WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 7, 1984-1991. Research Article ISSN 2277– 7105

# SYNTHETIC AND PHARMACOLOGICAL EVALUATION OF SOME 3-(4-{[(SUBSTITUTEDPHENYL) METHYLENE] AMINO} PHENYL)-6-BROMO-2-METHYL QUINAZOLIN-4-ONE DERIVATIVES

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Article Received on
10 May 2015,

Revised on 05 June 2015,
Accepted on 28 June 2015

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## ABSTRACT

A series of ten novel compounds **(3a)** 3-(4-{[(2-chlorophenyl) methylene] amino}phenyl)-6-bromo-2-methylquinazolin-4-one; **(3b**) 3-(4-{[(4-chlorophenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one; **(3c)** 3-(4-{[(3,4-dimethoxyphenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one; **(3d)** 3-(4-{[(phenylmethylene] amino}phenyl)-6-bromo-2- hylquinazolin-4-one; **(3e)** 3-(4-{[(2-ydroxyphenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one; **(3f**) 3-(4-{[(4-hydroxy-3-methoxyphenyl) methylene] amino} phenyl)-6-bromo-2 methylquinazolin-4-one; **(3g)** 3-(4-{[(4-hydroxyphenyl)methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one; **(3h)** 3-[4-{[(4-(dimethylamino) phenyl) methylene] amino) phenyl]-6-bromo-2-methylquinazolin-4-one; **(3i)** 3-(4-{[(4-methoxyphenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one **; (3j)** 3-(4-{[(3-nitrophenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one (3a -3j) have been synthesized by the reaction between 3-(4-aminophenyl)-6-bromo-2-methylquinazolin-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) 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:** **4**-Quinazolinone, 4-Benzoxazinone, Synthesized & Characterized, antibacterial, antifungal.

## INTRODUCTION

In recent years Quinazoline and quinazolinone derivatives have attracted significant attention due to their diverse pharmacological activities.[1] such as antimalarial.[2] antimicrobial.[3-5] anti-inflammatory.[6-10] anticonvulsant.[11-15] antihypertensive.[16-18] anti-diabetic.[19] cholinesterase inhibition.[20] and anticancer activities.[21-26] Especially quinazolin-4-one motifs are having many interesting activity profiles namely EOX – 1 inhibitors.[27] Inhibitors of the bacterial enzyme Mur – B.[28] non- nucleosides inhibitors of HfV-RT.[29] and anti histamine agents.[30] Quinazolin-4-one compounds are the derivatives of quinazoline which belong to an important group of heterocyclic compounds containing nitrogen in a six member ring.[31-36] 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-methyl-3, 1-benzoxazin-4-one and 3-(4-aminophenyl)-6-bromo-2-methyl quinazolin-4-one was prepared accordingly to the literature method.[10] The aromaticbenzaldehyde and substituted benzeldehydes were B.D.H. regents. Chemicals and solventsused 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 was used as control in this method. The area of inhibition of zone is measured in percentage.

**PREPARATION**

**(1) Preparation of 6-bromo-2-methyl-3,1-benzoxazin-4-one**

2-(acetyl amino)-5-bromobenzoic acid (0.01ml) in pyridine was added with 36 ml of acetic anhydride and the mixture was refluxed for 1 hour in a round bottom flask . A solid product was separated on cooling. The yield of the product was 55% and the products melts at 123°C.

**(2) Preparation of 3-(4-aminophenyl)-6-bromo-2-methyl quinazolin-4-one**

In a 250 ml conical flask (equipped with a reflux condenser) a mixture of 6-bromo-2-methyl-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 78% and the product melts at 220°C.

**(3) Preparation of 3-(4-{[(2-chlorophenyl) methylene] amino} phenyl)-6-bromo-2-methylquinazolin-4-one (3a-3j)**

To a solution of 3-(4-aminophenyl)-6-bromo-2-methylquinazolin-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-chloro phenyl) methylene] amino} phenyl) -6-bromo-2-phenylquinazolin-4-one. The yield of the product was 78% and the product melts at 142°C.The characterizations of all other (3a-3j) compounds were shown in **Table-1**.

**Table – 1.**

| Physical Constant 3-(4-{[(substitutedphenyl)methylene]amino}phenyl)-6-bromo-2-methylquinazolin-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 | $C_{22}H_{15}BrClN_3O$ | 452.73 | 78 | 142 | 58.3 | 58.36 | 3.28 | 3.34 | 9.23 | 9.28 |
| 2 | 3b | -4Cl | $C_{22}H_{15}BrClN_3O$ | 452.73 | 79 | 140 | 58.3 | 58.36 | 3.3 | 3.34 | 9.22 | 9.28 |
| 3 | 3c | -3$OCH_3$, -4$OCH_3$ | $C_{24}H_{20}BrN_3O_3$ | 478.33 | 85 | 150 | 60.2 | 60.26 | 4.14 | 4.21 | 8.7 | 8.78 |
| 4 | 3d | -H | $C_{22}H_{16}BrN_3O$ | 418.28 | 79 | 180 | 63.1 | 63.17 | 3.2 | 3.86 | 9.95 | 10.05 |
| 5 | 3e | -2OH | $C_{22}H_{16}BrN_3O_2$ | 434.28 | 81 | 168 | 60.76 | 60.84 | 3.65 | 3.71 | 9.6 | 9.68 |
| 6 | 3f | -3$OCH_3$, -4OH | $C_{23}H_{18}BrN_3O_3$ | 464.31 | 80 | 130 | 59.45 | 59.5 | 3.85 | 3.91 | 8.97 | 9.05 |
| 7 | 3g | -4OH | $C_{22}H_{16}BrN_3O_2$ | 434.28 | 75 | 145 | 60.75 | 60.84 | 3.64 | 3.71 | 9.6 | 9.68 |
| 8 | 3h | -4-$N(CH_3)_2$ | $C_{24}H_{21}BrN_4O$ | 461.35 | 77 | 127 | 62.4 | 62.48 | 4.5 | 4.59 | 12.05 | 12.14 |
| 9 | 3i | -4$OCH_3$ | $C_{23}H_{18}BrN_3O_2$ | 448.31 | 76 | 118 | 61.55 | 61.62 | 3.97 | 4.05 | 9.28 | 9.37 |
| 10 | 3j | -3$NO_2$ | $C_{22}H_{15}BrN_4O_3$ | 463.28 | 82 | 160 | 56.73 | 57.04 | 3.18 | 3.26 | 11.96 | 12.09 |

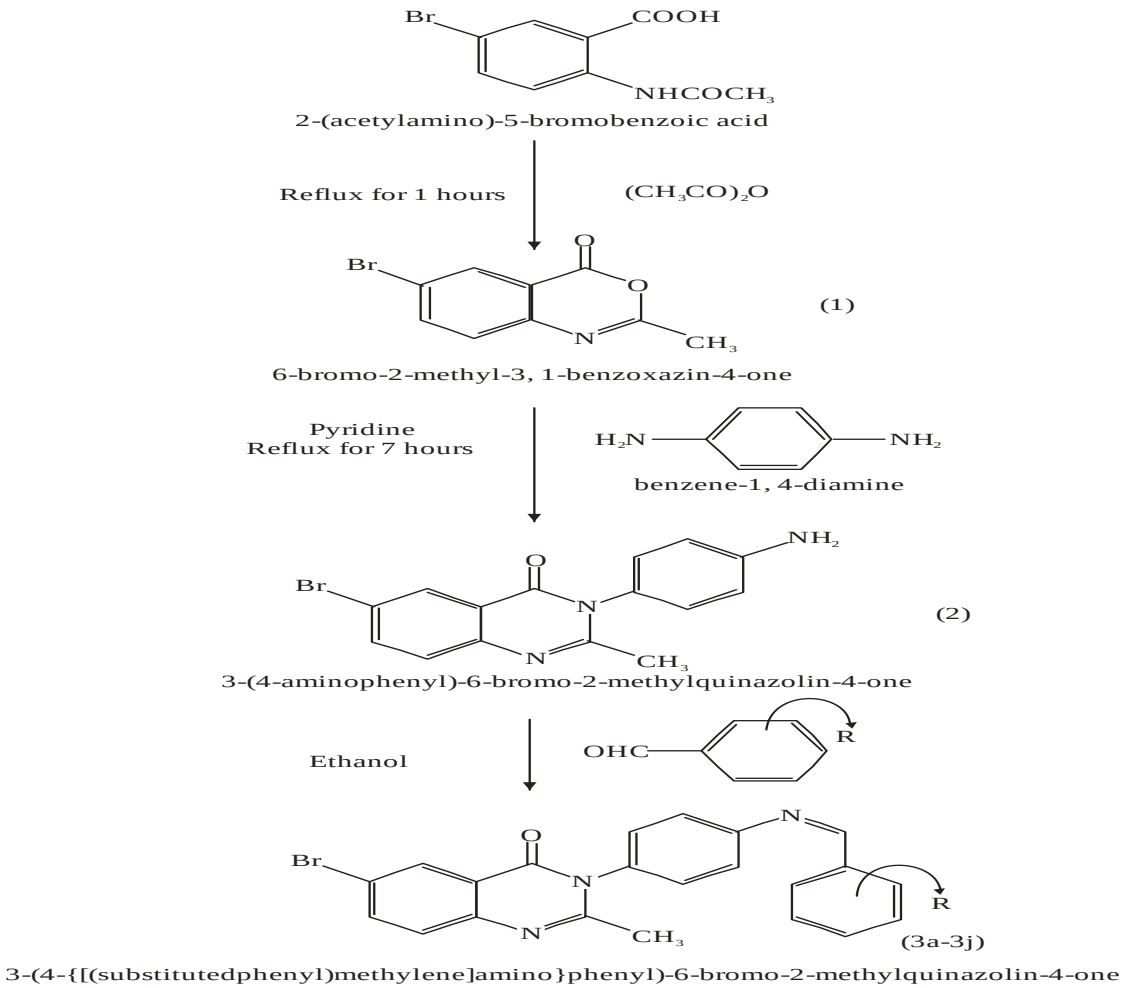
## ANTIBACTERIAL ACTIVITY

The antibacterial activities of the series (3a-3j) have been carried out against some strain of bacteria shown in **(Table-2)**. The result shows that the prepared compounds are toxic against the bacteria. 3a, 3b, 3c, 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. | Sample Code | Microorganisms | | | | | | | Yeast |
|---|---|---|---|---|---|---|---|---|---|
| | | E.coll. | S. aureus | B. spizinzenii | P. aeruginosa | S. paratyphi | B. pumillus | K.pneumoniae | C.albicns |
| 1 | 3a | 16 | 21 | 21 | 18 | 21 | 23 | 17 | 21 |
| 2 | 3b | 18 | 20 | 23 | 16 | 19 | 21 | 16 | 20 |
| 3 | 3c | 20 | 18 | 21 | 15 | 18 | 18 | 18 | 20 |
| 4 | 3d | 17 | 14 | 18 | 16 | Nill | 14 | 15 | 15 |
| 5 | 3e | 17 | Nill | 17 | 17 | 19 | 19 | 17 | 17 |
| 6 | 3f | 20 | 17 | 18 | 17 | 18 | 19 | 19 | Nill |
| 7 | 3g | 18 | 18 | 15 | 18 | 17 | 15 | 14 | 17 |
| 8 | 3h | 19 | 20 | Nill | 17 | 17 | 20 | 16 | 20 |
| 9 | 3i | 20 | 18 | 20 | 17 | 15 | 18 | 20 | 21 |
| 10 | 3j | 21 | 22 | 20 | 16 | 18 | 18 | 18 | 17 |

**Reaction Scheme**




**Where R is referred 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.

## RESULT AND DISCUSSION

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds 3a, 3b, 3c, 3f, 3i and 3j showed very good activity against the tested organisms. Compounds 3d, 3e, 3g and 3h are moderate antibacterial activity. The compounds 3a, 3b, 3c, 3h and 3i showed good antifungal activity and 3d, 3e, 3g and 3j showed moderate antifungal 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.

## ACKNOWLEDGEMENT

We are thankful to the Head, Department of Chemistry LRPG College Sahibabad and Head, Department of Chemistry GKV, Haridwar, for literature survey and providing experimental facilities. We are also thankful to IPC Ghaziabad and JNU New Delhi, providing spectral data for IR and NMR spectra.

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