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

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A series of 2-phenyl-3-(substituted methyl amino) quinazolin-4(3*H*)-ones were synthesized from 3-amino-2-phenyl quinazolin-4(3*H*)-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 the compounds **1** (IC_{50} 0.59×10^3 ng/ml) and **5** (IC_{50} 0.49×10^3 ng/ml) were found to be two fold potent when compared to standard chlorpheniramine maleate. These compounds show less sedation (compound **1** shows 4%, compound **5** shows 7%) than the standard (33%). Hence they could serve as prototype molecules for future development.

1. Introduction

The prevalence of asthma and other allergic diseases is increasing [1–3] providing a rapidly expanding market for antiallergic drugs. The first generation antihistamines penetrate the blood brain barrier and also possess anticholinergic properties and this has led to the development of a second generation [4] of H_1-antagonists such as terfenadine, cetrizine and astemizole. They are labelled as "non sedative antihistamines" and may also bind more selectively to the H_1-receptor and do not bind to serotonin, muscarinic or alpha adrenergic receptors [5]. First generation compounds are usually characterized by two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain [6] (eg. diphenhydramine, pheniramine maleate), the second generation compounds (terfenadine and cetrizine) also contain many of the structural features of first generation compounds. A literature survey reveals reports on excellent antihistaminic activity [7–9] of 2,3-disubstituted quinazolones. It has been proposed that for H_1-anithistaminic 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). In view of these requirements a series of 2-phenyl-3-(substitutedmethyl amino) quinazolin-4(3*H*)-ones was prepared. These substituted quinazolones containing putative pharmacophore shown good antihistaminic activity.

2. Investigations, results and discussion

Compounds **1**–**10** (Table 1) were prepared as shown in the Scheme. The data presented in Table 2 revealed that all the test compounds show H_1-receptor blocking activity. Compound **1** with dimethyl substitution show good activity (IC_{50} 0.59×10^3 ng/ml), with increased lipophilicity (i.e., diethyl compound **2** and pyrrolidine compound **3**) activity decreased (IC_{50} 0.71, 1.23×10^3 ng/ml respectively), introduction of an oxygen atom (compound **4**) leads to a further decrease in activity (IC_{50} 1.41×10^3 ng/ml) whereas introduction of an additional nitrogen atom gave better activity (compound **5** IC_{50} 0.49×10^3 ng/ml). Aryl or heteroaryl substitution decreases the activity of alicyclic compounds with a small side chain (methyl) and with an additional nitrogen atom (piperazine) seems to provide optimum activity.

Scheme 1

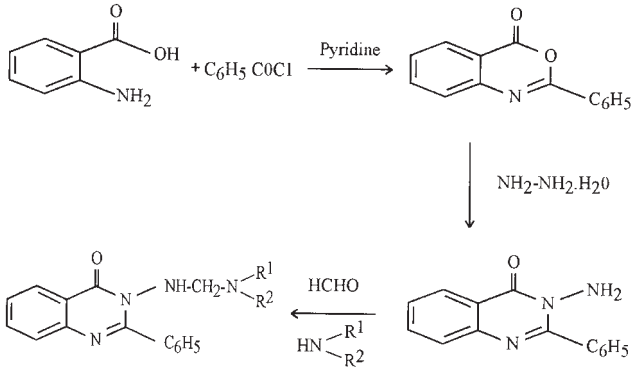
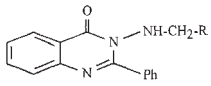
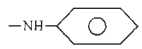
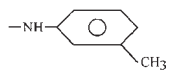
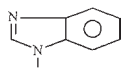
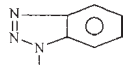


Table 1: Physical data for 2-phenyl-3-(substituted methyl amino) quinazolin-4(3*H*)-ones



Compd.	R	Mol. Formula*	Mol. Weight **	M.P. °C	% Yield
1		$C_{17}H_{18}N_4O$	294	110	70
2		$C_{19}H_{22}N_4O$	322	155	67
3		$C_{19}H_{20}N_4O$	320	195	65
4		$C_{19}H_{20}N_4O_2$	336	135	69
5		$C_{19}H_{21}N_5O$	335	120	68
6		$C_{20}H_{18}N_5O$	344	119	64
7		$C_{22}H_{20}N_4O_2$	372	100	60
8		$C_{22}H_{20}N_4O$	356	115	61
9		$C_{22}H_{17}N_5O$	367	105	60
10		$C_{21}H_{16}N_6O$	368	118	63

* All the compounds gave satisfactory elemental analysis ±0.4% of the theoretical values

** Mol. Wt. determinations by mass spectra

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

Compd.	IC_{50}(ng/ml)	Percent CNS depression		
		30 min	1st h	2nd h
1	$0.59 \times 10^3 \pm 2.14^{+}$	3.13 $\pm 2.12^{+++}$	0.5.14 $\pm 1.69^{++}$	05.11 $\pm 2.39^{+}$
2	$0.71 \times 10^3 \pm 3.13^{++}$	5.93 $\pm 2.54^{+}$	10.13 $\pm 5.53^{++}$	12.81 $\pm 5.11^{+++}$
3	$1.23 \times 10^3 \pm 4.21^{++}$	4.82 $\pm 4.10^{+}$	08.44 $\pm 3.93^{++}$	11.35 $\pm 3.11^{++}$
4	$1.41 \times 10^3 \pm 2.35^{++}$	4.15 $\pm 3.19^{++}$	06.19 $\pm 4.12^{+}$	07.45 $\pm 5.14^{+}$
5	$0.49 \times 10^3 \pm 1.80^{++}$	5.53 $\pm 5.79^{+}$	07.33 $\pm 4.75^{+}$	08.01 $\pm 6.18^{++}$
6	$1.12 \times 10^3 \pm 1.19^{++}$	4.55 $\pm 5.56^{+}$	08.11 $\pm 5.33^{++}$	09.38 $\pm 3.99^{++}$
7	$1.81 \times 10^3 \pm 1.38^{+++}$	4.48 $\pm 4.55^{+}$	0.9.14 $\pm 3.38^{++}$	10.13 $\pm 6.58^{+}$
8	$2.94 \times 10^3 \pm 4.69^{++}$	6.53 $\pm 1.11^{++}$	11.14 $\pm 1.39^{+}$	13.01 $\pm 6.31^{+}$
9	$3.77 \times 10^3 \pm 1.18^{+}$	0.4.33 $\pm 4.14^{+}$	06.19 $\pm 3.36^{++}$	07.58 $\pm 3.80^{++}$
10	$3.96 \times 10^3 \pm 2.08^{+++}$	3.18 $\pm 1.55^{++}$	07.68 $\pm 1.39^{+}$	07.77 $\pm 2.56^{++}$
Chlorphenir-amine maleate	$1 \times 10^3 \pm 2.44^{++}$	26.19 $\pm 3.13^{++}$	34.19 $\pm 2.56^{+}$	39.44 $\pm 3.55^{++}$

$^{+}$ denotes significant differences from control at $p \leq 0.05$

Of the 10 compounds tested for sedative-hypnotic activity, compounds **2**, **3**, **6**, **7**, and **8** exhibited mild activity (9–13%) less than the standard chlorpheniramine maleate whereas the compounds **1**, **4**, **5**, **9**, and **10** showed negligible activity (4–8%). It appears that compounds with a small side chain (or) cyclic structures with an additional hetero atom show a decrease in sedation due to lower lipophilicity.

The principle aim of the present study was to modify and optimize the structural features of our earlier reported series of 2-mercapto-3-(substitutedmethyl amino) quinazolin-4(3*H*)-ones [10] which has shown good antihistaminic activity but are associated with CNS depression (15–20%). In order to reduce sedation, the mercapto group (which may in principle be responsible for sedation) in the C-2 was substituted by phenyl. Compound **5** was the most active (with least IC_{50} and sedation), and could therefore serve as a lead molecule for further modification to obtain a clinically useful antihistamine.

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 were performed on Carlo erba 1108.

3.1.1. Synthesis of 2-phenyl-3,1-benzoxazin-4-one

To a solution of anthranilic acid (0.1 mol) dissolved in pyridine (60 ml), benzoyl chloride (0.2 mol) was added. The mixture was stirred for 0.5 h followed by treatment with 5% $NaHCO_3$ (15 ml). The separated solid was crystallised from ethanol (80%), m.p. 120 °C; IR (KBr): 3350 (NH), 1780 (C=O), 1680 (cyclic C=O) and 1620 (C=N) cm^{-1}; NMR ($CDCl_3$) (δ ppm): 86.8–7.5 (m, 9 H, ArH); MS (m/e) 223 (M^+).

3.1.2. Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one

A mixture of 2-phenyl-3-benzoxazin-4-one (0.05 mol) and hydrazine hydrate (0.05 ml) in ethanol was refluxed for 3 h and cooled. The separated solid was crystallized from ethanol (85%), m.p. 196 °C; IR(KBr): 3300 (NH_2), 1680 (cyclic C=O), 1620 (C=N) and 1600 (C=C) cm^{-1}; NMR ($CDCl_3$) (δ ppm): 4.5 (s, 2 H, NH_2), 6.7–7.4 (m, 9 H, ArH); MS (m/e) 237 (M^+).

3.1.3. Synthesis of 2-phenyl-3-(N,N-dimethylaminomethyl amino)quinazolin-4(3H)-one (**1**)

To a slurry of 3-amino-2-phenyl quinazolin-4(3*H*)-one (0.005 mol) in dimethyl-formamide (15 ml), a mixture of formalin (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 30 min. After cooling it was poured into ice water, the solid obtained was filtered, washed with water, dried and recrystallized from an alcohol (95%) – chloroform mixture. IR (KBr): 1690 (C=0), 2850 ($-CH_2$), 3260 (NH) cm^{-1}; NMR ($CDCl_3$) (δ ppm): 2.3 (s, 6 H, $N(CH_3)_2$), 5.1 (s, 2 H, CH_2), 7.1–7.8 (m, 9 H, Ar-H), 8.9 (t, 1 H, NH); Anal. ($C_{17}H_{18}N_40$) C, H, N. Compounds **2**–**10** were prepared similarly.

3.2. Antihistaminic activity

Antihistaminic activity of the test compounds **1**–**10** was performed on isolated guinea pig ileum [12, 13]. After washing thoroughly with tyrode solution, concentration response curves of histamine in the presence of standard, test compounds and vehicle were recorded, six determinations were made for each compound. The IC_{50} of test compounds and the standard required to block the histamine induced contraction were determined and the datas were analysed statistically by student's t-test (Table 2).

3.3. Sedative-hypnotic activity

Sedative-hypnotic activity was determined by measuring the reduction in motor activity, using an actophotometer [14, 15]. Mice were choosen as test animals in a group of 6. Basal activity score was taken and then compounds **1**–**10** and standard chlorpheniramine maleate were administered intraperitonially at the 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 the data was analysed statistically by student's t-test (Table 2).

$$\% \text{ Reduction in motor activity} = [(A - B)/A] \times 100$$

where A-Basal score, B-score after drug treatment.

References

1 Peat, J. K. : Clin. Exp. Allergy **24**, 797 (1994)
2 Bummy, P.; Chin, S.; Rona, R. J.: Brit. Med. J. **300**, 1306 (1990)
3 Naliagimi, T.; Itaya, H.; Tominga, T.; Yamaki, H.; Hisamatsu, S.; Nakagomi, O.: Lancet **343**, 121 (1994)
4 Simons, F. E. R.; Simons, K. J.: N. Engl. J. Med. **330**, 1663 (1994)
5 Snyder, S. H.; Snowman, A. M.: Ann. Allergy **59**, 4 (1994)
6 Ellis, E. F.; Adkinson, N. F.; Yungingen, J. W.; Bussc, W. W. (Eds): Allergy, Principles and practice, L. Ed., Vol. 1, P. 856, Musby – Year book, Inc., St. Louis
7 Kottke, K.; Kühmstedt, M.; Hagen, U.; Renner, H.; Schnitzler, S.: DE. Pat. 139, 715 (1978); C.A. **99**, 70757 (1983)
8 Wade, J. J.: U.S. Pat. 4, 528288 (1984); C.A. **104**, 5889 (1986)
9 West. W. R.; Jully, W. R.: EP. Pat. 34, 529 (1981); C.A. **96**, 20114 (1982)
10 Alagarsamy, V.; Prabakaran, L.; Duraimurugan, R.; Gurumurthy, G.; Bindu, P.; Arunkumar, M.; Bothiraja, C.: Acta. Pharm. Turc. **13**, 33 (2000)
11 Deshmukh, M. B.; Deshmukh, D. S.: J. Ind. Chem. Soc. **72**, 847 (1995)
12 Menta, A. K.; Kulkarni, S. K.: Arch. Int. Pharmacodyn. Therap. **264**, 187 (1983)
13 Parale, M. P.; Kulkarni, S. K.: Arch. Int. Pharmacodyn. Therap. **275**, 53 (1985)
14 Devis, P. B.: Brit. J. Pharmacol. Chemotherap. **8**, 46 (1953)
15 Kulkarni, S. K.; Dandiya, P. C.: Int. J. Med. **63**, 462 (1975)

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