ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL EVALUATION OF A SERIES OF QUINAZOLINE ANALOGS

Gaurav Agrawal*[1], Neelam Khan[1], Shivendra Dwivedi[1], Ritesh Patel[2], Gurdeep Singh[3]

[1]*Department of Pharmaceutical Chemistry, Oriental College of Pharmacy and Research, Oriental University, Indore, Madhya Pradesh, India*

[2]*Indore Institute of Pharmacy, Indore, Madhya Pradesh, India*

[3]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*

**Corresponding author: gauravpharma_iip@yahoo.co.in*

ABSTRACT

A series of substituted 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4(3H)-one has been synthesized and evaluated for their biological activity. The title compounds (G_1-G_{10}) were prepared by the reaction of 5-bromo anthranilic acid with acetic anhydride to form 6-bromo-2-methyl-4H-benzo[1,3]oxazin-4-one which upon treatment with hydrazine hydrate in the presence of anhydrous pyridine form 3-amino-6-bromo-2-methylquinazolin-4(3H)-one. The resulting intermediate underwent Schiff reaction with different aromatic aldehyde followed by reflux with chloroacetyl chloride and triethylamine. Ten different quinazoline derivatives (G_1-G_{10}) were synthesized. Structural assignments of these compounds have been made by elemental analysis, FTIR, ^{1}HNMR & Mass spectral data and the purity of the compounds was determined by TLC. The anti-microbial activity of the newly isolated heterocyclic compounds was evaluated against Gram-positive, Gram-negative bacteria and fungi. Most of the compounds showed a moderate degree of anti-microbial activity. The study concluded that the compound G_4 & G_6 were found to exhibit significant anti-bacterial activity when compared to Amoxicillin as standard drug while compound G_7 exhibit significant anti-fungal activity when compared to Fluconazole as standard drug.

Keywords: Amoxicillin, Anti-microbial activity, Aziridine, 5-bromo anthranilic acid, Fluconazole, Schiff base.

1. INTRODUCTION

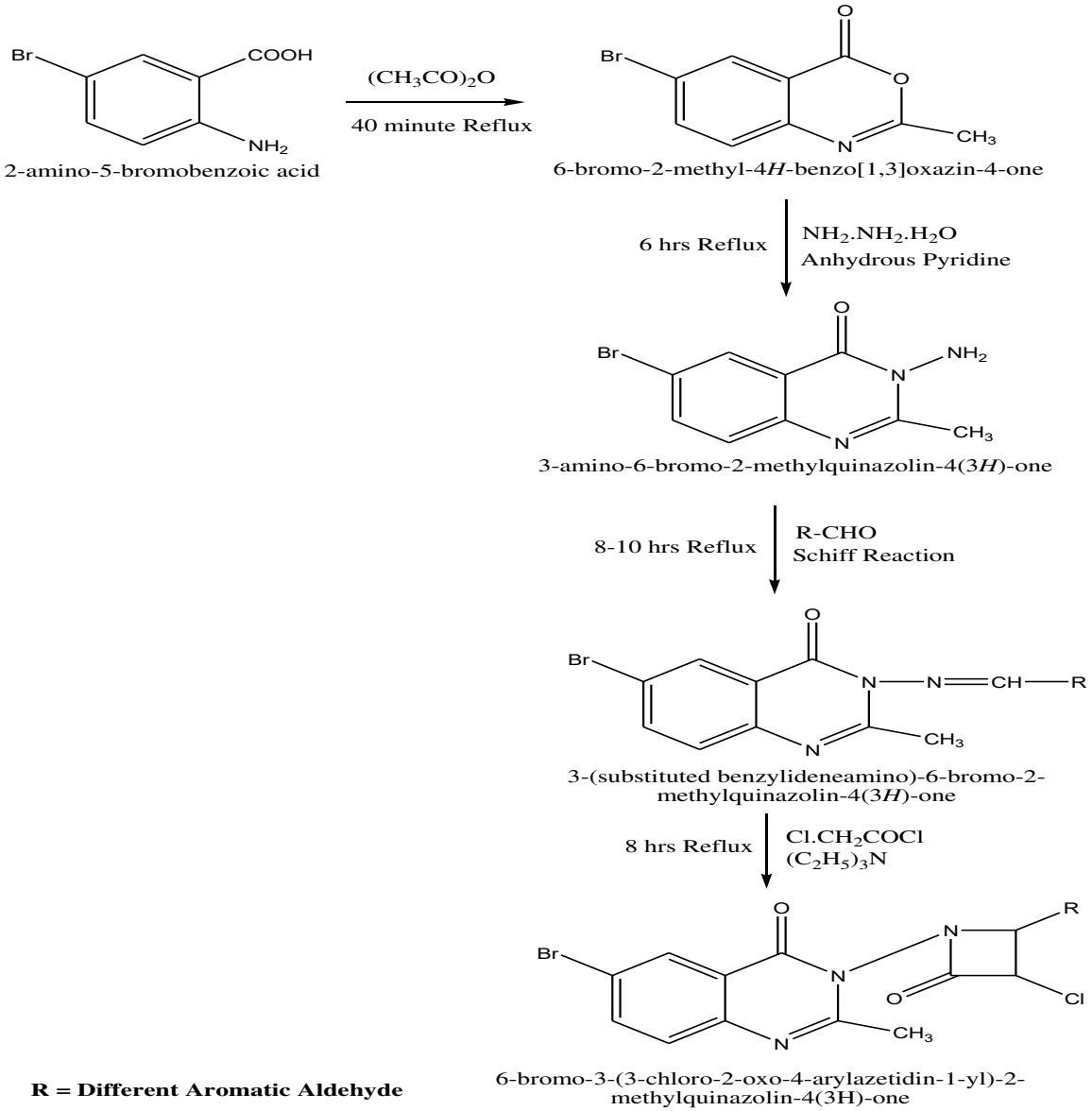
Quinazoline is a fused six-member aromatic ring (a benzene ring and a pyrimidine ring are fused). Quinazoline is a fused bicyclic compound earlier known as benzo 1, 3-diazine [1]. It was first prepared in the laboratory in 1903 by Gabriel. Although its derivative were known much earlier. The name quinazoline (German: Chinazolin) was first proposed for this compound by weddige on observing that this was isomeric with the compounds cinnoline and quinoxaline. Paal and Bush suggested the numbering of quinazoline ring system, which is currently used [2-4]. The other less commonly used names for this ring system are 'phenmiazine' and 5, 6-benzopyrimidine. However, the name quinazoline is now universally accepted. Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [5-8], anti-inflammation [9-10], anti-bacterial [11-14], analgesic [9,13], anti-viral [15], anti-cytotoxin [16], anti-spasmodic [13, 17], antitubercular [18], anti-oxidant [19], anti-malarial [20], anti-hypertensive [21], anti-obesity [22], anti-psychotic [23], anti-diabetic [24] etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. Potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored. Quinazoline derivatives have attracted much attention for their various biological and medicinal properties. For example, they act as the potent tyrosine kinase and cellular phosphorylation inhibitors [25] and they are also used as ligands for benzodiazepine and GABA receptors in the central nervous system [26] or as DNA binders [27-29]. Some of them show remarkable activity as anticancer [30], antiviral [31] and anti-tubercular agents [32-33]. Molecules containing the

Quinazoline unit have been popular drugs. For example, Erlotinib is used in the treatment of several types of tumors [34], Prazosin acts as an adrenergic blocker [35] and Iressa as an epidermal growth factor receptor inhibitor was approved by the Food and Drug Administration in USA for the treatment of lung cancer [36]. Encouraged by the diverse biological activities of Quinazoline Heterocyclic compounds, it was decided to prepare a new series of Quinazoline derivatives. Literature survey revealed that incorporation of different groups in Quinazoline Heterocyclic ring enhanced antibacterial and antifungal activity.

Recently quinazolinone derivatives seek great attention of researchers in organic and medicinal chemistry due to their prompt biological activities. Encouraged by the therapeutic diversity of quinazolinone containing moiety and the comparative ease of convertibility of anthranilic acid to quinazolinone, we took up the synthesis of certain novel quinazolinone from 5-bromo anthranilic acid and evaluated their anti-microbial activity.

2. MATERIAL AND METHODS

All the chemicals used in the synthesis of the intermediates and final derivatives were of A.R grade and procured from the Merck and LOBA chemicals. All the synthesized quinazoline derivatives were characterized by melting point determination using Veergo digital melting point apparatus in open capillary tubes and were uncorrected.



Scheme of Synthesis

IR Spectra were recorded using Perkin Elmer FTIR spectrophotometer using KBr pellets techniques and ^{1}HNMR spectra of the synthesized compounds in deuteriated DMSO were recorded on Bruker Avance II 400MHz NMR Spectrometer instrument using TMS as the internal standard. Mass Spectra were recorded using LC-MSD-Tranp-SL2010A Shimadzu using Dimethyl-sulphoxide (DMSO) as solvent. TLC was performed using silica gel GF_{254} coated plates of 0.25 mm thickness. Petroleum ether & Ethyl acetate (1:2) were used as solvent system and iodine vapours as visualizing agent.

Table 1: List of Various Aromatic Aldehydes

S. No.	Compounds Code	Substituted Aromatic Aldehyde (Ar)
1	G_1	Benzaldehyde
2	G_2	o-Chloro Benzaldehyde
3	G_3	m-Chloro Benzaldehyde
4	G_4	o-Nitro Benzaldehyde
5	G_5	m-Nitro Benzaldehyde
6	G_6	m-Fluoro Benzaldehyde
7	G_7	p-Fluoro Benzaldehyde
8	G_8	o-Hydroxy Benzaldehyde
9	G_9	o,p-DimethoxyBenzaldehyde
10	G_{10}	2-Chloro-5-Nitro Benzaldehyde

2.1. The Experimental Work completed in Four Steps.

Step-I: Synthesis of 6-bromo-2-methyl-4H-benzo [1, 3] oxazin-4-one from 5-bromo anthranilic acid.

Step-II: Synthesis of 3-amino-6-bromo-2-methyl-quinazolin-4(3H)-one.

Step-III: Synthesis of 3-(substituted benzylideneamino) -6-bromo-2-methylquinazolin-4(3H)- one. (Preparation of Schiff base derivatives)

Step-IV: Synthesis of 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4(3H)-one.

2.1.1. General Procedure for the synthesis of 6-bromo-2-methyl-4H-benzo [1, 3] oxazin-4-one from 5-bromo anthranilic acid (Intermediate-I):

5-bromo anthranilic acid (5 gm, 0.023 moles) was allowed to mix with acetic anhydride (100ml, 0.979 moles) and refluxed for 40 min. The solution was cooled to room temperature and excess acetic anhydride was removed under reduce pressure and the crude product was filtered and dried. The dried crude product then recrystallized from cyclohexane. Yield: 78.51%, M.P.: 167-169°C.

2.1.2. General Procedure for the synthesis of 3-amino-6-bromo-2-methylquinazolin-4-(3H)-one (Intermediate-II):

3-amino-6-bromo-2-methylquinazolin-4(3H)-one was prepared by adding dropwise a solution of hydrazine hydrate (3.204 ml, 0.1 mol) in anhydrous pyridine (25 ml) to cold solution of 6-bromo-2-methyl-4H-benzo [1,3] oxazin-4-one (12 gm, 0.05 mol) in anhydrous pyridine (25 ml), with constant stirring. When the addition was completed, the resultant reaction mixture was stirred vigorously for 30 min at room temperature and subsequently heated under reflux for 6 h under anhydrous reaction conditions. It was allowed to cool at room temperature and poured into ice cold water containing dilute hydrochloric acid on standing for 1 h, solidification occur which was allowed to settle down. It was then filtered off, washed repeatedly with water and dried in vacuum. Yield: 74.39%, M.P.: 202-204°C.

2.1.3. Synthesis of 3-(substituted benzylidene-amino)-6-bromo-2-methylquinazolin-4 (3H) -one: (Preparation of Schiff base derivatives)

To a solution of the appropriate substituted benzal-dehyde (0.001 mol) in ethanol (15 ml), 3-amino-6-bromo-2-methylquinazolin-4(3H)-one (0.001 mol) and a few drops of acetic acid (0.05 mol) were added. The reacting mixture was then refluxed for 8-10 hrs and the course of the reaction was monitored by TLC {petroleum ether/ethyl acetate (*V/V*=1:2)} to its completion. The reacting mixture was then allowed to cool. The crude product was recrystallized from 95% ethanol to obtain title compounds.

2.1.4. Synthesis of 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4 (3H)-one: (General Procedure)

A mixture of Schiff bases of quinazolinone (0.01 mol), 1, 4-dioxan (50 ml), Chloroacetyl chloride (0.01 mol) and triethylamine (0.01 mol) was refluxed on water bath for 8 hrs. The resultant mixture was then transferred to the beaker and ice cold water was added. The separated solid was then filtered off, washed with water and recrystallized from ethanol to give different substituted quinazolinone compounds [G_1 to G_{10}].

2.2. Biological Study

2.2.1. Evaluation of Anti-microbial Activity [37-39]

2.2.1.1. Anti-bacterial studies

The newly prepared compounds were screened for their antibacterial activity against *Bacillus subtilis, Staphy-*

lococcus aureus, Klebsiella pneumonia and *Escherichia coli* (clinical isolate) bacterial strains by disc diffusion method [40-41]. A standard inoculum (1-2×107cfu/ml 0.5 Mc Farland standards) was introduced on to the surface of sterile agar plates and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6 mm in diameters were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. Amoxicillin (30 µg) was used as positive control and the disk poured in DMSO was used as negative control and the test compounds were dissolved in DMSO at concentration of 100 and 50µg/mL. The plates were inverted and incubated for 24h at 37°C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition of zone of measured and compared with controls. The bacterial zones of inhibition values are given in Table 2.

2.2.1.2. Antifungal studies

The newly prepared compounds were screened for their antifungal activity against *Candida albicans* and *Aspergillus flavus* in DMSO by agar diffusion method. Sabouraud agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make suspension of corresponding species. Twenty milliliters of agar media was poured into each Petridish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h using an agar punch, wells were made and each well was labelled. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The fungal activity of each compound was compared with Fluconazole as a standard drug. Inhibition zone were measured and compared with the controls. The fungal zone of inhibition values are given in Table 3.

3. RESULTS AND DISCUSSION

3.1. Chemistry

All the novel quinazolinone derivatives were synthesized, purified and separated by using column chromatography or recrystallization method. Synthesized compounds were characterized by using Elemental analysis, FT-IR, ^{1}HNMR and Mass Spectrometric studies. The integration curves fully support the orientation of protons in the analyzed compounds. Furthermore, all the compounds demonstrated the characteristic chemical shifts for the quinazolinone nucleus. Additionally, synthesized compounds were analyzed by mass spectra and indicated no difference in the fragmentation pattern among the set of synthesized series.

3.2. Spectral analysis of different derivatives

3.2.1. G1: *6-bromo-3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-methylquinazolin-4(3H)-one (G1)*

Off white colored solid, Molecular formula: $C_{18}H_{13}BrClN_3O_2$, Molecular weight: 418.67, Yield: 76.55%, M.P.: 126-128°C, R_f value: 0.68, **FT-IR (KBr, cm^{-1}):** 3052.41 (=C-H Str.), 2862.23 (C-H in CH_3 Str.), 1572.09 (C=C Str.), 1648.58 (C=O Str.), 1268.65 (C-N Str.), 727.25 (Ar C-H Bend.), 525.31 (C-Br Bend.), 1598.60 (C=N Str.), 1743.17 (C=O in β-lactum), 584.28 (C-Cl Bend.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.18-8.23 (m, 8H, Ar H), 0.92 (s, 3H, CH_3), 5.38 (d, 1H, CH), 4.98 (d, 1H, CH). **Elemental Analysis, % found (% required):** C 51.58 (51.64); H 3.08 (3.13); Br 19.02 (19.09); C l8.40 (8.47); N 10.01 (10.04); O 7.56 (7.64).

3.2.2. G2: 6-bromo-3-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G2)

Yellowish brown colored solid, Molecular formula: $C_{18}H_{12}BrCl_2N_3O_2$, Molecular weight: 453.12, Yield: 67.38%, M.P.: 132-134°C, R_f value: 0.86, **FT-IR (KBr, cm^{-1}):** 3023.33 (=C-H Str.), 2925.12 (C-H in CH_3 Str.), 1593.33 (C=C Str.), 1673.42 (C=O Str.), 1284.83 (C-N Str.), 739.40 (Ar C-H Bend.), 534.25 (C-Br Bend.), 1592.45 (C=N Str.), 1752.14 (C=O in β-lactum), 628.54 (C-Cl Bend.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.06-8.14 (m, 8H, Ar H), 0.94 (s, 3H, CH_3), 5.43 (d, 1H, CH), 5.12 (d, 1H, CH). **Mass Spectra: m/z:** 454.92 (M^{+2}). **Elemental Analysis, % found (% required):** C 47.58 (47.71); H 2.62 (2.67); Br 17.58 (17.63); Cl 15.58 (15.65); N 9.22 (9.27); O 7.02 (7.06).

3.2.3. G3: 6-bromo-3-(3-chloro-2-(3-chlorophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G3)

Creamish yellow colored solid, Molecular formula: $C_{18}H_{12}BrCl_2N_3O_2$, Molecular weight: 453.12, Yield: 70.18%, M.P.: 136-138°C, R_f value: 0.82, **FT-IR**

(KBr, cm^{-1}): 3045.64 (=C-H Str.), 2874.45 (C-H in CH_3 Str.), 1587.23 (C=C Str.), 1686.71 (C=O Str.), 1320.25 (C-N Str.), 724.75 (Ar C-H Bend.), 629.52 (C-Br Bend.), 1601.25 (C=N Str.), 1754.75 (C=O in β-lactum), 678.28 (C-Cl Bend.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.01-8.18 (m, 8H, Ar H), 0.89 (s, 3H, CH_3), 5.42 (d, 1H, CH), 5.16 (d, 1H, CH). **Mass Spectra: m/z:** 466.57 (M^{+2}). **Elemental Analysis, % found (% required):** C 47.10 (47.71); H 2.61 (2.67); Br 17.59 (17.63); Cl 15.55 (15.65); N 9.24 (9.27); O 7.01 (7.06).

3.2.4. G4: 6-bromo-3-(3-chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G4)

Pale yellow colored solid, Molecular formula: $C_{18}H_{12}BrClN_4O_4$, Molecular weight: 463.67, Yield: 68.48%, M.P.: 129-131°C, R_f value: 0.73, **FT-IR (KBr, cm^{-1}):** 3012.54 (=C-H Str.), 2942.43 (C-H in CH_3 Str.), 1621.57 (C=C Str.), 1657.27 (C=O Str.), 1338.43 (C-N Str.), 730.38 (Ar C-H Bend.), 645.74 (C-Br Bend.), 1604.76 (C=N Str.), 1662.25 (C=O in β-lactum), 720.15 (C-Cl Bend.), 1521.47 (C-NO_2 Str.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.32-8.16 (m, 8H, Ar H), 0.91 (s, 3H, CH_3), 5.41 (d, 1H, CH), 5.14 (d, 1H, CH). **Mass Spectra: m/z:** 465.18 (M^{+2}). **Elemental Analysis, % found (% required):** C 46.57 (46.63); H 2.58 (2.61); Br 17.18 (17.23); Cl 7.57 (7.65); N 12.02 (12.08); O 12.72 (13.80).

3.2.5. G5: 6-bromo-3-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G5)

Pale red colored solid, Molecular formula: $C_{18}H_{12}BrClN_4O_4$, Molecular weight: 463.67, Yield: 74.24%, M.P.: 155-157°C, R_f value: 0.76, **FT-IR (KBr, cm^{-1}):** 3062.48 (=C-H Str.), 2961.32 (C-H in CH_3 Str.), 1637.27 (C=C Str.), 1642.35 (C=O Str.), 1276.08 (C-N Str.), 729.58 (Ar C-H Bend.), 667.20 (C-Br Bend.), 1607.35 (C=N Str.), 1767.45 (C=O in β-lactum), 815.64 (C-Cl Bend.), 1536.31 (C-NO_2 Str.,).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.34-8.12 (m, 8H, Ar H), 0.96 (s, 3H, CH_3), 5.48 (d, 1H, CH), 4.18 (d, 1H, CH). **Elemental Analysis, % found (% required):** C 46.60 (46.63); H 2.56 (2.61); Br 17.18 (17.23); Cl 7.58 (7.65); N 12.01 (12.08); O 13.75 (13.80).

3.2.6. G6: 6-bromo-3-(3-chloro-2-(3-fluorophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G6)

Light red colored solid, Molecular formula: $C_{18}H_{12}BrClFN_3O_2$, Molecular weight: 436.66, Yield: 76.36%, M.P.: 142-144°C, R_f value: 0.68, **FT-IR (KBr, cm^{-1}):** 3034.26 (=C-H Str.), 2912.53 (C-H in CH_3 Str.), 1648.21 (C=C Str.), 1634.73 (C=O Str.), 1272.45 (C-N Str.), 728.96 (Ar C-H Bend.), 681.25 (C-Br Bend.), 1609.28 (C=N Str.), 1748.49 (C=O in β-lactum), 766.18 (C-Cl Bend.), 1241.07 (C-F Bend.**)**. **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 6.82-8.20 (m, 8H, Ar H), 0.95 (s, 3H, CH_3), 5.52 (d, 1H, CH), 5.16 (d, 1H, CH). **Mass Spectra: m/z:** 438.25 (M^{+2}). **Elemental Analysis, % found (% required):** C 49.50 (49.51); H 2.71 (2.77); Br 18.74 (18.30); Cl 8.08 (8.12); F 4.31 (4.35); N 9.56 (9.62); O 7.20 (7.33).

3.2.7. G7: 6-bromo-3-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)-one (G7)

Greyish red colored solid, Molecular formula: $C_{18}H_{12}BrClFN_3O_2$, Molecular weight: 436.66, Yield: 69.82%, M.P.: 143-145°C, R_f value: 0.69, **FT-IR (KBr, cm^{-1}):** 3058.16 (=C-H Str.), 2885.12 (C-H in CH_3 Str.), 1579.25 (C=C Str.), 1628.41 (C=O Str.), 1312.52 (C-N Str.), 732.15 (Ar C-H Bend.), 577.45 (C-Br Bend.), 1605.87 (C=N Str.), 1746.75 (C=O in β-lactum), 834.31 (C-Cl Bend.), 1356.23 (C-F Bend.**)**. **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 6.95-8.17 (m, 8H, Ar H), 0.93 (s, 3H, CH_3), 5.46 (d, 1H, CH), 5.17 (d, 1H, CH). **Mass Spectra: m/z:** 438.40 (M^{+2}). **Elemental Analysis, % found (% required):** C 49.49 (49.51); H 2.72 (2.77); Br 18.22 (18.30); Cl 8.07 (8.12); F 4.32 (4.35); N 9.54 (9.62); O 7.21 (7.33).

3.2.8. G8: 6-bromo-3-(3-chloro-2-(2-hydroxyphenyl) -4-oxoazetidin-1-yl)-2-methylquinazolin-4 (3H)z one (G8)

Dark Brown colored solid, Molecular formula: $C_{18}H_{13}BrClN_3O_3$, Molecular weight: 434.67, Yield: 66.30%, M.P.: 156-158°C, R_f value: 0.82, **FT-IR (KBr, cm^{-1}):** 3074.16 (=C-H Str.), 2984.42 (C-H in CH_3 Str.), 1609.51 (C=C Str.), 1679.27 (C=O Str.), 1306.25 (C-N Str.), 737.21 (Ar C-H Bend.), 591.35 (C-Br Bend.), 1594.75 (C=N Str.), 1764.70 (C=O in β-lactum), 742.83 (C-Cl Bend.), 3249.85 **(**C-OH

Str.). **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 6.71-8.19 (m, 8H, Ar H), 0.96 (s, 3H, CH_3), 5.43 (d, 1H, CH), 5.19 (d, 1H, CH). **Elemental Analysis, % found (% required):** C 49.66 (49.74); H 2.94 (3.01); Br 18.32 (18.36); Cl 8.09 (8.16); N 9.58 (9.67); O 10.96 (11.04).

3.2.9. G9: 6-bromo-3-(3-chloro-2-(2,4-dimethoxy-phenyl)-4-oxoazetidin-1-yl)-2-methylquina-zolin 4(3H)-one (G9)

Pale Brown colored solid, Molecular formula: $C_{20}H_{17}BrClN_3O_4$, Molecular weight: 478.72, Yield: 71.84%, M.P.: 182-184°C, R_f value: 0.78, **FT-IR (KBr, cm^{-1}):** 3084.60 (=C-H Str.), 2936.67 (C-H in CH_3 Str.), 1632.27 (C=C Str.), 1683.24 (C=O Str.), 1316.25 (C-N Str.), 734.36 (Ar C-H Bend.), 614.15 (C-Br Bend.), 1591.15 (C=N Str.), 1758.38 (C=O in β-lactum), 594.62 (C-Cl Bend.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 6.26-8.27 (m, 8H, Ar H), 0.97 (s, 3H, CH_3), 5.56 (d, 1H, CH), 5.20 (d, 1H, CH), 3.71 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3). **Mass Spectra: m/z:** 480.61 (M^{+2}). **Elemental Analysis, % found (% required):** C 50.09 (50.18); H 3.52 (3.58); Br 16.63 (16.69); Cl 7.37 (7.41); N 8.71 (8.78); O 13.29 (13.37).

3.2.10. G10: 6-bromo-3-(3-chloro-2-(2-chloro-5-nitrophenyl)-4-oxoazetidin-1-yl)-2 methyl-quinazolin-4(3H)-one (G10)

Creamish Brown colored solid, Molecular formula: $C_{18}H_{11}BrCl_2N_4O_4$, Molecular weight: 498.11, Yield: 64.96%, M.P.:163-165°C, R_f value: 0.89, **FT-IR (KBr, cm^{-1}):** 3091.25 (=C-H Str.), 2957.14 (C-H in CH_3 Str.), 1599.14 (C=C Str.), 1639.47 (C=O Str.), 1293.78 (C-N Str.), 731.05 (Ar C-H Bend.), 582.94 (C-Br Bend.), 1596.48 (C=N Str.), 1769.25 (C=O in β-lactum), 642.41 (C-Cl Bend.),1547.45 (C-NO_2 Str.).**^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.46-8.23 (m, 8H, Ar H), 0.91 (s, 3H, CH_3), 5.49 (d, 1H, CH), 5.20 (d, 1H, CH). **Elemental Analysis, % found (% required):** C 43.32 (43.40); H 2.16 (2.23); Br 16.01 (16.04); Cl 14.14 (14.23); N 11.18 (11.25); O 12.76 (12.85).

3.3. Anti-microbial studies

The newly synthesized compounds (G_1-G_{10}) were screened for their *in vitro* anti-bacterial activity against *Bacillus subtilis, Staphylocouccus aureus, Klebsiella pneumonia* and *Escherichia coli* using Amoxicillin as standard by disc diffusion method (zone of inhibition). The test compounds were dissolved in dimethyl Sulfoxide (DMSO) at concentrations of 50 and 100µg/mL. The antibacterial screen revealed that all the tested compounds showed good inhibition against various tested microbial strains compared to the standard drug. Along with the synthesized compounds G_4 & G_6 were found to be more active against tested bacterial strains as compared to the standard. The *in vitro* antifungal activities for compounds G_1-G_{10} were determined by agar diffusion method. The results indicate that, among the tested compounds only G_7 were active against all tested fungal strains. The Tables 2 and 3 depict the antimicrobial screening results of the final compounds.

Table 2: Anti-Bacterial Activity of Novel Quinazoline Derivatives

Compounds	Zone of inhibition (mm)							
	Gram positive				Gram negative			
	B. subtilis		*S. aureus*		*K. pneumonia*		*E. coli*	
	100 µg/mL	50 µg/mL	10 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
G_1	6.3	4.3	7.4	7.2	8.5	8.6	10.7	9.7
G_2	7.8	5.8	8.9	5.6	9.9	5	8.6	4.3
G_3	5.2	2.8	4.7	4	8	7.2	7.5	7.5
G_4	14	12	13.8	12.9	16.4	13.7	19.7	14.7
G_5	8.5	6.4	9.1	6.9	10.7	10.7	12.4	10.9
G_6	13	10.5	14.2	11.7	15	14.6	17.3	13
G_7	9	8.7	10.4	9.2	10.3	9.8	13.2	8.6
G_8	8.3	9.2	8.7	8.6	7.5	11.3	10.2	8
G_9	7.2	3.5	9.6	10	8.1	9.2	7.4	9.2
G_{10}	10.3	8.1	10.7	7.8	11.3	8	11.8	10.1
Amoxicillin	17.2	13.8	16	14.7	19	15.7	21.5	16.8
Control **(DMSO)**	---	---	----	-----	----	-----	-----	-----

Table 3: Anti-Fungal Activity of Novel Quinazoline Derivatives

Synthesized Compounds	Zone of inhibition measure in mm			
	Candida albicans		*Aspergillus flavus*	
	100µg/mL	50µg/mL	100µg/mL	50µg/mL
G_1	7.8	8.2	6.9	4
G_2	8.3	7.8	7	6.8
G_3	9.5	9.1	7.3	8.1
G_4	10.5	9.8	10.2	9.8
G_5	8.4	7.6	8.8	7.2
G_6	6.7	8.3	5.4	5
G_7	16.2	13.8	12.8	11.2
G_8	9.1	10.4	9.7	8.8
G_9	4.8	5.1	6	5.6
G_{10}	7.7	6.7	8.5	6.1
Flucanazole	18.3	16.2	15	13.8
Control (DMSO)	--	--	--	--

4. CONCLUSION

The main focus of this research work was to synthesize novel series of quinazolinone derivatives, characterization and evaluation of their anti-microbial activity. From the results, it can be concluded that the modified quinazolinone show significant biological evaluation as anti-microbial agents. However, further evaluation of quinazolinone will be undertaken, concerning the structural arrangements in ring for anti-microbial activity.

5. ACKNOWLEDGEMENT

The authors are thankful to Department of Pharmaceutical Chemistry, Oriental College of Pharmacy and Research, Oriental University, Indore for providing chemicals and facilities to conduct research work.

Conflict of interest

The authors declared no conflict of interest.

6. REFERENCES

1. Gabriel P. *Berichte der Deutschen Chemischen Gesellschaft* 1903; **36:**800.
2. Oriefs: Berichte der Deutschen Chemischen Gesellschaft 1869; **2:**416.
3. Weddige J. *Journal für praktische Chemie,* 1887; **2:**141
4. Paal B. *Berichte der Deutschen Chemischen Gesellschaft,* 1889; **22:**2683.
5. Chandregowda V, Kush AK, Chandrasekara RG. *European Journal of Medicinal Chemistry,* 2009; **44:** 3046-3055.
6. Al-Rashood ST, Aboldahab IA, Nagi MN, Abouzeid LA, Abdel-Aziz AA, et al. *Bioorganic & Medicinal Chemistry,* 2006; **14:**8608-8621.
7. Vasdev N, Dorff PN, Gibbs AR, Nandanan E, Reid LM, et al. *Journal of Labelled Compounds and Radiopharmaceuticals,* 2005; **48:**109-115.
8. Wakeling AE, Guy SP, Woodburn JR, Ashton SE, Curry BJ, et al. *Cancer Research,* 2002; **62:**5749-5754.
9. Alagarsamy V, Solomon VR, Dhanabal K. *Bioorganic & Medicinal Chemistry,* 2007; **15:**235-241.
10. Baba A, Kawamura N, Makino H, Ohta Y, Taketomi S, et al. *Journal of Medicinal Chemistry* 1996; **39:**5176-5182.
11. Rohini R, Muralidhar RP, Shanker K, Hu A, Ravinder V. *European Journal of Medicinal Chemistry,* 2010; **45:**1200-1205.
12. Antipenko L, Karpenko A, Kovalenko S, Katsev A, Komarovska-Porokhnyavets E, et al. *Chemical and Pharmaceutical Bulletin,* 2009; **57:**580-585.
13. Jatav V, Kashaw S, Mishra P, Gupta V. *Medicinal Chemistry Research,* 2008; **17:**205-211.
14. Aly AA. *Chinese Journal of Chemistry,* 2003; **21:**339-346.
15. Li H, Huang R, Qiu D, Yang Z, Liu X. *Progress in Natural Science,* 1998; **8:**359-365
16. Chandrika PM, Yakaiah T, Narsaiah B, Sridhar V, Venugopal G. *Indian Journal of Chemistry,* 2009; **48B:** 840-847.
17. Paneersalvam P, Raj T, Ishar PSM, Singh B, Sharma V. *Indian Journal of Pharmaceutical Sciences,* 2010; **72:** 375-378.
18. Nandy P, Vishalakshi MT, Bhat AR. *Indian*

Journal of Heterocyclic Chemistry, 2006; **15:**293-294.
19. Saravanan G, Alagarsamy V, Prakash CR. *International Journal of Pharmacy and Pharmaceutical Sciences,* 2010; **2:**83-86.
20. Lakhan R, Singh OP, Singh JRL. *Journal of the Indian Chemical Societ,y* 1987: **64:**316-318.
21. Hess HJ, Cronin TH, Scriabine A. *Journal of Medicinal Chemistry,* 1968; **11:**130-136.
22. Sasmal S, Balaji G, Kanna Reddy HR, Balasubrahmanyam D, Srinivas G, et al. *Bioorganic & Medicinal Chemistry Letters,* 2012; **22:**3157-3162.
23. Alvarado M, Barceló M, Carro L, Masaguer CF, Raviña E. *Chemistry & Biodiversity,* 2006; **3:**106-117.
24. Malamas MS, Millen J. *Journal of Medicinal Chemistry,* 1991; **34:**1492-1503.
25. Fry DW, Kraker AJ, McMichael A, Ambroso LA, Nelson JM, et al. *A J Science,* 1994; **265:**1093.
26. Colotta V, Catarzi D, Varano F, Lenzi O, Filacchioni G. *Journal of Medicinal Chemistry,* 2006; **49:**6015-6026.
27. Doyle LA, Ross DD. *Oncogene,* 2003; **22:**7340-7358.
28. Henderson EA, Bavetsias V, Theti DS, Wilson SC, Clauss R, et al. *Bioorganic & Medicinal Chemistry,* 2006; **14:**5020-5045.
29. Foster A, Coffrey HA, Morin MJ, Rastinejad F. *Science,* 1999; **286:**2507-2510.
30. Chien TC, Chen CS, Yu FH, Chern JW. *Chemical and Pharmaceutical Bulletin,* 2004; **52:**1422.
31. Herget T, Freitag M, Morbitzer M, Kupfer R, Stamminger T, et al. *Antimicrobial Agents and Chemotherapy,* 2004; **48:**4154-4162.
32. Waisser K, Gregor J, Dostal H, Kunes J, Kubicova L, et al. *Journal Farmaco,* 2001; **56:**803
33. Kunes J, Bazant J, Pour M, Waisser K, Slosarek M, et al. *Journal Farmaco,* 2000; **55:**725-729.
34. Gundla R, Kazemi R, Sanam R, Muttineni R, Sarma JARP. *N Journal of Medicinal Chemistry,* 2008; **51:**3367-3377.
35. Mendes da Silva JF, Walters M, Al-Damluji S, Ganellin CR. *Bioorganic & Medicinal Chemistry,* 2008; **16:**7254.
36. Rewcastle GW, Palmer BD, Bridges AJ, Showalter HD, Sun L, et al. *Journal of Medicinal Chemistry,* 1996; **39:**918-928.
37. C.Nisha shri, Ajithadas Aruna, T. Vetrichelvan. *International Journal Of Scientific Research,* 2015; **4(8):** 714
38. Mehta et al. *BMC Chemistry,* 2019; **13:**113
39. Reda A Haggam, Essam A Soylem, Mohamed G. Assy, Marium F Arastiedy. *Journal of the Iranian Chemical Society,* 2020; **17:**1715-1723
40. Collins CH (1976) Microbiological methods. Butterworth, London, UK.
41. Varma RS (1998) Anti-fungal agents: past, present and future prospects. National Academy of Chemistry & Biology, Lucknow, India.