DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 1,2,4-TRIAZOLOPHENYL QUINOLINE-2-ONE DERIVATIVES

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ABSTRACT: Heterocyclic compounds containing triazole ring are important targets in synthetic and medicinal chemistry because this key moiety is responsible for numerous biological activity. An efficient method for synthesis of novel derivatives of Substituted-1,2,4-triazolo phenyl quinolone was adopted by reacting various substituted aniline and cinnamic acid. The synthesized derivatives were designed to have an electron donating and electron with drawing groups to figure out which group is influencing probable pharmacological activity. During designing of the scheme the site of action for antibiotic activity i.e. disruptions of bacterial cell wall in case of bacteria and interfering with enzymes (cytochrome p450) required for cell membrane synthesis for fungal inhibition was targeted. The structures of these newly synthesized compounds were established by their Elemental analysis, IR, 1H NMR and Mass spectral data. All the synthesized compounds were then evaluated for their antimicrobial potentials using standard drug fluconazole and clotrimazole for antifungal activity and ampicillin anhydride for antibacterial activity. Moderate to good antimicrobial activity was presented by the targeted final derivatives (3a-3j) against pathogenic fungal and bacterial strains.

INTRODUCTION: Due to inappropriate use of antibiotics the problem of antibiotic resistance is now recognized as a serious and permanent public health concern and it needs to be addressed seriously. Latest report by economist tells that the true cost of antimicrobial resistance (AMR) will be 300 million premature deaths and up to $100 trillion lost to global economy by 2050. Microorganisms have mutated within last few decades and resulted in the generations of multidrug-resistant (MDR) which are increasingly difficult to treat with antibiotics currently available.
designed (Fig. 1), synthesized by convenient and effective method. Then all the targeted molecules were purified, characterized and screened to study their antimicrobial efficacy by zone of inhibition and minimal inhibitory concentration (MIC).

MATERIALS AND METHODS:
General materials:
The required chemicals for the synthesis and other experimental work were purchased from Merck, Sigma Aldrich, Lobachem, Rankem chemical company and used without further purification. Melting points of compounds were determined on a Veego, MPI melting point apparatus and are uncorrected. The purity of the compounds was routinely checked in each step by TLC using Silica Gel 60G and visualization was made with UV light or with iodine vapor.

IR spectra were recorded on FTIR-8400S spectrophotometer (Schimadzu, Kyoto, Japan), all data are given for stretching frequencies. 1H NMR spectra were recorded by Bruker DRX – 300 MHz FT NMR using the solvents CDCl3& DMF. Chemical shifts are reported in δ ppm downfield from TMS as internal standard and signals are expressed as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Mass spectra were determined using Agilent 6520 Q-TOF (ESI-MS) and Elemental analysis was performed by Elemental Analyzer: Vario EL-III.

Synthetic procedure:
A series of ten novel derivatives (3a-3j) of 1,2,4-triazolophenyl quinoline-2-one derivatives were synthesized by following scheme 1. Cyclocondensation 29, 30 of aniline derivatives with cinnamic acid by refluxing for 4h in the presence of absolute ethanol, 4 to 5 drops of con. H2SO4 and 1ml of nitro benzene gave phenyl quinolin-2-one derivatives (1a-1j).

Equimolar concentration i.e., 0.02mol of compound (1a-1j) on further reaction with mono chloroacetic acid in the presence of alkaline medium (NaHCO3) refluxing with water for 2h yielded phenylquinolin-acetic acid derivatives (2a-2j).Then the targeted molecules 1-[(4-amino-5-sulfanyl - 4H - 1,2,4- triazol – 3 - yl) methyl]-[R]-4-phenylquinolin-2(1H)-one (3a-3j) were obtained by fusing phenylquinolin-acetic acid derivatives(2a-2j) with thiocarbohydrazide at its melting point temperature. The purity of compound and completion of the reaction was routinely checked by thin layer chromatography, melting point of the various synthesized derivatives were determined and are uncorrected (Table 1). The structure of these new derivatives was established by their elemental and spectral data.

1-[(4-amino-5-sulfanyl-4H-1,2,4 – triazol – 3 - yl) methyl]-4-phenylquinolin-2(1H)-one [3a]:
White crystalline Solid; Yield 84%; IR(KBr, cm-1): 3378(Ar N-H Str), 3042(Ar C-H str), 2658(S-H str), 1703(C=O str), 1614(C=N str), 1578(C=C str), 1305(Ar C-N str); 1H NMR (CDCl3, 300MHz): δ(ppm): 5.24 (s, 2H, NH2), 5.78 (s, 2H, CH2), 6.99 (s, 1H, CH=), 7.41-7.44 (m, 3H, Ar-H), 7.46-7.58 (q, 5H, J = 7.5Hz, Ar-H), 7.77 (m, 1H, Ar-H), 9.64 (s, 1H, SH). ESI-MS(m/z) calcd. for C18H15N5OS is 349.40 found 350.35[M + H]+.

1-[(4-amino-5-sulfanyl - 4H - 1,2,4-triazol - 3yl) methyl]-8-chloro-4-phenylquinolin - 2(1H) - one [3b]:
White needled crystal; Yield 82%; IR (KBr, cm-1): 3369(Ar N-H Str), 3038 (Ar C-H str), 2655(S-H str), 1709(C=O str), 1610(C=N str), 1549(C=C str), 1335(Ar C-N str), 756(C-Cl); 1H NMR (CDCl3, 300MHz): δ(ppm): 5.81 (s, 2H, NH2), 5.82 (s, 2H, CH2), 6.81 (s, 1H, CH=), 7.24 (t, 1H, Ar-H), 7.41-7.45 (q, 2H, J=7.5Hz, Ar-H), 7.46-7.48 (q, 4H, J=1.5Hz, Ar-H), 7.64 (q, 1H, J=7.5Hz Ar-H), 9.68 (s, 1H, SH). ESI-MS(m/z) calcd. for C18H14ClN5OS is 383.45 found 389.78[M + H]+.

1-[(4-amino-5-sulfanyl-4H-1,2,4 – triazol – 3-yl) methyl]-7-chloro-4-phenylquinolin - 2(1H) - one [3c]:
White needled crystal; Yield 84%; IR (KBr, cm-1): 3355(Ar N-H Str), 3035(Ar C-H str), 2656(S-H str), 1748(C=O str), 1608(C=N str), 1532(C=C str), 1342(Ar C-N str), 752(C-Cl); 1H NMR (CDCl3, 300MHz): δ(ppm): 6.85 (s, 2H, NH2), 5.81 (s, 2H, CH2), 7.21 (s, 1H, CH=), 7.41-7.46 (t, 3H, Ar-H), 7.48-7.85 (q, 3H, J = 7.5Hz Ar-H), 8.22-8.45 (d, 2H, J = 8.5Hz, Ar-H), 9.68 (s, 1H, SH). ESI-MS(m/z) calcd. for C18H14ClN5OS is 383.85 found 389.86[M + H]+.
1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl) methyl]-6-chloro-4-phenylquinolin-2(1H)-one [3d]:
White needled crystal; Yield 86%; IR (KBr, cm\(^{-1}\)): 3312(Ar N-H Str), 3032(Ar C-H str), 2659(S-H str), 1745(C=O str), 1610(C=N str), 1531(C=C str), 1336(Ar C-N str), 756(C-Cl); \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\)(ppm): 5.47 (s, 2H, NH\(_2\)), 5.80 (s, 2H, CH\(_2\)), 6.81 (s, 1H, CH=), 7.45 (t, 3H, Ar-H), 7.47-7.48 (q, 3H, J = 7.5Hz, Ar-H), 8.73 (d, 2H, J = 8.5Hz, Ar-H), 9.68 (s, 1H, SH). ESI-MS(m/z) calcd. for C\(_{19}\)H\(_{17}\)N\(_5\)OS is 383.45 found 384.46[M + H]\(^+\).

1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl) methyl]-8-methoxy-4-phenylquinolin-2(1H)-one [3e]:
Sharp white needled crystal; Yield 69%; IR (KBr, cm\(^{-1}\)): 3343(Ar N-H Str), 2894, 3014(Ar C-H str), 2690(S-H str), 1708(C=O str), 1610(C=N str), 1558(C=C str), 1302(Ar C-N str); \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\)(ppm): 2.61 (s, 3H, CH\(_3\)), 5.36 (s, 2H, NH\(_2\)), 5.74 (s, 2H, CH\(_2\)), 6.80 (s, 1H, CH=), 7.28 (m, 1H, Ar-H), 7.41-7.45 (q, 2H, J = 7.5Hz, Ar-H), 7.46-7.48 (t, 5H, Ar-H), 9.69 (s, 1H, SH). ESI-MS(m/z) calcd. for C\(_{19}\)H\(_{17}\)N\(_5\)OS is 374.43 found 380.44[M + H]\(^+\).

1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl) methyl]-7-methoxy-4-phenylquinolin-2(1H)-one [3f]:
Sharp white needled crystal; Yield 65%; IR (KBr, cm\(^{-1}\)): 3323(Ar N-H Str), 2885,3009(Ar C-H str), 2692(S-H str), 1710(C=O str), 1608(C=N str), 1560(C=C str), 1306 (Ar C-N str); \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\)(ppm): 2.43 (s, 3H, CH\(_3\)), 5.37 (s, 2H, NH\(_2\)), 5.79 (s, 2H, CH\(_2\)), 7.19 (s, 1H, CH=), 7.41-7.48 (q, 5H, J = 7.5Hz, Ar-H), 7.68 (m, 1H, Ar-H), 8.30 (d, 2H, J = 7.5Hz, Ar-H), 9.69 (s, 1H, SH). ESI-MS(m/z) calcd. for C\(_{19}\)H\(_{17}\)N\(_5\)OS is 363.43 found 364.46[M + H]\(^+\).

1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl) methyl]-6-methoxy-4-phenylquinolin-2(1H)-one [3g]:
Sharp white needled crystal; Yield 62%; IR (KBr, cm\(^{-1}\)): 3325(Ar N-H Str), 2894,3004(Ar C-H str), 2689(S-H str), 1708(C=O str), 1610(C=N str), 1562(C=C str), 1304(Ar C-N str); \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\)(ppm): 2.48 (s, 3H, CH\(_3\)), 5.36 (s, 2H, NH\(_2\)), 5.78 (s, 2H, CH\(_2\)), 6.81 (s, 1H, CH=), 7.40-7.41 (m, 3H, Ar-H), 7.46-7.48 (q, 4H, J = 7.5Hz, Ar-H), 8.30 (d, 1H, J=8.5Hz, Ar-H), 9.69 (s, 1H, SH). ESI-MS(m/z) calcd. for C\(_{19}\)H\(_{17}\)N\(_5\)OS is 363.43 found 364.41[M + H]\(^+\).
Antimicrobial Assay (CLSI):
Minimal Inhibitory Concentration:
(MICs, µg/mL) were determined on different microbes using Broth Micro Dilution procedure according to recommendations of Clinical and Laboratory Standards Institute (CLSI formerly NCCLS). Strains of gram (–ve) bacteria Pseudomonas aeruginosa (MCCB 0035), Escherichia coli (ATCC 8739) and Strains of gram (+ve) bacteria Staphylococcus aureus (ATCC 29213) and fungal strains Aspergillus fumigatus (NCIM 2081), Aspergillus niger (NCIM 2191), Candida albicans (NCIM 2087) were used for testing antibacterial and antifungal activity respectively. Bacterial strains were grown in Mueller-Hinton Broth and fungal strains were grown in Sabouraud Liquid medium.

The inoculum densities of 5 x 10^5 CFU/ml for bacteria and 0.5-2.5 x 10^5 CFU/ml for fungi were prepared. Ampicillin Anhydride and fluconazole were used as standard antibiotic powder. Each of the test compounds was dissolved in DMSO and further dilutions were prepared in sterile distilled water. Ampicillin anhydride and fluconazole were diluted in sterile distilled water. Two fold dilutions of the compound and standards were prepared as 512-0.5 µg/ml and 64-0.0625 µg/ml concentrations respectively. After dilution was completed, microbe suspensions were inoculated into each well of row. MIC values were given as µg/mL. It was determined that solvent had no antimicrobial activity against any of the test compound (Table 2).

Agar Disk Diffusion:
Testing method as per CLSI guidelines was used to evaluate antifungal activity and antibacterial activity with some modification. Mueller-Hinton Agar (MHA) petri plates were prepared, standardized and then it was inoculated with test organism suspension. It was ensured that the inoculum suspension was evenly distributed. The stock solution of synthesized compounds were prepared in DMSO and further diluted with distilled water. Working concentration of test compounds was 100µg/ml. Similarly standard antibiotic solution of ampicillin (100µg/ml) and Clotrimazole (100µg/ml) to evaluate antibacterial and antifungal actively respectively were prepared. Disc of 8mm in diameter were prepared from no. 1 Whatman filter paper. These discs were sterilized by keeping in hot air oven at 140 °C for 60 min. then the standard and test solution were added to each disc and air dried. Then the discs containing the test compounds (100µg/8mm disc) was placed with the help of sterile forceps to stick them to the agar plate one at a time. Three disks were applied in one plate in triplicate manner down firmly to ensure complete, level contact with the agar.

The bottom of the agar plates were labeled and were incubated a temperature of 35°C for 24 hours for bacterial strains and 48 hours for fungal strains in BOD incubator. At the end Zone of inhibition produced by test compounds were measured using a scale. The zone of inhibition obtained by different test compounds was compared with that of standard given in (Table 3) and activity of some compounds have been shown in Fig. 4, 5, 6, 7, 8 and 9.

RESULT AND DISCUSSION:
Chemistry:
Final targeted compounds were synthesized by following synthetic procedure enumerated in scheme 1 and structures of compounds (3a-3j) were established by IR, 1H-NMR, Mass and elemental analysis. Formation of cyclized product (triazoles) were confirmed by its IR spectrum which showed peak at 3378-3312 cm^{-1} due to NH_2- group, 2693-2655 cm^{-1} due to SH- group and 1614-1643 cm^{-1} due to -C=N group.

Further its 1H-NMR spectra of synthesized compounds showed three broad singlet at δ(ppm) 5.24-6.10 due to NH_2 proton, 5.78-6.06 due to CH_2 proton and 9.64-10.12 due to SH- proton. The appearance of triplets and quartet at δ(ppm) 7.26-7.48 due to four aromatic quinoline protons and appearance all other aromatic protons at expected region confirms formation of cyclized triazole compound.

Mass spectra (ESI-MS) of all the synthesized compounds showed molecular ion peaks which is in agreement with their molecular formula. The physicochemical data of all the synthesized derivatives (3a-3j) were summarized in Table 1.
Antimicrobial activity:  
All the targeted compounds showed moderate-to-good antimicrobial activity (Table 2 & 3) which can be depicted in Fig.4, 5, 6, 7, 8 and 9. The inhibition was seen to increase by increasing compound concentration. Compound code 3b, 3c, 3d, 3i and 3j were found to be effective against both bacterial and fungal species as revealed from the data obtained from MIC (Table 2), zone of inhibition (Table 3) and Fig. 2 and 3 as compared with reference compound. Compound 3d was the most potent among all the synthesized derivatives whereas compound code 3e, 3f and 3g showed least significant activity against both fungal and bacterial species. Compound 3d and 3j showed good activity against S. aureus and compound 3c and 3i was seen to show effective against P. aeruginosa, whereas compound 3b, 3i and 3j were moderately active against E. coli. In case of fungal species compound 3b, 3d, 3i and 3j have shown to possess good activity against C. albicans, compound 3b, 3c and 3i showed comparable activity against A. niger when compared with the standard drug.

### Table 1: Physicochemical Data of 1,2,4-Triazoleophenyl Quinoline-2-Onederivatives (3a-3j).

<table>
<thead>
<tr>
<th>Comp. Code</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Yield (%)</th>
<th>M.p (°C)</th>
<th>% Analysis of C, H, N found (calculated)</th>
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<tr>
<td>3a</td>
<td>H</td>
<td>C15H13N2O5S</td>
<td>84</td>
<td>203-204</td>
<td>C 61.84(61.87) H 4.30(4.33) N 20.02(20.04)</td>
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<tr>
<td>3b</td>
<td>2-Cl</td>
<td>C15H13N2O5S</td>
<td>82</td>
<td>182-183</td>
<td>C 56.30(56.32) H 3.67(3.68) N 18.22(18.24)</td>
</tr>
<tr>
<td>3c</td>
<td>3-Cl</td>
<td>C15H13N2O5S</td>
<td>84</td>
<td>185-187</td>
<td>C 56.29(56.32) H 3.63(3.68) N 18.21(18.24)</td>
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<tr>
<td>3d</td>
<td>4-Cl</td>
<td>C15H13N2O5S</td>
<td>86</td>
<td>186-188</td>
<td>C 56.31(56.32) H 3.65(3.68) N 18.22(18.24)</td>
</tr>
<tr>
<td>3g</td>
<td>4-CH3</td>
<td>C15H13N2O5S</td>
<td>62</td>
<td>200-201</td>
<td>C 62.75(62.79) H 4.69(4.71) N 19.25(19.27)</td>
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<td>3h</td>
<td>2-OCH3</td>
<td>C15H13N2O5S</td>
<td>68</td>
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<td>C 60.09(60.14) H 4.48(4.52) N 18.41(18.46)</td>
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<td>3i</td>
<td>3-OCH3</td>
<td>C15H13N2O5S</td>
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</tr>
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<td>4-OCH3</td>
<td>C15H13N2O5S</td>
<td>66</td>
<td>248-249</td>
<td>C 60.10(60.14) H 4.49(4.52) N 18.42(18.46)</td>
</tr>
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### Table 2: Minimum inhibitory concentration (MIC) in μg/ml of 1,2,4-Triazoleophenyl Quinoline-2-Onederivatives(3a-3j)* against bacterial and fungal strains.

<table>
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<tr>
<th>Comp. Code</th>
<th>R</th>
<th>Ec</th>
<th>Pa</th>
<th>Sa</th>
<th>Af</th>
<th>An</th>
<th>Ca</th>
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<td>3a</td>
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<td>128</td>
<td>64</td>
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<td>3-OCH3</td>
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<td>64</td>
<td>32</td>
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<td>16</td>
<td>32</td>
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</table>

*Minimum inhibitory concentration were determined by micro-broth dilution method.

**Ec:** Escherichia coli; **Pa:** Pseudomonas aeruginosa; **Sa:** Staphylococcus aureus; **Af:** Aspergillus fumigatus; **An:** Aspergillus niger; **Ca:** Candida albicans.

### Table 3: Zone of inhibition of compounds 1,2,4-Triazoleophenyl Quinoline-2-one(3a-3j)* in the concentration of 100 μg/ml MM disc compared with broad spectrum antibacterial standard drug Ampicillin(AA) and Clotrimazole(CL) 100 μg/ml MM disc.

<table>
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<tr>
<th>Comp. Code</th>
<th>R</th>
<th>Ec</th>
<th>Pa</th>
<th>Sa</th>
<th>An</th>
<th>Ca</th>
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<td>3a</td>
<td>H</td>
<td>10</td>
<td>07</td>
<td>12</td>
<td>10</td>
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</table>
*Zone of Inhibition of compounds were determined by micro-broth dilution method.

**Ec:** *Escherichia coli*; **Pa:** *Pseudomonas aeruginosa*; **Sa:** *Staphylococcus aureus*; **An:** *Aspergillusniger*; **Ca:** *Candida albicans*; **AA:** Ampicillin anhydride; **CL:** Clotrimazole.

**SCHEME 1:** REAGENTS AND CONDITIONS: (a) ABSOLUTE ETHANOL, NITROBENZENE, Conc. H$_2$SO$_4$, REFLUX, 80°C, 4 h; (b) CHLOROACETIC ACID, NaHCO$_3$, CuO, DIST. WATER, REFLUX, 100°C, 2 h; (C) FUSED AT 180°C to 280°C
FIG. 2: ZONE OF INHIBITION OF COMPOUNDS (3a-3j) AND STANDARD DRUG AMPICILLIN AGAINST BACTERIAL SPECIES

FIG. 3: ZONE OF INHIBITION OF COMPOUNDS (3a-3j) AND STANDARD DRUG CLOTRIMAZOLE AGAINST FUNGAL SPECIES.

FIG. 4: ZONE OF INHIBITION OF COMPOUND 3a AGAINST C. ALBICANS

FIG. 5: ZONE OF INHIBITION OF COMPOUND 3c AGAINST C. ALBICANS
CONCLUSION: In this research work ten new scaffolds of 4-amino-5-sulfanyl-1,2,4-triazolophenylquinolin-2-one derivatives (3a-3j), were successfully synthesized and the structures were established from their elemental and spectral data. From the antimicrobial study it was revealed that the compounds containing halogen group (Cl) and methoxy groups are potent antimicrobial agent against the studied microbes. Particularly analogues containing substitution at para position (3d, 3j) were most potent compounds against all the studied bacterial and fungal strains in relative to standard drug ampicillin and fluconazole respectively.

Whereas the compounds having methyl groups substitution at all the three places seen to be least significant. This investigation showed that derivatives of 4-amino-5-sulfanyl-1,2,4-triazolophenylquinolin-2-one may be considered as valuable chemical analogues for design and development of effective antimicrobial agent.

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