CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.6798506

Available online at: http://www.iajps.com *Research Article*

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF STYRYL MOIETIES BASED NEW 4(3H)-QUINAZOLINONE DERIVATIVE

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Article Received: May 2022 **Accepted:** June 2022 **Published:** July 2022

Abstract:

Objective: *The objective of the paper is synthesis and characterization of new 4(3H)- quinazolinone derivative based on styryl moieties and evaluate them for the antimicrobial activity.*

Material and methods: *The derivatives have been synthesized by the three steps process, in first step 2-methyl-4H-3,1-benzoxazin-4-one compounds was synthesized, in step 2, 2-methyl-3-peptido quinazolin-4-(3H)-ones compound was synthesized and in last step, 2-styryl-3-peptido quinazolin-4-(3H) ones compound have been synthesized by the reaction of synthesized compound of step 2, with different substituted aldehyde to from the final compounds. Total Sixteen compounds have been synthesized and characterized by physicochemical and spectral analysis. The final compounds (QP-1 to QP-16) have been evaluated for anti-microbial activity i.e., antibacterial and antifungal activity by agar based disk diffusion method.*

Result and Discussion: *The IR spectrum of the final compound QP-1 to QP16 have shown the IR spectrum with characteristics peak at 3442,57 (N-H str.); 1702.33 (C=O str., amide); 1457.55 (C=N str.); 1368.32 (N-O str.); 1565.22 (N=O str.); 852.22 (C-Cl); 1015.32 (C-Br); 1102.22 (C-F). The 1HNMR spectrum of the compound QP-1 to QP16 have shown the characteristics peak at 7.48-8.02 (4H, 1-benzene); 8.15 (1H, s ethylene); 6.66 (1H, s, ethylene), 1.46 (3H, s, methylene); 2.85 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine). The Data of antibacterial activity against the gram-positive bacterial strains suggested that compound QP-1, QP-4, QP-6, QP-9, QP12 have shown best activity against gram positive bacteria. The Data of antibacterial activity against the gram-negative bacterial strains (Escherichia Coli, Klebsiella Penumoniae) suggested that among substituted quinazolinone derivatives, compound QP-1, QP-4, QP-6, QP-9, QP12 have shown best activity against gram positive bacteria. The compounds possessed the halogens on the aromatic ring reveals the positive contribution of electron withdrawing groups to the antibacterial and antifungal activity. Presence of electronegative group (Cl, NO_2) is required for the potent antimicrobial activity.*

Keywords: *antimicrobial activity, quinazolinone, peptides, disk diffusion method, antibacterial, antifungal*

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Please cite this article in press Manmohan Gupta et al, ***Synthesis, Characterization And Antimicrobial Evaluation Of Styryl Moieties Based New 4(3h)- Quinazolinone Derivative.,*** *Indo Am. J. P. Sci, 2022; 09(7).*

INTRODUCTION:

Quinazolinone ring is an aromatic benzo-pyrimidine system, earlier known as benzo-1,3-diazine was prepared in the laboratory by Gabriel in 1903. It is yellow and crystalline in nature.[1] Compounds containing a fused quinazolinone ring belong to a broad class of compounds which have received a considerable attention over the past years due to their wide range of biological activities.[2] Some of amino-quinazolinone derivatives were found to be cardiac stimulants, they were also found as inhibitors of the tyrosine kinase or dihydrofolate reductase enzymes so they work as potent anticancer agents. [3] They are also used for hypertension, malaria and to fight infections involving AIDS.

The drug available in the market having the quinazolinone derivatives are, afloqualone as sedatives, hypnotics and anticancer potential, Albendazole used as antifungal drug, fluproquazone used as antipyretic and NSAID drug, methaqualone was used as hypnotic agent, Halofuginone used in immune disorder and diproqualone is used as effective agent against the rheumatoid arthritis. [4]

The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities such as anti-cancer, antibacterial, anti-HIV, anti-inflammatory, antifungal, analgesic, antihyperglycemic, anticonvulsant. But in-spite of this, an increasing number of infections are untreatable due to antimicrobial resistance (AMR). [5] An estimated 214,000 new born die every year from sepsis caused by antibiotic resistant bacteria, and lack of effective antibiotics threatens both basic and advanced medicine. The negative impact also extends well beyond health with serious implications on poverty reduction and inequality, animal welfare, the environment, food safety and security.

Antimicrobial peptides (also called host defence peptides) are an evolutionarily conserved component of the innate immune response and are found among all classes of life. Fundamental differences exist between prokaryotic and eukaryotic cells that may represent targets for antimicrobial peptides. [6] These peptides are potent, broad-spectrum antibiotics which demonstrate potential as novel therapeutic agents. Antimicrobial peptides have been demonstrated to gram negative and gram-positive bacteria, mycobacteria, enveloped viruses, fungi and even transformed or cancerous cells. [7]

Antimicrobial peptides are generally between 12 and 50 amino acids. In addition to killing bacteria directly, they have a number of immunomodulatory functions that may be involved in the clearance of infection, including the ability to alter host gene expression, act as chemokines and/or induce chemokine production, inhibiting lipopolysaccharide induced pro-inflammatory cytokine production, promoting wound healing, and modulating the responses of dendritic cells and cells of the adaptive immune response. [8] The increase of antimicrobial resistance (AMR) and antimalarial resistance are complex and severe health issues today, as many microbial strains have become resistant to market drugs Based on their reports, we have planned to synthesize the quinazoline by incorporating dipeptide and derive a set of peptide-quinazolinones and to screen for antimicrobial activities. [9]

The objective of the paper was to design, synthesis, characterization and biological evaluation of new derivatives of 4(3H)-quinazolinone carrying peptide and styryl moieties and evaluate for antimicrobial activity by agar Disk-diffusion method.

MATERIAL AND METHOD:

The 2-amino benzoic acid, acetic anhydride was purchased from Merck, India. The methyl 3-(2-aminopentanamido)-2-methylpropanoate, ethyl 3-(2-aminopentanamido)-2-methyl propanoate, glacial acetic acid, and substituted aldehydes were procured from sigma Aldrich, India. All the chemicals were purchased from Sigma Aldrich and Merck India are analytical grade and solvents used for the reactions were distilled before use. The melting points of the synthesized compounds were determined in open glass capillaries. IR spectra were recorded on Bruker-alpha FTIR spectrometer. Elemental analysis was performed and found values were within 0.4% of theoretical values. 1HNMR spectra were recorded at 400 MHz, Mass Spectra were recorded using Mass Spectrometers Jeol FSX-112 (FAB) by ESI.

Chemistry:

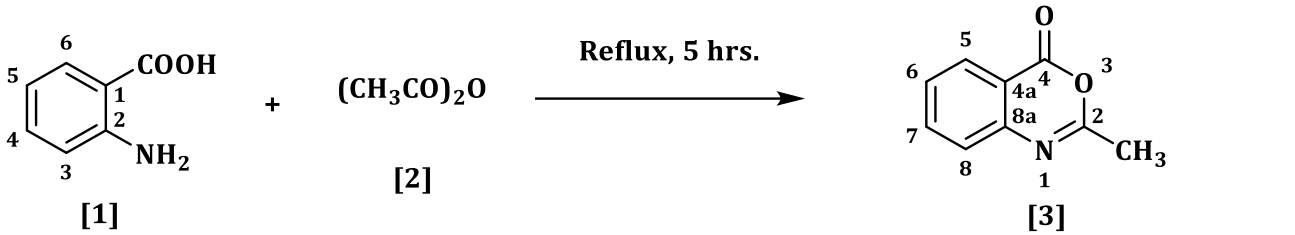
Synthesis of new 4(3H)-quinazolinone derivatives involves the following three steps.

Step 1: Synthesis of 2-methyl-4H-3,1-benzoxazin-4-one

Step 2: Synthesis of 2-methyl-3-peptido quinazolin-4-(3H)-ones

Step 3: Synthesis of 2-styryl-3-peptido quinazolin-4-(3H) ones

(a) Synthesis of 2-methyl-4H-3,1-benzoxazin-4-one

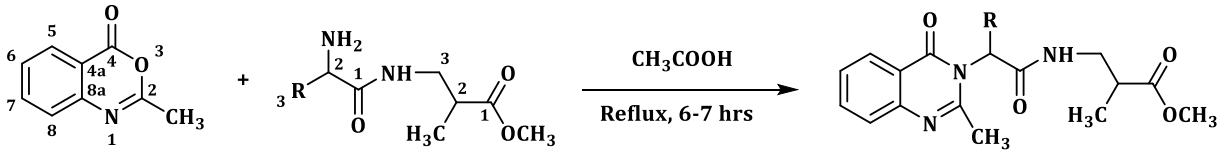


[1] **[2]** **[3]**

2-aminobenzoic acid **acetic anhydride** **2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one**

Procedure: This reaction carried-out under anhydrous conditions, in this reaction anthranilic acid (2-aminobenzoic acid) (0.01M) **[Compound 1]** and acetic anhydride (0.02M) **[Compound 2]** were refluxed for 5 hours and the excess acetic anhydride was removed under pressure. Due to its instability for a longer period of time, the product (2-methyl-4H-benzo[d][1,3]oxazin-4-one) **Compound 3** was quickly cooled to room temperature and used for the next phase. [10]

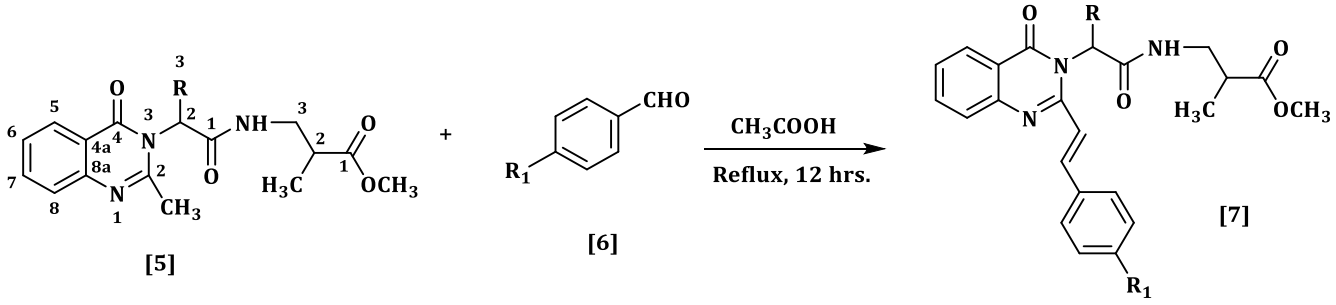
Step 2: Synthesis of 2-methyl-3-peptido quinazolin-4-(3H)-ones



[3] **[4]** **[5]**

Procedure: This reaction is carried out in anhydrous condition, in this reaction 2-methyl-4H-benzo[d][1,3]oxazin-4-one (0.01M) **Compound 3**, was dissolved in glacial acetic acid and methyl 3-(2-aminopentanamido)-2-methylpropanoate (0.01M) **Compound 4** was added to reaction mixture. The reaction mixture was refluxed for 6-7 hrs. under controlled environment. The reaction was monitored by the TLC technique by using solvent system; n-hexane: ethyl acetate (8:2). The reaction mixture was allowed to cool at room temperature and poured into crushed ice; the crude solid product[11] **Compound 5** obtained was recrystallized from ethanol**.**

Step 3: Synthesis of 2-styryl-3-peptido quinazolin-4-(3H) ones



[5] **[6]** **[7]**

Procedure: A mixture of substituted-2-methyl-3-peptido quinazolin-4-(3H)-ones (0.01M), **Compound 5** and various 4-substituted benzaldehyde (0.01M), **Compound 6** was dissolved in glacial acetic acid (50 ml) and refluxed for 12 hrs. The reaction was monitored by the thin layer chromatographic (TLC) technique by using solvent system **(**n-hexane: ethyl acetate (7:3). The reaction mixture was poured into ice cold water to obtained the solid product (**Compound 7, QP-1 to QP16)**, filtered, dried and recrystallized from ethanol.[12]

PHARMACOLOGICAL SCREENING:

Antimicrobial activity

The sixteen compounds naming as QP-1 to QP16 was subjected to pharmacological screening for

antibacterial and antifungal activity by agar-based disk diffusion method. In antibacterial screening of compounds, both gram positive and gram-negative strains were utilized in that case of Gram-positive strains (*Micrococlus luteus* ATCC 9341 and *Staphylococcus aureus* MTCC 96); Gram negative Organisms (*Klebsiella pneumoniae* ATCC 29665 and *Escherichia coli* MTCC-40) were used respectively. In other screening as antifungal activity, two fungal strains naming as *Candida albicans* ATCC 10231 and *Fusarium oxysporum* MTCC 284 were utilized. Disc diffusion method is applied for the determination of zone of inhibition. [13] Ciprofloxacin and ketoconazole were used as standard drug for the antibacterial and antifungal activity respectively. The antibacterial and antifungal activity of projected synthesized compounds was evaluated by dissolving the compound in dimethyl formamide (DMF) at two different concentrations of 50 and 100µg/ml by disc diffusion method. [14] The inhibition of zones caused by the synthesized compounds and standard drug were examined and the diameter of zone of inhibition was observed and recorded. [15]

RESULT AND DISCUSSION:

Chemistry:

The Sixteen compounds (QP-1 to QP-16) have been synthesized and was characterized by IR, 1HNMR, mass spectral and elemental analyses. The compound 3 (2-methyl-4H-3,1-benzoxazin-4-one) have been synthesized by the reaction of anthranilic acid with acetic anhydride. The compound 3 was synthesized with yield on 78.54% and having Rf value 0.51. The compound 3, was further reacted with the methyl 3-(2-aminopentanamido)-2-methylpropanoate to form the 2 2-methyl-3-peptido quinazolin-4-(3H)-one derivatives represented as compound 5. The IR spectrum of the compound 5, shown the characteristics peak at 3382.12 (N-H str.); 1702.55 (C=O str., amide); 1456.55 (C=N str.); 1652.25 (C=C str., aromatic); 1090.63 (C-O str.); 2920.32 (C-H str. in CH3); 2854.20 (-CH2 str.); 850.16 (C-Cl). The final compound (Compound 7, QP-1 to QP16) was obtained by the reaction of Compound 5 with eight different substituted benzaldehyde compounds (Compound 6). The IR spectrum of the final Compound 7 (QP-1 to QP16) have shown the IR spectrum with characteristics peak at 3442,57 (N-H str.); 1702.33 (C=O str., amide); 1457.55 (C=N str.); 1662.78 (C=C str., aromatic); 1064.11 (C-O str.); 3210.12 (C-H str. in CH3); 2920.19 (-CH2 str.); 1368.32 (N-O str.); 1565.22 (N=O str.); 852.22 (C-Cl); 1015.32 (C-Br); 1102.22 (C-F). The 1H NMR spectrum of the Compound 7 (QP-1 to QP16) shown the characteristics peak at 7.48-8.02 (4H, 1-benzene); 7.56-7.68 (2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.66 (1H, s, ethylene), 1.46 (3H, s, methylene); 2.85 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine). Mass spectrum of all sixteen compound were recorded and it almost similar to the compounds molecular weight. The elemental analysis and melting point of compound were also recorded and analysed and have in the accepted limit.

QP-1: Methyl-(E)-3-(2-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)propan amido)-2-methyl propanoate

Chemical Formula: C24H24ClN3O4; Molecular Weight: 453.92; IR (cm-1): 3428.15 (N-H str.); 1702.33 (C=O str., amide); 1456.55 (C=N str.); 1652.23 (C=C str., aromatic); 1092.32 (C-O str.); 2922.32 (C-H str. in CH3); 2854.23 (-CH2 str.); 852.22 (C-Cl); 1HNMR (400 MHz, DMSO-*d6*, ppm): 7.48-8.02 (4H, 1-benzene); 7.56-7.68 (2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.66 (1H, s, ethylene), 1.46 (3H, s, methylene); 2.85 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 453.15.

QP-2: Methyl (E)-3-(2-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)propan-amido) -2-methylpropanoate

Chemical Formula: C24H24BrN3O4; Molecular weight: 498.38**;** IR (cm-1): 3438.15 (N-H str.); 1705.33 (C=O str., amide); 1453.55(C=N str.); 1653.23 (C=C str., aromatic); 1092.32 (C-O str.); 2928.32 (C-H str. in CH3); 2852.23 (-CH2 str.); 1015.32 (C-Br); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (4H, 1-benzene); 7.62-7.70 (2H, Phenylic proton in 2-position of quinazolinone); 8.06 (1H, s, secondary amide in 3-propionamidopropanoate); 8.12 (1H, s ethylene); 6.65 (1H, s, ethylene), 1.48 (3H, s, methylene); 2.88 (1H, s, methine), 3.52 (3H, s, methyl), 4.64 (1H, s, methine); Mass (m/z): 497.10.

QP-3: Methyl-(E)-3-(2-(2-(4-fluorostyryl)-4-oxoquinazolin-3(4H)-yl)propan- amido)-2-methylpropanoate

Chemical formula: C24H24FN3O4; Molecular Weight: 437.47; IR (cm-1): 3439.15 (N-H str.); 1705.33 (C=O str., amide); 1458.55 (C=N str.); 1652.23 (C=C str., aromatic); 1090.32 (C-O str.); 2922.32 (C-H str. in CH3); 2854.23 (-CH2 str.); 1102.22 (C-F); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (4H, 1-benzene); 7.62-7.70 (2H, Phenylic proton in 2-position of quinazolinone); 8.06

(1H, s, secondary amide in 3-propionamidopropanoate); 8.12 (1H, s ethylene); 6.65 (1H, s, ethylene), 1.48 (3H, s, methylene); 2.88 (1H, s, methine), 3.52 (3H, s, methyl), 4.64 (1H, s, methine); Mass (m/z): 437.18.

QP-4: Methyl-(E)-2-methyl-3-(2-(2-(4-nitrostyryl)-4-oxoquinazolin-3(4H)-yl)-propan-amido)propanoate

Chemical formula: C24H24N4O6; Molecular weight: 464.48; IR (cm-1): 3445.15 (N-H str.); 1702.33 (C=O str., amide); 1450.55 (C=N str.); 1650.23 (C=C str., aromatic); 1092.32 (C-O str.); 2925.32 (C-H str. in CH3); 2852.23 (-CH2 str.); 1368.32 (N-O str.); 1565.22 (N=O str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (4H, 1-benzene); 7.62-7.70 (2H, Phenylic proton in 2-position of quinazolinone); 8.06 (1H, s, secondary amide in 3 propionamidopropanoate); 8.12 (1H, s ethylene); 6.65 (1H, s, ethylene), 1.48 (3H, s, methylene); 2.88 (1H, s, methine), 3.52 (3H, s, methyl), 4.64 (1H, s, methine); Mass (m/z): 464.17.

QP-5: Methyl-(E)-2-methyl-3-(2-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl) propan-amido)propanoate

Chemical Formula: C25H27N3O4; Molecular weight: 433.51; IR(cm-1): 3442.57 (N-H str.); 1702.33 (C=O str., amide); 1457.55 (C=N str.); 1662.78 (C=C str., aromatic); 1064.11 (C-O str.); 3210.12 (C-H str. in CH3); 2920.19 (-CH2 str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.54-8.12 (4H, 1-benzene); 7.62-7.70 (2H, Phenylic proton in 2-position of quinazolinone); 8.06 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (1H, s, ethylene), 1.45 (3H, s, methylene); 2.86 (1H, s, methine), 3.51 (3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 433.20.

QP-6: Methyl-(E)-3-(2-(2-(4-methoxystyryl)-4-oxoquinazolin-3(4H)-yl)propan- amido)-2-methylpropanoate

Chemical Formula: C25H27N3O5; Molecular Weight: 449.51; IR (cm-1): 3437.15 (N-H str.); 1702.33 (C=O str., amide); 1452.55 (C=N str.); 1656.23 (C=C str., aromatic); 1098.32 (C-O str.); 2930.32 (C-H str. in CH3); 2856.23 (-CH2 str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.50-8.10 (4H, 1-benzene); 7.62-7.74 (2H, Phenylic proton in 2-position of quinazolinone); 8.03 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (1H, s, ethylene), 1.45 (3H, s, methylene); 2.85 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 449.20.

QP-7: Methyl-(E)-3-(2-(2-(4-ethylstyryl)-4-oxoquinazolin-3(4H)-yl)propan amido)-2-methylpropanoate

Chemical formula: C26H29N3O4; Molecular weight: 447.54; IR (cm-1): 3438.35 (N-H str.) 1705.23 (C=O str., amide); 1458.65 (C=N str.); 1652.13 (C=C str., aromatic); 1095.42 (C-O str.); 2920.12 (C-H str. in CH3); 2858.23 (-CH2 str.); 850.03 (C-Cl); 1HNMR (400 MHz, DMSO-d6, ppm): δ 7.54-8.16 (4H, 1-benzene); 7.62-7.70 (2H, Phenylic proton in 2-position of quinazolinone); 8.03 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (1H, s, ethylene), 1.52 (3H, s, methylene); 2.85 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 447.22.

QP-8: Methyl-(E)-3-(2-(2-(4-ethoxystyryl)-4-oxoquinazolin-3(4H)-yl)propan-amido)-2-methylpropanoate

Chemical formula: C26H29N3O5; Molecular weight: 463.53; IR (cm-1): 3423.15 (N-H str.); 1708.33 (C=O str., amide); 1450.55 (C=N str.); 1652.23 (C=C str., aromatic); 1093.32 (C-O str.); 2922.32 (C-H str. in CH3); 2856.23 (-CH2 str.); 850.46 (C-Cl); 1HNMR (400 MHz, DMSO-d6, ppm): δ 7.50-8.15 (4H, 1-benzene); 7.62-7.68 (2H, Phenylic proton in 2-position of quinazolinone); 8.03 (1H, s, secondary amide in 3-propionamidopropanoate); 8.12 (1H, s ethylene); 6.65 (1H, s, ethylene), 1.45 (3H, s, methylene); 2.86 (1H, s, methine), 3.50 (3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 463.45.

QP-9: Methyl-(E)-3-(2-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)butanamido)-2-methyl propanoate

Chemical formula: C25H26ClN3O4; Molecular weight: 467.95; IR (cm-1); 3423.15 (N-H str.); 1702.33 (C=O str., amide); 1456.55 (C=N str.); 1652.23 (C=C str., aromatic); 1090.32 (C-O str.); 2922.32 (C-H str. in CH3); 2850.23 (-CH2 str.); 849.22 (C-Cl); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (m, 4H, 1-benzene); 7.62-7.70 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.21 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.46 (m, 3H, s, methylene); 2.86 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.64 (1H, s, methine); Mass (m/z): 467.16.

QP-10: Methyl-(E)-3-(2-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)butan-amido) -2-methylpropanoate

Chemical formula: C25H26BrN3O4; Molecular weight: 512.40; IR (cm-1): 3438.25 (N-H str.); 1705.13 (C=O str., amide); 1450.45 (C=N str.);

1652.63 (C=C str., aromatic); 1092.32 (C-O str.); 2920.42 (C-H str. in CH3); 2852.13 (-CH2 str.); 1012.38 (C-Br); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (m, 4H, 1-benzene); 7.62-7.66 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.05 (1H, s, secondary amide in 3-propionamidopropanoate); 8.16 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.45 (m, 3H, s, methylene); 2.82 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 512.02.

QP-11: Methyl (E)-3-(2-(2-(4-fluorostyryl)-4-oxoquinazolin-3(4H)-yl)butan amido)-2-methylpropanoate

Chemical formula: C25H26FN3O4; Molecular weight: 451.50; IR (cm-1): 3438.15 (N-H str.); 1705.13 (C=O str., amide); 1450.25 (C=N str.); 1652.53 (C=C str., aromatic); 1097.32 (C-O str.); 2920.62 (C-H str. in CH3); 2852.33 (-CH2 str.); 1102.22 (C-F); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.12 (m, 4H, 1-benzene); 7.62-7.75 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.45 (m, 3H, s, methylene); 2.84 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.62 (1H, s, methine); FAB Mass (m/z): 451.19.

QP-12: Methyl-(E)-2-methyl-3-(2-(2-(4-nitrostyryl)-4-oxoquinazolin-3(4H)-yl)-butan amido)propanoate

Chemical formula: C25H26N4O6; Molecular weight: 478.51; IR (cm-1): 3422.15 (N-H str.); 1700.33 (C=O str., amide); 1453.55 (C=N str.); 1654.23 (C=C str., aromatic); 1094.32 (C-O str.); 2925.32 (C-H str. in CH3); 2854.23 (-CH2 str.); 1365.32 (N-O); 1564.22 (N=O); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.13 (m, 4H, 1-benzene); 7.60-7.72 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.04 (1H, s, secondary amide in 3-propionamido propanoate); 8.12 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.45 (m, 3H, s, methylene); 2.85 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 478.16.

QP-13: Methyl-(E)-2-methyl-3-(2-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl) butanamido)propanoate

Chemical formula: C26H29N3O4; Molecular weight: 447.54; IR (cm-1): 3442.15 (N-H str.); 1702.33 (C=O str., amide); 1453.55 (C=N str.); 1650.23 (C=C str., aromatic); 1092.32 (C-O str.); 2920.32 (C-H str. in CH3); 2852.23 (-CH2 str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (m, 4H, 1-benzene); 7.62-7.72 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.05 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.46 (m, 3H, s, methylene); 2.85 (1H, s, methine), 3.51 (m, 3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 447.22.

QP-14: Methyl-(E)-3-(2-(2-(4-methoxystyryl)-4-oxoquinazolin-3(4H)-yl)butanamido)-2-methylpropanoate

Chemical formula: C26H29N3O5; Molecular weight: 463.53; IR (cm-1): 3438.15 (N-H str.); 1705.33 (C=O str., amide); 1452.55 (C=N str.); 1652.23 (C=C str., aromatic); 1090.32 (C-O str.); 2920.32 (C-H str. in CH3); 2856.23 (-CH2 str.); 849.32 (C-Cl); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (m, 4H, 1-benzene); 7.62-7.70 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.16 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.45 (m, 3H, s, methylene); 2.83 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 463.21.

QP-15: Methyl-(E)-3-(2-(2-(4-ethylstyryl)-4-oxoquinazolin-3(4H)-yl)butanamido)-2-methyl propanoate

Chemical formula: C27H31N3O4; Molecular weight: 461.56; IR (cm-1): 3440.15 (N-H str.); 1705.33 (C=O str., amide); 1450.55 (C=N str.); 1652.23 (C=C str., aromatic); 1092.32 (C-O str.);2920.32 (C-H str. in CH3); 2852.23 (-CH2 str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.15 (m, 4H, 1-benzene); 7.62-7.70 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.05 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.68 (s, 1H, ethylene), 1.42 (m, 3H, s, methylene); 2.86 (1H, s, methine), 3.50 (m, 3H, s, methyl), 4.64 (1H, s, methine); Mass (m/z): 461.23.

QP-16: Methyl-(E)-3-(2-(2-(4-ethoxystyryl)-4-oxoquinazolin-3(4H)-yl)butanamido)-2-methylpropanoate

Chemical formula: C27H31N3O5; Molecular weight: 477.56; IR (cm-1): 3439.15 (N-H str.); 1708.33 (C=O str., amide); 1452.55 (C=N str.); 1650.23 (C=C str., aromatic); 1092.32 (C-O str.); 2923.32 (C-H str. in CH3); 2856.23 (-CH2 str.); 1HNMR (400 MHz, DMSO-d6, ppm): 7.52-8.16 (m, 4H, 1-benzene); 7.60-7.72 (m, 2H, Phenylic proton in 2-position of quinazolinone); 8.02 (1H, s, secondary amide in 3-propionamidopropanoate); 8.15 (1H, s ethylene); 6.62 (s, 1H, ethylene), 1.45 (m, 3H, s, methylene); 2.85 (1H, s, methine), 3.51 (m, 3H, s, methyl), 4.62 (1H, s, methine); Mass (m/z): 477.23.

Pharmacological evaluation:

The antibacterial activity of synthesized compounds **(Compound 7, QP-1 to QP16)** was screened against

each gram positive *Micrococlus luteus* ATCC 9341 & *Staphylococcus aureus* MTCC 96 and Gram-negative Organisms (*Klebsiella pneumoniae* ATCC 29665 & *Escherichia coli* MTCC-40) by disc diffusion method using ciprofloxacin as standard drug. The data of antibacterial activity of synthesized quinazolinone derivatives against gram-positive and gram-negative bacteria was represented in Table 1.

Antibacterial activity:

The Sixteen synthesized compounds (QP-1 to QP-16) were evaluated for the antibacterial screening and data obtained by the result stated that substituted quinazolinone derivatives has shown the mild to best activity against tested organism's strains. The screening carried out on both Gram positive and gram-negative bacteria separately. The Data of antibacterial activity against the gram-positive bacterial strains (*S. Aureus* and *M. Luteus*) suggested that among substituted quinazolinone derivatives (QP-1 to QP-16), compound QP-16, QP-15, QP-14, QP-11, QP-3, QP-8, QP-10 have shown mild activity while as compound QP-2, QP-7, QP-5, QP-13 shown moderate activity and compound QP-1, QP-4, QP-6, QP-9, QP12 have shown best activity against gram positive bacteria (Table 5.3).

The compound QP-1 (12.42±0.3; 12.52±0.2), QP-4 (11.22±0.6; 11.42±0.8), QP-6 (9.22±0.3; 7.42±0.3), QP-9 (11.72±0.3; 13.28±0.3), QP12 (10.22±0.7; 10.14±0.5) have shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 17.22±0.3; 17.25±0.5) has shown good activity at 50µg concentration against gram-positive bacterial strains (*S. Aureus* and *M. Luteus*) respectively, The compound QP-1 (14.10±0.8; 17.62±0.6), QP-4 (13.62±0.8; 15.22±0.3), QP-6 (10.62±0.6; 8.54±0.4), QP-9 (13.15±0.4; 15.32±0.2), QP12 (10.14±0.5; 13.32±0.7) have shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 19.45±0.5; 21.52±0.4) has shown good activity at 100µg concentration against gram-positive bacterial strains (*S. Aureus* and *M. Luteus*), The representation of zone of inhibition on gram positive and gram negative bacterial strains was shown in Figure 1 & 2.

The Data of antibacterial activity against the gram-negative bacterial strains (*Escherichia Coli*, *Klebsiella Penumoniae*) suggested that among substituted quinazolinone derivatives (QP-1 to QP-16), compound QP-16, QP-15, QP-14, QP-11, QP-3, QP-8, QP-10 have shown mild activity while as compound QP-2, QP-7, QP-5, QP-13 shown moderate activity and compound QP-1, QP-4, QP-6, QP-9, QP12 have shown best activity against gram positive bacteria.

Table 1: Antibacterial activity of synthesized quinazolinone derivatives against gram-positive and gram-negative bacteria

Compound	Zone of Inhibition (mm)							
	GRAM POSITIVE BACTERIA				GRAM NEGATIVE BACTERIA			
	Staphylococcus Aureus		*Micrococlus luteus*		*Klebsiella pneumoniae*		*Escherichia coli*	
Conc.	**50µg/ml**	**100µg/ml**	**50µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**
QP-1	12.42±0.3	14.10±0.8	12.52±0.2	17.62±0.6	14.15±0.5	16.22±0.3	15.32±0.8	17.62±0.7
QP-2	7.42±0.7	9.32±0.3	8.22±0.1	10.54±0.6	7.22±0.6	9.14±0.7	7.13±0.4	8.56±0.3
QP-3	5.32±0.1	6.62±0.7	6.22±0.5	6.12±0.7	6.32±0.7	6.26±0.2	6.14±0.3	6.23±0.4
QP-4	11.22±0.6	13.62±0.3	11.42±0.8	15.22±0.5	12.12±0.3	14.52±0.7	12.52±0.2	14.22±0.5
QP-5	8.52±0.5	9.22±0.4	6.22±0.5	7.15±0.5	5.32±0.2	6.15±0.5	6.54±0.5	7.11±0.5
QP-6	9.22±0.3	10.62±0.6	7.42±0.7	8.54±0.4	6.13±0.5	8.44±0.3	6.25±0.2	7.32±0.6
QP-7	7.62±0.8	8.02±0.7	8.55±0.2	10.12±0.4	6.62±0.4	8.12±0.8	7.07±0.3	8.17±0.7
QP-8	6.22±0.2	7.52±0.5	5.52±0.3	6.02±0.3	4.42±0.3	6.46±0.4	6.06±0.5	7.22±0.7
QP-9	11.72±0.3	13.15±0.4	13.28±0.5	15.32±0.2	12.03±0.5	13.37±0.6	13.42±0.3	15.17±0.5
QP-10	6.36±0.3	6.12±0.2	6.12±0.3	6.22±0.3	6.12±0.3	6.14±0.4	6.02±0.2	6.14±0.3
QP-11	4.42±0.6	5.22±0.6	6.32±0.3	6.32±0.2	6.52±0.6	6.15±0.7	6.14±0.4	6.16±0.8
QP-12	10.22±0.7	12.52±0.2	10.14±0.5	13.32±0.7	9.42±0.8	11.32±0.4	10.32±0.7	12.62±0.3
QP-13	8.42±0.8	9.22±0.4	9.55±0.3	11.42±0.8	7.52±0.7	9.42±0.9	8.52±0.4	9.52±0.2
QP-14	05.22±0.2	6.42±0.3	6.22±0.5	6.32±0.5	6.22±0.2	6.22±0.7	6.22±0.7	6.22±0.8
QP-15	04.72±0.8	6.62±0.5	6.22±0.7	6.12±0.3	6.02±0.5	6.22±0.4	6.12±0.3	6.22±0.3
QP-16	3.22±0.4	4.52±0.2	6.22±0.4	6.02±0.5	5.69±0.7	6.12±0.7	6.02±0.6	6.35±0.8
Ciprofloxacin (25µg/ml)	17.22±0.3	19.45±0.5	17.25±0.5	21.52±0.4	16.64±0.3	17.45±0.3	17.64±0.2	20.65±0.4

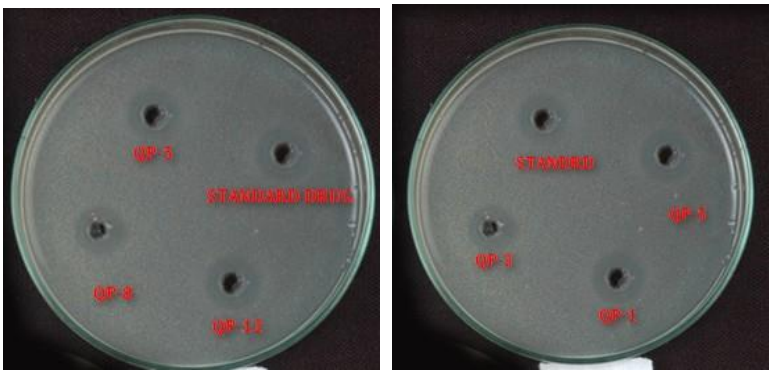


Figure 1: The pictorial representation of Zone of inhibition of compound against gram-positive bacteria (*Micrococlus luteus* ATCC 9341)

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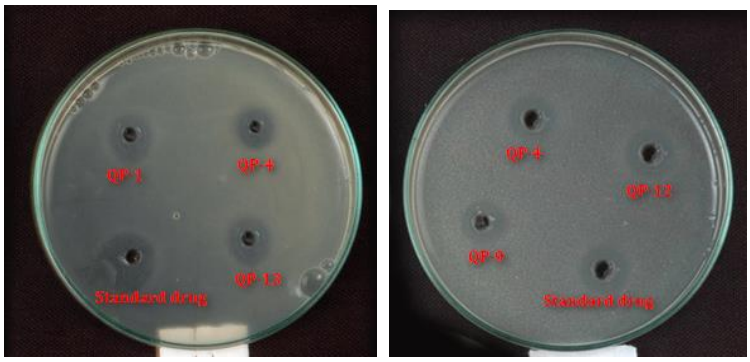

Figure 2: The pictorial representation of Zone of inhibition of compound against gram negative bacteria

Antifungal activity

The Sixteen synthesized compounds (QP-1 to QP-16) were evaluated for the antifungal screening and data obtained by the result stated that substituted quinazolinone derivatives has shown the mild to best activity against tested organism's strains. The screening carried out on two fungal strains i.e., *S. Cerevisiae* and A. *Niger*. The result data have represented in Table 2. The graphical representation of zone of inhibition was shown in Figure 3 & 4.

Table 2: Antifungal activity of the Synthesized compound (QP-1 to QP-16)

Compound	Zone of inhibition in mm			
	S. Cerevisiae		*A. Niger*	
Conc.	**50 µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**
QP-1	14.75±0.53	17.65±0.83	13.34±0.78	18.25±0.32
QP-2	7.32±0.55	7.65±0.45	3.42±0.52	6.25±0.55
QP-3	04.22±0.26	5.52±0.32	3.62±0.55	5.32±0.53
QP-4	12.45±0.28	16.32±0.26	12.23±0.63	16.35±0.65
QP-5	8.32±0.33	8.72±0.64	4.52±0.76	7.64±0.42
QP-6	5.32±0.22	6.62±0.53	2.62±0.37	5.12±0.33
QP-7	6.32±0.84	7.12±0.75	5.65±0.22	9.22±0.44
QP-8	4.32±0.14	5.72±0.72	3.32±0.57	5.22±0.73
QP-9	11.72±0.34	12.20±0.82	9.62±0.23	16.72±0.68
QP-10	9.62±0.72	11.62±0.23	7.24±0.53	12.52±0.72
QP-11	6.32±0.77	8.42±0.36	5.32±0.13	9.64±0.65
QP-12	10.42±0.67	12.72±0.37	8.52±0.85	14.32±0.546
QP-13	10.32±0.32	12.25±0.45	10.38±0.54	14.42±0.25
QP-14	5.32±0.37	5.22±0.27	3.22±0.34	5.32±0.36
QP-15	07.32±0.88	8.32±0.44	6.65±0.36	10.52±0.82
QP-16	3.32±0.63	4.332±0.67	3.42±0.35	5.42±0.27
Ketoconazole	15.25±0.32	20.35±0.26	14.24±0.32	19.23±0.23

The Data of antibacterial activity against two fungal strains i.e., *S. Cerevisiae* and A. *Niger* suggested that among substituted quinazolinone derivatives (QP-1 to QP-16), compound QP-3, QP-6, QP-8, QP-10, QP-16, QP-15, QP-14, QP-11, have shown mild activity while as compound QP-2, QP-5, QP-7 shown moderate activity and compound QP-1, QP-4, QP-9, QP-QP-10, 12, QP-13 have shown best activity against both fungal strains (Table 2).

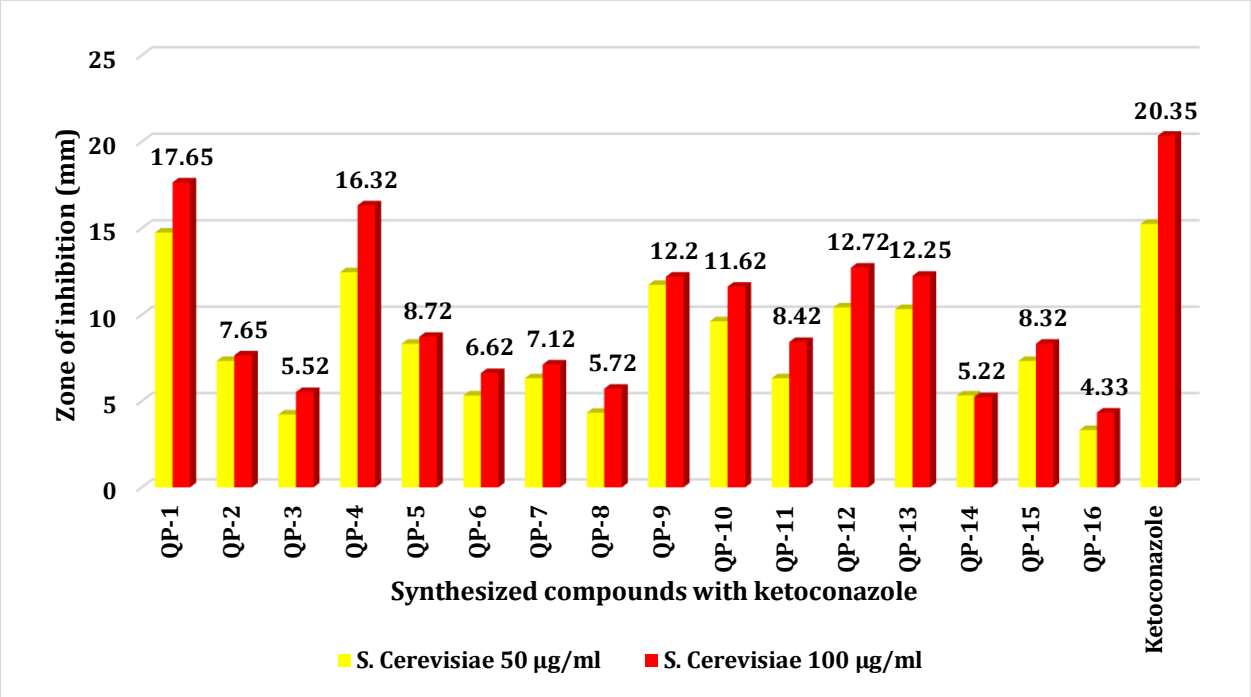

Figure 3: Zone of inhibition (mm) of synthesized compounds (QP-1 to QP-16) on *S. Cerevisiae* at 50 µg/ml and 100 µg/ml concentration.

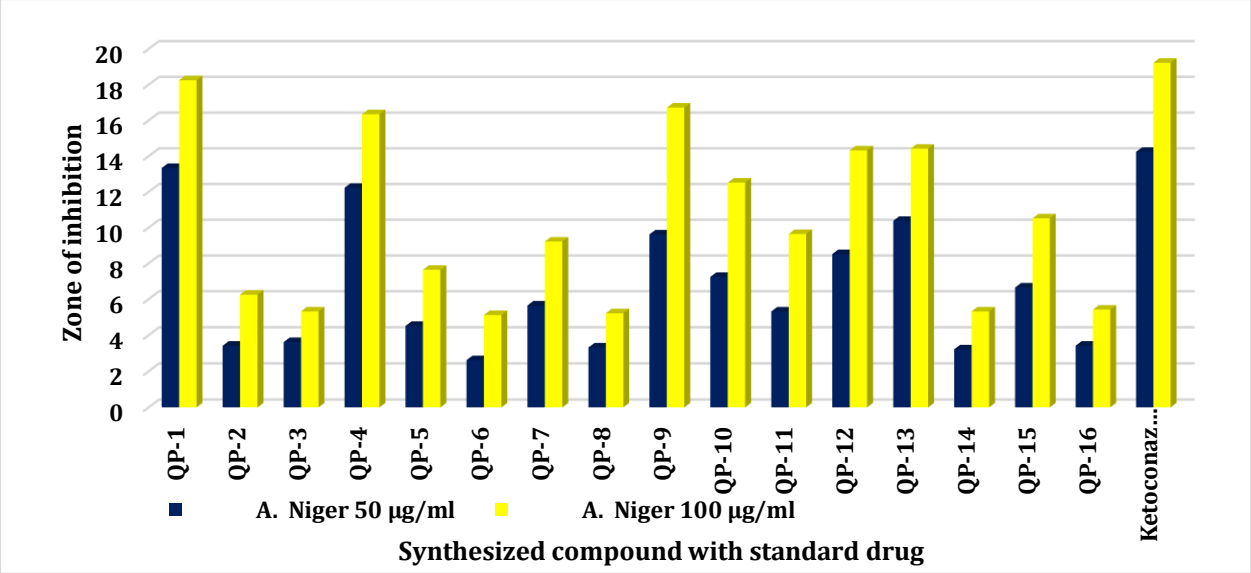

Figure 4: Zone of inhibition (mm) of synthesized compounds (QP-1 to QP-16) on *A. Niger* at 50 µg/ml and 100 µg/ml concentration.

The compound QP-1 (14.75±0.53; 17.65±0.83), QP-4 (12.45±0.28; 12.23±0.63), QP-9 (11.72±0.34; 9.62±0.23), QP-10 (9.62±0.72; 7.24±0.53), QP-12 (10.42±0.67; 8.52±0.85), QP-13 (10.32±0.32; 10.38±0.54) have shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 15.25±0.32; 14.24±0.32) has shown good activity at 50µg concentration against both the fungal strains (*S. Cerevisiae* and A. *Niger*) respectively, The compound QP-1 (17.65±0.83; 18.25±0.32), QP-4 (16.32±0.26.; 16.35±0.65), QP-9 (12.20±0.82; 16.72±0.68), QP-10 (11.62±0.23; 12.52±0.72), QP12 (12.25±0.45; 14.42±0.25), QP-13 (12.25±0.45; 14.42±0.25) have shown zone of

inhibition (mm) in comparison to standard drug (Ciprofloxacin, 20.35±0.26; 19.23±0.23) has shown good activity at 100µg concentration against fungal strains (*S. Cerevisiae* and A. *Niger*).

DISCUSSION:

The antibacterial activity of synthesized compounds **(Compound 7, QP-1 to QP16)** was screened against each gram positive *Micrococlus luteus* ATCC 9341 & *Staphylococcus aureus* MTCC 96 and Gram-negative Organisms (*Klebsiella pneumoniae* ATCC 29665 & *Escherichia coli* MTCC-40) by disc diffusion method using ciprofloxacin as standard drug as well as antifungal screening carried out on two fungal strains i.e., *S. Cerevisiae* and A. *Niger* by using ketoconazole drug as standard.

The antibacterial activity data of quinazolinone indicated that the compounds have significant inhibitory activity on all the bacteria at both 50 µg/ml and 100 µg/ml dose levels when compared with standard. Among all the compounds tested, compounds QP-1, QP-4, QP-6, QP-9, QP-12 possessed maximum activity. These compounds possessed the halogens on the aromatic ring and thus reveal the positive contribution of electron withdrawing groups to the antibacterial and antifungal activity. Presence of electronegative group (Cl, NO_2) is required for the potent antimicrobial activity.

Acknowledgement:
I would like to thank SAIF, Punjab University, Chandigarh for carried out the IR, 1HNMR, and mass spectroscopy for characterization of synthesized compounds.

Conflicts of Interest:
The author declares no conflicts of interest

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