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Synthesis of Some 2-Methyl-3-(Arylthiocarbamido) Quinazol-4-Ones and 2-Methyl-3-(Arylidencarboxamido) Quinazol-4-Ones as Potential Antimicrobial Agents

B. D. Gupta
Department of Chemistry, Northern India Engineering College, Lucknow 226001, India

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Abstract. Some quinazolone derivatives of 2-methyl-3-(arylthiocarbamido) quinazol-4-ones **(2)** and 2-methyl-3-(arylidencarboxamido) quinazol-4-ones **(3)** have been synthesized and assayed for their possible antibacterial activity against *Bacillus subtilis, Bacillus cereus, Salmonella aureus, Salmonella lutae* and antiviral activity against *Gomphrena mosaic* virus. Some of these compounds show notable activity.

Keywords: quinazol-4-ones, antibacterial activity, antiviral activity

Introduction

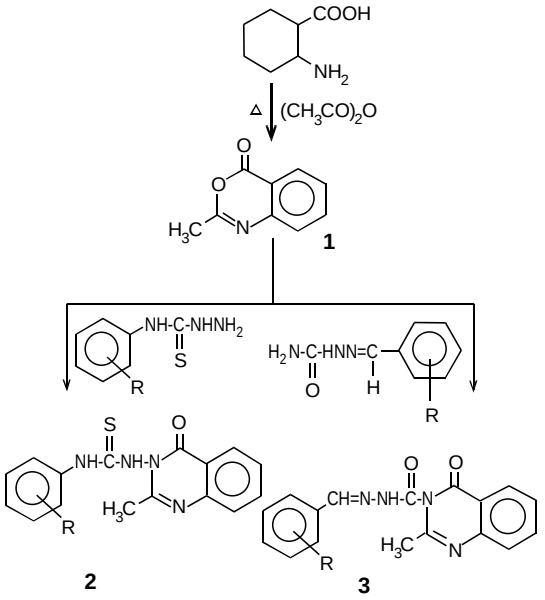
Quinazolone derivatives exhibit a wide range of activity such as dopamine receptor (Srivastva *et al.,* 1987) anthelmintic (Gupta *et al.,* 1988; Alaimo, 1972) anti-inflammatory (Alagarsamy *et al.,* 2003), antimicrobial (Pandey *et al.,* 2004; Alagarsamy *et al.,* 2000) CNS deprcssant (Saksena and Khan, 1989; Kacker and Zaheer, 1951) neuroleptic (Mukerji *et al.,* 1980) hypotonic (Gujral *et al.,* 1955) and analgesic (Ram *et al.,* 1990). Pharmacological activity of this class of compounds is beyond any doubt, thus it was decided to synthesize some new title quinazolones in order to study their antibacterial and antiviral activities.

Materials and Methods

Melting points were determined in open glass capillary and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer-157 spectrometer and ^{1}HNMR (60 MHz) spectra on Varian EM 360 spectrometer.

2-Methyl-1,3-benzo [d] oxazin-4-one called acetanthranil was obtained essentially by the method of Zentmyer and Wagner (1949).

2-Methyl-3-(4-chlorophenylthiocarbamido)-quinazol-4-one (**2**, R=4-CI). (Scheme I) Acetanthranil (1.6 g) and 4-chlorophenylthiosemicarbazide (1.8 g) in methanol (20 ml) were heated together upto 3 h. The reaction mixture was cooled. The solid thus obtained was washed with dil. Na_2CO_3 followed by dil. HCl and the product was finally crystallised from ethanol; yield 75%. m.p. 168°C; MS: m/z: M^+ 344; IR(KBr) cm^{-1} : 1150, 1595, 1570, 1440, (Ar-H), 1620 (C=N), 1660 (C=O), 3250 (NH); ^{1}HNMR (DMSO-d_6): δ 2.1 (s, 3H. CH_3), 7.0-7.5 (m, 8H, Ar-H), 8.2 (s, 2H, NH); Anal. found: C 55.61; H 3.64; N 16.12. ca1cd: C 55.73; H 3.79; N 16.25% (Table 1).



Scheme 1

2-Methyl-3-(4-methoxybenzylidencarboxamido) quinazol-4-one (**3**, R=4-OCH_3). Acetanthranil (1.6 g) and 4-methoxybenzaldehydesemicarbazone (1.7 g) in presence of excess of acetic anhydride (10 ml) were heated together on a water bath for 3 h. The reaction mixture was cooled. The solid thus obtained was washed with dil. Na_2CO_3 followed by dil. HCI and the product was finally crystallised from ethanol; yield 79%, m.p. 166 °C; MS m/z : M^+ 336; IR (KBr) cm^{-1}: 1595, 1570, 1460 (Ar-H), 1650 (C-NH), 1670 (C=O), 3400 (NH); ^{1}HNMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 4.2 (s, 3H, OCH_3), 6.1 (s, 1H, N=CH), 7.2-7.6 (m, 8H, ArH), 8.6 (s, 1H, NH);

E-mail: bdgupta_chem@rediffmail.com

Table 1. Characterization data of compounds **2** and **3**

Compound	R	M.P. °C	Yield (%)	M. F.	Found (calcd. %) C	H	N
2a	H	140	72	$C_{16}H_{14}N_4OS$	61.8	4.39	17.86
					(61.91	4.54	18.04)
2b	2-CH_3	120	78	$C_{17}H_{16}N_4OS$	62.83	4.83	17.03
					(62.94	4.96	17.27)
2c	3-CH_3	149	72	$C_{17}H_{16}N_4OS$	62.84	4.82	17.01
					(62.94	4.96	17.27)
2d	4-CH_3	178	75	$C_{17}H_{16}N_4OS$	62.82	4.81	17.02
					(62.94	4.96	17.27)
2e	4-OCH_3	164	70	$C_{17}H_{16}N_4O_2S$	59.87	4.6	16.31
					(59.99	4.73	16.45)
2f	2-Cl	210	77	$C_{16}H_{13}N_4OSCl$	55.62	3.63	16.13
					(55.73	3.79	16.25)
2g	4-Cl	168	75	$C_{16}H_{13}N_4OSCl$	55.62	3.63	16.13
					(55.73	3.79	16.25)
2h	2,4-Cl_2	162	75	$C_{16}H_{12}N_4OSCl_2$	50.55	3.1	14.62
					(50.67	3.18	14.77)
2i	2,6-$(CH_3)_2$	175	72	$C_{18}H_{18}N_4OS$	63.8	5.22	16.39
					(63.88	5.36	16.55)
3a	H	148	70	$C_{17}H_{14}N_4O_2$	66.56	4.46	18.24
					(66.67	4.6	18.28)
3b	4-CH_3	203	78	$C_{18}H_{16}N_4O_2$	67.38	4.88	17.35
					(67.49	5.03	17.48)
3c	4-OCH_3	166	79	$C_{18}H_{16}N_4O_3$	64.2	4.64	16.52
3d	2-Cl	194	80	$C_{17}H_{13}N_4O_2Cl$	59.8	3.71	16.29
					(59.92	3.84	16.44)
3e	4-Cl	191	77	$C_{17}H_{13}N_4O_2Cl$	59.89	3.7	16.28
					(59.92	3.84	16.44)
3f	2-OH	211	72	$C_{17}H_{14}N_4O_3$	63.22	4.23	17.23
					(63.35	4.37	17.38)
3g	2-OH, 3-OCH_3	297	74	$C_{18}H_{16}N_4O_4$	61.24	4.4	15.78
					(61.36	4.57	15.90)

Anal. found: C 64.20; H 4.64; N 16.52. calcd: C 64.28; H 4.79; N 16.66% (Table 1).

Pharmacology. ***Antibacterial screening.*** The *in vitro* antibacterial activity of the synthesised compounds was determined by the method of Verma and Nobbles (1968), at a concentration of 100 µmg/ml. A standard tetracycline was also tested under similar conditions to compare the results. The inhibition zone (in cm) against four species *viz.*: *B. subtilis*, *B. cereus*, *S.aureus* and *S. lutes* were measured. The results are recorded in Table 2.

Antiviral screening. The *in vitro* antiviral activity of all the synthesized compounds reported here was determined by the method of Verma and Awasthi (1978) on *Gomphrena mosaic* virus, taking gaur leaves as host. The concentration of each sample was 3.0 mg/mole. The percentage activity is recorded in Table 2.

Results and Discussion

Antibacterial activity. All the compounds of this report have been screened for their antibacterial activity. Perusal of the

Table 2. Antibacterial and antiviral activities of compounds **2** and **3**

Compound	R	Inhibition zone (in cm)				% inhibition of
		a	b	c	d	*Gomphrena mosaic* virus
2a	H	1.3	-	1.1	1.3	40
2b	2-CH_3	1.5	1	1.4	1.7	52
2c	3-CH_3	2	0.8	0.9	2.1	48
2d	4-CH_3	1.8	2.2	1.6	1.7	52
2e	4-OCH_3	2.6	-	0.9	0.8	22
2f	2-Cl	1.7	1.1	1.5	1.6	60
2g	4-Cl	2.8	2.2	2.7	2	65
2h	2,4-Cl_2	2.4	2	2.9	2	77
2i	2,6-$(CH_3)_2$	2.6	-	0.8	1.1	20
3a	H	0.6	0.6	0.8	1.1	24
3b	4-CH_3	1.2	0.8	0.9	1	50
3c	4-OCH_3	-	-	1.5	0.7	15
3d	2-Cl	-	1.7	1.2	1.6	18
3e	4-Cl	2.1	-	0.8	1.8	27
3f	4-OH	1.8	1.6	1.5	1.3	61
3g	4-OH, 3-OCH_3	2.2	1.6	1.9	1.9	80
Tetracycline*		3.2	2.4	2.4	2.4	-

a = *B. subtilis*; b = *B. cereus*; c = *S. aureus*; d = *S. lutae;** = standard drug for antibacterial activity; - = no activity.

results (Table 2) indicates that the range of inhibition zones produced by these compounds are 0.6 to 2.8 cm on *Bacillus subtilis;* 0.6 to 2.2 cm on *Bacillus cereus;* 0.6 to 2.9 cm on *Salmonella aureus* and 0.7 to 2.1 cm on *Salmonella lutes*, respectively, whereas, the standard drug (tetracycline) could inhibit the bacteria in the zones of 3.2, 2.4, 2.4, 2.4, respectively. Compounds **2g**, **2h**, **3e** and **3g** showed good activity on all the four species as compared to the standard drug. So further screening of these compounds on wider range of bacteria as well as on more dilutions is desirable. On the basis of above, the following conclusion can be drawn:

(i) The presence of -OCH_3 group in the phenyl ring does not impart any activity.
(ii) Presence of alkyl group (-CH_3) in phenyl ring works better than unsubstituted phenyl ring.
(iii) The position of -CH_3 group in the phenyl ring played a role in the activity. The order of activity is 4-CH_3 > 2-CH_3 > 3-CH_3.
(iv) The presence of one -Cl group played notable activity while two chlorine atoms together work better.
(v) Presence of -OH group alone or in presence of -OCH_3 group imparts better antibacterial activity.

Antiviral activity. All the compounds have been screened for their antiviral activity against *Gomphrena mosaic* virus. The results (Table 2) indicate that the activity was between 15 to 80%. Compounds **2f**, **2g**, **3f** and **3g** have activities greater than 60%, while two compounds **2h** and **3g** had activities 77% and 80%, respectively. Further screening of these two compounds on wider range of viruses as well as more dilutions is in progress. These results lead to the following conclusion.

(i) Presence of -Cl and -OH groups in phenyl ring alone and presence of -OH with -OCH_3 group increases activity.
(ii) As the number of Cl-atom increases, the activity also increases.
(iii) Presence of phenolic -OH at position-4 in the phenyl ring imparts much more activity than if it is at position-2.

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