Acta Pharmaceutica Turcica
XLII (1) (33-38) 2000

SYNTHESIS AND ANTIHISTAMINIC ACTIVITY OF SOME NOVEL 2-MERCAPTO-3-(SUBSTITUTEDMETHYLAMINO)QUINAZOLIN-4(3H)-ONES

V.ALAGARSAMY*, L. PRABAKARAN, R. DURAI MURUGAN, G. GURUMURTH, P. BINDU, M. ARUNKUMAR, and C.BOTHIRAJA

Medicinal Chemistry R&D Laboratory, S.B. College of Pharmacy, Sivakasi-626 130 INDIA

A series of novel 2-mercapto-3-(substituted methylamino)quinazolin-4(3H)-one have been synthesized by condensing the active hydrogen atom of 3-amino of 3-amino-2-mercaptoquinazolin-4-(3H)-one with formaldehyde and the desired amines. The compounds synthesized were screened for antihistaminic activity. While all the test compounds exhibited antihistaminic activity, the Compounds I and V were found to possess antihistaminic activity equipotent to that of standard pheniramine maleate. Sedative potentiality of the test compounds were also evaluated and was found to be lesser than the standard pheniramine maleate.

Keywords : *Quinazoline; Mannich base; Antihistaminic activity*

Introduction

Quinazoline nucleus have attracted the attention of medicinal chemists due to their wide range of biological activities as analgesic & antiinflammatory (1-3), antibacterial (4-7), antiviral (8,9), antiepileptic(10), antihypertensive (11,12) and anticancer (13) activities. Of the various quinazolines reported, the C-2 and N-3 substituted quinazolines(14-16) exhibit interesting pharmacologial activities. In spite of a large number of quinazolines that have been synthesized and studied for various pharmacologial activities, the antihistaminic activity of quinazolines is relatively unexplored (17-19). In the present study we aimed to synthesize a series of hitherto unreported 2-mercapto-3-(substituted methyl-amino) quinazolin – 4 (3H) - ones and these compounds were evaluated for their antihistaminic activity. Since sedation is the major draw back associated with most of the clinically useful antihistamines, the compounds were also evaluated for their sedative potentiality.

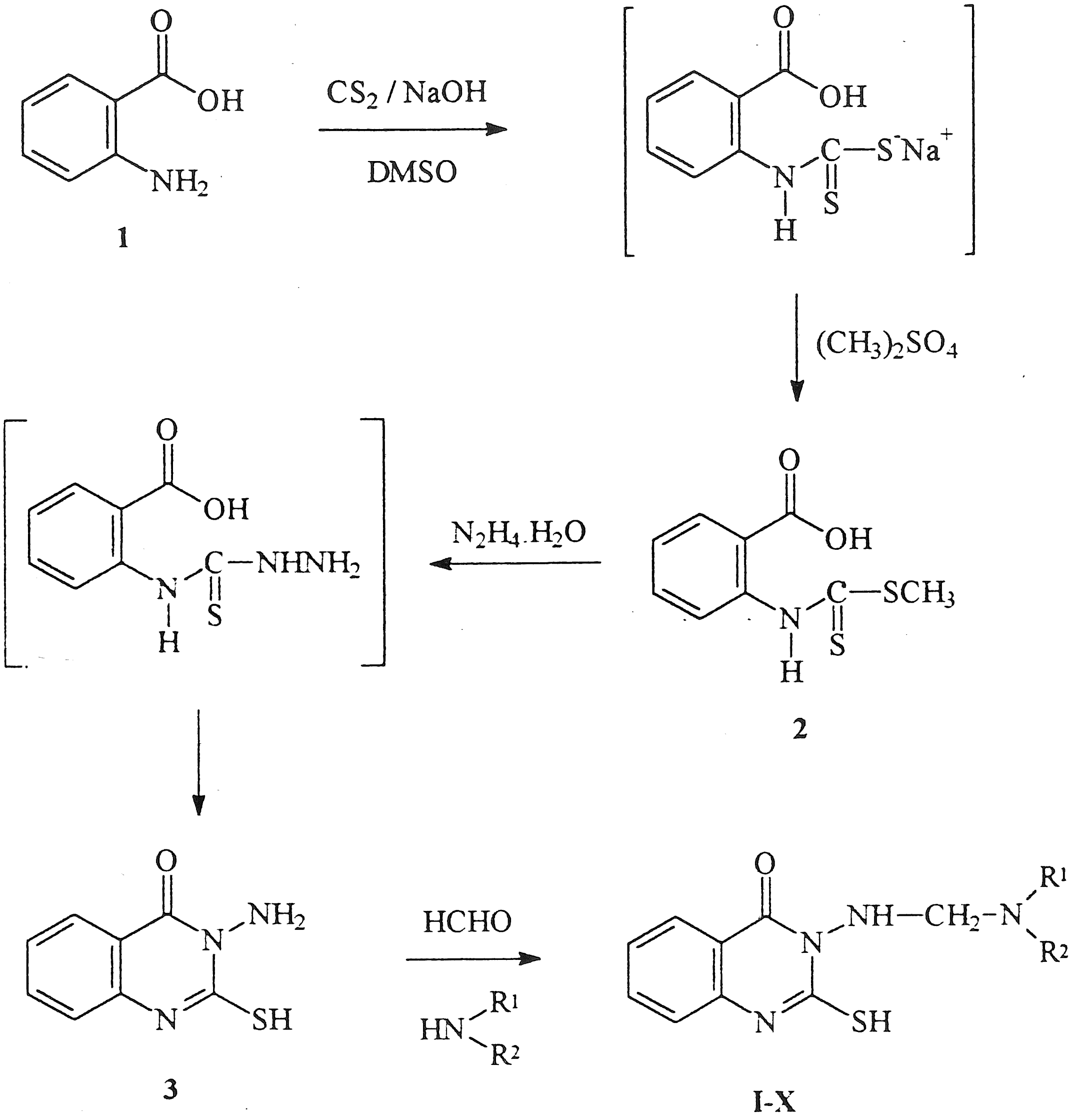
Literature survey reveals only a few reports on the synthesis of condensed 3-amino-2-mercapto pyrimidin – 4 – ones. Santagati *et al* (20) have reported the synthesis of 1, 2, 3, 4, 5, 6, 7, 8-octahydro – 3 –amino-2-mercaptobenzothieno (2,3-d) pyrimidin-4-one from the reaction of the corresponding 3-carbethoxy-2-isothiocyanatothiophene with hydrazine hydrate. However this route was not much attractive as it involves the use of a highly toxic chemical thiophosgene making it less friendly to the environment. Moreover the yield was low (40%).

Herein, a novel, simple and more ecofriendly route for the preparation of 3-amino-2-mercaptoquinazolin–4-3(H)-one (**3**) is described. This route not only curtails the use of thiophosgene but also affords the desired o-amino mercapto compound (**3**) in good yield (90%).

An alternate route reported (21) for the preparation of 3-amino-2-mercaptoquinazolin-4(3H)-ones was adopted for preparing **3**. However it yielded **3** in negligible amount (10%). Hence improvisation was carried on this method. Dimethyl sulfoxide was substituted for acetone as the reaction solvent and aq. NaOH (20 molar solution)

---

*Correspondence

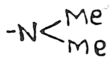
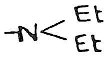
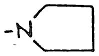
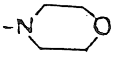
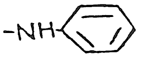
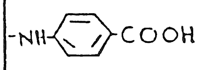
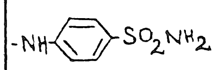
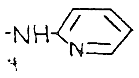
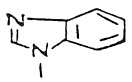


Scheme 1.

was used as the base instead of anhydrous K_2CO_3.

Anthranilic acid reacts with carbondisulphide to give dithiocarbamate salt **2a** which was methylated with dimethyl sulfate to afford the dithiocarbonate methyl ester **2b.** Compound **2b**, on reaction with hydrazine hydrate, gave the desired **3** in excellent yield and in a short reaction time (Scheme 1). The use of DMSO as the reaction solvent can enhance the rate of reaction and the use of alkali in higher concentration helped in preventing the hydrolysis of the intermediate **2a** probably due to less solvation. The target compounds, 2-mercapto-3-(substituted-methylamino)quinazolin-4(3H)-ones (**1-X**), were synthesized by condensing the active hydrogen atom of 3-amino of 3-amino-2-mercapto quinazolin-4(3H)-one with formaldehyde and the desired amines. (Mannich Reaction). All compounds (Table 1) gave satisfactory elemental analysis. IR and NMR spectra were consistant with the assigned structure.

Table 1. Physical data for 2-mercapto-3-(substitutedmethylamino)quinazolin-4(3H)-ones (**I-X**)

Compound No.	R	Molecular Formula	Molecular Weight	MP°C	Yield %	Rf Value
I	 $-N<^{Me}_{Me}$	$C_{11}H_{14}N_4OS$	250	142	75	0.33
II	 $-N<^{Et}_{Et}$	$C_{13}H_{18}N_4OS$	278	149	80	0.51
III		$C_{13}H_{16}N_4OS$	276	156	77	0.46
IV		$C_{13}H_{16}N_4O_2S$	292	146	73	0.39
V		$C_{13}H_{17}N_5OS$	291	151	80	0.49
VI		$C_{15}H_{14}N_4OS$	298	139	76	0.50
VII		$C_{16}H_{14}N_4O_3S$	342	162	79	0.58
VIII		$C_{15}H_{15}N_5O_3S_2$	377	169	77	0.61
IX		$C_{14}H_{13}N_5OS$	299	130	81	0.38
X		$C_{16}H_{13}N_5OS$	323	179	82	0.41

Materials and Methods

Melting points were taken in open capillary tubes on a Thomas Hoover melting point apparatus and were uncorrected. IR spectra were recorded in KBr on Perkin Elmer-841 Grating Spectrometer (γ max in cm^{-1}); Mass spectra on Varian Atlas CH-7 Mass Spectrometer at 70 eV and NMR spectra on Varian A-60 or EM-360 spectrometer at 60 MHZ, using TMS as internal standard.

Synthesis of 3-amino-2-mercapto quinazolin-4-3(H) one 3

To a vigorously stirred solution of anthranilic acid (2.75 g; 0.02 mole) in DMSO (10 ml) at room temperature, carbondisulphide (1.6 ml; 0.026 mole) and aqueous sodium hydroxide (1.2 ml; 20 mole) were added dropwise. After thirty minutes, dimethyl sulfate (2.5 g; 0.02 mole) was added dropwise under cooling within an ice bath. Stirring was continued for 3 hrs, then the reaction mixture was poured into water and extracted with chloroform. The solvent was removed by distillation under reduced pressure. Thus the obtained methyl-N-(2-carboxyphenyl)dithiocarbamate was used for further reaction without purification. Hydrazine hydrate (8.6 g; 0.2 mole; 80%) was added dropwise to a stirred methyl-N-(2-carboxyphenyl)dithiocarbamate in cold condition. After the completion of addition, stirring was continued for 1.5 hrs at 50°C and then the mixture was poured into ice water. The solid so obtained was filtered, washed with water, dried and recrystallised from DMF-ethanol to yield **3** as a white crystalline product.

Yield-3.4 g (90%); M.P.-236-237°C (Lit(22)-236-237); IR (KBr) 3300, 3220 (NH), 2990 (CH), 2560 (SH), 1680 (C=O); NMR- ($CDCl_3$) δ ppm-3.21 (s, 1H, $S\underline{H}$), 5.12 (s, 2H, $N\underline{H}_2$, D_2O exchangable), 7.14 (m, 4H, Ar-$\underline{H}$); Anal. ($C_8H_7N_3OS$)C, H, N.

Synthesis of 2-mercapto-3-(N,N-dimethylamino-methylamino) quinazolin-4(3H)-one(I)

To a slurry of 3-amino-2-mercaptoquinazolin-4-(3H) one 3 (0.96 g; 0.005 mole) in dimethylformamide, 15 ml of the mixture of 37% formalin (1ml) and dimethylamine, (0.23 g; 0.005 mole) was added dropwise while stirring. The reaction mixture was then warmed on a water bath by stirring for thirty minutes and poured into ice-water. The solid so formed was filtered, washed with water, dried and recrystallized from alcohol-chloroform mixture to yield 0.94 g (75%) of **I**; M.p. 142C°: IR (KBr): 3380 (NH), 3050 (C-H), 2850 (C-H), 2500 (SH), 1700 (C=O); NMR ($CDCl_3$) δ ppm: 1.9 (s, 2H, $C\underline{H}_2$), 2.1 (s, 6H, $N(C\underline{H}_3)_2$), 7.1 (m, 4H, Ar-$\underline{H}$), 8.6 (t, 1H, $N\underline{H}$) Anal. ($C_{11}H_{14}N_4OS$) C, H, N.

Compounds (**II-X**) were also prepared by the same methodology.

ANTIHISTAMINIC ACTIVITY

Antihistaminic activties of the compounds (**I-X**) were performed in isolated guinea pig ileum (23,24).

Concentration dependent response due to histamine was recorded after washing thoroughly with tyrode solution. Concentration responce curve of histamine in the presence of standard and test compounds were recorded and the minimum effective concentrations (MEC) of the test compounds and the standard (pheniramine maleate) required to block the histamine induced contraction were determined as shown in Table 2.

Table 2. Antihistaminic activity of Compounds **I-X**.

Compound No	MEC. (µg/ml)
I	0.1
II	0.2
III	0.2
IV	0.1
V	0.1
VI	0.1
VII	16
VIII	16
IX	0.1
X	0.1
Standard (Pheniramine maleate)	0.1

CNS DEPRESSANT ACTIVITY

Test for CNS depressant activity was done by measuring the reduction in motor activity using Actophotometer (25,26). Mice were chosen as test animals. Basal activity score was taken and then test compounds (**I-X**) and standard pheniramine maleate were administered intraperitoneally at the dose of 7 mg/kg. Scores were recorded at 0.5, 1 and 2 hours after drug administration. The percent reduction in motor activity was calculated by using the following formula:

Reduction in motor activity %= [(A-B)/A]x100

Where;

A= Basal score

B= Score after drug treatment

Percent reductions in motor activity of test compounds and standard are shown in Table 3.

Table 3. Percent CNS depressant activity of compounds (**I-X**)

Compound No.	30 mins	1st hr	2nd hr
I	8.18	15.14	17.26
II	7.96	13.32	20.26
III	6.02	12.12	21.56
IV	5.88	14.58	20.46
V	12.42	14.62	21.18
VI	8.21	16.12	19.42
VII	5.12	13.98	18.11
VIII	6.41	14.19	18.96
IX	7.82	13.16	19.99
X	10.66	18.68	18.51
Standard (Pheniramine maleate)	28.38	40.31	38.69

Results and Discussion

The Compound **II** with dimethylamino substitution exhibited good antihistaminic activity, when the lipophilicity was increased ie. diethylamine (Compound **II**) and pyrrolidine (Compound **III**) substitution resulted in decreased activity. Introduction of a second hetero atom leads to retaining of the potency (Compound **V**), but the addition of more hetero atom (Compound **VII** and **VIII**) lead to a decrease in activity showing that lipophilicity/hydrophilicity and molecular size should be within certain limits to get optimal antihistaminic activity.

The results of CNS depressant activity showed that, all the test compounds exhibited sedation, but lesser than the standard pheniramine maleate.

It was concluded that these classes of agents were equipment in their antihistaminic activity, but lesser sedative than standard pheniramine maleate. Hence further study is needed to increase the antihistaminic activity and eliminate the sedative potentiality in order to develop clinically useful antihistamines.

Acknowledgement

The authors are grateful to the management, S.B. College of Pharmacy, Sivakasi- 626 130, India., for providing the necessary infrastructure to carry out this research.

References

1. Nigam, R., Swarup, S., Saxena, V.K.: Indian Drugs 27(4) 238 (1990)
2. Koizomi, M., Marakuni, Y.: Japan Kokai 77, 51 (1917)
3. Hitkari, A., Bhalla, M., Saxena, A.K., Verma, M., Gupta, M.M.: Boll. Chem. Farm. 134 (11) 609 (1995)
4. Khalil, M.A., Alexandria, A.: J. Pharm. Sci. 3(2) 221 (1989)
5. Dash, B., Prasana, K.: J.Int.Chem. 55(6) 216 (1983)
6. Shiba, S.A., Kharmy, A.A.: Pharmazie 52(3) 189 (1997)
7. Jantava, S., Hudecova, D., Stankovsky, S.: Folia. Microbial.Praha. 40(6) 611 (1995)
8. Agiholri, A.K., Shukla, S.K.: Arch. Pharm. 315, 701 (1972)
9. Desai, N.C., Bhatt, J.J., Undavia, N.K.: Farmaco. 51(5) 361 (1996)
10. Manabu, H., Ryvichi, I., Hideaki, H.: Chem. Pharm. Bull. 38(3) 618 (1990)
11. Vanholltte, R.M.: J. Cardiovasc. Pharmacol. 7(7) 5105 (1985)
12. Kotto, K., Koeshmstedt, H., Konke, D., Wahlam, H., Heder, G.: Ger. Patent 31, 225 (1985)

13. Robbam, M., Cagniant Sevricourt, M., Lecomte, J.M.: J.Heterocycl. Chem. 12(3) 525 (1975)
14. Shukla, J.S., Agrawal, V.K. : Ind. J.Chem. 24 B(8) 886 (1985)
15. Kumar, P., Agrawal, J.C., Nath, C., Bhargava, K.P.: Pharmazie 36, 780 (1981)
16. Kulkarni, Y.D., Abdi, S.H.R., Sharma, V.L.: J. Ind.Chem. Soc. 61(B) 720 (984)
17. Lemura, R., Manabe, H., Saito, T.: Chem.Pharm.Bull. 30(10) 2723 (1989)
18. Anil, K., Saxena, M.: Arzenium. Forsch. 39, 35 (1992)
19. Doria, G., Romco, C., Shlerze, P., Cadelly, G.: Eur. J. Med. Chem. 23, 247 (1979)
20. Santagati, A., Santagati, M., Medica, M.: Heterocycles 36, 1315 (1993)
21. Pathak, U.S., Devani, M.B., Shishoo, C.J., Kulkarni, P.P., Rakhalia, V.M., Bhadti, V.S., Anathan, S., Dave, M.G., Shah, V.A.: Ind. J. Chem. 25B 489 (1986)
22. Cherbulies, E., Willhalm, B., Jacard, S., Rabia, S.: J.Het. Chim. Acta 50, 2563 (1967)
23. Menta, A.K., Kulkarni, S.K.: Arch. Int. Pharmacodyn. Therap. 264, 187 (1983)
24. Parale, M.P., Kulkarni, S.K.: Ibid. 275, 53 (1985)
25. Dews, P.B.: Brit.J.Pharmac. and Chemotherap. 8, 46 (1953)
26. Kulkarni, S.K., Dandiya, P.C.: Int. J. Med. 63, 462 (1975)

Accepted: 22.07.1999