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Synthesis and pharmacological investigation of some novel 2-methyl-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones as histamine H_1-receptor blockers

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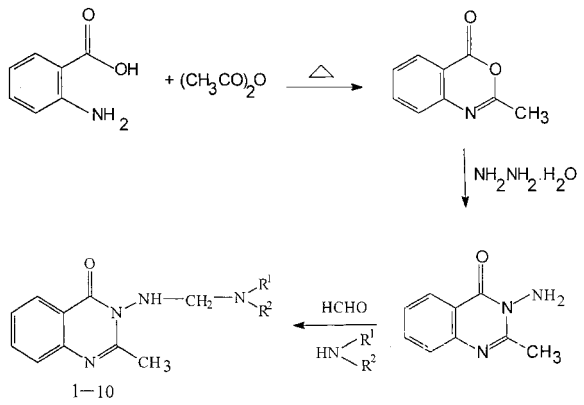
A series of 2-methyl-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones were synthesized from 3-amino-2-methyl-(3*H*)-quinazolin-4-one. Their structures were confirmed by spectral data (IR, NMR and MS) and the purity was ascertained by microanalysis. When tested for H_1-receptor blocking activity on isolated guinea pig ileum all the test compounds inhibited histamine induced contraction whereas compound **5** (IC_{50} 0.22 · 10^3 ng/ml) was found to be four times more potent than chlorpheniramine maleate (IC_{50} 1 · 10^3 ng/ml) and it showed lesser sedation (8%) than the standard (32%).

1. Introduction

The first generation anti-histamines penetrate the blood brain barrier and also possess anticholinergic properties and this has led to the development of a second generation (Simons and Simons 1994) of H_1-antagonists such as terfenadine, cetirizine and astemizole, known as "non sedative antihistamines". These may also bind more selectively to the H_1-receptor and do not bind to serotonin, muscarinic or alpha adrenergic receptors (Snyder and Snowman 1987). A common feature of first generation compounds includes two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain (Ellis et al. 1985) (e.g. diphenhydramine, pheniramine), the second generation compounds (terfenadine and cetirizine) also contain many of the structural features of first generation compounds. A literature survey reveals excellent antihistaminic activity (Kottke et al. 1978; Wade 1984; West and Jully 1981) in 2,3-disubstituted quinazolones. It has been proposed that for H_1-antihistaminic activity, a compound should have the above mentioned pharmacophore (two aryl (or) hetero aryl rings linked to an aliphatic tertiary amine via the side chain). From these studies and to develop earlier reported 2-substituted-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones (Alagarsamy et al. 2000, 2002), which exhibited good antihistaminic activity, in the present study a series of 2-methyl-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones were prepared.

Scheme



2. Investigations, results and discussion

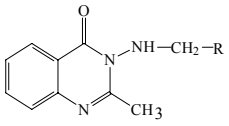
The title compounds were prepared by condensing the active hydrogen atom of the 3-amino group of 3-amino-2-methyl-(3*H*)-quinazolin-4-one with formaldehyde and appropriate amines. The starting material was synthesized as presented in the Scheme. The chemical structures of the synthesized compounds (Table 1) were confirmed by ^{1}H NMR, IR and MS data, the purity was ascertained by elemental analysis. The synthesized compounds were tested for their antihistaminic activity on isolated guinea pig ileum.

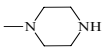
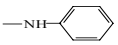
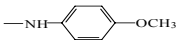
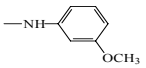
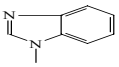
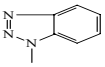
The data presented in Table 2 revealed that all the test compounds show H_1-receptor blocking activity. Compound **1** with dimethyl substitution shows good antihistaminic activity (IC_{50} 0.42 · 10^3 ng/ml); with increased lipophilicity (i.e. diethyl compound **2** and pyrrolidine compound **3**) activity was retained (IC_{50} 0.46, 0.48 · 10^3 ng/ml respectively), introduction of an oxygen atom (compound **4**) leads to a decrease in activity (IC_{50} 0.62 · 10^3 ng/ml) whereas introduction of an additional nitrogen atom gave better activity (compound **5** IC_{50} 0.22 · 10^3 ng/ml). Aryl or heteroaryl substitution decreases activity. A small alkyl side chain (methyl and ethyl) and alicyclic groups with an additional nitrogen atom (piperazine) seem to provide optimum activity.

When the title compounds were evaluated for their sedative-hypnotic activity all compounds were found to exhibit only weak sedation.

The principle aim of the present study was to modify and optimize the structural features of our earlier reported series of 2-mercapto-3-(substituted methylamino)-(3*H*)-quinazo-

Table 1: Physical and preparative data for 2-methyl-3-(substituted methylamino)-3*H*-quinazolin-4-ones



Code	R	Molecular formula	Molecular weight*	M.p. (°C)	Yield (%)
1	—$N(CH_3)_2$	$C_{12}H_{16}N_4O$	232	116	71
2	—$N(C_2H_5)_2$	$C_{14}H_{20}N_4O$	260	159	70
3		$C_{14}H_{18}N_4O$	258	215	71
4		$C_{14}H_{18}N_4O_2$	274	116	73
5		$C_{14}H_{19}N_5O$	273	139	65
6		$C_{16}H_{16}N_4O$	280	107	69
7		$C_{17}H_{18}N_4O_2$	310	115	60
8		$C_{17}H_{18}N_4O_2$	310	136	63
9		$C_{17}H_{15}N_5O$	305	101	59
10		$C_{16}H_{14}N_6O$	306	128	67

+ All Compounds gave satisfactory elemental analysis (± 0.4% of theoretical values)
* Molecular weight determination by mass spectra

Table 2: Antihistaminic and sedative-hypnotic activities of compounds 1–10

Compound	IC_{50} (ng/ml)	Percent CNS depression		
		30 min	1 h	2 h
1	$0.42 \cdot 10^3 \pm 1.12$*	6 ± 5.76*	7±3.81*	8 ± 3.86**
2	$0.46 \cdot 10^3 \pm 3.46$*	8 ± 6.17**	13 ± 5.13*	14 ± 3.38***
3	$0.48 \cdot 10^3 \pm 2.41$**	5 ± 3.63*	10 ± 6.18**	14 ± 3.19*
4	$0.62 \cdot 10^3 \pm 1.17$**	5 ± 5.13**	7 ± 4.33***	10 ± 6.39**
5	$0.22 \cdot 10^3 \pm 2.67$***	5 ± 4.43**	9 ± 3.18**	10 ± 2.16*
6	$1.24 \cdot 10^3 \pm 4.26$*	7 ± 1.44**	12 ± 2.36**	11 ± 1.18***
7	$1.12 \cdot 10^3 \pm 2.39$**	5 ± 3.92***	11 ± 4.14**	12 ± 4.12**
8	$1.64 \cdot 10^3 \pm 1.19$*	10 ± 1.36**	13 ± 3.24**	14 ± 3.17*
9	$1.46 \cdot 10^3 \pm 4.17$**	9 ± 4.14*	11 ± 1.15**	12 ± 3.95**
10	$1.22 \cdot 10^3 \pm 6.13$*	6 ± 4.14**	10 ± 3.41**	12 ± 4.5*
Chlorpheniramine maleate	$1 \cdot 10^3 \pm 3.16$*	25 ± 1.19***	33 ± 5.36*	39 ± 2.19*

Each value represents the mean ± SEM (n = 6). Significance levels * $p < 0.5$, ** $p < 0.01$ and *** $p < 0.001$ as compared with the respective control

lin-4-ones (Alagarsamy et al. 2000), which has shown good antihistaminic activity and is associated with CNS depression (15–20%). When the mercapto group (which may be principally responsible for sedation) in the C-2 was substituted by phenyl, an increase in antihistaminic activity with negligible sedation was observed (Alagarsamy et al. 2002). In order to further increase the antihistaminic activity the C-2 phenyl group was substituted by methyl which led to a two-fold increase in activity. Compound **5** (IC_{50} 0.22 10^3 ng/ml) was the most active (with lowest IC_{50} and sedation) and it is two-fold as potent as our earlier reported phenyl series lead molecule (IC_{50} $0.49 \cdot 10^3$ ng/ml).

3. Experimental

3.1. Chemistry

Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer-841 grating spectrometer (cm^{-1}), mass spectra on a Varian Atlas CH-7 mass spectrometer at 70 eV and NMR spectra on a Varian A-60 or EM-360 spectrometer, using TMS as internal standard. Elemental analysis was performed on Carlo Erba 1108.

3.1.1. 2-Methyl-3,1-benzoxazin-4-one

A mixture of anthranilic acid (0.01 mol) and acetic anhydride (0.1 mol) was refluxed on gentle flame for 1 h. The excess acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether and kept aside for 1 h, m.p. 182 °C; IR (KBr): 3350 (NH), 1700 (C=O) and 1640 cm^{-1} (C=N); NMR ($CDCl_3$) (δ ppm): 2.5 (s, 3 H, CH_3), 6.9–7.4 (m, 4 H, ArH); MS (m/z) 161 (M^+); Anal. ($C_9H_7NO_2$) C, H, N.

3.1.2. 3-Amino-2-methyl-(3H)-quinazolin-4-one

A mixture of 2-methyl-3,l-benzoxazin-4-one (0.01 mol) and hydrazine hydrate (0.03 mol) in ethanol was refluxed for 3 h and cooled. The separated solid was recrystallized from ethanol, m.p. 140–142 °C; IR (KBr): 3300–3260 (NH_2), 1680 (C=O), 1640 (C=N) and 1600 cm^{-1} (C=C); NMR ($CDCl_3$) (δ ppm): 2.6 (s, 3H, CH_3), 4.6 (s, 2H, NH_2), 6.6–7.2 (m, 4 H, ArH); MS (m/z) 175 (M^+); Anal. ($C_9H_9N_3O$) C, H, N.

3.1.3. 2-Methyl-3-((dimethylamino) methylamino)-(3H)-quinazolin-4-one **(1)**

To a slurry of 3-amino-2-methyl-(3*H*)-quinazolin-4-one (0.005 mol) in dimethylformamide (15 ml), a mixture of formalin (37–41%; 1 ml) and dimethylamine (0.005 mol) was added drop by drop with stirring. The reaction mixture was heated on a water bath for about 25 min. After cooling it was poured into ice-water, the solid obtained was filtered, washed with water, dried and recrystallized from ethanol, m.p. 116 °C; IR (KBr): 3280 (NH), 2860 (−CH_2), 1700 cm^{-1} (C = O); NMR ($CDCl_3$) (δ ppm): 2.3 (s, 6 H, $N(CH_3)_2$), 2.6 (s, 3 H, CH_3), 5.1 (s, 2 H, CH_2) 7.2–7.7 (m, 4 H, Ar-H), 9.0 (t, 1 H, NH); MS (m/z) 232 (M^+); Anal. ($C_{12}H_{16}N_4O$) C, H, N.
Compounds **2**–**10** were prepared similarly.

3.2. Antihistaminic activity

Antihistaminic activity of compounds **1**–**10** was determined on isolated guinea pig ileum (Mehta and Kulkarni 1983). The segments (1 cm) of ileum containing tyrode solution were suspended in an organ bath. The contractile response to histamine ($5.4 \cdot 10^{-7}$ mol/L) was measured with an isotonic transducer. Each test compound was added in the organ bath 5 min before the addition of histamine. Concentration dependent response due to histamine was recorded. After washing thoroughly with tyrode solution, concentration response curve of histamine in presence of standard, test compounds and vehicle were recorded, 6 such determinations were made for each compound. The IC_{50} of test compounds and the standard required to block the histamine induced contraction were determined (Table 2).

3.3. Sedative-hypnotic activity

Sedative-hypnotic activity was determined by measuring the reduction in motor activity, using an actophotometer (Dews 1953; Kuhn and Van Mannen 1961). Mice were chosen as test animals in a group of 6. Basal activity score was taken and then compounds **1**–**10** and standard chlorpheniramine maleate were administered intraperitoneally at a dose of 5 mg/kg. Scores were recorded at 0.5, 1 and 2 h after the drug administration. The

percent reduction in motor activity was calculated by the following formula and shown in Table 2.

% Reduction in motor activity = [(A-B)/A] × 100

Where A-basal score, B-score after drug treatment.

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