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Synthesis and biological evaluation of some novel oxo-quinazoline derivatives for their anti bacterial activity.

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ABSTRACT

A number of substituted oxoquinazolines are known for their biological importance like anti-bacterial and anti-inflammatory 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)methly-1,3,4-triazin-2-thiol and to carry out their biological activity. 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 by standard methods. The compound shows anti-bacterial activity in comparison with the standard.

Key words: Oxoquinazoline, Bromo substitution, Anti bacterial activity.

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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 bacteria [1-8], anti fungal [9-10], anti cancer[11-12],anti-inflammatory[13-17],antiviral [18], anti tuberculosis[19],CNS depressant activity [20], Anti-parkinsonism [21-23] , bronchodilator activity [24] 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)methly-1,3,4-triazin-2-thiol yielded accordingly to scheme no.1.and 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.

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 and cooled below 15^0C. Then bromine 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 containing concentrated hydrochloric acid and filtered while hot under suction. The insoluble residue was extracted twice with boiling water. The filtrate, upon cooling yielded an abundant precipitate of the monobrome anthranilic-acid.

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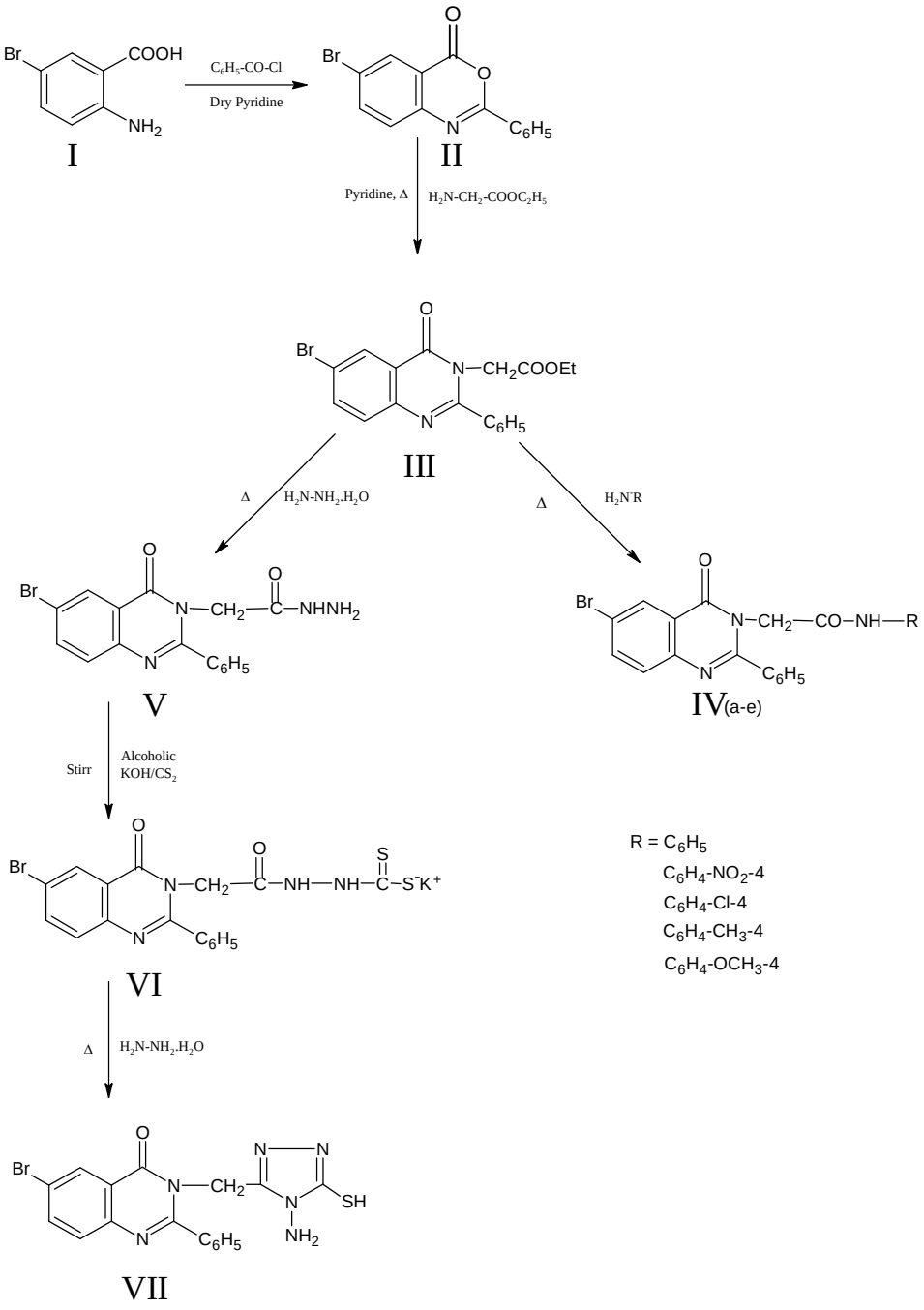
2. Synthesis of 6-Bromo-2-phenyl-1, 3, 4-benzoxazinone (II):

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^{o}-80^{o}C) to get a color less crystalline solid.

Scheme: 1



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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^{o}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 distilled 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 dithiocarbazinate (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 solid.

Antibacterial activity [25]

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. Test solutions of synthesized compounds IV & VII were 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^{0}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-3.

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Table No 1: Elemental analysis of some novel oxoquinazoline derivatives.

No	Compound	R	M.F	Yield (%)	M.P (^{0}C)	%Analysis Calc. (Found) C	H	N
1	IV_a	$-C_6H_5$	$C_{22}H_{16}N_3O_2Br$	81	180	60.84	3.71	9.68
2	IV_b	$-C_6H_4-NO_2$	$C_{22}H_{15}N_4O_4Br$	75	175	55.13	3.15	11.69
3	IV_c	$-C_6H_4-Cl$	$C_{22}H_{15}N_3O_2ClBr$	60	178	56.37	3.23	8.96
4	IV_d	$-C_6H_4-CH_3$	$C_{23}H_{18}N_3O_2Br$	72	190	61.62	4.05	9.37
5	IV_e	$-C_6H_4-OCH_3$	$C_{23}H_{18}N_3O_3Br$	68	205	56.37	3.23	8.96

Table No. 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)	3326, 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_6H_5, s, 2H, N-CH_2 – CO, s 1H, D_2O 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	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		
VII	3614,3317 , 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_6H_5, s 2H, -N-CH_2- s,NH and NH_2 d, 1H, J=9.0Hz; C_8-H dd, 1H, J=2.0 H_z & J=9.0 H_z, C_7-H d, 1H, J=9.0 Hz, C_5-H

RESULTS AND DISCUSSION

A series of oxoquinazoline derivatives II,III, IV(a-e) VI and VII were synthesized and their structure was elucidated by elemental analysis, IR, 1H-NMR and Mass spectra, yields melting points, calculated in table1, 2. The compounds were screened for antibacterial activity against *E.coli* (Gram negative) and *S. aureus* (Gram positive) by Cup plate method. All the observations are given in table 3.

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Table No.3.Antimicrobial activity of some novel oxoquinazoline derivatives.

S.No.	Compound	Zone of Inhibition (in mm)				
		E.coli	*B. subtills*	*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 - Ampicillin
B - Blank - DMF

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