Asian Journal of Chemistry Vol. 17, No. 1 (2005), 57–65

Synthesis and Biological Activity of Some Substituted 2-Phenyl-quinazolin-4-ones

N.M. RAGHAVENDRA*, M.S. NIRANJAN, P. VENKATESH†, B.R. PRASHANTHA KUMAR, NARENDRA B. GOWDA and M.S. SRIPATHI
Department of Pharmaceutical Chemistry
Government College of Pharmacy,
Subbiah Circle, Bangalore-560 027, India
Ph. (M) 9448419058
E-mail: nmraghu 76@yahoo.co.in; nmraghu76@hotmail.com

Synthesis of nine 2,3,6-trisubstituted quinazolin-4-ones is reported. The nine compounds contain a bromine atom at position 6, a phenyl group at position 2 while at position 3, one compound has free amino group and the remaining eight compounds have substituted benzalamino group. The synthesized compounds were screened for their anticancerous activity by evaluating the percentage increase in life span in mice bearing Ehrlich ascites carcinoma at different dose, *viz.*, 2, 50, 100 and 250 μg/mouse/day on alternate days for a total period of 10 days. Synthesized compounds were also investigated for their antimicrobial activity against two gram +ve and two gram –ve microorganisms using agar cup diffusion method.

Key Words: Synthesis, Biological activity, Substituted 2-phenyl-quinazolin-4-ones.

INTRODUCTION

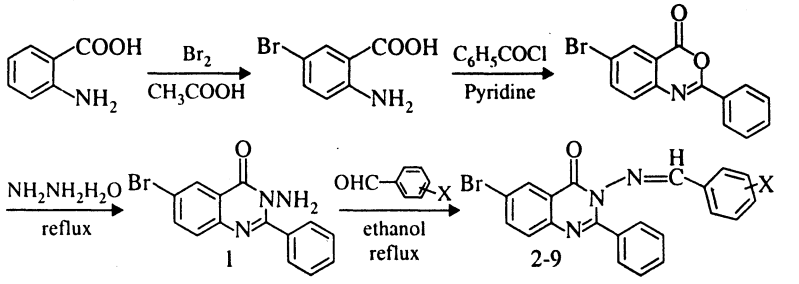
Quinazolinone derivatives exhibit a wide range of activities such as antiparkisonism, antitremor, antibacterial[1], anthelmintic[2], CNS depressant[3], neuroleptic[4], antitubular[5], anticonvulsant, analgesic[6] and fungicidal[7]. Antitumor activities of 2,3-dihydro-2-aryl-4-quinazolinones were reported around 1970[8,9] Recent re-evaluation of this type of compound by NCI against human tumor cell lines reconfirmed that, like colchicines, they are effective inhibitors of tubulin polymerization. 2-Styryl quinazolin-4-ones (SQZ)[10,11] were also identified as potent inhibitors of tubulin polymerization. As per the SAR information of phenyl quinazolinone derivatives (PQZ), single substitution at the sixth position seemed to be beneficial for increased antitumor activities[12]. Much work has also been done at third position of PQZ derivatives for antitumor activity[13].

†Department of Pharmacology, Government College of Pharmacy, Subbiah Circle, Bangalore-560 027, India.

In continuation of the above works, 2,3,6-trisubstituted quinazolinones have been synthesized in order to get better anticancerous activity. All the synthesized compounds were screened for their anticancer and antibacterial activity.

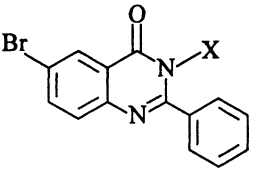
RESULTS AND DISCUSSION

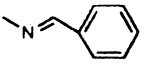
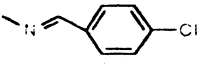
Synthesis of nine novel 2-aryl, 6-bromo-3-substituted benzalamino quinazolinone involves four steps, namely, bromination, Schotten-Baumann reaction, cyclization, condensation and Schiff base formation. Anthranilic acid was brominated by the method of Wheeler, *et al.*[14] and then treated with benzoyl chloride in the presence of pyridine to undergo cyclization forming 6-bromo, 2-phenyl-3,1-benzoxazin-4-one, which on condensation with hydrazine hydrate yielded 6-bromo, 2-phenyl-3-amino, quinazolin-4-one:

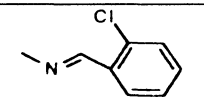
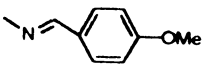
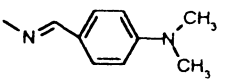
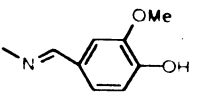
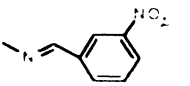
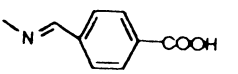


The latter was treated with different substituted benzaldehydes in presence of ethanol to form corresponding 2-phenyl, 6-bromo-3-substituted benzalamino quinazolinones (Table-1).

TABLE-1
2,3,6-TRISUBSTITUTED QUINAZOLIN-4-ONES



Compound	Chemical name	Susbstituent X	m.w.	Yield (%)
1	6-Bromo, 2-phenyl-3-amino, quinazolin-4(3H)-one	NH_2	315	26
2	6-Bromo, 2-phenyl-3-benzalamino-quinazolin-4(3H)-one		403	66
3	6-Bromo, 2-phenyl-3-(4-chloro-benzalamino)-quinazolin-4(3H)-one		437	32.89

Compound	Chemical name	Susbstituent X	m.w.	Yield (%)
4	6-Bromo, 2-phenyl-3-(2-chloro-benzalamino)-quinazolin-4(3H)-one		437	31.9
5	6-Bromo, 2-phenyl-3-(4-methoxy-benzalamino)-quinazolin-4(3H)-one		433	52
6	6-Bromo, 2-phenyl-3-(4-N,N'-dimethylaminobenzalamino)-quinazolin-4(3H)-one		446	62.41
7	6-Bromo, 2-phenyl-3-(4-hydroxy, 3-methoxybenzalamino)-quinazolin-4(3H)-one		449	42.25
8	6-Bromo, 2-phenyl-3-(3-nitro-benzalamino)-quinazolin-4(3H)-one		448	70
9	6-Bromo, 2-phenyl-3-(4-carboxybenzalamino)-quinazolin-4(3H)-one		447	66.7

Control group: Mice bearing EAC administered with 1% tragacanth suspension.

Standard group: Mice bearing EAC treated with Vincristine 26 µg/mouse/week for two times.

Number of animal in each group: Seven.

Route of administration: Intra peritoneal.

Mode of treatment: Treatment started 24 h after inoculation of the tumour. A different dose of the synthesized compounds was given in single dose intra-peritonially on alternate days for 10 days.

The percentage increase in life span was calculated from the formula:

$$\% \text{ Increase in life span} = \left(\frac{\text{MST of treated group}}{\text{MST of control group}} \times 100 \right) - 100$$

None of the compounds showed significant therapeutic efficacy by increasing the mean survival time. However, compounds **2, 9** and **8** at 50 µg/mouse/day has increased the life span by 9.48, 7.62 and 4.43% respectively (Table-2).

Compound-**2** showed good antibacterial activity against *B. subtilis* and *P. aeruginosa*; Compound-**6** showed good antibacterial activity against *B. subtilis* and *E. coli* while Compound-4 showed good antibacterial activity against E. coli (Table-3).

TABLE-2
ANTICANCER EFFECTS OF 2,3,6-TRISUBSTITUTED QUINAZOLIN-4-ONES (1-9)

Compound	Dose	MST[a] ± SEM[b]	% ILS[c]	t-Test	Compound	Dose	MST ± SEM	% ILS	t-test
Control	⊗	22.57 ± 0.429	0.00	—	5	250 µg	22.29 ± 1.286	–1.24	—
						100 µg	22.14 ± 1.61	–1.905	—
Vincristine	26 µg	38.14 ± 0.705	+68.98	—		50 µg	21.14 ± 1.895	–6.335	—
						02 µg	21.43 ± 0.528	–5.05	—
1	250 µg	18.29 ± 1.985	–18.96	—	6	250 µg	16 ± 1.234	–29.1	—
	100 µg	22.29 ± 0.993	–1.24	—		100 µg	16.59 ± 2.08	–28.62	—
	50 µg	20.29 ± 1.569	–10.10	—		50 µg	19.29 ± 1.769	–14.66	—
	02 µg	18.14 ± 0.261	–19.62	—		02 µg	20 ± 1.414	–11.38	—
2	250 µg	17.29 ± 1.911	–23.39	—	7	250 µg	20.14 ± 3.446	–10.76	—
	100 µg	22.57 ± 2.258	0.00	—		100 µg	15.71 ± 2.201	–30.39	—
	50 µg	24.71 ± 2.298	+9.48	—		50 µg	13.14 ± 13.14	–41.78	—
	02 µg	20.86 ± 2.154	–7.56	—		02 µg	19.29 ± 1.848	–14.53	—
3	250 µg	12.29 ± 0.606	–45.55	—	8	250 µg	16.14 ± 0.885	–29.64	—
	100 µg	15.43 ± 2.759	–31.63	—		100 µg	20.86 ± 1.534	–7.58	—
	50 µg	18 ± 2.41	–20.24	—		50 µg	23.57 ± 0.896	+4.43	ns
	02 µg	13.7 ± 0.565	–39.25	—		02 µg	16.57 ± 1.962	–26.58	—
4	250 µg	20 ± 1.543	–11.38	—	9	250 µg	20.29 ± 2.337	–10.1	—
	100 µg	20.29 ± 1.267	–10.10	—		100 µg	21.86 ± 1.850	–3.145	—
	50 µg	19.57 ± 1.757	–13.29	—		50 µg	24.29 ± 1.107	+7.62	ns
	02 µg	18 ± 2.44	–20.29	—		02 µg	20.29 ± 1.714	–10.1	—

[a]Mean survival time. [b]Standard error mean. [c]Percentage increase in life span. ⊗ 0.5 mL 1% tragacanth suspension.
Statistics: t-test; df = 12, * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$. ns = Not Significant.

TABLE-3
ANTIMICROBIAL ACTIVITY OF 2,3,6-TRISUBSTITUTED QUINAZOLIN-4-ONES

Group	Zone of inhibition (mm)			
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*
Streptomycin	30	22	30	22
Compound-1	10	—	10	—
Compound-2	17	—	10	15
Compound-3	10	—	13	—
Compound-4	—	—	14	—
Compound-5	—	—	12	08
Compound-6	13	—	14	07
Compound-7	10	—	13	—
Compound-8	12	—	13	—
Compound-9	09	—	13	—
Control (DMF)	—	—	—	—

EXPERIMENTAL

The melting points were recorded on the conventional melting point apparatus. Purity of the compounds was checked by TLC on ready made precoated TLC plates having silica gel F28 as adsorbent using pet ether and ethyl acetate (8 : 2) as mobile phase. IR spectra were recorded in KBr on a Shimadzu FTIR 8400 spectrophotometer as KBr pellets. ^{1}H NMR spectra were obtained on the AMX-400 liquid state spectrometer at 440 MHz in $CDCl_3$. Mass spectra were measured with an FAB mass spectrometer (LSIMS).

5-Bromo-anthranilic acid: To a solution of 40 g of anthranilic acid in 500 mL of glacial acetic acid, 19 mL of bromine was added at a temperature of 16°C. The resulting mixture was extracted with 1 L of water containing 50 mL of concentrated HCl, followed by filtration. 5-Bromo anthranilic acid crystallized out as pale creamish crystals by cooling the filtrate; m.p. 212°C; yield 31.75%; R_f = 0.13. IR (cm^{-1}): 1670 ν(C=O) of carboxylic acid, 3030 ν(CH) of aromatic ring, 3383, 3363 ν(NH). ^{1}H NMR: 7.7–7.8 δ (d, 2H, of —NH_2), 7.3–7.4 δ (dd, 2H, of —ArH) and 6.73 δ (d, 1H, of —ArH). MS m/z = 215 (M^+).

Synthesis of 6-Bromo, 2-phenyl-3,1-benzoxazin-4(3H)-one: 0.065 M of 5-bromo anthranilic acid (14 g, 0.065 M) was dissolved in 75 mL of pyridine. To this reaction mixture benzoyl chloride (8.7 mL, 0.075 M) was added with stirring at room temperature (27°C). Stirring continued for 20 min at the same temperature. The reaction mixture was subjected to vacuum pump filtration to collect the precipitate, which was washed with distilled water and pet. ether 60/80 to remove traces of pyridine. The pale yellowish crystals obtained were dried at 60°C; m.p. 179–183°C; yield 30%; R_f = 0.8. IR (cm^{-1}): 1751 ν(C=O) of lactone), 3040–3000 ν(CH) of hetero-aromatic ring, 686 ν(C—Br). ^{1}H NMR: 8.37 δ (d, 1H, of

—ArH), 7.89–7.93 δ (dd, 2H, of —ArH) and 7.4–8.32 δ (m, 5H, of —ArH). MS m/z = 302 (M^+).

Synthesis of 6-Bromo, 2-phenyl-3-amino, quinazolin-4(3H)-one (1): 6-Bromo, 2-phenyl-3,1-benzoxazin-4(3H)-one (11 g, 0.037 M) was refluxed with 75 mL of hydrazine hydrate for 3 h at 120–130°C. The reaction mixture was allowed to cool to room temperature. Pale yellowish crystals developed were collected through filtration by using vacuum pump. The crystals were recrystallized from super dry ethanol; m.p. 147–150°C; yield 26%; R_f = 0.59, IR (cm^{-1}): 1666 ν(C=O) of ketone; 3070 ν(CH) of hetero-aromatic ring, 686 ν(C—Br), 3309, 3217 ν(NH). 1H NMR: 8.45 δ (d, 1H, of —ArH), 7.75–7.82 δ (dd, 2H, of —ArH) and 7.49–7.9 δ (m, 5H, of —ArH), 5.0 δ (s, 2H, of —NH_2); MS m/z = 315 (M^+).

Synthesis of 6-bromo, 2-phenyl-3-benzalamino-quinazolin-4(3H)-one (2): 6-Bromo, 2-phenyl-3-amino, quinazolin-4(3H)-one (2 g, 0.0065 M) was dissolved in 100 mL of super dry ethanol. To this reaction mixture, a few drops of concentrated sulphuric acid and benzaldehyde (0.65 mL, 0.0065 M) was added and refluxed for 5 h. Then the reaction mixture was allowed to cool to room temperature to get shining milky white crystals. The crystals obtained were then filtered by using vacuum pump and recrystallized from super dry ethanol; m.p. 175–180°C; yield 66%; R_f = 0.91, IR (cm^{-1}): 1681 ν(C=O) of ketone, 3030 ν(CH) of hetero-aromatic ring, 686 ν(C—Br), 1681 ν(C=N); ^{1}H NMR: 9.04 δ (s, 1H, of =CH), 8.45–8.5 δ (d, 1H, of —ArH), 7.8–7.9 δ (dd, 2H, of —ArH) and 7.35–7.75 δ (m, 10H, of —ArH); MS m/z = 404 (M^+).

The method used to prepare **2** was used with indicated substituted benzaldehyde and 6-bromo, 2-phenyl-3-amino, quinazolin-4(3H)-one **(1)** to afford **3–9.**

Synthesis of 6-bromo, 2-phenyl-3-(4-chlorobenzalamino)-quinazolin-4(3H)-one (3): **(1)** (1.1 g, 0.0034 M) and 4-chlorobenzaldehyde (0.48 g, 0.0034 M), cream coloured crystals; m.p. 220–222°C; yield 32.89%; R_f = 0.86. IR (cm^{-1}): 1681 ν(C=O) of ketone, 3030 ν(CH) of hetero aromatic ring, 686 ν(C—Br), 763 ν(C—Cl), 1681 ν(C=N). ^{1}H NMR: 9.05 δ (s, 1H, of =CH), 8.4–8.5 δ (d, 1H, of —ArH), 7.8–7.9 δ (dd, 2H, of —ArH) and 7.3–7.72 δ (m, 9H, of —ArH).

Synthesis of 6-bromo, 2-phenyl-3-(2-chlorobenzalamino)-quinazolin-4(3H)-one (4): **(1)** (0.6 g, 0.0019 M) and 2-chlorobenzaldehyde (0.22 mL, 0.0019 M), shining white crystals; m.p. 216–220°C; yield 31.9%; R_f = 0.75. IR (cm^{-1}): 1689 ν(C=O) of ketone, 3030 ν(CH) of hetero-aromatic ring, 694 ν(C—Br), 763 ν(C—Cl), 1689 ν(C=N). ^{1}H NMR: 9.52 δ (s, 1H, of =CH), 8.51 δ (d, 1H, of —ArH), 7.8–7.9 δ (dd, 2H, of —ArH) 7.6–7.7 δ (t, 3H, of —ArH) and 7.2–7.7 δ (m, 5H, of —ArH).

Synthesis of 6-bromo, 2-phenyl-3-(4-methoxybenzalamino)-quinazolin-4(3H)-one (5): **(1)** (0.7 g, 0.0022 M) and 4-methoxy benzaldehyde (0.3 mL, 0.0022 M), cream-coloured crystals; m.p. 210°C; yield 52%; R_f = 0.77. IR (cm^{-1}): 2939, 2839 ν(OCH_3), 1033 ν(C—O—C), 1674 ν(C=O) of ketone 3030 ν(CH) of hetero-aromatic ring, 694 ν(C—Br), 1674 ν(C=N). ^{1}H NMR: 8.85 δ (s, 1H, of =CH), 8.48 δ (d, 1H, of —ArH), 7.8–7.9 δ (dd, 2H, of —ArH) 7.2–7.75 δ (m, 7H, of —ArH), 6.9–7.0 δ (d, 2H, of —ArH) and 3.85 δ (s, 3H, of —OCH_3).

Synthesis of 6-bromo, 2-phenyl-3-(4-N,N-dimethylaminobenzalamino)-quinazolin-4(3H)-one (6): **(1)** (1.0 g, 0.0032 M) and 4-N,N-dimethylamino benzaldehyde (Ehrlich reagent) (0.5 g, 0.0032 M), shining yellow crystals; m.p. 218°C; yield 62.41%; $R_f = 0.57$, IR (cm^{-1}): 2825 (CH_3), 1674 ν(C=O) of ketone, 3030 ν(CH) of hetero-aromatic ring, 686 ν(C—Br), 1674 ν(C=N). ^1H NMR: 8.63 δ (s, 1H, of =CH), 8.48 δ (d, 1H, of —ArH), 7.8–7.87 δ (dd, 2H, of —ArH) 7.55–7.6 δ (d, 2H, of —ArH), 7.25–7.8 δ (m, 5H, of —ArH), 6.65–6.7 δ (d, 2H, of —ArH) and 3.15 δ (s, 6H, of —$N(CH_3)_2$).

Synthesis of 6-bromo, 2-phenyl-3-(4-hydroxy,3-Methoxybenzalamino)-quinazolin-4(3H)-one (7): **(1)** (1.0 g, 0.00317 M) and 4-hydroxy, 3-methoxy benzaldehyde (vanillin) (0.49 g, 0.00317 M), white amorphous powder; m.p. 238°C; yield 42.25%; $R_f = 0.35$, IR (cm^{-1}): 2931 ν(OCH_3) of alkane, 3386 ν(OH) of phenol, 1674 ν(C=O) of ketone, 3030 ν(CH) of hetero-aromatic ring, 686 ν(C—Br), 1674 ν(C=N). ^1H NMR: 8.85 δ (s, 1H, of =CH), 8.49 δ (d, 1H, of —ArH), 7.8–7.9 δ (dd, 2H, of —ArH) 7.15–7.8 δ (m, 7H, of —ArH), 6.9–7.0 δ (d, 1H, of —ArH) and 3.83 δ (s, 3H, of —OCH_3).

Synthesis of 6-bromo, 2-phenyl-3-(3-nitrobenzalamino)-quinazolin-4(3H)-one (8): **(1)** (0.7 g, 0.0023 M) and 3-nitrobenzaldehyde (0.35 g, 0.0023 M), white amorphous powder; m.p. 242°C; yield 70%; $R_f = 0.69$, IR (cm^{-1}): 1535 ν(C—NO_2), 1681 ν(C=O) of ketone, 3085 ν(CH) of hetero-aromatic ring, 686 ν(C—Br), 1681 ν(C=N). ^1H NMR: 9.4 δ (s, 1H, of =CH), 8.4–8.5 δ (s, 1H, of —ArH), 8.3–8.39 δ (d, 1H, of —ArH), 7.85–8.0 δ (dd, 2H, of —ArH), 7.2–7.7 δ (m, 7H, of —ArH) and 7.6 δ (t, 1H, of —ArH).

Synthesis of 6-bromo, 2-phenyl-3-(4-carboxybenzalamino)-quinazolin-4 (3H)-one (9): (1) (0.7 g, 0.0023 M) and 4-carboxy benzaldehyde (0.345 g, 0.0023 M), pale cream-coloured amorphous powder; m.p. 240°C; yield 66.7%; $R_f = 0.78$. IR (cm^{-1}): 3500 ν(OH) of acid, 1681 ν(C=O) of ketone, 3030 ν(CH) of hetero-aromatic ring, 694 ν(C—Br), 1681 ν(C=N). ^1H NMR: 8.89 δ (s, 1H, of =CH), 8.1–8.2 δ (d, 1H, of —ArH), 7.7–7.8 δ (d, 2H, of —ArH) and 7.1–7.85 δ (m, 9H, of —ArH).

Anticancer activity: Synthesized trisubstituted quinazolin-4-ones were evaluated for their anticancerous activity[15, 16] by counting the mean survival time at different doses ranging from 2 to 250 μg in mice bearing Ehrlich ascites carcinoma (EAC).

Animals: Adult Swiss albino mice, 7–9 weeks of age, weighing 20–25 g of either sex were used. They were housed in polypropylene cages and were given standard mouse pellet and water *ad libitum*.

Tumour cells: Ehrlich ascites carcinoma was procured from Department of Radiobiology, Kasturba Medical College, Manipal, India. Tumour cells were maintained and propagated intraperitoneally by serial transplantation in adult Swiss albino mice.

Preparation of drug solution

All nine synthesized compounds were made into four groups each having four

different doses, namely, 250, 100, 50 and 02 μg. Weighed amounts of synthesized compounds were triturated with 1% of tragacanth in distilled water, so that the required doses were present in 0.5 mL of drug suspension. Fresh drug suspensions were prepared every day.

Experimental design

The ascetic fluid of the donor animal bearing 8–10 days old tumour was collected by drawing the fluid from the peritoneal cavity using a sterile disposable 1 mL syringe with 26-gauge needle under strictly aseptic conditions. The fluid was diluted immediately with normal saline. Dilution was followed by the determination of percentage viable cells adopting tryphan blue exclusion method. This was followed by the cell count using Wright's stain in Neubaurs chamber. Counting was done similar to that of white blood cells and the dilution was made with normal saline to get a concentration of 5×10^6 cells per mL so that 0.5 mL of ascetic fluid contains 1×10^6 cells (challenging dose required to induce the development of cancer). The experimental animals were injected intraperitonially with 0.5 mL suspension of ascetic fluid.

Antimicrobial activity

1. *Standard antibiotic solution*: Streptomycin (100 μg/mL).
2. *Synthesized compound solutions*: Nine compound solutions are made in the dimethyl formamide (100 μg/mL) solution.
3. *Chemicals*: Sodium chloride, dimethyl formamide (DMF), rectified spirit and 70% alcohol.
4. *Apparatus/facilities*: Hot air oven, autoclave, laminar air flow, incubator, etc.
5. *Test organisms*: Gram +ve: *Bacillus subtilis*, *Staphylococcus aureus*. Gram –ve : *Escherichia coli*, *Pseudomonas aeruginosa*.
6. *Culture media*: Nutrient agar from Himedia.

Assay method

Nine compounds were screened for their antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa* by cup-plate method[17]. Nutrient agar was melted in a water bath and cooled to 45°C with gentle shaking before pouring into the sterilized petri dishes (20–25 mL each petri dish). The poured material was allowed to set (1–1.5 h) and thereafter the 'Cups' (10 mm diameter) were made by punching into the agar surface with a sterile cork-borer and scooping out the punched part of the agar. Into these cups were added 0.1 mL portions of the test compound (100 μg/mL) in solvent with the help of a sterile syringe. The drug solution was allowed to diffuse for about 1 h into the medium. The plates were incubated at 37°C for 48 h and the zone of inhibition was measured. A solvent control was also run to know the activity of the blank (solvent). This was carried out in DMF at a concentration of 100 μg/mL. The standard drug streptomycin was also screened under similar conditions for comparison at a concentration of 100 μg/mL.

Conclusion

We hereby conclude that the synthesized 2,3,6-trisubstituted quinazolin-4-ones are ineffective in mice bearing Ehrlich ascites carcinoma. All the synthesized compounds of trisubstituted quinazolin-4-ones can be studied for: (1) their anticancerous activity evaluating percentage increase in life span for other varieties of cancer, (2) antibacterial activity against other microorganisms.

ACKNOWLEDGEMENT

We thank Professor M. Lakshmana, Principal, Government College of Pharmacy, Bangalore for helping to get financial grants from various pharmaceutical industries in Bangalore, Karnataka, India.

REFERENCES

1. V.K. Srivastava, S. Singh, A. Gucati and K. Shankar, *Indian J. Chem.*, **26B**, 652 (1987).
2. D.P. Gupta. S. Ahmad, A. Kumar and K. Shankar, *Indian J. Chem.*, **27B**, 1060 (1988).
3. M.R. Chaurasia and A.K. Sharma, *J. Indian Chem. Soc.*, **62**, 308 (1985).
4. D.D. Mukherji, S.R. Nautiyal, C.R. Prasad and B.N. Dhawan, *Indian J. Med. Res.*, **71**, 480 (1980).
5. V. Joshi and R.P. Chaudari, *Indian J. Chem.*, **26B**, 602 (1987).
6. V.J. Ram, R.C. Srimal, D.S. Kushwaha and L.J. Mishra, *J. Prakt. Chem.*, **332**, 629 (1990).
7. N. Tiwari, B. Chaturvedi and Nizamuddin, *Indian J. Chem.*, **28B**, 200 (1989).
8. H.J. Yale and M. Kalkstein, *J. Med. Chem.*, **10**, 334 (1967).
9. G.L. Neil, L.H. Li, H.H. Buskirk and T.E. Moxley, *Cancer Chemotherapy*, **56**, 163 (1972).
10. J.B. Jiang, D.P. Hesson, B.A. Dusak, D.L. Dexter, G.J. Kang and E. Hamel, *J. Med. Chem.*, **33**, 1721 (1990).
11. C.M. Lin, G.J. Kang, M.C. Roach, J.B. Jiang, D.P. Hesson, R.F. Luduena and E. Hamel, *Molecular Pharmacol.*, **40**, 827 (1991).
12. M.J. Hour, L.J. Huang, S.C. Kuo, Y. Xia, K. Bestow, Y. Nakanishi, E. Hamel and K.H. Lee, *J. Med. Chem.*, **43**, 4479 (2000).
13. B.R. Shah, J.J. Bhatt, H.H. Patel, N.K. Undavia, P.B. Trivedi and N.C. Desai, *Indian J. Chem.*, **34B**, 201 (1995).
14. A.S. Wheeler and W.M. Oates, *J. Am. Chem. Soc.*, 770 (1910).
15. A.C. Sharada, F.E. Solomon, P. Uma Devi, N. Udupa and K.K. Srinivasan, *Acta Oncologica*, **35**, 95 (1996).
16. J.K. Khanam, S.P. Bag, B. Sur and P. Sur, *Indian J. Pharmacol.*, **29**, 157 (1997).
17. R. Cruickshank, J.D. Dugid, D.P. Marmion and R.H.A. Swain, Medical Microbiology, Vol. 2, Churchill-Livingstone, Edinburgh-London (1975).

(*Received*: 16 October 2003; *Accepted*: 6 July 2004) AJC-3493