 8.18 (s, 1 H, ph-2-H), 7.99 (d, ³J = 8 Hz, 1 H, ph-6-H), 7.59 (d, ³J = 8 Hz, 1 H, 1 ph-4-H), 7.47 (dd, ³J = 8 Hz, 1 H, ph-5-H), 7.17 (s, 1 H, imi-5-H), 3.27 (t, ³J = 7.4 Hz, 2 H, CH₂CH₂NH₂⁺CH₃), 2.96 (t, ³J = 7.4 Hz, 2 H, CH₂CH₂NH₂⁺CH₃), 2.69 (s, 3 H, CH₃).
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