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# Synthesis, Characterization and Evaluation of Anti-microbial Activity of Quinazolinone Derivatives

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**ABSTRACT**
Quinazolinone also called as quinazolindiones, chemically known as Quinazolin-4(3H)-one. Chemicals with two conjoined aromatic rings incorporating two nitrogen atoms and one of the carbons oxidized with keto oxygen. Quinazolinone is a heterocyclic chemical compound. The designed prototypes which are fused ring of quinozolinones with the substituted benzene linked via Schiff base thiosemicarbazides were synthesized by using our previous approach with a slight modification in the reaction conditions. Total, five compounds of newly modified quinazolin-4 (3H)-ones were synthesized. The completion of the reaction was checked by TLC in the n-haxane:ethyl acetate (1:3) mixture. Quinazolinones derivatives were recrystallized from ethanol. The %Yield was calculated. Quinazolinones were characterized by molecular formula, molecular weight, physical state, color, melting point, solubility and $R_f$ -Value. Also IUPAC name and Elemental Analysis was done. The structures of the synthesize compounds were elucidated and confirmed with FT-IR, and $^1$H NMR spectroscopy. The synthesize compounds were screened for their antimicrobial activity for the gram positive, gram negative and fungal strains by disc diffusion method and the inhibition of microorganism were compared with the standard drugs ciprofloxacin and Clotrimazole respectively. Novel synthesized Quinazolinones derivatives were exhibited anti-bacterial activity against B. subtilis, E. coli. and Against C. Albicans and A. Niger. Overall, all the synthesized compounds are moderate to significantly active against both bacterial and fungal strains. Significantly compounds Q-2 and Q-4 had the highest activity against both bacterial and fungal strains. For this heterocyclic incorporate series, among the substitutions on quinazolones, substituted chlorine and methyl group substituted compounds are more active than others. May be the electron withdrawing group or electron donating groups are required to enhance the biological action of the quinazolones.

**KEYWORDS:** Quinazolinone, quinazolindiones, thiosemicarbazides, NMR, FT-IR,

## I. INTRODUCTION

The emergence of antimicrobial resistance is a broadly identified public health threat[1]. The search for novel antibacterial drugs is an attractive purpose for medicinal chemists Bacterial resistance to existing drugs is a growing problem in the world[2]. Considerable researches have been performed on the synthesis of new quinazolinone derivatives with potent antimicrobial activity. These derivatives possess antibacterial activities, especially against the gram positive strains, and fungi through their interaction with the cell wall and DNA structures[3].

Quinazolinone also called as quinazolindiones, chemically known as Quinazolin-4(3H)-one. Chemicals with two conjoined aromatic rings incorporating two nitrogen atoms and one of the carbons oxidized with keto oxygen[4]. Quinazolinone is a heterocyclic chemical compound[5]. Carbonyl linkage on the quinazoline ring will give rise to quinazolinone (4(3H)-quinazolinone & 2(1H)-quinazolinone). There are two structural isomers, 2-quinazolinone and 4-quinazolinone, with the 4-isomer being the more common. Quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties[6]. Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoan,

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anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules[7].

Schiff bases have also shown to exhibit a wide range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, andantipyretic properties. Imine or azomethine groups arepresent in various natural, natural-derived, and non-natural compounds[8].

In the exploration of various chemical classes for developing new antibacterial agents, we found quinazolinone to be a promising scaffold which could be considered as a privileged structure by virtue of its wide range of biological properties such as anti-inflammatory, anti-HIV, anticancer, antibacterial, antifungal, anticonvulsant, and analgesic activities and also scope to develop structural diversity. Potent anti-bacterial activity of various quinazolinone derivatives have been reported by several groups. Therefore our aim is to synthesize different quinazolinone derivatives as anti-microbial agents by substitution of different electron donating and electron withdrawing groups and evaluate them for their anti-inflammatory activity.

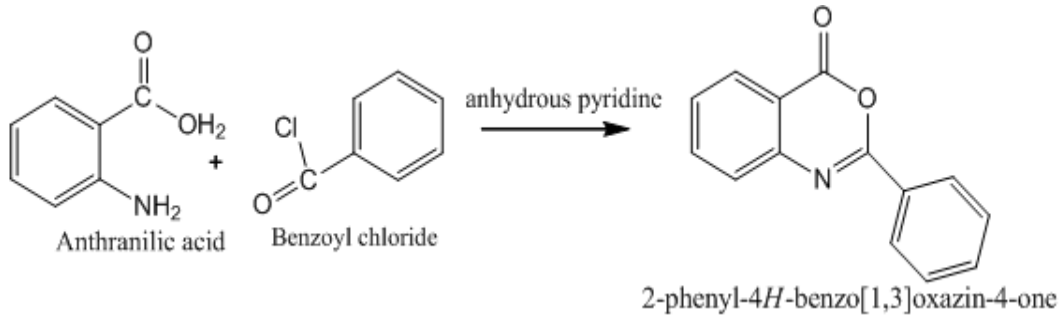
## II. MATERIALS AND METHOD

Anthranilic acid, Acetic Acid glacial, Acetophenone, were purchased from Himedia Mumbai and 1-(p-tolyl)ethanone, 1-(4-hydroxyphenyl) ethanone, 1-(4-aminophenyl) ethanone, 1-(4-Chlorophenyl) ethanone, were purchased from Sigma Aldrich Co. All other reagents and solvent used during experiment were belongs to L.R. grade.

**Methods of Synthesis of Quinazolinone derivatives**

**6.2.1 Step-1: General Procedure for the Synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one (Q)**

Anthranilic acid (2.7g, 0.02mol) was dissolved in 30ml of anhydrous pyridine with stirring at room temperature. The mixture was cooled to 0°C and a second solution of benzoyl chlorides (2.3ml, 0.02mol) in anhydrous pyridine (30ml) was slowly added to this solution with constant stirring for 30min and set aside for 1 hour. The pasty mass obtained was diluted with water and the resulting mixture was treated with 5% sodium bicarbonate solution to remove the unreacted acid. When effervescence was ceased, the solid material was filtered off and washed with water to remove the inorganic materials and the adhered pyridine. The crude benzoxazine thus obtained was dried and re-crystallized from ethanol[9].




**6.2.2 Step-2: Synthesis of 4-oxo-2-phenylquinazoline-3(4H)-carbothiohydrazide (Q-0)**

2-phenyl-4H-3,1-benzoxazin-4-one(2.25g, 0.01mol) and Thiosemicarbazide (9.11g, 0.01mol) was dissolved in ethanol. The reaction mixture was made acidic with glacial acetic acid and resulting mixture was refluxed on a hot plate for 5-6 hours. The mixture was cooled at room temperature and poured into ice containing beaker and solid residue was collected. The precipitate were filtered, dried and recrystallized from ethanol[10].

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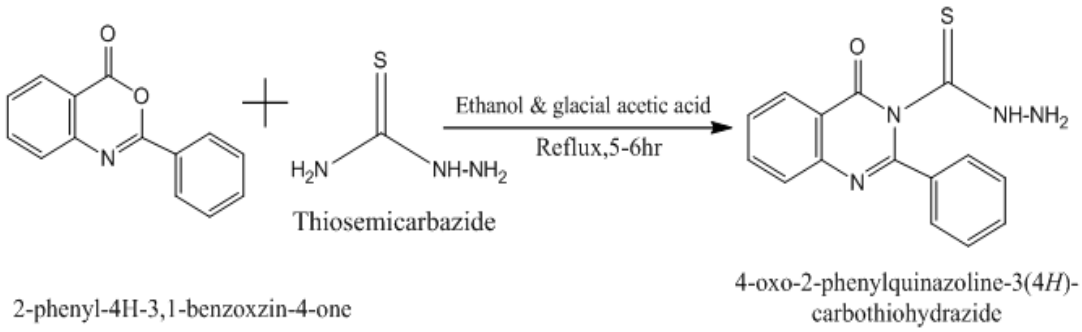
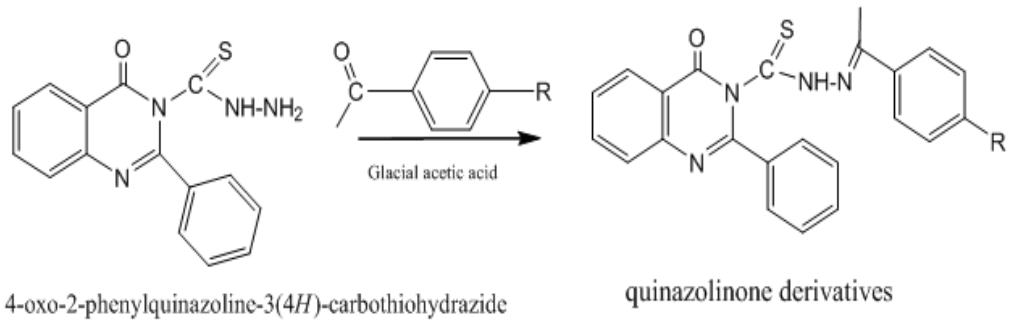



**6.2.3 Step-3: Synthesis of Quinazolinone derivatives**

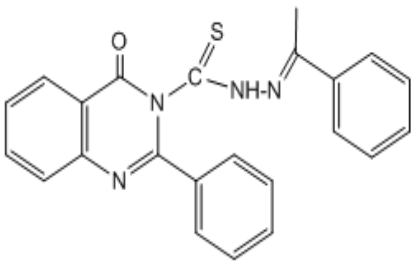
4-oxo-2-phenylquinazoline-3(4H)-carbothiohydrazide (2.97g, 0.01mol) and substituted aromatic ketones (0.01mol) were dissolved in ethanol. It pH was adjusted to 4.0-4.5 with glacial acetic acid. The content of the mixture was refluxed for 03 hour. The reaction mixture was poured into ice cooled water and filtered. The obtained solid was dried and recrystallized from ethanol[11].




## III. RESULTS AND DISCUSSION

**Characterization and Structural Elucidation of Novel Synthesized Quinazolinones**

**(A) 4-oxo-2-phenyl-N'-(1-phenylethylidene)quinazoline-3(4H)-carbothiohydrazide (Q-1):** $C_{23}H_{18}N_4OS$; Dark Yellow, Crystalline solid; Melting Point (162-164$^{O}$C), Yield (62.53%,); **Elemental Analysis calculated (Found) %:** C, 69.32(68.90); H, 4.55(4.36); N, 14.06(14.01); O, 4.02(4.02); S, 8.05(8.02).; **FT-IR (KBr):** cm$^{-1}$ 3289 N-H str.; 1693 C=O str.; 1673 C=N str.(imine), 1643 C=N str. (Pyrimidine), 1557 C=C str. (Ar), 1489 C-H str., 1303 C-N str.; **$^{1}$H NMR ($CDCL_3$, 400 MHz):** δ 8.03(d, 1H, J= 8.4, CH-Ar.), 7.94(d, 2H, J= 6.96, CH-Ar), 7.83(d, 2H, J= 7.68, CH-Ar), 7.70-7.63(m, 3H, CH-Ar), 7.52(t, 6H, J= 5.64, 4.68, CH-Ar), 7.1(s, 1H, NH), 2.43(s, 3H, $CH_3$), ppm.



**(B) 4-oxo-2-phenyl-N'-(1-(p-tolyl) ethylidene) quinazoline-3(4H)-carbothiohydrazide (Q-2): $C_{24}H_{20}N_4OS$**; Yellowish, Crystalline solid; Melting Point (143-145$^{O}$C), Yield (54.12%); **Elemental Analysis calculated (Found) %:** C, 69.88(69.57); H, 4.89(4.73); N, 13.58(13.49); O, 3.88(3.79); S, 7.77(7.63); **FT-IR (KBr): cm$^{-1}$** 3314 N-H str.; 1787 C=O str., 1648 C=N str.(imine), 1590 C=N str. (Pyrimidine), 1548 C=C str. (Ar), 1480 C-H str., 1312 C-N str.; **$^{1}$H NMR ($CDCL_3$, 400 MHz):** δ 8.03(d, 1H, J= 9.28, CH-Ar.), 7.83(d, 2H, J=

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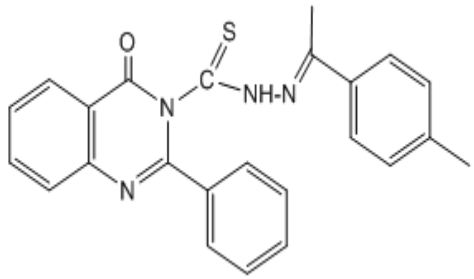
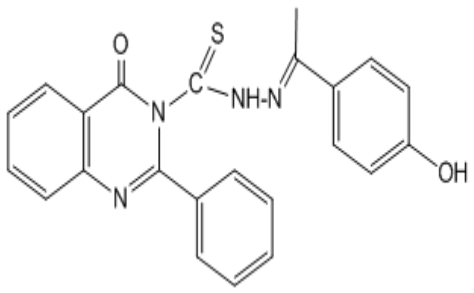
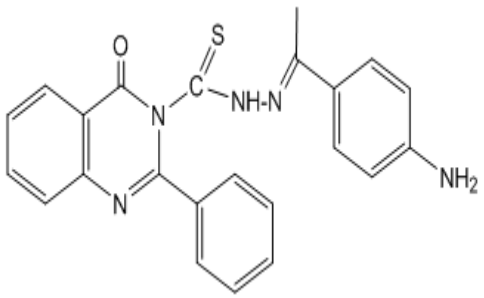
9.36, CH-Ar), 7.71(d, 2H, J= 4.44, CH-Ar), 7.70-7.63(m, 3H, CH-Ar), 7.52(t, 3H, J= 4.44, 3.80, CH-Ar), 7.28(d, 2H, J= 8.36, CH-Ar), 7.1(s, 1H, NH), 2.43(s, 3H, $CH_3$), 2.34(s, 3H, $CH_3$), ppm.



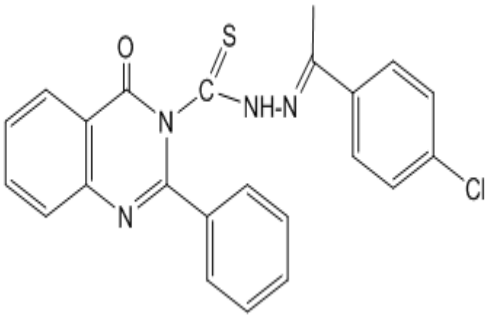

**(C) 4-N'-(1-(4-hydroxyphenyl) ethylidene) -4-oxo-2-phenylquinazoline-3 (4H)-carbothiohydrazide (Q-3): $C_{23}H_{18}N_4O_2S$**; Light Yellow, Crystalline solid; Melting Point (165-166 $^{O}$C), Yield (65.76 %); **Elemental Analysis calculated (Found) %:** C, 66.65(66.47); H, 4.38(4.32); N, 13.52(13.47); O, 7.72(7. 64); S, 7.74(7.62).; **FT-IR (KBr): cm$^{-1}$** 3396 N-H str.; 3310 O-H str.; 1650 C=O str., 1606 **C=N** str. (Pyrmidine), 1567 C=C str. (Ar), 1487 C-H str., 1387 C-N str.; **$^{1}$H NMR (CDCL$_3$, 400 MHz):** δ 8.03(d, 1H, J= 8.08, CH-Ar.), 7.85(d, 2H, J= 5.08, CH-Ar), 7.83(d, 2H, J= 8.72, CH-Ar), 7.70-7.63(m, 3H, CH-Ar), 7.52(t, 3H, J= 2.64, 5.52, CH-Ar), 7.1(s, 1H, NH), 6.85(d, 2H, J= 8.88, CH-Ar), 5.35(s, 1H, OH), 2.34(s, 3H, $CH_3$), ppm.




**(D) N'-(1-(4-aminophenyl) ethylidene)-4-oxo-2-phenylquinazoline-3 (4H)- carbothiohydrazide (Q-4): $C_{23}H_{18}N_4O_2S$**; Light Yellow, Crystalline solid; Melting Point (165-166 $^{O}$C), Yield (64.70 %); **Elemental Analysis calculated (Found) %:** C, 66.81(66.73); H, 4.63(4.60); N, 16.94(16.82); O, 3.87(3.75); S, 7.75(7.71); **FT-IR (KBr): cm$^{-1}$** 3747 N-H str.; 1679 C=N str.(imine), 1634 C=N str. (Pyrimidine), 1534 C=C str. (Ar); **$^{1}$H NMR (CDCL$_3$, 400 MHz):** δ 8.03(d, 1H, J= 7.52, CH-Ar.), 7.83(d, 2H, J= 4.64, CH-Ar), 7.70-7.63(m, 3H, CH-Ar), 7.58(d, 2H, J= 8.32, CH-Ar), 7.52(t, 3H, J= 2.48, 4.00, CH-Ar), 7.1(s, 1H, NH), 6.68(d, 2H, J= 6.08, CH-Ar), 6.27(s, 2H, $NH_2$), 2.43(s, 3H, $CH_3$), ppm.




**(E) N'-(1-(4-chlorophenyl) ethylidene) -4-oxo-2-phenylquinazoline-3 (4H)-carbothiohydrazide (Q-5): $C_{23}H_{17}ClN_4OS$**; Light Yellow, Crystalline solid; Melting Point (158-161$^{O}$C), Yield (64.11%); **Elemental Analysis calculated (Found) %:** C, 63.81(63.52); H, 3.96(3.48); Cl, 8.19(8.13); N, 12.94(12.85); O, 3.70(3.62); S, 7.41(7.32); **FT-IR (KBr): cm$^{-1}$** 3280 N-H str.; 1662 C=O str., 1652 C=N str.(imine), 1606 C=N str. (Pyrimidine), 1552 C=C str. (Ar), 1489 C-H str., 1307 C-N str.; **$^{1}$H NMR (CDCL$_3$, 400 MHz):** δ 8.03(d, 1H, J= 6.96, CH-Ar.), 7.98(d, 2H, J= 6.76, CH-Ar), 7.83(d, 2H, J= 6.88, CH-Ar), 7.70-7.63(m, 3H, CH-Ar), 7.52(t, 5H, J= 4.44, 4.24, CH-Ar), 7.1(s, 1H, NH), 2.43(s, 3H, $CH_3$), ppm.



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**In-vitro Evaluation of Anti-Microbial Activity by Disc Diffusion Method**

**Antibacterial activity**

**Table No. 1: Antibacterial activity of Quinazolinone Q-1 to Q-5**

| Sample applied | Diameter of zone of inhibition (mm) | |
|---|---|---|
| | **B. subtilis** | **E. coli** |
| Q-1 | 18(25) | 8(6.25) |
| Q-2 | 15(25) | 23(6.25) |
| Q-3 | 12(6.25) | 11(6.25) |
| Q-4 | 19(6.25) | 20(6.25) |
| Q-5 | 10(6.25) | 12(6.25) |
| **Control(C)** | **-** | **-** |
| **Ciprofloxacin(S)** | **21(6.25)** | **22(6.25)** |

[a] Values in brackets are MIC values (µg $ml^{-1}$)


**Figure 1: Antibacterial activity of Quinazolinone Q-1 to Q-5**

**Antifungal activity**

**Table No. 2: Antifungal activity of Quinazolinone Q-1 to Q-5**

| Sample applied | Diameter of zone of inhibition (mm) | |
|---|---|---|
| | **C. Albicans** | **A. Niger** |
| Q-1 | 17(25) | 11(6.25) |
| Q-2 | 16(25) | 12(6.25) |
| Q-3 | 16(6.25) | 13(6.25) |
| Q-4 | 10(6.25) | 8(6.25) |
| Q-5 | 17(6.25) | 10(6.25) |
| **Control (C)** | **-** | **-** |
| **Clotrimazole (S)** | **18(6.25)** | **20(6.25)** |

[a] Values in brackets are MIC values (µg $ml^{-1}$)

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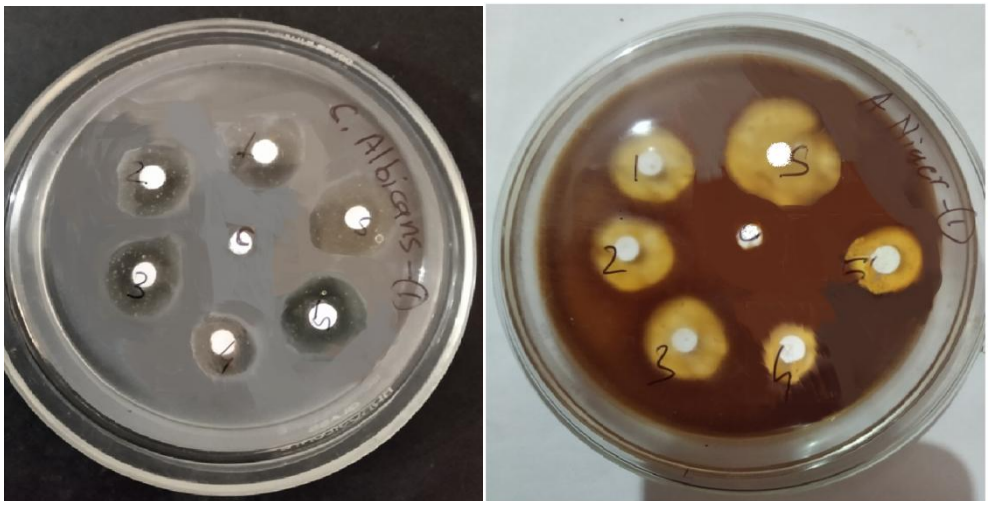


**Figure 2: Antibacterial activity of Quinazolinone Q-1 to Q-5**

## DISCUSSION

The designed prototypes which are fused ring of quinozolinones with the substituted benzene linked via Schiff base thiosemicarbazides were synthesized by using our previous approach with a slight modification in the reaction conditions. The structures of the synthesize compounds were elucidated and confirmed with FT-IR, $^{1}H$ NMR and Mass spectroscopy. Characteristic peaks of functional groups involved in Quinazolinones were found in FT-IR spectroscopy, like 3289 N-H str.; 1693 C=O str.; 1673 C=N str.(imine), 1643 and C=N str. (Pyrimidine). $^{1}H$ NMR spectroscopy was obtained using 400MHz spectroscope, sample were dissolved in deuterated chloroform ($CDCl_3$). Fixed characteristic 'δ' – values were found which are correct according to structure e.g. doublet at 8.03 and multiplet at 7.70-7.63 of represents the hydrogen of Quinazolinones and singlet at 7.1 represents the hydrogen of N-H of thiosemicarbazide, also 2.43 of $CH_3$. The synthesize compounds were screened for their antimicrobial activity for the gram positive, gram negative and fungal strains by disc diffusion method and the inhibition of microorganism were compared with the standard drugs ciprofloxacin and Clotrimazole respectively. Novel synthesized Quinazolinones derivatives were exhibited anti-bacterialactivity against B. subtilis, Q-1, Q-4 were possessed significant effect, Q-2, Q-3 and Q-5 were possessed moderate effect. Against E. coli, Q-2, have excellent activity, Q-4 possessed significant effect and Q-3, Q-5 possessed moderate effect. Novel synthesized Quinazolinones derivatives were exhibited anti-fungal activity. Against C. Albicans Q-1, Q-2, Q-3 and Q-4 has significant activity and Q-4, has moderate activity. Against A. Niger Q-1, Q-2, Q-3 and Q-5 showed significant activity and Q-4 has moderate activity. Overall, all the synthesized compounds are moderate to significantly active against both bacterial and fungal strains.

## IV. CONCLUSION

The quinazolones derivatives were synthesized and evaluated. The antimicrobial activities are moderately significant. Clean reaction profiles, simplicity, use of readily available reagents, no use of any solvent, mild conditions, high yields of the products, and low reaction times are the main advantages of this protocol. In the biological assay, all the synthesized compounds exhibited significant to moderate antibacterial and antifungal activities. Significantly compounds Q-2 and Q-4 had the highest activity against both bacterial and fungal strains. For this heterocyclic incorporate series, among the substitutions on quinazolones, substituted chlorine and methyl group substituted compounds are more active than others. May be the electron withdrawing group or electron donating groups are required to enhance the biological action of the quinazolones.

## CONFLICTS OF INTERESTS

There are no conflicts of interests

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