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Design, Synthesis and *In Silico* Studies of Some Novel Quinazoline Derivatives as Antimicrobial Agents

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Abstract
Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have triggered established issues due to their extensively and distinct biopharmaceutical sports. Quinazoline derivatives encompass a huge spectrum of pharmaceutical hobby profile inclusive of antitumor, anti-HIV, antimicrobial, antibacterial, anti-inflammatory, CNS activity and cardiovascular activity. The overall goal of this study has a look at ways to increase efficient artificial techniques for the synthesis of oxadiazole substituted quinazoline analogues. Based on in silico research, ten analogues have been taken for wet lab synthesis. The synthesized compounds were screened for antibacterial activity. The systems of the synthesized compounds were characterized by way of FT-IR, 1H NMR and MASS spectroscopy.

Keywords
Antimicrobial activity, Agar well diffusion method, Schrodinger, FT-IR.

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INTRODUCTION:
Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two different elements as number of rings. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. 4(3H)-Quinazolinones and related quinazolines are classes of fused heterocyclic that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities [1- 6]. Quinazoline pharmacophore has been selected for drug design because of great importance in their biological as well as synthetic approach of medicinal chemistry. Though the parent quinazoline molecule is rarely mentioned by itself in technical literature, substituted derivatives have been synthesized for medicinal purposes such as anti -malarial, anti - cancer and anti- bacterial agents. Quinazoline substituted oxadiazole derivatives were designed for anti-bacterial activities based on multi target drug design approach. For anti- bacterial studies, the target proteins selected were DNA gyrase and β-ketoacyl-acyl carrier protein synthase III (FabH). Molecular docking studies were supported to synthesize novel quinazoline derivatives which target more than one receptor for the same activity in order to increase their pharmacological efficacy [7-9].

MATERIALS AND METHODS:

All the reagents and solvents used were of analytical or synthetic grade and obtained from commercial sources. The newly synthesized compounds were characterized by Melting point, IR, 1HNMR and Mass spectral analysis. The melting points of the synthesized analogues were determined with an electro thermal melting point apparatus. The purity of the compounds were ascertained by TLC over precoated, pre-activated glass plates with solvent system ethyl acetate: petroleum ether (3:7). Purity of the compounds was confirmed by single spot in TLC and consistency in the Rf value. FT-IR spectra of the synthesized compounds were recorded using KBr pellets in the range of 4000-500cm-1 on Agilent Cary 630 FTIR spectrometer, at College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram. NMR spectra of compounds were recorded on Bruker Avance AV 500 NMR spectrometer at 500 MHz, at National Institute for Interdisciplinary Science and Technology (NIIST), Council of Scientific and Industrial Research (CSIR), Govt. of India, Thiruvananthapuram. Mass spectra (LC-MS) were recorded by thermo exactive orbitrap FTMS instrument in Department of Applied Chemistry, CUSAT, Kochi.

Synthetic procedure

Step 1. Synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one

A mixture of anthranilamide (1 mmol), benzaldehyde (1 mmol) and ammonium chloride (5mol %) in 20 ml ethanol was refluxed at 120 °C for 15 minutes. The progress of the reaction was monitored by TLC (ethyl acetate/ n- hexane). After completion of the reaction, a solid was obtained. It was washed with water and recrystallized from ethanol**.** TLC was performed by using mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.68, yield 85%, m.p 197º C.

Step 2. Synthesis of ethyl [(2-phenyl-1, 2-dihydroquinazolin-4-yl) oxy] acetate (2)

In 500 ml round bottom flask, take 15-20 ml dry DMF (dimethyl formamide). To this add 2-methyl 2, 3-dihydroquoinazolinone (0.01 mol, 1.6 g) and ethyl chloro acetate (0.01 mol, 1.25 ml) and anhydrous potassium carbonate (0.1 mol, 1.38 g). The resultant mixture was stirred and refluxed for 9-10 hours at 80°C. After completion of the reaction, the reaction mixture was filtered and poured into large amount of water. The solid separated was filtered and washed with water, the solid was dried and recrystallized from ethanol. TLC; mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.63, yield 82%, m.p 183ºC.

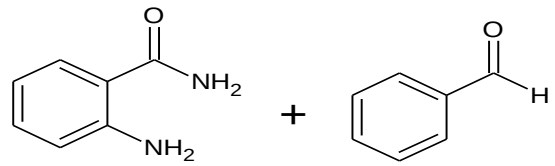
Step 3. Synthesis of 2-[(2-phenyl-1, 2-dihydroquinazolin-4-yl] oxy) acetohydrazide

Compound 2(0.01mol) and hydrazine hydrate (0.01mol, 0.9ml) in ethanol(20ml) were placed in round bottom flask and microwave irradiated (350W, 76-78°C) for 3.5 min. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol. TLC; mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.55, Yield 80%, MP 175°C.

Step 4. Synthesis of 2-[(2-phenyl-1, 2-dihydroquinazolin-4-yl) oxy]-N-[(E)-phenylmethylidene] acetohydrazide (4)

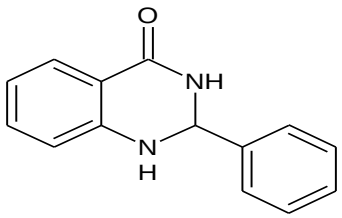
A mixture of compound 3 (0.01mol), aromatic aldehyde (0.01 mol) and 2-3 drops of glacial acetic acid in ethanol (20ml) were placed in round bottom flask and microwave irradiated (400W, 76-78°C) for 3 minute. After completion of the reaction, the solvent was removed and residue recrystallized from ethanol.

SCHEME



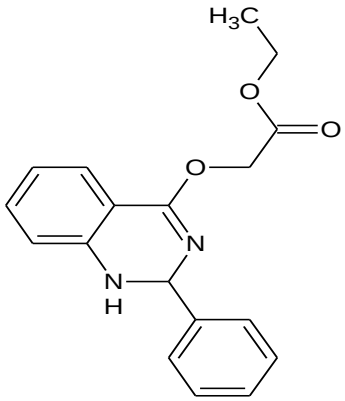
2-aminobenzamide + benzaldehyde

Ethanol
120^{0}C, 15 min, Reflux
STEP I

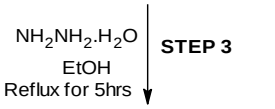


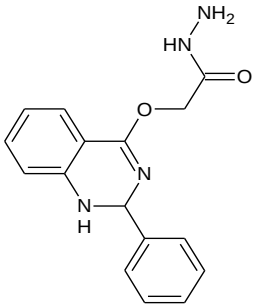
2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one

$ClCH_2COOC_2H_5$, DMF
80^{0}C, 9$^-$10 hrs, stirr & Reflux
STEP 2

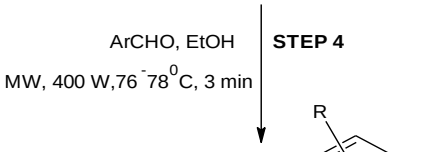


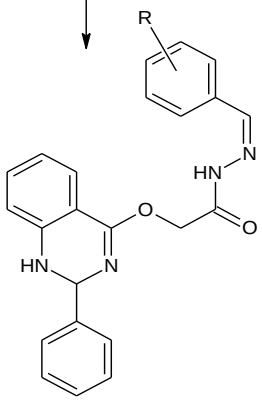
ethyl [(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetate



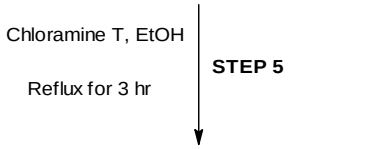


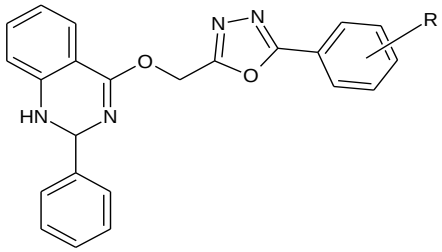
2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide





2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]-*N*'-[(*Z*)-phenylmethylidene]acetohydrazide





2-phenyl-4-[(5-phenyl-1,3,4-oxadiazol-2-yl)methoxy]-1,2-dihydroquinazoline

- Recrystallization solvent-ethanol
- TLC; mobile phase-ethyl acetate: petroleum ether(3:7)

General procedure was adapted for the synthesis of all analogues and thus following compounds are synthesized,

- **QS-1**: 2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]-*N*'-[(*E*)phenylmethylidene] acetohydrazide

Aldehyde: ***benzaldehyd***e; MW Irradiation (400W, 78°C, 3 minute).

- **QS-2**:N'-[(E)-(4-chlorophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide
  Aldehyde: ***P- Chlorobenzaldehyde***; MW Irradiation (400W, 78°C
  3 min)
- **QS-3**: *N*'-[(*E*)-(4-bromophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide
  Aldehyde:***P-Bromobenzaldehyde***; MW Irradiation(400W, 78°C, 3 minute).
- **QS-4**: *N*'-[(*E*)-(4-hydroxy phenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide
  Aldehyde: ***P-hydroxybenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-5**: *N*'-[(*E*)-(4-nitrophenyl) methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl) oxy] Aceto hydrazide
  Aldehyde: ***4-nitrobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-6**: *N*'-[(*E*)-(3-nitrophenyl) methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl) oxy] acetohydrazide
  Aldehyde: ***3-nitrobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-7**: *N*'-[(*E*)-(2-methoxyphenyl) methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl) oxy]acetohydrazide
  Aldehyde: ***2-methoxybenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-8** : *N*'-[(*E*)-(4-aminophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide
  Aldehyde: ***P-aminobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-9**: *N*'-[(*E*)-(2-hydroxyphenyl) methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide
  Aldehyde: ***Salicylaldehyde***; MW Irradiation (400W, 78°C, 3 minute).
- **QS-10** :*N*'-[(*E*)-(4-dimethylamino)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***P-dimethylaminobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

Step 5. Synthesis of 2-phenyl-4-[(5-phenyl-1, 3, 4-oxadiazol-2-yl) methoxy]-1, 2-dihydroquinazoline

To a solution of compound 4 (schiff base) (0.01mol) and chloramine T (0.05 mol) in ethanol (20ml) was refluxed for 3 hour. After completion of the reaction, it was filtered to remove sodium chloride. The filtrate along with washings was concentrated to a small volume and left at room temperature. A solid mass so obtained was filtered and crystallised from ethanol to yield oxadiazole substituted quinazoline derivatives (QO).

Biological screening

Antibacterial screening

The antibacterial screening on synthesized analogues was carried out by agar well diffusion method at Microbiology Laboratory of College of Pharmaceutical Sciences, Medical College, Thiruvananthapuram. All the synthesized analogues were dissolved in 5% DMSO to make the concentrations of 1000µg/ml. Gentamicin (100µg/ml) was used as standard drug. The micro-organisms were procured from Microbiology lab, Govt. Medical College, Trivandrum. (*Staphylococcus aureus* (gram positive bacteria) and *Escherichia coli* (gram negative bacteria).

Petriplates containing 20ml Muller Hinton Agar Medium were seeded with bacterial culture of *E.coli,* and *Staphylococcus aureus* (growth of culture adjusted according to McFards Standard, 0.5%). Wells of approximately 10mm was bored using a well cutter and sample of 25, 50, and100 µg concentrations were added. The plates were then incubated at 37°C for 24 hours. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well (**NCCLS, 1993**). Gentamicin was used as a positive control.

RESULTS AND DISCUSSIONS:

The *in-silico* molecular modelling studies of oxadiazole substituted quinazoline analogues were carried out successfully with the aid of different software for selection of suitable drug candidates prior to wet lab synthesis. *In-silico* studies were performed on 15 analogues by means of ACD Lab Chemsketch 12.0, ChemDraw, Molinspiration, PASS, and Schrodinger. Out of 15 proposed analogues, 10 candidates were chosen for wet lab synthesis. The synthesized analogues were characterized by FT-IR, 1H NMR and MASS spectral analysis. All the proposed analogues were subjected to flexible docking using GLIDE XP (Extra Precision) on DNA gyrase and β ketoacyl-acyl carrier Protein Synthase II (FabH) which indicates the antimicrobial activity. Among these compounds two analogues (QO-4, QO-5) were selected for in vitro antibacterial screening against S.aureus and E.coli. Antibacterial activity of selected analogue QO-4 showed more activity towards S.aureus and E.coli than QO-5 and is less than that of standard drug Gentamicin at a concentration of 100µg/ml. The compound QO-4 showed more antibacterial activity due to the presence of hydroxyl group at para position. The hydroxyl group interacts with bacterial cell wall and leads to bactericidal action.

Table 1. Characterization of step 4 product

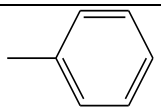
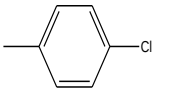
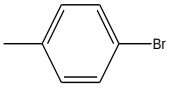
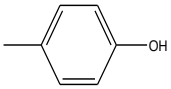
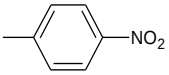
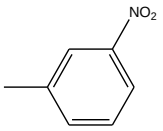
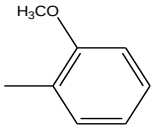
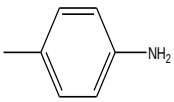
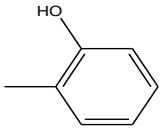
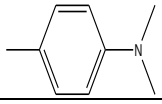
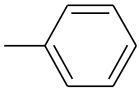
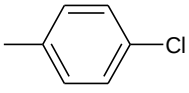
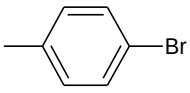
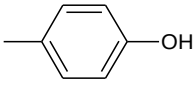
Compound code	R	Molecular formula	Molecular weight	Melting point	% yield	R_f
QS-1		$C_{23}H_{20}N_4O_2$	384.43	176°C	68	0.55
QS-2		$C_{23}H_{19}ClN_4O_2$	418.87	173°C	65	0.58
QS-3		$C_{23}H_{19}BrN_4O_2$	463.32	171°C	63	0.56
QS-4		$C_{23}H_{20}N_4O_3$	400.42	168°C	69	0.41
QS-5		$C_{23}H_{19}N_5O_4$	429.42	175°C	70	0.49
QS-6		$C_{23}H_{19}N_5O_4$	429.42	169°C	66	0.40
QS-7		$C_{24}H_{22}N_4O_3$	414.45	164°C	62	0.44
QS-8		$C_{23}H_{21}N_5O_2$	399.44	165°C	66	0.46
QS-9		$C_{23}H_{20}N_4O_3$	400.42	167°C	71	0.43
QS-10		$C_{25}H_{25}N_5O_2$	427.49	172°C	73	0.50

Table 2. Characterization of oxadiazole-quinazoline analogues

Compound code	R	Molecular formula	Molecular weight	Melting point	% yield	R_f value
QO-1		$C_{23}H_{18}N_4O_2$	382.41	82°C	62	0.45
QO-2		$C_{23}H_{17}ClN_4O$	416.85	71°C	60	0.43
QO-3		$C_{23}H_{17}BrN_4O$	461.31	94°C	67	0.42
QO-4		$C_{23}H_{18}N_4O_3$	398.41	75°C	69	0.26

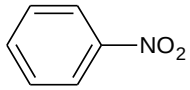
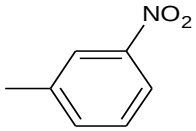
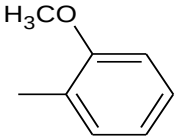
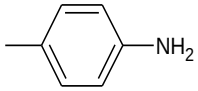
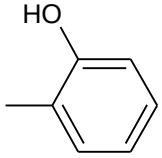
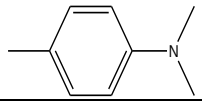
QO-5		$C_{23}H_{17}N_5O_4$	427.41	95°C	72	0.39
QO-6		$C_{23}H_{17}N_5O_4$	427.41	97°C	64	0.45
QO-7		$C_{24}H_{20}N_4O_3$	412.44	95°C	73	0.38
QO-8		$C_{23}H_{19}N_5O_2$	397.42	85°C	67	0.44
QO-9		$C_{23}H_{18}N_4O_3$	398.41	96°C	75	0.36
QO-10		$C_{25}H_{23}N_5O$	425.48	91°C	61	0.47

Table 3. Docking score of Oxadiazole-quinazoline analogues for anti-bacterial activity

Compound Code	Glide score	
	Target: DNA gyrase PDB ID: 1KZN	Target: β ketoacyl-acyl carrier Protein Synthase III (FabH) PDB ID: 1HNJ
QO-1	-5.4	-6.3
QO-2	-5.2	-5.7
QO-3	-4.4	-6.1
QO-4	-5.8	-7.5
QO-5	-5.2	-6.4
QO-6	-5.4	-6.2
QO-7	-4.8	-5.4
QO-8	-5.8	-6.0
QO-9	-4.5	-5.9
QO-10	-4.5	-5.8

Table 4. FT-IR Spectral data of the compounds

Compound	FT-IR (KBr υ cm^{-1})
Q-1(Step 1)	3308 (N-H str), 1653 (C=O, carboxamide), 1609 (C-N)
Q-2(Step 2)	1653 (C=O), 1609 (C=N), 1291 (C-O ether), 2851(CH aliphatic)
Q-3(Step 3)	3304- 2922 (NH, NH_2), 2848 (C-H aliphatic), 1653 (CO, Carboxamide), 1615 (C=N), 1300 (C-O-C)
QS-7	3394 (NH str.), 3022 (Aromatic CH str.), 1653 (C=O str.), 1617 (C=N str.), 1252 (Asymmetric C-O-C str.), 1026 (Symmetric C-O-C str.),

QO-7	3320 (NH str.), 2960 (Aromatic CH str.), 1302 (Asymmetric C-O-C str.), 1097 (Symmetric C-O-C str.), 1158 (C-O-C ring str.).
QS-6	3308 (NH str.), 3046 (Ar-CH str.), 1654 (C=O str.), 1615(C=N str.), 860 (aliphatic CH stretching of N=CH), 1300 (C-O-C ether), 1257 (C-N str.), 1485 (Ar C-C str.), 1511 (N=O, asymmetric), 1363 (N=O, symmetric)
QO-6	3385 (Aromatic CH str.), 1531 (Ar NO_2, N=O str. asymmetric), 1302 (N=O srt. symmetric), 1674 (C=N str.), 1158(C-O-C ring str.), 817(CN str. Ar NO_2), 1455(CN str. ring)
QO-5	3423 (Aromatic CH str.), 1526 (Ar NO_2, N=O str. asymmetric),1342 (N=O, symmetric), 1158(C-O-C ring str.), 817 (CN str. Ar NO_2),
QO-4	1528 (C=C aromatic str.), 3463 (OH phenolic str.), 3428 (NH str.), 1305 (OH bending), 1677 (C=N str.), 1158 (C-O-C ring asymmetric str.), 1097 (C-O-C ring symmetric str.)

Table 5. ^{1}HNMR Spectral Analysis of QO-4

Compound	^{1}HNMR
QO-4	OH (s, 5.0), CH_2 (s, 4.79), NH (s, 4.0), CH- methine (s, 5.55), Aromatic protons (m, 6.61-7.31)

Table 6. Mass Spectral Analysis of QO-4

Compound	Molecular ion peak (m/z)	Base peak (m/z)
QO-4	398.40	237.1

Table 7. Antibacterial activity of oxadiazole- quinazoline analogues on *Staphlyococcus aureus*

Group	Drug	Zone of inhibition (cm)		
		25µg/ml	50µg/ml	100µg/ml
Control	DMSO	-	-	-
Standard	Gentamicin	-	-	2.6
Test	QO-4	1.0	1.2	1.3
	QO-5	0.9	1.0	1.2

Table 8. Antibacterial activity of oxadiazole- quinazoline analogues on *E. coli*

Group	Drug	Zone of inhibition (cm)		
		25µg/ml	50µg/ml	100µg/ml
Control	DMSO	-	-	-
Standard	Gentamicin	-	-	2.8
Test	QO-4	1.3	1.7	2.2
	QO-5	1.0	1.1	1.2

Figure 1. 2D interactions of QO-4 with the binding site of 1KZN

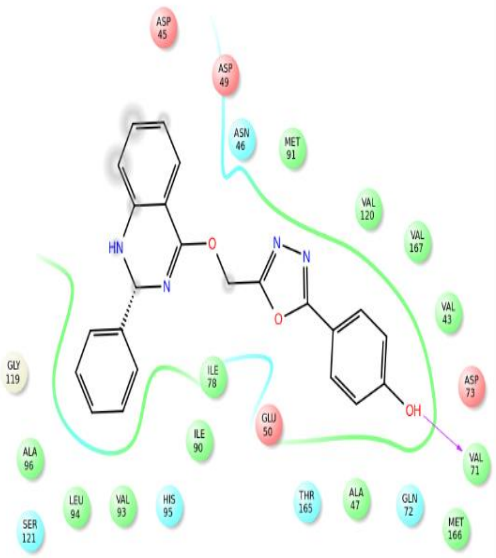


Figure 2. Docking image of QO-4 to 1KZN

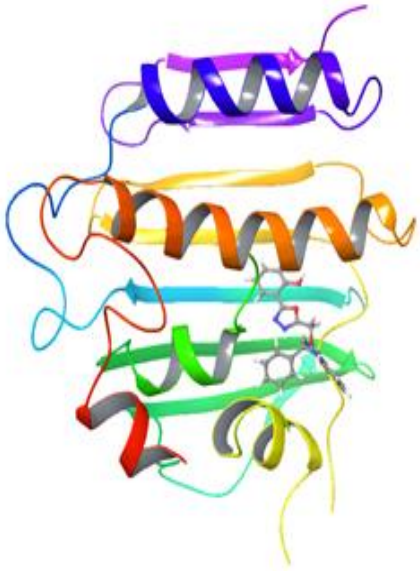


Figure 3. 2D interactions of QO-4 with the binding site of 1HNJ

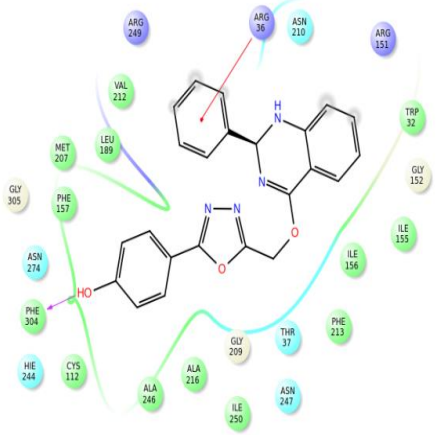


Figure 4. Docking image of QO-4 to IHNJ

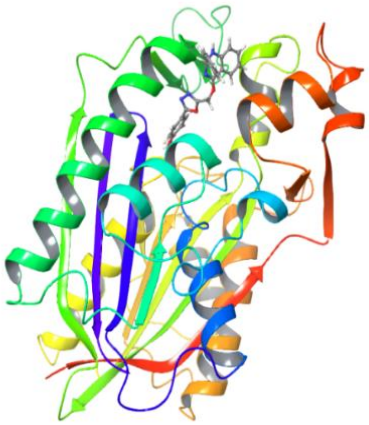


Figure 5. Graphical analysis of QO-4 and QO-5 on *staphylococcus aureus*

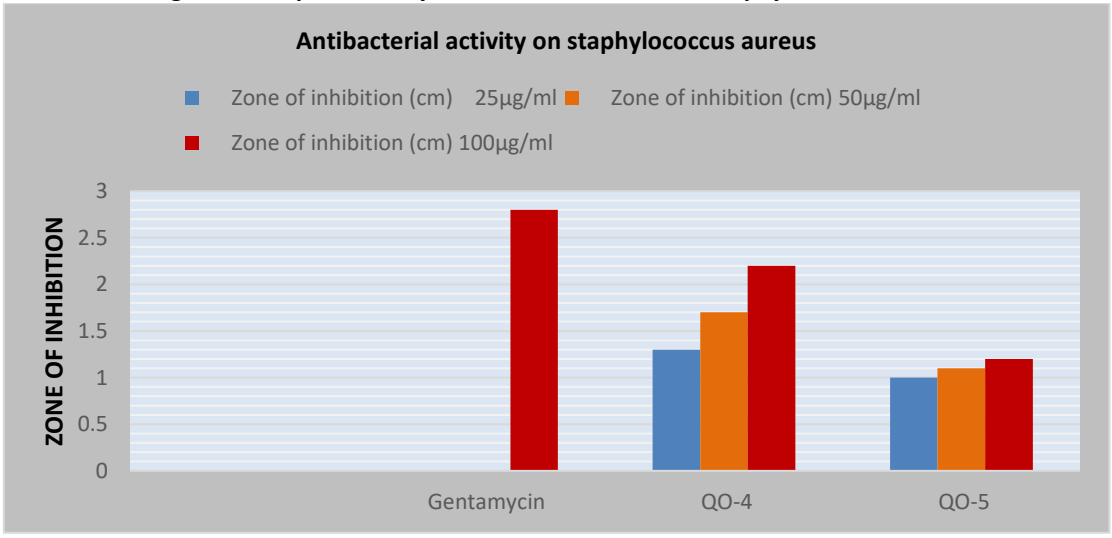


Figure 6. Graphical analysis of QO-4 and QO-5 on *E. Coli*

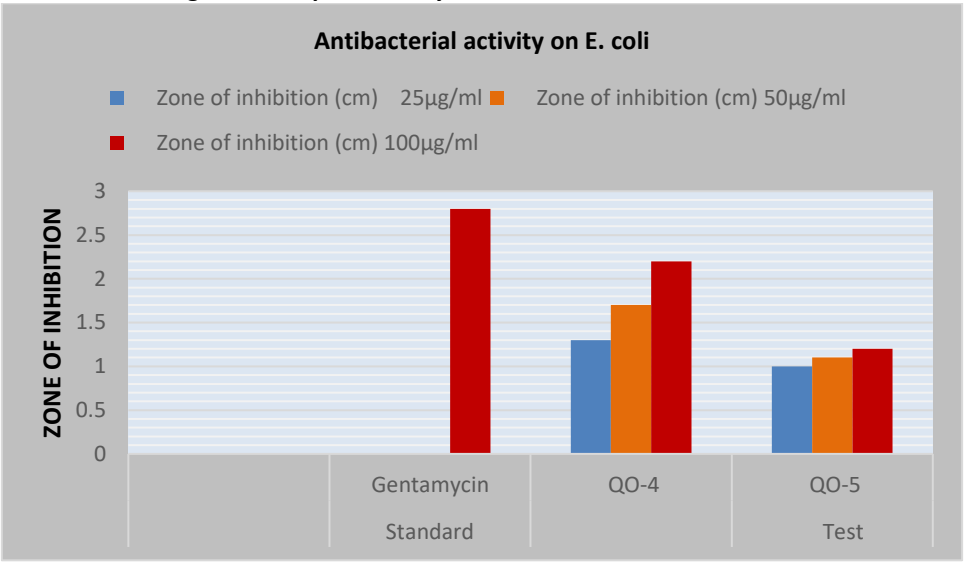


Figure 7. Photographic images of antibacterial evaluation of QO-4 on *S. aureus* and *E.coli*

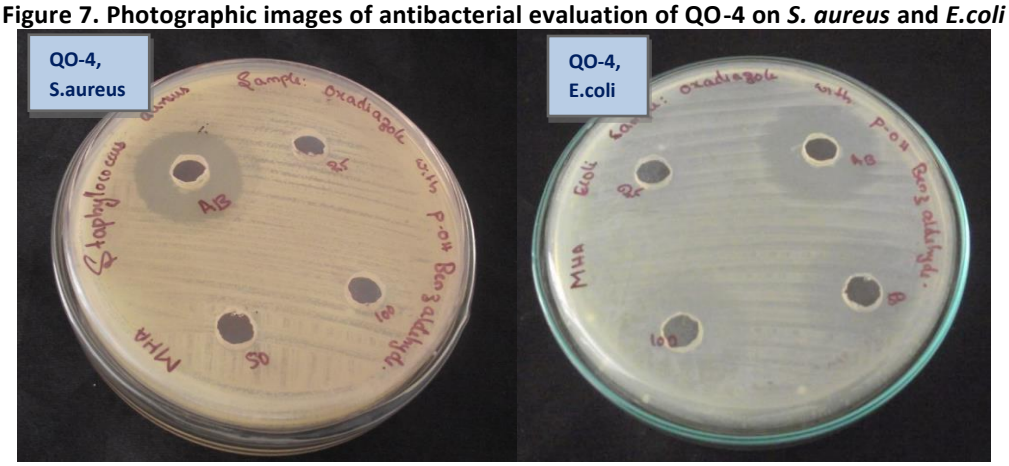


Figure 8. Photographic images of antibacterial evaluation of QO-5 on *S .aureus* and *E. coli*

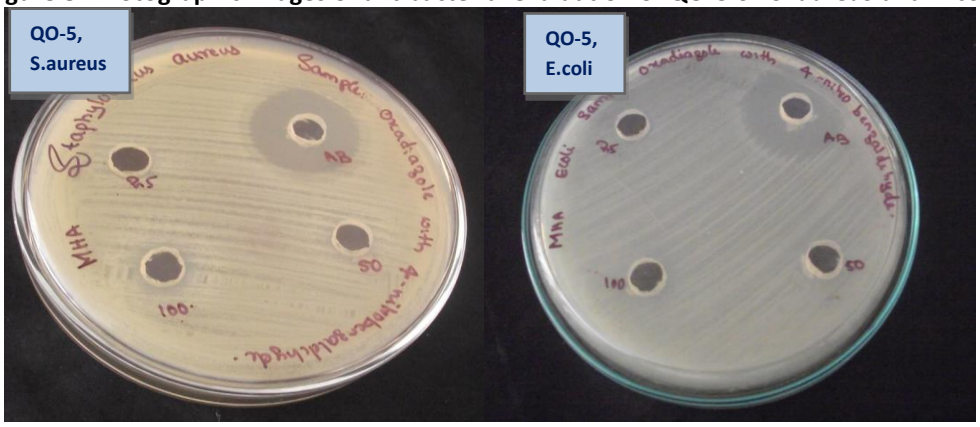


Figure 9. Mass spectra of compound qo-4

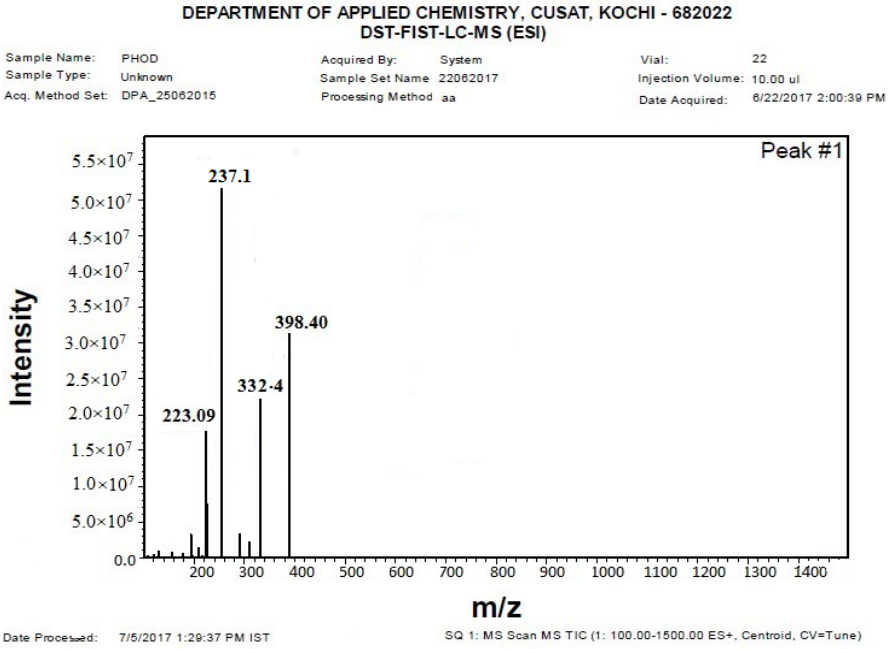
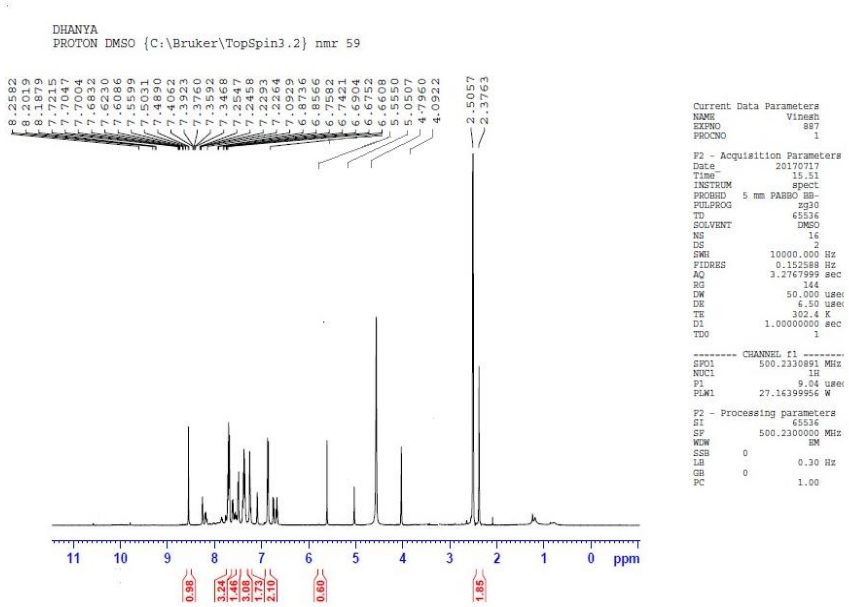
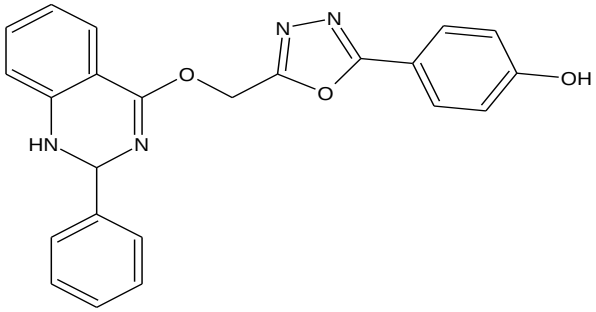


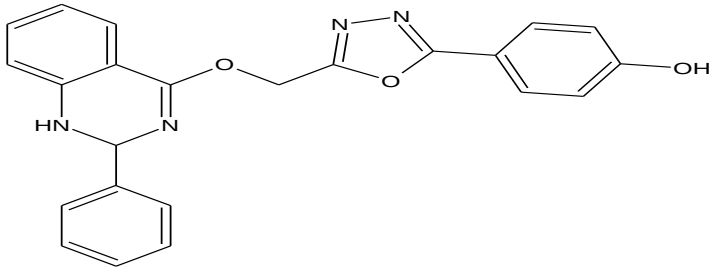
Figure 10. ^{1}H NMR SPECTRA OF COMPOUND QO-4





c\21ccccc1NC(/N=C/2OCc3nnc(o3)c4ccc(cc4)O)c5ccccc5

4-(5-{[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)phenol



c\21ccccc1NC(/N=C/2OCc3nnc(o3)c4ccc(cc4)O)c5ccccc5

4-(5-{[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)phenol

CONCLUSION:

The present work involved in the preliminary *In-silico* screening of quinazolineanalogues, for quantifying their molecular descriptors using computational software. Molecular docking was performed for ten analogues using Schrodinger Maestro and multi targeting drug design was carried out by choosing two proteins for antimicrobial activity. The proteins selected were 1KZN and 1HNJ. All analogues showed good protein interactions.

The compounds were selected for the wet lab synthesis on the basis of desired physicochemical properties, obeying Lipinski Rule of five and good docking score. Ten analogues were synthesized by both conventional and microwave method and the purity of synthesized analogues were ascertained by consistency in melting point and R_f value. The compounds were characterized by IR, ^1H NMR and Mass spectral analysis.

The synthesized compounds were subjected to *in-vitro* screening for antibacterial evaluation. The respective results were analysed and evaluated for the potency of the synthesized compounds. Two analogues (QO-4 and QO-5) were selected for antibacterial screening. Antibacterial activity on both gram positive organism *(S.aureus)* and gram negative organism *(E.coli)* reveal that QO-4 derivative have better inhibitory activity than QO-5 and is lesser than that of standard drug Gentamicin (100µg/ml)..

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