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Synthesis and Biological Activity of 2-Methyl-3-(Substituted Thiocarbamido/Carbamido)-4(3H) Quinazolones

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Abstract: Several new 2-Methyl-3-(substituted thiocarbamido/cabamido)-4(3H) quinazolones were synthesized by the reaction of 2-Methyl-3-(N acyl- thiocarbamido/cabamido)-4(3H) quinazolone in methanol and substituents in the presence of 2%NaOH solution. Acetanthranil was starting material. The structures of the newly synthesized compounds were confirmed with the help of elemental and spectral studies. Some of these synthesized compounds were screened for their cardiovascular/dilatory effect with CNS depressant activities.

Keywords: CNS depressant, inflammatory, ALD, cardiovascular, SMA.

I. INTRODUCTION

Compounds having quinazolones nucleus are reported to exhibit a wide spectrum of biological activities. These derivatives also pass a variety of pharmacological properties viz. anticonvulsent5-6CNS depressant7, antibactrial8, antifungel9, neuroleptic10, hypnotic11 and analgestic12activities. In this paper we report the synthesis of quinazol-4-ones derivatives having substituted thiosemicarbazide/semicarbazide group. With these modifications we hope to prepare -4(3H) quinazolones derivatives, which have the potential or acting as drug associates cardiovascular/dilatory effect, CNS depressant activities.

II. MATERIALS AND METHODS (EXPERIMENTAL)

A. *Chemistry*

The melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC (silica gel absorbent) using iodine vapour as visualizing agent. The structures of the desired products were ascertained by IR, ^{1}H NMR spectral analytical data. IR Spectra were recorded on Perkin-Elmer-881 Spectrophotometer in KBr, ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruckner DPX-300 MHz.

B. *Synthesis*

The following steps of scheme for the synthesis of the derivatives of quinazol-4-ones, were used:

1) Synthesis of 2-Methyl -3- (thiocarbamido/carbamido) -4(3H) quinazolone [2,2']
2) Synthesis of 2-Methyl-3-(N acyl- thiocarbamido/carbamido) -4(3H) quinazolone [3,3']
3) Synthesis of 2-Methyl-3-(substituted thiocarbamido/carbamido) -4(3H) quinazolones [4,4']

2-Methyl-3-(1,4-benzoxazone) called acetanthranil was obtained essentially by the method of David *et al.*[13]

C. *2-methyl-3-(thiocarbamido)-4(3H)quinazolone- 2*

A mixture of compound **1** [2-Methyl-3-(1,4-benzoxazone)] (0.075 mole, 12.08 gms) and thiosemicarbazide (0.075 mole, 6.83 gms) in methanol (60 ml) was refluxed on water-bath for about 10 hours, concentrated, cooled, powered onto crushed ice, filtered and recrystallised from ethanol water.

m.p.l65°C, yield 60% (Found C, 51.09; H, 4.12; N, 23.4 Calcd. For .$C_{10}H_{10}ON_4S$,C 51.26; H, 4.30; N, 23.91%)

IR(KBr) : 3160 (N–H), 3025 (C–H aromatic), 2920 (C–H aliphatic), 1150, 1595, 1570, 1440 (Ar–H) , 1620 (C=N), 1660 (C=O), 3250 (NH), 1600 (C=C) of aromatic ring, 1180 cm^{-1} (C=S).

^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar-H), 7.5 (q, 1H, CH–Ar), 7.9 (d, 1H, CH–Ar), 2.0 (s, 3H, NH).

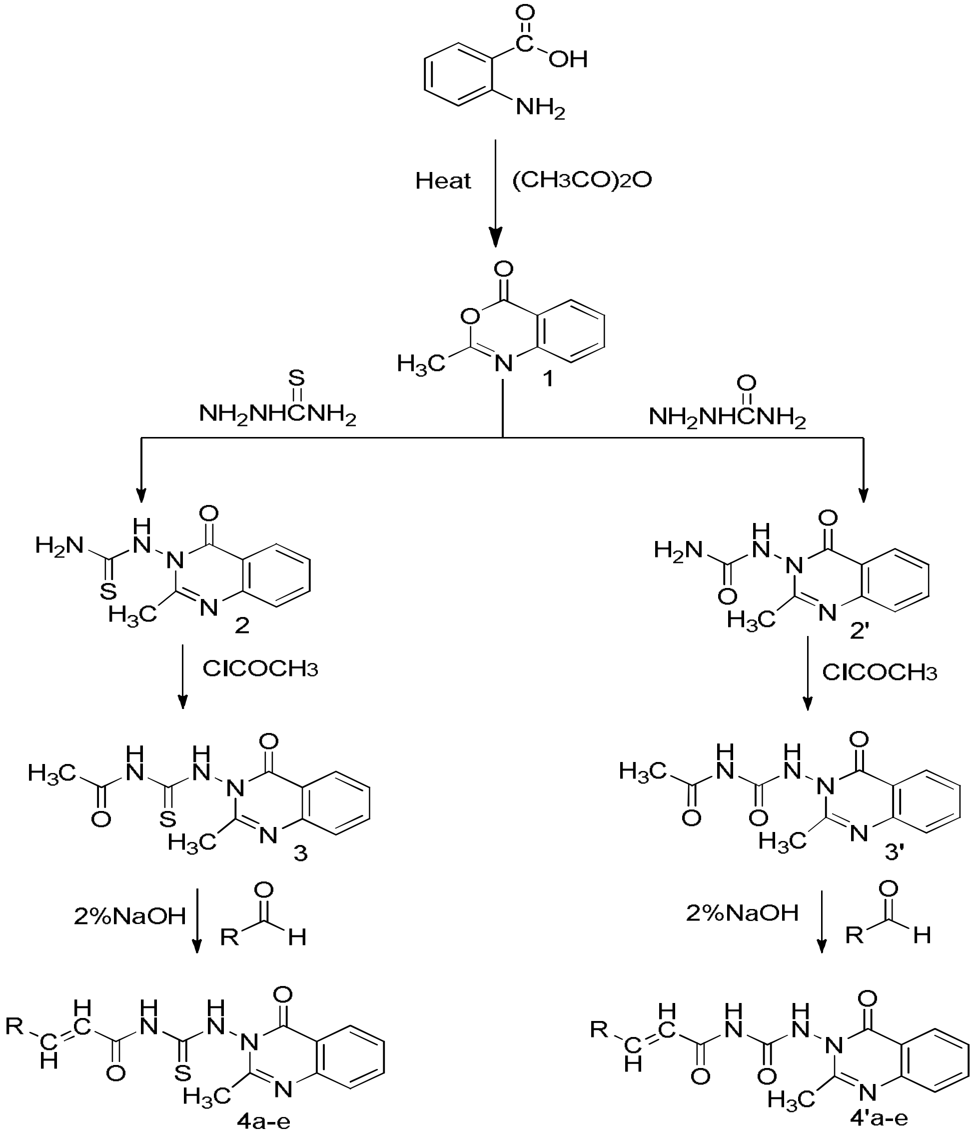
D. *2-methyl-3-(carbamido)-4(3H) quinazolone-2'*

A mixture of compound **1** [2-Methyl-3-(1,4-benzoxazone)] (0.075 mole, 12.08 gms) and semi carbazide (0.075 mole, 8.36 gms) in methanol (60 ml) was refluxed on water-bath for about 10 hrs., concentrated, cooled, powered onto crushed ice, filtered and recrystallised from ethanol water.

m.p. 160°C, yield 62% (Found C, 54.5; H, 4.09; N, 24.9 Calcd. for $C_{10}H_{10}O_2N_4$C, 55.04; H, 4.61; N, 25.67%).

IR(KBr): 3160 (N-H), 3025 (C-H aromatic), 2920 (C-H aliphatic), 1150, 1595, 1570, 1440 (Ar-H), 1620 (C=N), 1660 (C=O), 3250 (NH), 1600 cm^{-1} (C=C) of aromatic ring.

^{1}H NMR($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar–H), 7.5 (q, 1H, Ar–H), 7.9 (d, 1H, CH–Ar), 6.0 (s, 3H, NH).



SCHEME

E. 2-methyl-3-(N acyl-thiocarbamido) - 4(3H)quinazolone- 3

A solution of acetyl chloride (0.02 mole, 1.5 ml) in dry chloroform (20 ml) was added drop wise at 0-5°C temperature to the vigorously stirred solution of 2-methyl-3-(thiocarbamido)- 4(3H)quinazolone- **2** (0.02 mole, 4.68) in dry chloroform (50 ml).

The reaction mixture further stirred with the help of mechanical stirrer for 2 hrs. at the room temperature and then refluxed for 6 hrs. on water bath. The excess of solvent was distilled off, cooled, powered onto crushed ice. The resulting mixture was filtered to afford solid product, washed with petroleum ether and recrystallised from ethanol-water.

m.p. 256°C, yield 55% (Found C, 51.91; H, 4.12; N, 19.92, Calcd. for$C_{12}H_{12}O_2N_4S$ C, 52.16; H, 4.37; N, 20.27%).

IR(KBr): 3160 (N–H), 3025 (C–H aromatic), 2920 (C–H aliphatic), 1150, 1595,1570, 1440 (Ar-H), 1620 (C=N), 1660 (C=O), 3250 (NH), 1600 (C=C) ofaromatic ring, 1860 cm^{-1} (C=S).

^{1}H NMR($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar–H), 7.5 (q, 1H, Ar-H), 7.9 (d, 1H, CH-Ar), 2.02 (s, 3H, CH_3), 8.0 (s, 1H, NH), 2.0 (s, 1H, CSNH).

F. 2-methyl-3-(N acyl-carbamido)- 4(3H)quinazolone- 3'

A solution of acetyl chloride (0.02 mole, 1.57 ml) in dry chloroform (20 ml) was added drop wise at 0-5°C temperature to the vigorously stirred solution of 2-methyl-3-(carbamido)- 4(3H)quinazolone- **2'** (0.02 mole, 4.36 gms) in dry chloroform (50ml).

The reaction mixture further stirred with the help of mechanical stirrer for 2 hrs at the room temperature and then refluxed for 6 hrs on water bath. The excess of solvent was distilled off, cooled, powered onto crushed ice. The resulting mixture was filtered to afford solid product, washed with pet. Ether and recrystallised from ethanol-water.

m.p. 238°C, yield 60% (Found C, 54.82; H, 4.02; N, 20.82, Calcd. for $C_{12}H_{12}O_3N_4$ C, 55.38; H, 4.64; N, 21.52%).

IR (KBr): 3160 (N-H), 3025 (C-H aromatic), 2920 (C-H aliphatic), 1150, 1595, 1570, 1440 (Ar-H), 1620 (C=N), 1660 (C=O), 3250 (NH), 1600 cm^{-1} (C=C) of aromatic ring.

^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar-H), 7.5 (q, 1H, Ar-H0, 7.9 (d, 1H, Ar-H), 2.4 (s, 3H, CH_3), 6.0 (s, 1H, NH), 10.0 (s, 1H, CONHCO-).

G. 2-methyl-3-(substituted thiocarbamido)- 4(3H)quinazolones- 4

To a solution of compound **3** (0.01 mole, 2.76 gms) in methanol (50 ml), substituted aldehyde (0.01 mole) was added in the presence of 2% NaOH solution. The reaction mixture was heated under reflux for 12 hrs. The excess of solvent distilled off, cooled, filtered and the compounds were thoroughly washed with cooled water and recrystallised with ethanol water.

IR (KBr): 3160 (N–H), 3025 (C–H aromatic), 2920 (OH aliphatic), 1150, 1595, 1570, 1440 (Ar–H), 1620 (C=N), 1660 (C=O), 1600 (C=C) of aromatic ring, 1860 cm^1 (C=S).

^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar-H), 7.5 (q, 1H, Ar-H), 6.54 (d, 2H, CH), 7.12 (d, 2H, CH), 6.84 (d, 1H, COCH=), 7.55 (d, 1H, =CH-Ar), 2.85 (s, 6H, $N(CH_3)_2$), 8.0 (s, 2H, CONHCS), 2.0 (s, 1H, CSNH).

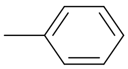
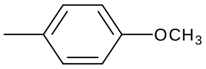
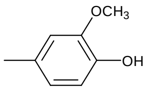
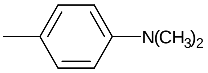
H. 2-methyl-3-(substituted carbamido)- 4(3H)quinazolones- 4'

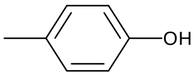
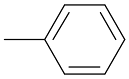
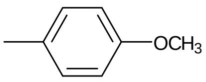
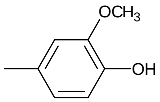
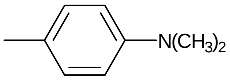
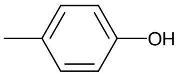
To a solution of compound **3'** (0.01 mole, 2.6 gms) in methanol (50 ml), substituted aldehyde (0.01 mole) was added in the presence of 2% NaOH solution. The reaction mixture was heated under reflux for 12 hrs. The excess of solvent distilled off, cooled, filtered and the compounds were thoroughly washed with cooled water and recrystallised with ethanol water.

IR (KBr): 3160 (N–H), 3025 (C–H aromatic), 2920 (C–H aliphatic), 1150, 1595, 1570, 1440 (Ar–H), 1620 (C=N), 1660 (C=O), 1600 (C=C) of aromatic ring.

^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.4 (q, 2H, Ar-H), 7.5 (q, 1H, Ar-H), 7.9 (d, 1H, Ar-H), 6.54 (d, 2H, CH), 7.12 (d, 2H, CH), 6.84 (d, 1H, COCH=), 7.55 (d, 1H, =CH-Ar), 2.85 (s, 6H, $N(CH_3)_2$), 6.0 (s, 1H, NH), 10.0 (s, 1H, CONHCO).

Table I: Characterization data of 2-Methyl-3-(substituted thiocarbamido/carbamido)-4(3H)-quinazolones

Compd.	R	m.p. (°C)	Yield (%)	Mol. for.	Found (Calcd.) %		
					C	H	N
4a		142	60	$C_{19}H_{16}O_2N_4S$	62.02 (62.62)	4.22 (4.42)	15.0 (15.37)
4b		123	57	$C_{20}H_{18}O_3N_4S$	60.2 (60.9)	4.12 (4.59)	13.90 (14.20)
4c		148	63	$C_{20}H_{18}O_4N_4S$	58.14 (58.52)	4.20 (4.42)	13.03 (13.64)
4d		163	60	$C_{21}H_{21}O_2N_5S$	60.03 (61.89)	4.95 (5.19)	17.03 (17.18)

Compd.	R	m.p. (°C)	Yield (%)	Mol. for.	Found (Calcd.) %		
					C	H	N
4e	 	208	47	$C_{19}H_{16}O_3N_4S$	59.06 (59.98)	3.90 (4.23)	14.01 (14.72)
4'a		140	51	$C_{19}H_{16}O_3N_4$	64.90 (65.5)	4.34 (4.62)	15.95 (16.08)
4'b	 	120	60	$C_{20}H_{18}O_4N_4$	62.92 (63.48)	4.05 (4.79)	13.95 (14.8)
4'c	 	146	49	$C_{20}H_{18}O_5N_4$	60.50 (60.91)	4.01 (4.60)	13.87 (14.2)
4'd	 	160	54	$C_{21}H_{21}O_3N_5$	60.85 (61.30)	4.85 (5.14)	16.86 (17.02)
4'e	 	200	44	$C_{19}H_{16}O_4N_4$	61.63 (62.63)	3.95 (4.42)	14.85 (15.37)

III. BIOLOGICAL STUDY

The methods employed during the course of investigation are given below:

The studies were carried out in Swiss Albino mice of either sex weighing between 15 to 20 g, each and experiments were conducted at a controlled room temperature of 25±1°C in an air conditioned laboratory. The compounds were administered i.p. as aqueous suspension in *gum acacia*.

A. *Acute Toxicity*

The ALD_{50} was determined in mice using the method of Horn[16]. Doses of the compounds were given in groups of 5 mice each in a geometrical progression starting with a dose of 464 mg/kg i.p. and mortality in 24 hours recorded. The ALD_{50} with fiducial limits was read out from the table given in the same method.

B. *Gross effects*

The method of Dua[17] was used. After i.p. administration of the compounds in groups of 5 mice each the animals were observed for gross behavioral effects. The animals were observed continuously for 3 hours after administration of the compound, then every thirty minutes for next three hours and finally after 24 hours. CNS stimulation was judged by increased spontaneous motor activity (SMA), piloerection, exophthalmoses, colonic and/or tonic convulsions, CNS depression by reduced SMA, sedation, ptosis, crouching, catalepsy and autonomic effects by piloerection, urination, defecation, salivation, lachrymation *etc.* At ½the ALD_{50} these effects were recorded using groups of 5 mice and effect on the body temperature was also recorded with a tele thermometer using YSI 402 physiological probe. SMA observed by the act photometer.

Table II

Compd. No.	Dose mg/kg i.v.	Fall in blood pressure (mm Hg)		ALD_{50} mg/kg i.p.	Effect on gross behaviour at 1/5th ALD_{50}i.p.
		Intermediate	Delayed		
4a	2	20	15	>1000	No effect
4b	2	25	20	>1000	No effect
4c	2	30	15	>1000	Depressant 28%
4d	2	30	20	>1000	Depressant 20%
4e	2	45	36	>1000	Depressant 15%

4'a	2	25	20	>1000	No effect
4'b	2	25	20	>1000	No effect
4'c	2	25	15	>1000	Depressant 25%
4'd	2	35	30	>1000	Depressant 21%
4'e	2	40	35	>1000	Depressant 10%

IV. RESULTS AND DISCUSSION

The author had synthesized ten 2-methyl-3-(substituted thiocarbamide)-4(3H) quinazolones and 2-methyl-3-(substituted carbamido)-4(3H) quinazolones compounds. The determination of the CNS activity of the synthesis compounds was performed on Albino mice and the results obtained there from are recorded in table All the compounds (Quinazolonesderivatives) were found to exhibit dilatory effect activities on cardio-vascular system (CVS).

However, only six compounds (out of the total of ten) showed the CNS depressant activity, the compounds are listed as under- 4c, 4d, 4e & 4'c, 4'd, 4'e.The maximum CNS depressant activity of the order of 28% was observed by the compound 4c. Interestingly, the same compound also showed the maximum dilatory effect in CVS.

A. Discussion (S.A.R.)

We have carefully examined the structure of six compounds, associated with CNS depressant activity (vide supra), it was observed that, the presence of methyl group at second position of quinazolone nucleus is essential for establishing CNS depressant activities and quinazolone derivatives having –OH group alone or in the presence of –OCH$_3$ group, –N(CH$_3$) group (4c, 4d, 4e, 4'c, 4'd, 4'e) showed good CNS depressant activities but those quinazolone derivatives having un substituted phenyl groups (4a, 4'a) and –OCH$_3$ substituted phenyl groups (4b, 4'b) showed no CNS depressant activities. So it is clear that quinazolone derivatives having strong activators substituents are responsible for CNS depressant activity and ring deactivating/moderate active atatingsubstituents are responsible for low/no CNS depressant activity.

V. ACKNOWLEDGEMENT

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