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Synthetic and Pharmacological Evaluation of some 4-Quinazolinone derivatives

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Abstract: A series of ten novel quinazolin-4-one 3a -3j have been synthesized by the reaction between 3-(4-aminophenyl)-6-bromo-2-phenylquinazolin-4-one and different substituted aldehydes by using ethanol as a solvent. The newly synthesized compounds were characterized by elemental, IR and mass spectra analysis. The synthesized compounds were evaluated for antibacterial and antifungal activities by Agar diffusion method. All the compounds 3a -3j at different concentrations and all compounds were screened for their antibacterial activity against E. coli, S. aureus, B. spizinzenii, P. aeruginosa, S. paratyphi, B. pumillus, K. pneumoniae, and yeast C. albicans by disk diffusion method. Compounds showed good antibacterial activity against *Staphylococcus aureus* and *Bacillus* spizinzenii. Compounds 3a -3j exhibited good antifungal activity against *Candida albicans* fungus.
Keywords: Quinazoline, Benzoxazine, Synthesized & Characterised, antibacterial, antifungal.

Introduction

In recent years there has been considerable interest in the synthesis of substituted quinazoline derivatives due to their pharmacological activities[1]. Especially quinazolin-4-one motifs are having many interesting activity profiles namely EOX – 1 inhibitors[2]. Inhibitors of the bacterial enzyme Mur – B[3], non-nucleosides inhibitors of HfV-RT[4] and anti histamine agents[5]. Quinazolin-4-one are the derivatives of quinazoline which belong to an important group of heterocyclic compounds containing nitrogen in a six member ring[6-9]. In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in quinazolin-4-one molecule and study their biological and pharmacological activity.

Experimental

Materials

6-bromo-2-phenyl-3, 1-benzoxazin-4-one and 3-(4-aminophenyl)-6-bromo-2-phenyl quinazolin-4-one was prepared accordingly to the literature method[10]. The aromatic benzaldehyde and substituted benzeldehydes were B.D.H. regents. Chemicals and solvents used were dried and purified by standard methods and moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes.

Measurements:

The melting points were determined in open capillary tubes and are uncorrected. IR- spectra were recorded on a Shimadzu FTIR-8400 instrument in KBr disc.

1H- NMR – spectra were recorded on a Bruker AC- 300 MHz FT NMR using TMS as internal standard, chemical shift are in δ-ppm, mass spectra were recorded on a Jeol D- 300 spectrometer. All the synthesized compounds gave satisfactory elementary analysis.

Antimicrobial activity of all the compounds were studied against E. coli, S. aureus, B. spizinzenii, P. aeruginosa, S. paratyphi, B. pumillus, K. pneumoniae microorganisms and yeast C. albicans at a concentration of 50µg/ml by agar cup method. Methanol system was used as control in the method[11]. The area of inhibition of zone is measured in percentage.

Preparation

(1) Preparation of 6-bromo-2-phenyl-3,1-benzoxazin-4-one: 5-bromo anthranilic acid (0.01m) in 30ml pyridine was added benzoyl chloride (0.02m) and the mixture was shaken for 5 minutes and then kept aside at room temperature for further 25 minutes with occasional shaking. The reaction mixture was treated with 15ml 5% $NaHCO_3$. The product separated as solid mass. The yield of the product was 58% and the products melts at 180°C.

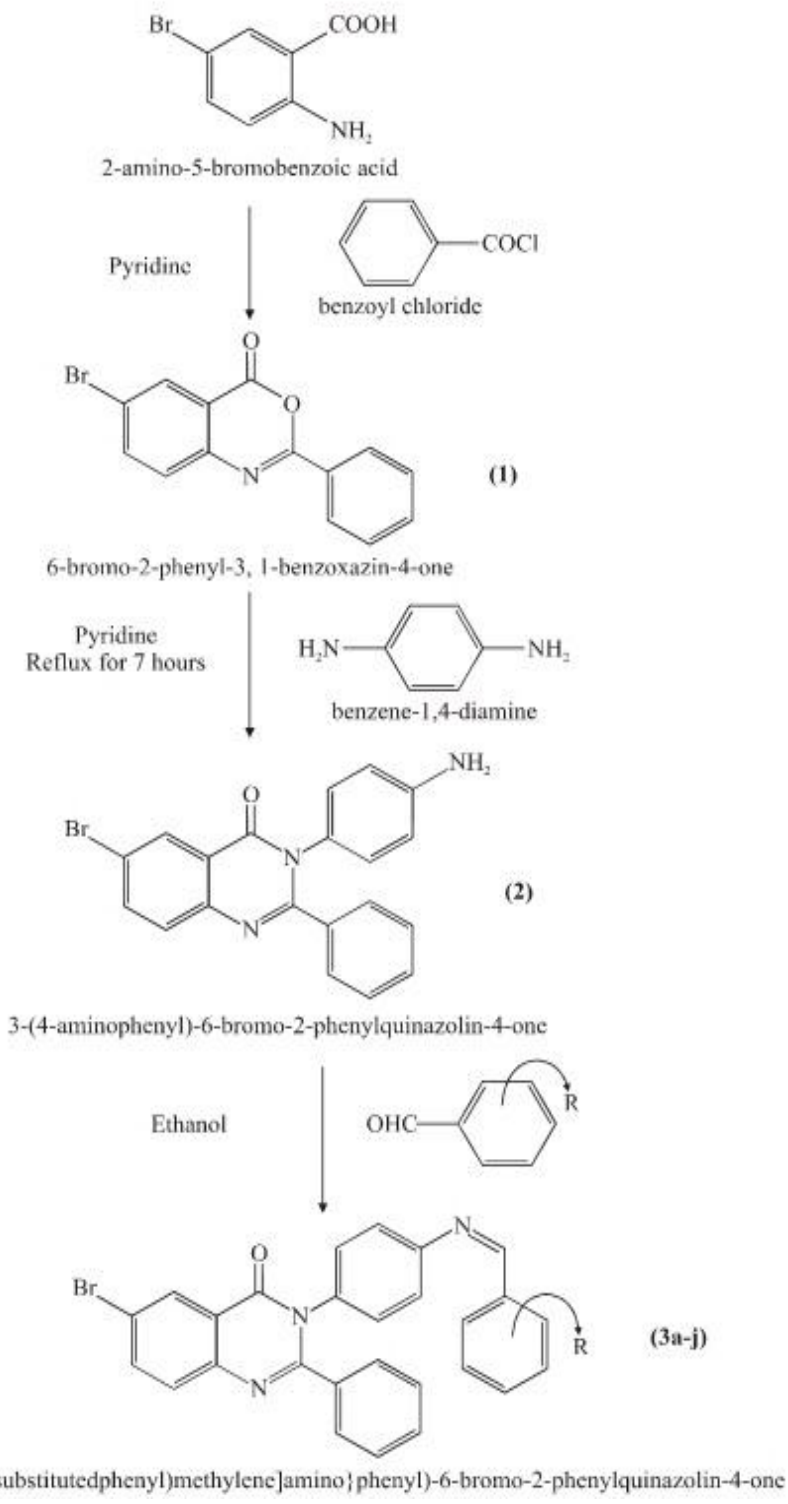
(2) Preparation of 3-(4-aminophenyl)-6-bromo-2-phenyl quinazolin-4-one: In a 250 ml conical flask (equipped with a reflux condenser) a mixture of 6-bromo-2-phenyl-3, 1-benzoxazin-4-one (0.1M), benzene-1, 4-diamine (0.1M), 25ml pyridine and about one pellet of KOH was placed and was heated on sand bath for 7-8 hours. The mixture was then poured in ice. The precipitates were collected, washed with 10% HCl and re-crystallized from ethanol. The yield of the product was 72% and the product melts at 210°C.

(3) Preparation of 3-(4-{[(substituted)methylene]amino} phenyl) -6-bromo-2-phenylquinazolin-4-one (3a-j) : To a solution of 3-(4-aminophenyl)-6-bromo-2-phenylquinazolin-4-one (0.01M) in absolute ethanol (60ml), 2-chlorobenzaldehye (0.01M) and a few drops of glacial acetic acid were added and the mixture refluxed for 10h. It was then cooled, concentrated and poured into crushed ice and filtered. The product thus obtained was purified by recrystallization from methanol to get compound 3-(4-{[(2-chlorophenyl)methylene] amino} phenyl) -6-bromo-2-phenylquinazolin-4-one. The yield of the product was 71% and the product melts at 240°C. The characterizations of compounds were shown in **Table-1**.

Table - 1

Physical Constant 3-(4-{[(substitutedphenyl)methylene]amino}phenyl)-6-bromo-2-phenylquinazolin-4-one												
S. No.	Sub No.	R	Molecular Formula	Mol. Wt. (g/m)	Yield (%)	M.P. °C	C (%) Required/ Found		H (%) Required/ Found		N% Required/ Found	
1	3a	-2Cl	$C_{27}H_{17}BrClN_3O$	514.8	71	240	62.9	63.0	3.25	3.33	8.10	8.16
2	3b	-4Cl	$C_{27}H_{17}BrClN_3O$	514.8	77	232	82.8	63.0	3.20	3.33	8.08	8.16
3	3c	-3OCH_3, -4OCH_3	$C_{29}H_{22}BrN_3O_3$	540.4	83	192	64.4	64.5	3.86	4.10	7.65	7.78
4	3d	-H	$C_{27}H_{18}BrN_3O$	480.4	75	212	67.5	67.5	3.68	3.78	8.65	8.75
5	3e	-OH	$C_{27}H_{18}BrN_3O_2$	496.4	80	225	65.3	65.3	3.56	3.66	8.36	8.47
6	3f	-3OCH_3, -4OH	$C_{28}H_{20}BrN_3O_3$	526.4	76	198	63.8	63.9	3.72	3.83	7.90	7.98
7	3g	-4OH	$C_{27}H_{18}BrN_3O_2$	496.4	78	204	65.3	65.3	3.55	3.66	8.40	8.47
8	3h	-4-$N(CH_3)_2$	$C_{29}H_{23}BrN_4O$	523.4	79	198	66.5	66.5	4.35	4.43	10.60	10.70
9	3i	-4OCH_3	$C_{28}H_{20}BrN_3O_2$	510.4	81	220	65.8	65.9	3.85	3.95	8.15	8.23
10	3j	-3NO_2	$C_{27}H_{17}BrN_4O_3$	525.4	79	185	61.6	61.7	3.20	3.26	10.51	10.66

Reaction Scheme



Where Ar is refered to as: (a) 2-Chloro (b) 4-Chloro (c) 3,4-di Methoxy (d) H (e) 2-hydroxy (f) 3-Methoxy-4-hydroxy (g) 4- hydroxy (h) 4- N,N-dimethyl (i) 4-Methoxy (j) 3-Nitro.

Antibacterial Activity

The antibacterial activities of the series (3a-j) have been carried out against some strain of bacteria. The result **(Table-2)** shows that the prepared compounds are toxic against the bacteria. 3a, 3c, 3f, 3h, 3i, 3j were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with yeast shows that these compounds have almost similar activity.

Table - 2

Sr. No.	Microorganisms								Yeast
	Sample Code	E.coli	S. aureus	B. spizinzenii	P. aeruginosa	S. paratyphi	B. pumillus	K. pneumoniae	C. albicans
1	3a	20	18	21	18	16	22	17	23
2	3b	17	23	21	14	17	20	17	20
3	3c	19	17	17	16	18	16	19	19
4	3d	15	15	16	Nill	14	16	16	17
5	3e	16	18	16	14	Nill	16	18	17
6	3f	18	18	14	17	19	17	18	20
7	3g	17	17	16	14	21	18	16	17
8	3h	18	20	18	15	20	16	20	Nill
9	3i	18	17	17	15	17	18	20	20
10	3j	20	18	21	14	16	21	17	20

Result and Discussion

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds 3a, 3c, 3f and 3h showed very good activity against the tested organisms.

Compounds 3b, 3e and 3g are moderate antibacterial activity. The compounds 3a, 3b and 3i showed good antifungal activity and 3c, 3f, 3dand 3j showed moderate antibacterial activity. All the compounds synthesized possess electron releasing groups, on both the aromatic rings. Therefore from the results it is evident that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities.

The compounds were characterized by elemental analysis IR and NMR- spectral studies. The IR spectra of the quinazolin-4-one derivatives show the prominent bands of 1630-20 cm^{-1} for the azomethene group. The structure of these were established on the basis of chemical analysis, IR (cyclic >C=O group, 1680 cm^{-1}) and NMR signals for different kinds of protons at their respective positions.

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