

SYNTHESIS OF SOME 6-BROMO QUINAZOLINONE DERIVATIVES FOR THEIR PHARMACOLOGICAL ACTIVITIES.**CH.RAJVEER^{1*}, D.KUMARASWAMY¹, S.SUDHARSHINI¹ AND B.STEPHEN RATHINARAJ¹.**

1. Department of Pharmaceutical chemistry, Vaagdevi College of Pharmacy, Warangal.Andhrapradesh.

Corresponding author* steaje@gmail.comABSTRACT**

A number of substituted 6-bromoquinazolinones are known for their pharmacological importance like anti-inflammatory, analgesic and anti-bacterial activity. In the present investigation is carried out for the synthesis of 2-(6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl)-N-substituted acetamides and 1-Amino-5-(6-bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3yl) methyl-1, 3, 4-triazin-2-thiol to carry out their pharmacological activities. A number of oxoquinazoline derivatives have been synthesized, purified and characterized with the help of their analytical and spectral data (IR, NMR & Mass).The required ethyl [6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl] acetate has been synthesized from 6-bromo-2-phenyl-1,3,4-benzoxazinone and ethyl glycinate. By the use of corresponding primary amines the N-substituted acetamides and by the use of hydrazine hydrate the 1-amino-5-[6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl] methyl 1, 3, 4-triazin-2-thiol were prepared. The synthesized compounds were screened for their anti-bacterial activity, anti-inflammatory activity and analgesic activity by standard methods. The compound shows Pharmacological activities in comparison with the standard.

KEY WORDS

Oxoquinazoline, Anti-inflammatory activity, Analgesic and Anti-bacterial activity.

INTRODUCTION

Quinazoline is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring having broad spectrum of medicinal values such as anti bacteria¹⁻⁸, anti fungal⁹⁻¹⁰, anti cancer¹¹⁻¹², anti-inflammatory¹³⁻¹⁷, antiviral¹⁸, anti tuberculosis¹⁹, CNS depressant activity²⁰, Anti-parkinsonism²¹⁻²³, bronchodilator activity²⁴ etc. In the present investigation is carried out for the synthesis of 2-(6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl)-N-substituted acetamides and 1-Amino-5-(6-bromo-3,4-dihydro-2-phenyl-4-oxoquinazolin-3yl)methyl-1,3,4-triazin-2-thiol yielded accordingly to

scheme no.1.and to carry out their biological activity.

MATERIAL AND METHODS

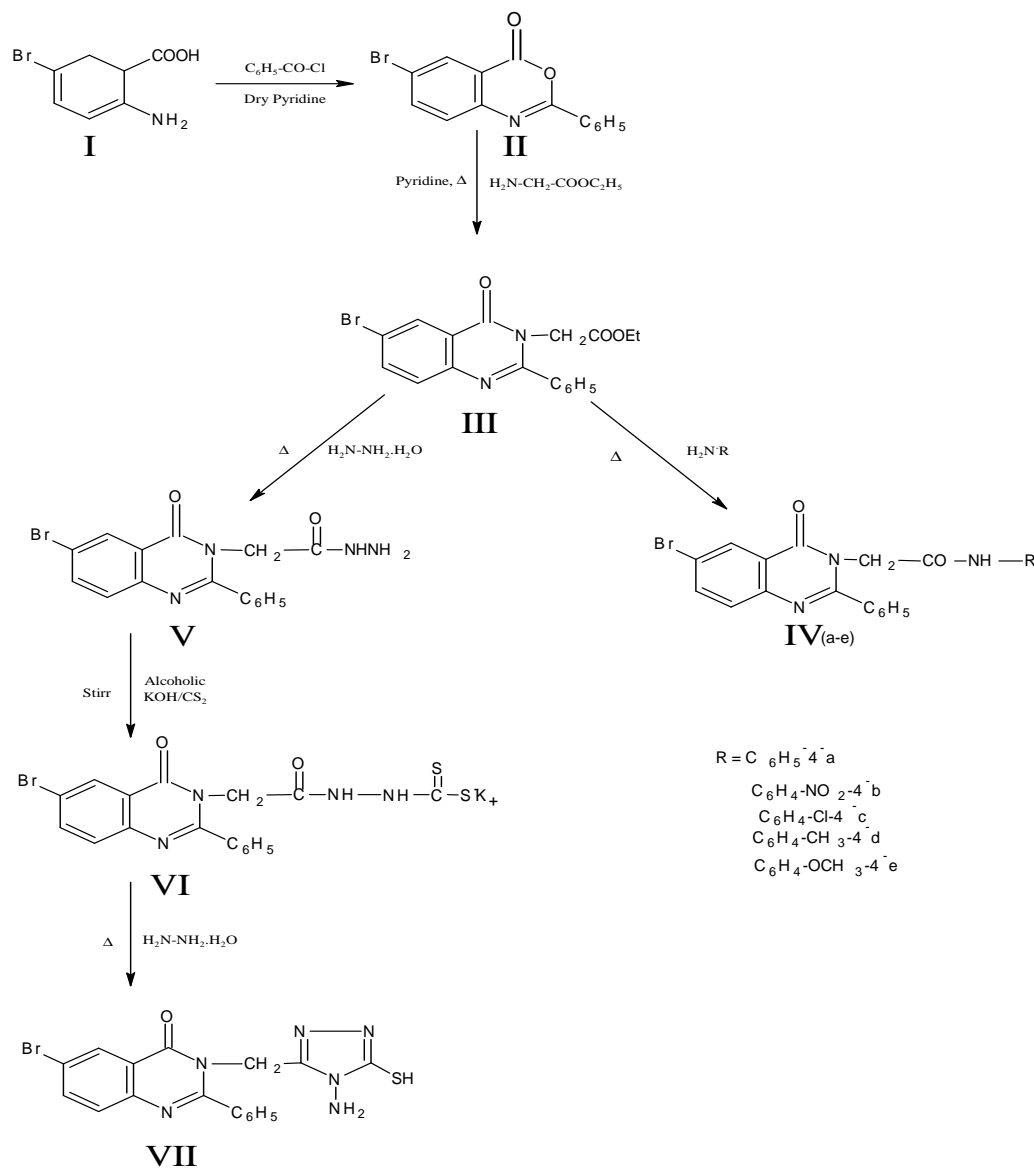
All chemicals were obtained from Center Drug House (CDH), New Delhi. All chemicals and solvents used were of analytical grade.

EXPERIMENTAL

All the melting all the melting points were determined in open capillary and are uncorrected. The purity is checked by TLC. IR spectras were recorded in KBr on shimadzu F.T. – IR 8300spectrophotometer.

Analytical data were also confirmed from its ¹H-NMR Spectra. The starting compound Ethyl (6-Bromo-3, 4-dihydro-2-phenyl-4-

oxoquinazolin-3-yl) acetate has been prepared according to known method.



Scheme 1

I - 5-Bromoanthranilic acid.

II - 6-Bromo-2-phenyl-1, 3, 4-benzoxazinone.

III - Ethyl (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3-yl) acetate.

IV- 2-[6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl]-N-substituted acetamide.

V- (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3yl) acetic acid hydrazide.

VI- Potassium-N (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3yl) acetyl dithiocarbazinate.

VII- 1-Amino-5-(6-bromo-3.4-dihydro-2-phenyl-4-oxoquinazolin-3yl) methyl-1, 3, 4-triazin-2-thiol

1. Synthesis of 5-Bromoanthranilic acid from Anthranilic acid (I) Bromination of anthranilic acid below the freezing point of glacial acetic acid

Anthranilic acid (20gms) was dissolved in glacial acetic acid (250cc) and cooled below 15°C. Then bromine (9.5 cc) in acetic acid has been run in, till the reddish-brown color of the bromine persisted. Before this point was reached the mixture had been converted into a thick mass of white glistening crystals consisting of the hydro bromides of the mono and dibromo anthranilic acids. The product was filtered off washed with benzene and after drying was found to weight 54.7 gm. It was then boiled up with water (500cc) containing concentrated hydrochloric acid (25cc) and filtered while hot under suction. The insoluble residue was extracted twice with boiling water (500cc). The filtrate, upon cooling yielded an abundant precipitate of the monobromo anthranilic-acid.

2. Synthesis of 6-Bromo-2-phenyl-1, 3, 4-benzoxazinone (II)

5-Bromoanthranilic acid (0.1mol) was dissolved in excess of freshly distilled benzoyl chloride and heated under reflux for 4 hrs. The excess of benzoyl chloride was distilled-off under reduced pressure. The compound obtained on cooling was repeatedly washed with small portions of pet. ether (60°-80°C) to get a color less crystalline solid

3. Synthesis of Ethyl (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3-yl) acetate (III)

6-Bromo 2-phenyl 1, 3, 4-benzoxazinone (0.01 mol) and glycine ethyl ester (0.01mol) are taken in a round bottom flask then pyridine (freshly distilled and dried) was added slowly while shaking. The mixture was heated under refluxed for 8 hrs. Excess of pyridine was distilled off under reduced pressure, then the solution was poured into a beaker contained crushed ice, to get the product. It was filtered under suction, washed with portions of ice cold water and dried at 100°C. The product was

purified by recrystallization with ethanol to get a colorless crystalline solid.

4. Synthesis of 2-[6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl]-N-substituted acetamide (IV) (a-e)

Ethyl [6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl] acetate (0.01 mol) and corresponding primary amines (0.01 mole) are taken in a round bottom flask then glacial acetic acid was added slowly while shaking. The mixture was heated under refluxed for 4-6 hrs. After cooling, the contents were poured into crushed ice. The resulting solid was washed with distill water, filtered, dried in vaccum and recrytallized from warm ethanol.

5. Synthesis of (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3yl) acetic acid hydrazide (V)

A mixture of ethyl ester (0.01mol) and hydrazine hydrate 99 % (0.01mol) in absolute ethanol was heated under reflux on a water bath of 30 min. The excess of ethanol was distilled-off to a possible extent and cooled. The resultant solid was separated by filtration and dried. It was purified by recrystallization from alcohol to get colorless flakes.

6. Synthesis of Potassium-N (6-Bromo-3, 4-dihydro-2-phenyl-4-oxoquinazolin-3yl) acetyl dithiocarbazinate (VI)

Carbon disulphide (12ml) was added drop wise to an ice cold solution of potassium hydroxide (0.015 mol) in absolute alcohol (20 ml) containing acid hydrazide (0.01mol). The mixture was diluted with absolute alcohol (15 ml) and stirred at room temperature for 14 hrs. Dry ether (20 ml) was then added and the separated solid was filtered, washed with portions of ether and re-crystallized with ethanol to get a colorless, crystalline solid.

7. Synthesis of 1-Amino-5-(6-bromo-3,4-dihydro-2-phenyl-4-oxoquinazolin-3yl) methyl-1, 3, 4-triazin-2-thiol (VII)

A mixture of dithiocarbazine (0.01mol), hydrazine hydrate 99%(0,02 mol) and water (2ml) was heated under reflux for 2 hrs then cold water (10 ml) was added and the mixture was neutralized with acetic acid. The resultant solid

thus separated was filtered, washed with small portion of cold water and dried. It was purified by recrystallization from ethanol to get a colorless, crystalline compound.

Table .1
Elemental analysis of some novel oxoquinazoline derivatives.

No	Compound	R	M.F	Yield (%)	M.P (°C)	C	%Analysis H	Calc. (Found) N	Br	O
1	IV _a	-C ₆ H ₅	C ₂₂ H ₁₆ N ₃ O ₂ Br	81	180	60.84	3.71	9.68	18.40	7.37
2	IV _b	-C ₆ H ₄ -NO ₂	C ₂₂ H ₁₅ N ₄ O ₄ Br	75	175	55.13	3.15	11.69	16.67	13.35
3	IV _c	-C ₆ H ₄ -Cl	C ₂₂ H ₁₅ N ₃ O ₂ ClBr	60	178	56.37	3.23	8.96	17.05	6.83
4	IV _d	-C ₆ H ₄ -CH ₃	C ₂₃ H ₁₈ N ₃ O ₂ Br	72	190	61.62	4.05	9.37	17.82	7.14
5	IV _e	-C ₆ H ₄ -OCH ₃	C ₂₃ H ₁₈ N ₃ O ₃ Br	68	205	56.37	3.23	8.96	17.21	10.34

Table .2
Spectral data of some novel oxoquinazoline derivatives

Compound	IR Bands (cm-1)	Types of Vibrations	d ppm	Proton nature
II	1759, 1647, 525.79, 3052.6	Cyclic lactonic carbonyl group, C=N str. C-Br, C-H Aromatic.		
III	1736, 1687.6, 1593.7, 3072	lactam carbonyl group, ester carbonyl group, C=N and C=C, -N-CH ₂ -Str.		
IV(a)	3288, 1686.6, 1653.1, 1596.7, 3052.1, 596.2.	-NH-Ar, carbonyl group of lactam (quinazolinone), C=N, C=C, C-H aromatic, C-Br	7.76 2.94 5.50 6.10 7.60 8.10 8.36	s, 5H, Ar-C ₆ H ₅ , s, 2H, N-CH ₂ -CO, s, 1H, D ₂ O exchangeable -NH-Ar, s, 5H, Ph, d, 1H, C ₈ -H, dd, 1H, C ₇ -H, d, 1H, C ₅ -H
IV (c)	1736.01, 1687.6, 1593.7, 3072.4, 798.8	Carbonyl group of lactam (Quinazolinone), C=O, Acetyl, C=C, Aromatic, -N-CH ₂ , Stretching, C-Cl.		
V	3230, 1703.5, 1624.0, 1599.8, 1567.3, 1213.6	-CO-NH-NH, C=O acid, C=O quinazolinone, C=N, C=C, C=S		
VI	3416, 3317, 1674, 1600, 1208.6, 6755	-NH and NH ₂ , C=O, quinazolinone, C=N, C=C, C-Br	6.70, 3.32, 5.50, 7.50, 7.82, 8.20	s, 5H, Ar-C ₆ H ₅ , s, 2H, -N-CH ₂ - s, NH and NH ₂ d, 1H, J=9.0Hz; C ₈ -H dd, 1H, J=2.0 Hz & J=9.0 Hz, C ₇ -H d, 1H, J=9.0 Hz, C ₅ -H
VII	3614, 3317, 1674, 1600, 1208.6, 6755	NH, NH ₂ , C=O, quinazolinone, C=N and C=C, C=S, C-Br	6.70, 3.22, 5.50, 7.50,	s, 5H, -C ₆ H ₅ s, 2H, -N-CH ₂

7.82,	s, 3H, NH and NH ₂
8.20	<u>d</u> , 1H, J=9.0Hz; C ₈ -H
	<u>dd</u> , 1H, J=2.0 Hz &
	J=9.0 Hz, C ₇ -H
	<u>d</u> , 1H, J=9.0 Hz, C ₅ -H

ANTI-INFLAMMATORY ACTIVITY²⁵

Carrageenan-induced Rat Hind –paw Edema Method

The anti-inflammatory activity of the test compounds was determined by the rat hind-Paw edema method. A 1% w/v solution of carrageenan (0.1ml) as the phlogistic agent was used to induce inflammatory. By measuring the change in the volume of mercury displaced by the inflamed paw in a "Plethysmograph" the extent of reduction was determined for each compound which in turn, reflects directly on the anti-inflammatory potency of the compounds. Indomethacin at a dose of 100mg/kg (b.W) was employed as the standard drug. The control group was maintained with normal saline.

Albino rats (100-150 g) were divided into six groups of four animals each. Initial paw volume (both right and left) of each rat was recorded using "Plethysmograph". Test compounds were prepared suspension in 0.3% carboxy methyl cellulose (CMC) and given by oral route at a dose of 100mg/kg (b.w). The animals of standard group was given indomethacin at a dose of 100mg/kg (b.w) subcutaneously. After 30 minutes of administration of the test and standard compounds, 0.1 ml of 1% carrageenan in 0.9% saline was injected subcutaneously in the sub plantar region of the left hind paw of each animal. After the lapse of 3 hours following the injection of carrageenan, the change in paw volume in each animal was measure, once again using plethysmograph. Control groups received 0.3 ml of normal saline (subcutaneously). paw volumes of control group were compared with the standard and test groups. The results are in presented in Table 3.

Tail Flick Method in Rats

Tail flick response in albino rats was adopted for the evaluations of analgesic activity of the new quinazoline derivatives. A hot-wire analgesiometer was used for the determination of the pain threshold of rats. Cold water was circulated through the water jacket of the instrument to avoid the heating of the area around the hot-wie. Albinorats were weighed and divided into six groups having four animals in each.

The animals were placed in a rat-holder and the tail protruded out through the slot of the lid. The normal reaction time i.e., the time taken flick the tail was noted and the current was adjusted so that more than 90% of the rats give the tail flick response with in 4nto 15 seconds and in no case it exceeded 20 seconds. Test dose (50 mg/kg (b.W) was administered orally to the albino rats of responsive group. After one hour, the pain threshold was measured by the same technique which was used for the determination of normal flick response time. Nimesulide at a dose of 50 mg/kg was employed as the standard drug and simultaneously, a control for the vehicle was maintained. The results are presented in Table 5.

Acetic acid-induced Writhing in Mice

This method was adopted for the evaluation of analgesic activity of the test compounds. An Intraperitoneal injection of acetic acid produces pain reaction which is characterized as a writhing response. Constriction of abdomen, turning of trunk (twist) and extension of hind legs as the reaction to chemically induced pain. Analgesic drugs should inhibit the induced writhing responses.

Mice (either sex) 20-25 g were weighed and divided in to six groups of four animals in each. Normal response i.e. ., administered volume of acetic acid solution (1% v/v, dose

1ml/10kg b.w) the onset of wriths were noted for a period of 20 min. Test dose (100mg/kg b.w) was injected and after 15 min, a solution of acetic acid was administered to these animals. Aspirin at a dose of 100mg/kg (b.w.) was employed as

a standard drug for comparison. The onset and severity of writhing responses for each compound was recorded. The results are presented in table 4.

Table 3.
Data on Anti-Inflammatory Activity of novel Oxoquinazoline Derivatives.

S.no	Compounds	No. of rats	Mean initial paw vol.	Mean final Vol.	Mean change in paw vol.	S.D	S.E	t-values	P-value
1.	Control	4	0.1	0.615	0.515	---	---	---	---
2.	Standard	4	0.09	0.3125	0.190	0.0234	0.0117	7.016	□<0.05
3.	Compound IV-a	4	0.095	0.3225	0.220	0.0221	0.0110	8.601	<0.05
4.	Compound IV-b	4	0.095	0.60	0.265	0.0318	0.0159	7.341	<0.05
5.	Compound IV-c	4	0.09	0.2075	0.1125	0.0320	0.0160	2.976	<0.05
6.	Compound IV-d	4	0.095	0.185	0.1125	0.0225	0.0112	4.233	<0.05
7.	Compound IV-e	4	0.09	0.2075	0.1125	0.0320	0.0160	2.976	<0.05
8.	Compound VII	4	0.095	0.60	0.265	0.0318	0.0159	7.341	<0.05

Table 4.
Data on Analgesic activity of Novel Oxoquinazoline Derivatives by Writhing method.

S.No	Compounds	No of Mice	No .Of Writhing	S.D	S.E	t-Value	P.Value
1.	Control	4	10	---	----	----	---
2.	Standard	4	8	1.0	0.5	6.92	<0.05
3.	Compound IV-a	4	9.25	1.1062	0.5531	7.232	<0.05
4.	Compound IV-b	4	7.5	0.644	0.322	10.0	<0.05
5.	Compound IV-c	4	7	0.9120	0.456	6.646	<0.05
6.	Compound IV-d	4	8.5	1.5540	0.777	4.736	<0.05
7.	Compound IV-e	4	9.25	1.1062	0.5531	7.232	<0.05
8.	Compound VII	4	7.5	0.644	0.322	10.0	<0.05

Standard-Diclofenac (100mg/Kg)

Test Dose (100mg/kg)

Table .5
Data on Analgesic Activity of new Oxoquinazoline Derivatives by Tail Flick method.

S.No	Compounds	No of rats	Mean of normal reaction in sec.	Mean of reaction time after drug admn (Sec)	S.D	S.E	t-Value	P.Value
1.	Control	4	4.2	3.175	----	----	----	---
2.	Standard	4	4.9	9.7	2.74	1.37	3.03	<0.05
3.	Compound IV-a	4	4.1	6.1	1.165	0.582	7.44	<0.05
4.	Compound IV-b	4	4.15	8.85	2.75	1.37	2.80	<0.05
5.	Compound IV-c	4	4.0	7.35	4.0	2.025	2.35	<0.05
6.	Compound IV-d	4	3.95	6.50	1.47	0.735	3.92	<0.05
7.	Compound IV-e	4	2.87	5.50	1.37	0.634	2.82	<0.05
8.	Compound VII	4	4.15	8.85	2.75	1.37	2.80	<0.05

Test Dose (50 mg/ kg)

Standard –Nimesulide (50 mg/Kg)

ANTIBACTERIAL ACTIVITY²⁶

The synthesized compounds were tested against gram positive bacteria *staphylococcus aureus* and *Bacillus cereus*, gram negative bacteria *E. coli*, *Candida albicans* and *Pseudomonas aeruginosa*. The glass Petri dishes were cleaned and sterilized. The nutrient agar media is mixed with sufficient quantity of distilled water and sterilized. The media were allowed to solidify at room temperature. A sterile borer was used to prepare 4 cups of 8mm diameter in the agar media. A test solution of synthesized compounds

IV was prepared at a concentration of 500 µg/ml with DMF. A solution of the standard drug Ampicillin was prepared at the same concentration. Accurately measured (0.1 ml) solution of the test and standard samples were added to the cups with a micropipette. All Petri dishes were incubated at $37 \pm 1^{\circ}\text{C}$ for 24 hrs. The solvent DMF was used as blank. The diameter of zone of inhibition was measured and recorded is presented in table-6.

Table .6
Antibacterial Activity of some novel oxoquinazoline derivatives.

S.No.	Compound	Zone of Inhibition (in mm)				
		E.coli	B. subtilis	P.aeruginosa	S.aureus	C. albicans
1	IV(a)	16	15	12	14	4
2	IV(b)	12	11	10	13	8
3	IV(c)	12	13	14	15	9
4	IV(d)	18	16	14	14	11
5	IV (e)	16	14	12	14	10
6	VII	20	18	20	16	13
7	S	32	21	31	28	22
8	B	0	0	0	0	0
S	- Standard	-	-	-	-	-
B	- Blank	-	-	-	-	-

RESULTS AND DISCUSSION

A series of oxoquinazoline derivatives II,III, IV(a-e) and VII were synthesized and their structure was elucidated by elemental analysis, IR, ¹H-NMR and Mass spectra, yields melting points, calculated in table-1, 2.

Anti-inflammatory activity

It is interesting to note from Table-3 that all the 6 new Oxoquinazoline derivatives possess a significant ($p < 0.05$) anti inflammatory activity at a oral dose of 100mg/kg (b.w) .Further their anti inflammatory potency was comparable to that of the standard indomethacin at the same dose based on the difference in the mean paw volume, in comparison with the standard, compounds IV-c, IV-d,IV-e and,VII were found to be more effective.

Analgesic activity

Tables -4 and 6 reveals the analgesic potency of new oxo quinazoline derivatives by two different **methods**. The test compounds were found to exhibit the analgesic activity in both the methods without any much variation. In the tail flick method, Nimesulide at equal dose, i.e., 50 mg/kg (b.w) was employed as the standard and the results are comparable. Like wise in the writhing method, Diclofenac was employed as the standard at an oral dose of 100mg/kg (b.w).At the same dose the analgesic activity of new oxoquinazoline derivatives was quiet comparable with the standard. But however the compound VII was found to be more superior in analgesic action by the tail-flick method and the next being compound IV-c. Interestingly almost the same two compounds showed to be effective in the writhing method as well except that compound IV-c being marginally superior that the compound VII.

Antibacterial Activity

Perusal of Table: 6 showing the data on Antibacterial activity of the compounds could reveal that all the 6 compounds could exhibit a

mild to moderate activity, against both Gram positive and Gram negative bacteria. Among the tested compounds 1-amino-2-mercaptotriazole derivative of Quinazolinone (VII) was found to show an appreciable zone of inhibition against both Gram positive and Gram negative bacteria and its activity was found to be comparable to that of the standard drug Ampicillin. The percentage activity of new quinazolinone derivatives were in the range of 66.16 % and 87.46% when compared to standard ampicillin, 100%.

REFERENCES

1. Mahadev B. Talawar, Shobha R. Desai, Marihal and Shankar C. Bennur, synthesis and antimicrobial activity of 1, 2, 4-triazoles, 1, 3, 4-oxadiazoles and 1, 3, 4 thiadiazoles. Indian J. Heterocycl.Chem., 5, 215, (1996).
2. Amir Badar MZ, Hassan El HA, Sheriff and Mohammed AM, synthesis and antibacterial activity of 6-bromo-3-aryl/alkyl-2-methyl-4(3H)-quinazolinones, thiaquinazolones and their 2-steryl derivatives. Bull. Chem. Soc. Japan, 53, 2389, (1980).
3. V. Alagarsamy, U.S. Pathak & R.K. Goyal synthesis and evaluation of some novel 2-mercapto-3- (substituted methyl amino) quinazolin-4(3H)-ones, I.J.P.S. 63 (2000).
4. Anil K, Sen Gupta and Hemant K Mishra, synthesis of new 6-bromo and 6, 8-dibromo-2-(N-(2-aryl-1, 3, 4-thiadiazol-5-yl) carbomoyl methyl thio)-3aryl/cyclohexyl-4(3H)-quinazolones J. Pharmac. Sci, 69 1313, (1980).
5. Amin Bader M.Z.Hassan E H & Sherief & Mohmoud A.M., the synthesis and antibacterial activity of 6-bromo-3-aryl/akyl-2-methyl-4(3H)-quinazolinones, thioquinazolinones and their 2-steryl derivatives Bull. Chem Soc. Japan, 53, 2389, (1980).
6. Surendra Bohadur, Srivastava Neeru & Saxena Mukta, synthesis of new 2-Phenyl-3-(4-N-substituted sulphonamido)

- phenyl-6, 8-disubstituted 4(3H)-quinazolinones J. Indian Chem. Soc., 60, 684, (1983).
7. N.A. Gangwal, U.R. Kothawade, A.P. Galande, D.S. Phande, A.S. Dhake, antimicrobial activity of 1-substituted-2-chloromethyl-4(1H)-quinazolinones. Indian J. Heterocycl. Chem., 10, 291, (2001).
 8. Ravishankar Ch, Devender Rao A, Jayasena Reddy E and Malla Reddy V the antimicrobial activity of 1-substituted-2-chloromethyl-4(1H)-quinazolinones. J.IndianChem.Soc, 60, 67, (1983).
 9. Giri.S and Singh .H, J. the synthesis and antibacterial activity of some 3-aryl-2-(N, N-disubstituted amino) methyl-4(3H)-quinazolinones and 3-aryl-2-(N⁴-arylsulfonamidomethyl)-4(3H)-quinazolinones and their 6, 8-dibromoanalogs from appropriate 3-aryl-2-chloromethyl-4(3H)-quinazolinone. Indian Chem. Soc. 49, 175, (1972).
 10. Chaurasia M.R., Sharma S.K. the synthesis of 6, 8-disubstituted-2-phenyl-3-(substituted benzothiazol-2-yl)-4(3H)-quinazolinones and their antifungal activity, J.Indian. Chem. Soc. 49, 370, (1972).
 11. Pandey V.K. & Lohani H.C. the anti-tremour activity of 2-aryl/alkyl-3(2-amino ethyl-1, 3, 4-thiadiazol-5-yl) quinazolin-4(3H) ones. J. Indian Chem. Soc., 56, 415, (1979).
 12. V. Murugan, N.P. Padmavaty, G.V.S. Ramasarma, Sunil V. Sharma & B. Suresh, the synthyesis of some quinazoline derivatives as possible anticancer agents. I.J.H.C. 13, 143 (2003).
 13. Ravi Shankar, Ch, Devender Rao, A, Malla Reddy V & Sattur P.B., the synthesis of new N⁴-(N-(6, 8-dibromo-2-methyl-3-quinazolin-4(3H)-one)-acetamido)-N¹-substituted sulfanilamides Curr.Sci. 53 1069, (1984).
 14. Ravi Shankar Ch, Devender Rao. A & Malla Reddy.V, the synthesis of 6,8-dibromo 2-methyl-3-(N-(5-alkyl-1,3,4-thiadiazol-2-yl)-carbamoyl methoxy)-4(3H)-quinazolinones and 6,8-dibromo-2-methyl-3-alkoxy-4(3H) quinazolinone Indian Drugs, 24B, 580, (1985).
 15. Abdel-Aim's, Abdel-Alim, Abdel-Nasser A, Shorbagi, Hosny.A.H, Shareif, The synthesis of 6-Bromo-2,3-disubstituted-4(3H) quinazolinones Indian J. Chem., 33B , 260, (1994).
 16. Mohd. Amir and Shalini Shahani, the synthesis and anti-inflammatory activity of naphthylmethyl oxadiazoles, thiadiazoles and triazoles. Indian J. Heterocycl. Chem. 8, 107, (1998).
 17. Saravanan, S. Mohan, K.S. Manjunatha, the synthesis and anti-inflammatory activity of some 6-bromo-2, 3-disubstituted-4(3H) quinazolinones.I.J.H.C. 8, 55, (1998).
 18. Mishra VS and Sunita Dhar, the synthesis of 2-phenyl-3-benzimidazolyl-alkyl/aryl-6-bromoquinazoline-4(3H)-ones. J.IndianChem.Soc, 55, 172, (1978).
 19. A.R. Bhat, G. Goutham Shenoy, Mohan Kotian, the synthesis and ant tubercular activity of 7-Nitro-2-methyl quinazolinones. Indian J. Heterocycl, Chem, 9, 319, (2000).
 20. R. Kumar, T.K. Gupta and Surendra S. Parmar, The synthesis of quinazolone azomethines using CNS depressant activity. Indian J. Pharm, 33, 108, (1970).
 21. Tiwari SS and Pandey VK, the synthesis of some new benzoxinones and their corresponding quinazolinones J. Indian Chem. Soc. 52, 736, (1975).
 22. S.Tiwardi SS and Rastogi RK, synthesis and antiparkinsonian activity of 2-aryl-3-(1, 3, 4-thiadiazol-2-yl)-quinazolones. J.IndianChem.Soc, 55, 477, (1978).
 23. Vijay K. Srivastava, I.P. Singh, Shrodha Singh M.B. Gupta and K. Shanker, Synthesis and anti-parkinsonism activity using 2-[2-(4-substituted phenyl) ethenyl]-3-(substituted phenyl)-4(3H)-quinazolinones Indian J. Pharmac. Sci. 48, 133, (1986).
 24. A. Raghu Ram Rao & Rajesh H Bahekar, the synthesis and bronchodilator activity of benzimidazo (1, 2,-c) quinazolines I.J.C., 38B, 434, (1999).

25. Drug discovery and Evaluation by H.Gerhard Vogel, Wolfgang H.Vogel, Springer – Verlag Berlin Heidelberg Newyork, 1997, pp.368-407.
26. Ananthnarayan R, Paniker J. Text book of microbiology. 5th Edition, Madras: orient Longman; 1997, pp- 36-44.