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Design, Synthesis and Characterization of a Series of 6-substituted-4-Hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-One Derivatives and Evaluation of Their In Vitro Anticancer and Antibacterial Activity †

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Abstract: The current research work deals with the design, synthesis and characterization of a series of 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl)quinolin-2(1*H*)-one derivatives [III(a-d)(1-3)] and evaluation of their in vitro anticancer activity against MDA-MB (Breast cancer) and A549 (Lung cancer) cell lines based upon MTT assay and In vitro antibacterial by the measurement of zone of inhibition and determining the Minimum Inhibitory Concentration (MIC). All the synthesized compounds were characterized by UV, IR, ^{1}H NMR and ^{13}C NMR spectral data. Molecular docking studies of the title compounds for 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl) quinolin-2(1*H*)-one derivatives [III(a-d)(1-3)] were carried out using Molegro Virtual Docker (MVD-2013, 6.0) software. The synthesized compounds exhibited well conserved hydrogen bonds with one or more amino acid residues in the active pocket of EGFRK tyrosine kinase domain (PDB ID: 1m17) for anticancer docking study and *S.aureus* DNA Gyrase domain complexed with a ciprofloxacin inhibitor (PDB ID: 2XCT) for antibacterial docking study. All synthesized derivatives were more potent against A549 (Lung cancer) cell line as compared to MDA-MB (Breast cancer) cell line. Compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIIc-3) was found to be the most cytotoxic as compared to the other synthesized derivatives, with IC_{50} values of 397.56 µg/mL against A549 (Lung cancer) cell line, however all synthesized derivatives were found to be a poor antibacterial agent when compared with standard norfloxacin. Thus, the synthesized derivatives possessed a potential to bind with some of the residues of the active site and can be further developed into potential pharmacological agents.

Keywords: Quinolin-2-one; anticancer; antibacterial; Molegro Virtual Docker; EGFRK protein; *S.aureus* DNA Gyrase protein

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1. Introduction

Cancer is characterized by an abnormal and uncontrolled division of cells, which produces tumours and invades adjacent normal tissues. Cancer is the second leading cause of death globally and is estimated to account for 9.6 million deaths in 2018. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and thyroid cancer are the most common among women [1].

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths [2]. Lung cancer claims more lives each year than do colon, prostate, liver, kidney, ovarian and breast cancers combined [3]. People who smoke have the greatest risk of lung cancer, though lung cancer can also occur in non-smokers [4]. Not surprisingly, smoking is a leading cause of lung cancer [5].

Scientists are constantly searching for new treatments based on the latest cancer research [6]. Quinoline compounds play an important role in anticancer drug development as they have shown excellent results through different mechanism of action such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration and modulation. A number of quinoline derivatives have been reported till date for their anticancer activity [7,8]. The main goal of many researchers is to synthesize novel quinolones with a profile of better performance, pharmacokinetics and tolerance to overcome existing drug limitations [8].

Antimicrobials are probably one of the most successful forms of chemotherapy in the history of medicine [9]. A bacterial infection is a proliferation of a harmful strain of bacteria on or inside the body. Bacteria can infect any part of the body. Pneumonia, meningitis, and food poisoning are just a few of the diseases that can be caused by harmful bacteria [10].

In recent decades the activity of conventional antibiotics against pathogenic bacteria has decreased due to the expansion of bacterial resistance [11]. Overuse and misuse of antibiotics has led to a rise in antibiotic resistance [10,11]. Therefore, antibiotic resistance problem demands continuous discovery and development of new antibacterial agents by modification of existing classes including fluoroquinolones, tetracyclines, aminoglycosides, β-lactams and identification of inhibitors against previously unexploited antibacterial targets by different mode of action [12–14]. Concern about the resistance increased in the late 1990's since then, many governmental and agency reports have been published regarding the agricultural use of antibacterials, advising less use of antibacterials, appropriate choice of antibacterials and regimens, prevention of cross-infection and development of new antibacterials [15].

The worldwide ever-increasing of bacterial resistance to the conventional medical antimicrobial agents is currently one of the most serious health crisis for modern medicine [15,16].

2. Material and Methods

All chemicals and reagents were purchased from SD Fine- Chem Limited, Mumbai. Melting points of synthesized compounds were determined by Thiele's melting point apparatus and are uncorrected. FT-IR spectra of the synthesized compounds were recorded on SHIMADZU IR AFFINITY- 1 spectrophotometer by using KBr pellets. The ^{1}H-NMR and ^{13}C-NMR spectral data of synthesized compounds were recorded on Bruker Advance II 400 NMR Spectrophotometer using DMSO-δ_6 as the solvent and TMS as internal standard, chemical shifts are expressed as delta (δ) values (ppm).

3. Procedure

1. Synthesis of 6-substituted-1-(2-chloroacetyl)-4-hydroxyquinolin-2(1*H*)-ones. (IIa/IIb/IIc/IId): [17]

In a clean, dry round bottom flask, 50 mmol of compound 6-substituted-4-hydroxyquinolin-2(1*H*)-ones Ia/Ib/Ic/Id**,** 30 mL of glacial acetic acid and 50 mmol of chloroacetyl chloride was mixed in an order under the fume hood. Then the mixture was gently warmed on a hot plate with swirling for 5–10 min. The product obtained was recrystallized.

2. Synthesis of 6-substituted-4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-ones [IIIa (1-3), IIIb(1-3), IIIc(1-3), IIId(1-3)]: [18–21]

A mixture of thiourea or thiamide (thiobenzamide/thiosemicarbazide) and iodine (0.28g, 0.0022 mol) was added with stirring to a solution of 6-substituted-1-(2-chloroacetyl)-4-hydroxyquinolin-2(1*H*)-ones IIa/IIb/IIc/IId (0.002 mol) in n-butanol (20 mL). The mixture was heated at 120 °C for 2 h in an open vessel. The crude residue was washed with ether (3 × 50 mL) and recrystallized.

MOLECULAR DOCKING STUDIES: [22–24]

In order to further validate the experimental results, molecular docking studies of the title compounds 6-substituted-4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-one derivatives [IIIa (1–3)/IIIb (1–3)/IIIc (1–3)/IIId (1–3)] were carried out using Molegro Virtual Docker (MVD-2013, 6.0).

The coordinate file and crystal structure of Epidermal Growth Factor Receptor tyrosine kinase (EGFRK) domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) obtained from the RCSB-PDB website for anticancer docking and *S.aureus* DNA Gyrase domain complexed with a ciprofloxacin inhibitor (PDB ID: 2XCT) were obtained from the RCSB-PDB website for antibacterial docking.

The MolDock Scores and the hydrogen bonding of the test compounds were compared with active ligands, 4-anilinoquinazoline ligand (PDB ID: 1m17) and Ciprofloxacin ligand (PDB ID: 2XCT).

Procedure for Docking Study

1. The selected compounds were built using Chemdraw 12.0.2.
2. The 2D structures were then converted into energy minimized 3D structures which were saved as MDL MolFile (.mol2).
3. The coordinate file and crystal structure of Epidermal Growth Factor Receptor tyrosine kinase domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) obtained from the RCSB-PDB website for anticancer docking and *S.aureus* DNA Gyrase domain complexed with a ciprofloxacin inhibitor (PDB ID: 2XCT) were obtained from the RCSB-PDB website for antibacterial docking.
4. The protein file was prepared by the removal of water molecules, addition of polar hydrogens, and removal of other bound ligands.
5. The site of binding of the complexed inhibitor was selected as the active site for docking of the molecules.
6. The docking protocol was carried out for synthesized compounds/ligands using MVD2013 (6.0) software using the standard operating procedure.
7. The MolDock Scores and the hydrogen bonding of the test compounds were compared with those of the 4-anilinoquinazoline ligand (anticancer docking) and ciprofloxacin inhibitor (antibacterial docking).

4. Biological Evaluation

Anticancer activity:

In vitro anticancer activity of 6-substituted-4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-one derivatives [III(a-d)(1-3)] was performed by [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) assay on MDA-MB (Breast cancer) and A549 (Lung cancer) cell lines by using following method in which Erlotinib was used as reference standard drug.

MTT solution preparation (stock solution): 5mg in 1ml of Phosphate buffered saline (PBS). (PBS—pH 7.4).

MTT (Cytotoxicity) Assay:

In vitro growth inhibition effect of test compound was assessed by colorimetric or spectrophotometric determination of conversion of MTT into "Formazan blue" by living cells.

Procedure for MTT assay:

a. 50 μL of 1 × 105 cells/mL cell suspension was seeded into each well in a 96 well micro titer plate and final volume was made to 150 μL by adding DMEM media.
b. Dilutions of the test compounds were prepared in DMEM media.
c. 100 μL of the test compounds of different concentrations was added to the wells and incubated for 24 h, in presence of 5% CO_2, at 37 °C into CO_2 incubator.
d. After 24 h, 20 μL of 5 mg/mL MTT reagent was added to the wells. The plate was kept for 4 h of incubation in dark place at room temperature. (The plate was covered with aluminum foil, since MTT reagent is photosensitive.)
e. The supernatant layer was carefully removed without disturbing the precipitated Formazan crystals and 100 μL of DMSO was added to dissolve the crystals formed.
f. The optical density (OD) was measured at wavelength of 492 nm.
g. The study was performed in triplicates and the result represents the mean of three readings.

Formula:

Surviving cells (%) = (Mean OD of test compound/Mean OD of negative control) ×100

Inhibiting cells (%) = 100- Surviving cells

Antibacterial activity:

In vitro antibacterial activity of 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl) quinolin-2(1*H*)-one derivatives [III(a-d)(1–3)] were determined by the measurement of zone of inhibition and determining the Minimum Inhibitory Concentration (MIC).

(a). Zone of inhibition.

Procedure:

1. A few colonies (3 to 10) of the organism to be tested are picked with a wire loop from a test tube containing 25 mL of Soya bean Casein Digest Medium (Trypton Soya Broth).
2. These tubes were incubated for 2–5 h to produce a bacterial suspension of moderate cloudiness.
3. The plates were dried for about 30 min before inoculation.
4. 10 mL of Mueller-Hinton medium was poured in each of the plates and was allowed to solidify.
5. The tubes containing culture were then poured into the plates and kept for 2 h to settle.
6. A well of 5 mm was bored and the drug solution of 10, 20, 30, 40 and 50 mg was added.
7. The plates were incubated for 24 h at 37 °C for bacterial growth.
8. The zone diameters were measured and compared with the standard drug Ciprofloxacin.

The bacterial strains used were as follows:

Gram Positive Bacteria	Gram Negative Bacteria
S.a = S. aureus	*E.c = E. coli*
B.s = B. subtilis	*P.a = P. aeroginosa*

(b). Minimum Inhibitory Concentrations (MIC): [25]

The Minimum Inhibitory Concentrations (MIC) of the synthesized 6-substituted-4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-one derivatives [III(a-d)(1–3)] were determined in the range of concentrations from 1–50 mg/mL.

Preparation of standard drug.

The concentration of standard drug Ciprofloxacin was 50 mg/10 mL (5 mg/mL = 5000 μg/mL i.e., 5000 μg/5000 μL). 51.2 μL of this solution contained 256 μg of the drug.

Preparation of stock solution of synthesized drugs.

The concentration of synthesized drugs IIIc-3, IIId-3 and IIIb-1 was 19,531.2 mg/10 mL (1953.12 mg/mL i.e., 1953.12 mg/1000 μL). 51.2 μL of this solution contained 100mg of the drug. The dilutions obtained were 50 mg/mL, 25 mg/mL, 12.5 mg/mL, 6.25 mg/mL, 3.125 mg/mL, 1.56 mg/mL, 0.78 mg/mL, 0.39 mg/mL, 0.195 mg/mL and 0.097 mg/mL respectively.

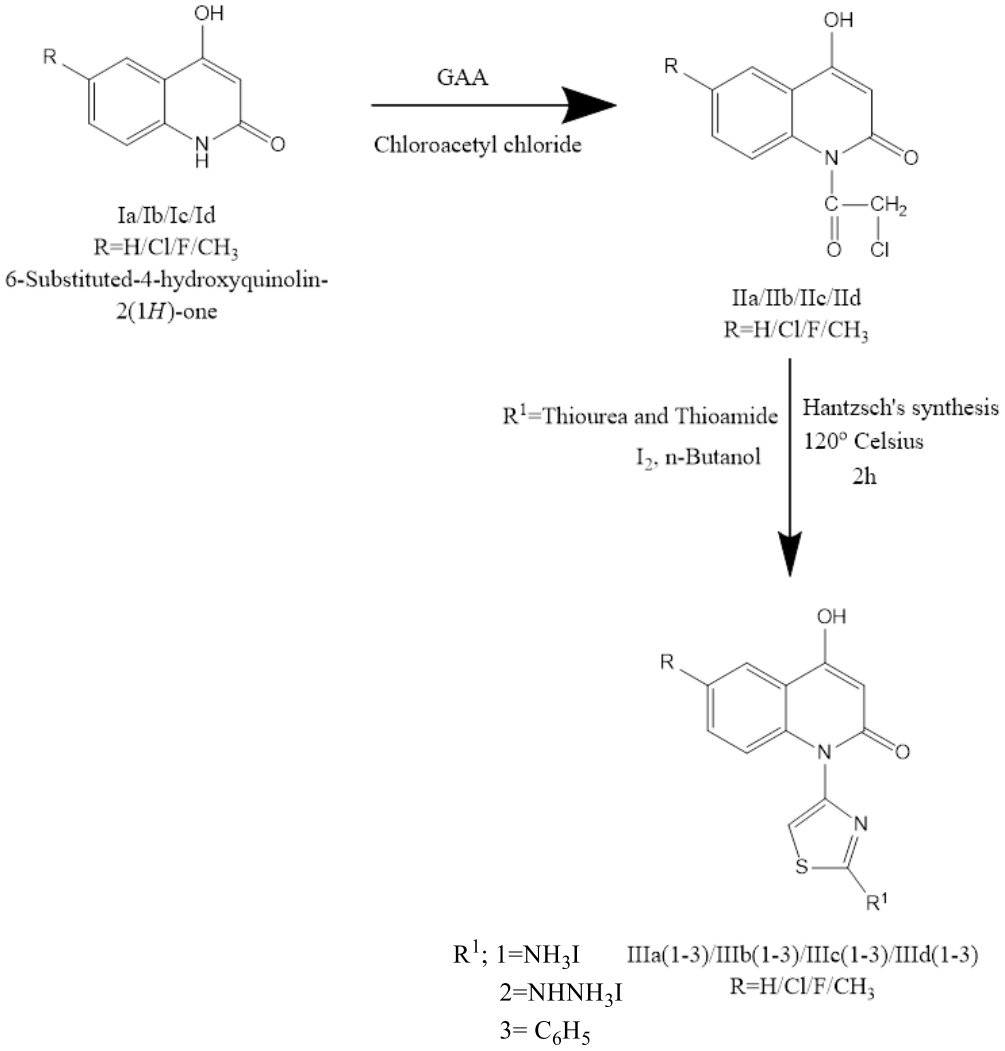
Procedure:

1. Twelve sterile T.T taken and numbered 1–12 (11th T.T—Positive control and 12th T.T—Negative control)
2. To 1st T.T 2000 μL Muller-Hinton broth added aseptically
3. Remaining T.T 1000 μL of MH was added
4. 51.2 μL MH broth was pipetted out and replaced with 51.2 μL of drug solution in 1st T.T
5. 1000 μL of mixed solution transferred from 1st to 2nd T.T aseptically and repeated till 10th T.T
6. From 10th T.T 1000 μL solution was discarded
7. Dilutions obtained were 50 mg/mL, 25 mg/mL, 12.5 mg/mL, 6.25 mg/mL, 3.125 mg/mL, 1.56 mg/mL, 0.78 mg/mL, 0.39 mg/mL, 0.195 and 0.097 mg/mL
8. 10 μL broth of culture to be tested was inoculated in all T.T except negative control and incubated at 37 °C for 24 h
9. After 24 h T.T were observed for inhibition of growth and MIC was reported.

The lowest concentration of the compound which causes apparently complete inhibition of the growth of the organism was taken as Minimum Inhibitory Concentration (MIC). Ciprofloxacin was used as the reference standard drug against *S. aureus, B. subtilis, E. coli and P. aeruginosa.*

5. Results and Discussion

The Scheme 1 for synthesis of derivatives initially involves, synthesis of substituted 4-hydroxyquinolin-2(1*H*)-ones **I(a–d)** as per the literature review [17]. Compound I(a–d) were further subjected to condensation with chloroacetyl chloride to give 6-substituted-1-(2-chloroacetyl)-4-hydroxyquinolin-2(1*H*)-ones II(a–d), the chloroacetyl chloride condenses with nitrogen at 1st position of quinoline ring with liberation of HCl to yield the corresponding compounds **(IIa/IIb/IIc/IId)**. Finally condensation with thiourea or thiamide through Hantzsch's thiazole synthesis yields twelve derivatives of 6-substituted- 4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1*H*)-ones **[III(a-d)(1-3)].** Physical data of all synthesized compounds are given in Table 1. All the synthesized compounds were characterized by UV, IR, ^{1}H NMR and ^{13}C NMR spectral data.



Scheme 1. Synthetic route for 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl) quinolin-2(1*H*)-one derivatives III[(a-d)(1–3)].

Table 1. Physical data of synthesized compounds.

Compound	Appearance	Mol. Formula	M.W	M.P(°C)	% Yield	Rf value	λ_{max}(nm)	Solubility
IIIa-1	White solid	$C_{12}H_{10}N_3O_2SI$	387	>300	71	0.74	231.8	DMSO
IIIa-2	White solid	$C_{12}H_{11}N_4O_2SI$	402	>300	89	0.77	216.8	DMSO
IIIa-3	White solid	$C_{18}H_{12}N_2O_2S$	320	>300	74	0.72	231.8	DMSO
IIIb-1	Orange solid	$C_{12}H_9ClN_3O_2SI$	421.5	>300	68	0.75	223.0	DMSO
IIIb-2	Orange solid	$C_{12}H_{10}ClN_4O_2SI$	436.5	>300	90	0.69	226.8	DMSO
IIIb-3	Orange solid	$C_{18}H_{11}ClN_2O_2S$	354.5	>300	76	0.71	232.8	DMSO
IIIc-1	White solid	$C_{12}H_9FN_3O_2SI$	405	>300	65	0.77	225.0	DMSO
IIIc-2	White solid	$C_{12}H_{10}FN_4O_2SI$	420	>300	95	0.70	230.0	DMSO
IIIc-3	White solid	$C_{12}H_{10}FN_4O_2S$	293	>300	75	0.73	229.8	DMSO
IIId-1	White solid	$C_{13}H_{12}N_3O_2SI$	401	>300	63	0.73	234.8	DMSO
IIId-2	White solid	$C_{13}H_{13}N_4O_2SI$	416	>300	88	0.71	218.6	DMSO
IIId-3	White solid	$C_{19}H_{14}N_2O_2S$	334	>300	66	0.68	232.4	DMSO

The in vitro anticancer activity of 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl)quinolin-2(1*H*)-one **[III(a–d)(1–3)]** was performed by MTT assay on MDA-MB (Breast cancer) and A549 (Lung cancer) cell lines as given in Tables 2 and 3 respectively. From the

obtained results, the synthesized compounds (IIIa-2), (IIIb-3), (IIIc-1), (IIId-3) showed IC_{50} values of 350.5 μg/mL, 354.2 μg/mL, 485.0 μg/mL, 452.15 μg/mL against MDA-MB (Breast cancer) cell line as compared to standard imatinib which showed IC_{50} value of 111.34 μg/mL as shown in Table 4. Compounds (IIIa-1), (IIIa-2), (IIIc-3), (IIId-1) showed IC_{50} values of 353.87 μg/mL, 377.82 μg/mL, 397.56 μg/mL, 346.12 μg/mL against A549 (Lung cancer) cell line as compared to standard imatinib which showed IC_{50} value of 337.61 μg/mL as shown in Table 5. Hence all synthesized derivatives were found to be more potent against A549 (Lung cancer) cell line as compared to MDA-MB (Breast cancer) cell line and compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one **(IIIc-3)** was the most potent compound with IC_{50} value of 397.56 μg/mL against A549 cell line.

Table 2. Cell viability of synthesized compounds [III(a–d)(1–3)] on MDA-MB (Breast cancer) cell line.

Concentration	**% Cell Viability (MDA-MB cell line)**					
μg/mL	**IIIa-1**	**IIIa-2**	**IIIa-3**	**IIIb-1**	**IIIb-2**	**IIIb-3**
500	60.09	**41.32**	80.23	72.98	65.5	**41.36**
250	60.11	**56**	83.04	73.1	68.34	**58**
125	61.5	**60.4**	83.1	75.04	70.3	**61.9**
62.5	62	**65.9**	88	75.23	71.23	**62.3**
31.25	68.32	**69.4**	90.54	86.1	77.6	**66.4**
Concentration	**% Cell Viability (MDA-MB cell line)**					
μg/mL	**IIIc-1**	**IIIc-2**	**IIIc-3**	**IIId-1**	**IIId-2**	**IIId-3**
500	**49.65**	60.15	61.22	73	70.2	**48.45**
250	**58.1**	62	63	74.2	71.3	**58.09**
125	**63.23**	63.1	64.86	75.41	75	**60.21**
62.5	**66.12**	64.3	70.65	80.3	75.09	**65.47**
31.25	**67.87**	65.8	73.42	81.9	78.9	**71.32**

Table 3. Cell viability of synthesized compounds [III(a–d)(1–3)] on A549 (Lung cancer) cell line.

Concentration	**% Cell Viability (A549 cell line)**					
μg/mL	**IIIa-1**	**IIIa-2**	**IIIa-3**	**IIIb-1**	**IIIb-2**	**IIIb-3**
500	**41.36**	**43.54**	63.8	55.54	70.15	66
250	**57.6**	**58.14**	65.4	65.2	73.9	68.13
125	**61**	**61.8**	68	68.49	74.5	70.05
62.5	**62.8**	**62**	70.5	70.4	75	71
31.25	**65.8**	**76**	71.5	70.49	77.3	72.02
Concentration	**% Cell Viability (A549 cell line)**					
μg/mL	**IIIc-1**	**IIIc-2**	**IIIc-3**	**IIId-1**	**IIId-2**	**IIId-3**
500	63.9	68.4	**40.35**	**46.26**	65.47	70.15
250	64.4	69	**58.21**	**55.19**	67.39	75.6
125	70.1	70.4	**62**	**61**	71.5	78
62.5	75	71	**64.32**	**65.19**	73	78.14
31.25	76.14	72.4	**66.30**	**68.14**	74.2	82.19

Table 4. IC_{50} values of synthesised compounds on MDA-MB cell line.

Compound	**IC_{50} (μg/mL)**
IIIa-2	**350.5**
IIIb-3	**354.2**
IIIc-1	**485.0**

IIId-3	**452.14**
Imatinib	**111.34**

Table 5. IC_{50} values of synthesised compounds on A549 cell line.

Compound	IC_{50} (μg/mL)
IIIa-1	**353.87**
IIIa-2	**377.32**
IIIc-3	**397.56**
IIId-1	**346.12**
Imatinib	**337.61**

All the twelve synthesized compounds 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl)quinolin-2(1*H*)-one **[III(a–d)(1–3)]** were screened for their in vitro antibacterial activity by measuring the zone of inhibition using agar diffusion method. Further Minimum Inhibitory Concentration (MIC) of the most active compound was determined by broth dilution method. The compounds were tested against Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli*, *P. aeruginosa* bacterial strains. Norfloxacin was used as the reference standard.

Total six derivatives out of twelve synthesized compounds showed antibacterial activity. However, except compound **IIIa-3** and **IIIb-3** which showed antibacterial activity only against Gram-negative *E. coli, P. aeruginosa* bacterial strains whereas all remaining four compounds **IIIc-3, IIId-3, IIIb-1, IIIc-1** showed activity against all strains of Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli, P. aeruginosa* bacterial strains as shown in Table 6. IIIc-3 and IIId-3 with phenylthiazole derivative and compound IIIb-1 with thiazol-2-aminium iodide exhibited highest values for zone of inhibition at 50, 40, 30, 20, 10 mg/mL in all strains as shown in Figures 1 and 2 and hence was further evaluated to determine its MIC.

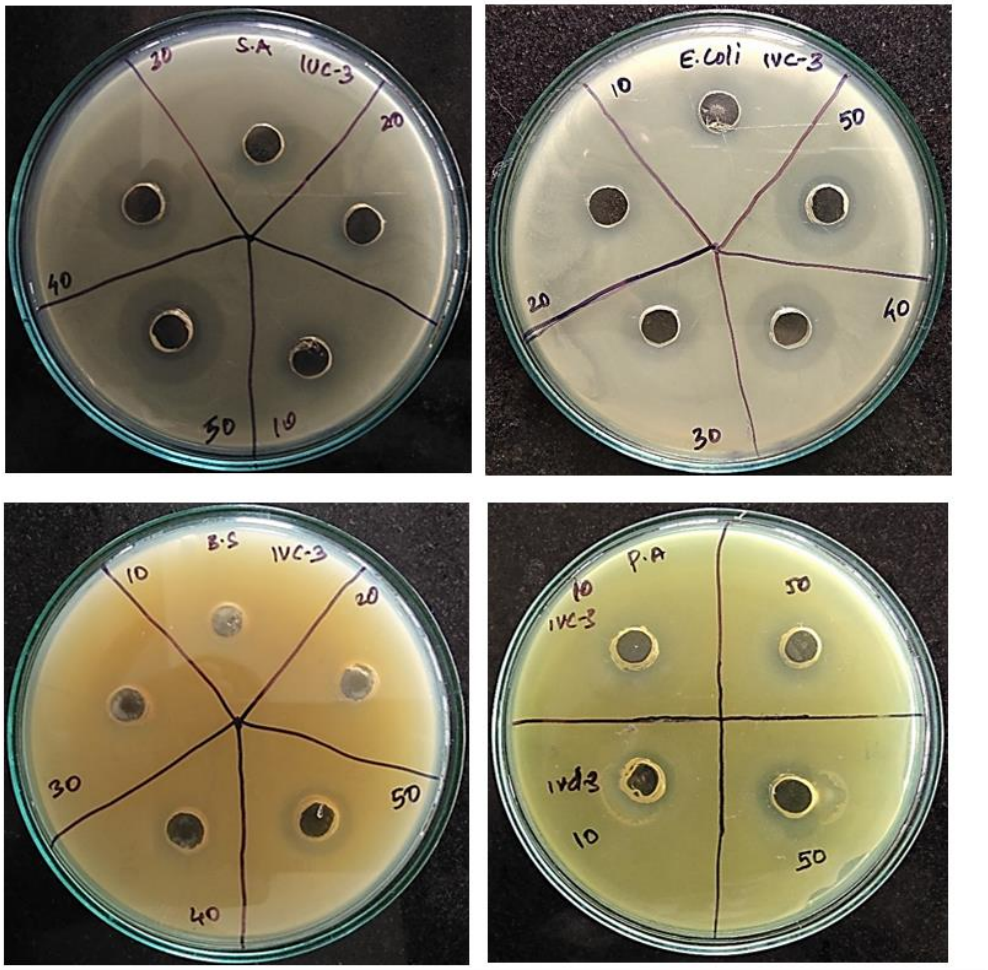


Figure 1. Antibacterial activity of compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) against *S. aureus, B. subtilus, E. coli, P. aeruginosa.*

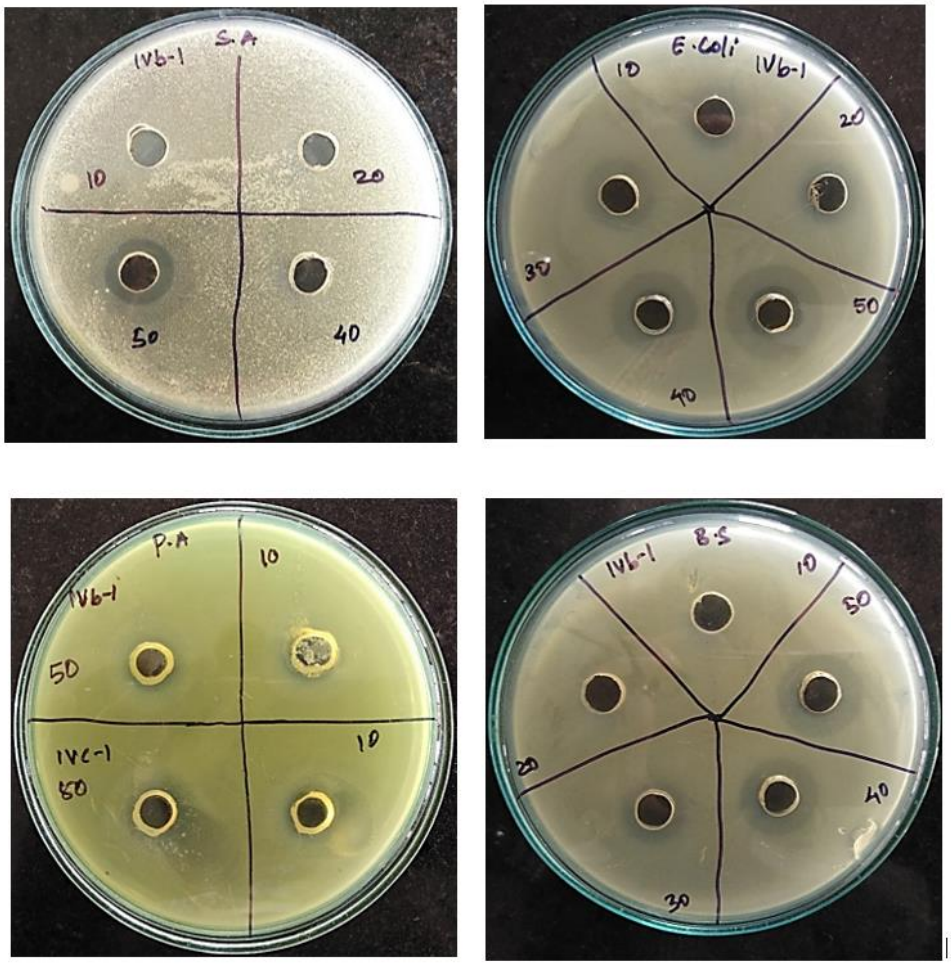


Figure 2. Antibacterial activity of compound 4-(6-chloro-4-hydroxy-2-oxoquinolin-1(2*H*)-yl)thiazol-2-aminium iodide (IIIb-1) against *S. aureus, B. subtilus, E. coli, P. aeruginosa.*

Compound 6-Fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one **IIIc-3** showed MIC of 6.25 mg/mL, 50 mg/mL, 12.5 mg/mL and 12.5 mg/mL against Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli, P. aeruginosa* bacterial strains respectively. Compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one **IIId-3** showed MIC of 25 mg/mL, 50 mg/mL, 12.5 mg/mL and 6.25 mg/mL against Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli, P. aeruginosa* bacterial strains respectively. Whereas compound 4-(6-chloro-4-hydroxy-2-oxoquinolin-1(2*H*)-yl)thiazol-2-aminium iodide **IIIb-1** showed MIC of 50 mg/mL, 25 mg/mL, 6.25 mg/mL and 50 mg/mL against Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli, P. aeruginosa* bacterial strains respectively as shown in Table 7.

Table 6. Antibacterial activity of synthesized 6-substituted-4-hydroxy-1-(2-substituted thiazol-5-yl) quinolin-2(1*H*)-one derivatives [III(a–d)(1–3)] by measuring the zone of inhibition.

Compound	Concentration mg	Zone of Inhibition in mm			
		Gram Positive Bacteria		Gram Negative Bacteria	
		S.a	***B.s***	***E.c***	***P.a***
IIIa-3	50	-	-	14	8
	40	-	-	12	-
	30	-	-	10	-
	20	-	-	9	-

	10	-	-	-	-
IIIb-3	50	-	-	14	18
	40	-	-	13	16
	30	-	-	12	13
	20	-	-	11	10
	10	-	-	10	8
IIIc-3	50	24	12	19	13
	40	20	-	18	11
	30	18	-	16	10
	20	17	-	15	9
	10	16	-	11	8
IIId-3	50	15	12	14	17
	40	12	-	13	16
	30	10	-	12	14
	20	9	-	11	13
	10	-	-	10	12
IIIb-1	50	20	17	15	14
	40	-	15	14	-
	30	-	14	13	-
	20	-	-	12	-
	10	-	-	10	-
IIIc-1	50	-	12	14	14
	40	-	11	11	13
	30	-	-	10	12
	20	-	-	-	11
	10	-	-	-	10
Norfloxacin	50	30	35	47	40
	40	28	33	46	38
	30	27	32	45	37
	20	26	31	44	36
	10	25	30	43	35

Table 7. Antibacterial activity of 4-hydroxy-1-phenyl/methyl-3-(2-(substituted thiazol)-4-yl) quinolin-2(1*H*)-one derivatives [III(a–d)(1–3)] by Minimum Inhibitory Concentration (MIC).

	Minimum Inhibitory Concentration (MIC) mg/mL			
Compound	**Gram Positive Bacteria**		**Gram Negative Bacteria**	
	S.a	***B.s***	***E.c***	***P.a***
IIIc-3	6.25	50	12.5	12.5
IIId-3	25	50	12.5	6.25
IIIb-1	50	25	6.25	50
Norfloxacin μg/ml	2	2	2	<4

Spectral data of synthesized compounds:

The spectral data of 4-hydroxyquinolin-2(1H)-one (Ia):

IR data (KBr,cm^{-1}): 3444.87 (-OH stretch), 3093.82 (Aromatic C-H stretch), 2953.02, 2902.87 (Aliphatic C-H stretch), 1658.78 (Amide C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.18 (s, 1H, -OH), 8.17 (s, 1H, -NH), 7.80–7.09 (m, 5H, Ar-H).

The spectral data of 6-chloro-4-hydroxyquinolin-2(1H)-one (Ib):

IR data (KBr,cm^{-1}): 3444.87 (-OH stretch), 3076.46 (Aromatic C-H stretch), 2974.23, 2883.58 (Aliphatic C-H stretch), 1678.07 (Amide C=O stretch), 747 (C-Cl stretch).

^{1}H NMR data (δ ppm, DMSO-*d6*): 11. 82(s, 1H, -OH), 8.09 (s, 1H, -NH), 7.73–7.26 (m, 4H, Ar-H)

^{13}C NMR data (δ ppm, DMSO-*d6*): 163.32 (1C, Amide -C=O), 161.44 (1C, -C-OH), 137.87 (1C, -C=C- of aromatic ring), 130.65 (1C, -C-Cl of aromatic ring), 125.06 (1C, -C=CH of aromatic ring), 121.72 (1C, -C=CH of aromatic ring), 117.08 (1C, -C=C- of aromatic ring), 116.36 (1C, -C=CH of aromatic ring), 99.11 (1C, -C=C)

The spectral data of 6-fluoro-4-hydroxyquinolin-2(1H)-one (Ic):

IR data (KBr,cm^{-1}): 3446.79 (-OH stretch), 3088.03 (Aromatic -CH stretch), 2972.31, 2893.22 (-CH stretch), 1654.92 (Amide -C=O stretch), 1197.79 (-C-F stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.73 (s, 1H, -OH), 8.27 (s, 1H, -NH), 7.48–7.27 (m, 4H, Ar-H)

^{13}C NMR data (δ ppm, DMSO-*d6*): 163.26 (1C, -C=O), 161.62 (1C, -C-OH), 157.88 (1C, -C-F of aromatic ring), 135.83 (1C, -C=C- of aromatic ring), 117.58 (1C, -C=CH of aromatic ring), 114.05 (1C, -C=CH of aromatic ring), 113.00 (1C, -C=C- of aromatic ring), 111.06 (1C, -C=CH of aromatic ring), 99.06 (1C, -C=C)

The spectral data of 6-methyl-4-hydroxyquinolin-2(1H)-one (Id):

IR data (KBr,cm^{-1}): 3442.94 (-OH stretch), 3030.17 (Aromatic -CH stretch), 2906.73, 2837.29 (Aliphatic -CH stretch), 1672.28 (Amide -C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.51 (s, 1H, -OH), 8.09 (s, 1H, -NH), 7.86–7.04 (m, 4H, Ar-H), 1.46 (s, 3H, $-CH_3$),

The spectral data of 1-(2-chloroacetyl)-4-hydroxyquinolin-2(1H)-one (IIa):

IR data (KBr,cm^{-1}): 3467.09 (-OH stretch), 3093.82 (Aromatic –CH stretch), 2953.02, 2858.51(-Aliphatic –CH stretch), 1666.50 (Amide -C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.19 (s, 1H, -OH), 7.11–7.78 (m, 5H, Ar-H), 4.25 (s, 2H, $-CH_2$)

The spectral 6-chloro-1-(2-chloroacetyl)-4-hydroxyquinolin-2(1H)-one (IIb):

IR data (KBr,cm^{-1}): 3467.54 (-OH stretch), 3088.03 (Aromatic –CH stretch), 2933.73, 2852.72 (Aliphatic –CH stretch), 1678.07 (Amide -C=O stretch), 819.75 (C-Cl stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 12.05 (s, 1H, -OH), 7.51–7.28 (m, 4H, Ar-H), 4.97 (s, 2H, $-CH_2$)

The spectral data of 6-fluoro-1-(2-chloroacetyl)-4hydroxyquinolin-2(1H)-one (IIc):

IR data (KBr,cm^{-1}): 3422.89 (-OH stretch), 3093.82(Aromatic –CH stretch), 2947.23, 2848.86 (Aliphatic -CH stretch), 1658.78(Amide -C=O stretch), 1197.79 (-C-F stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.24 (s, 1H, -OH), 7.98–7.34 (m, 4H, Ar-H), 4.48 (s, 2H, $-CH_2$)

The spectral data of 6-methyl-1-(2-chloroacetyl)-4-hydroxyquinolin-2(1*H*)-one (IId):

IR data (KBr,cm^{-1}): 3446.79 (-OH stretch), 3064.89 (Aromatic –CH stretch), 2927.94, 2852.72 (Aliphatic -CH stretch), 1658.78(Amide -C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.45 (s, 1H, -OH), 7.51-7.28 (m, 4H, Ar-H), 4.97 (s, 2H, $-CH_2$)

The spectral data of 4-(4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-aminium iodide (IIIa-1):

IR data (KBr,cm^{-1}): 3446.79 (-OH stretch), 3093.82 (Aromatic –CH stretch), 2993.52, 2864.29(Aliphatic -CH stretch), 1666.50 (Amide -C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.20 (s, 1H, -OH), 7.79-7.11 (m, 5H, Ar-H), 6.31 (s, 1H, -CH thiazole), 4.05 (s, 3H, N)

^{13}C NMR data (δ ppm, DMSO-*d6*): 163.55 (1C, -C=O), 162.41 (1C, -C-OH), 159.01 (1C, -C=N of thiazole ring), 139.15 (1C, -C=N of thiazole ring), 130.80 (1C, -C=C of thiazole ring), 122.61–114.96 (6C,-C-Ar), 98.19 (1C, 3rd C of Quinolin-2-one)

The spectral data of 2-(4-(4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-yl)hydrazin-1-ium iodide (IIIa-2):

IR data (KBr,cm^{-1}): 3446.79 (-OH stretch), 3093.82 (Aromatic –CH stretch), 2960.73(Aliphatic -CH stretch), 1631.78 (-C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.20 (s, 1H, -OH), 8.04 (s, 3H, NH_3), 7.93–7.01 (m, 5H, Ar-H), 5.38 (s, 1H, -CH thiazole), 3.98 (s, 3H, N-H)

The spectral data of 4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1H)-one (IIIa-3):

IR data (KBr,cm^{-1}): 3432.79 (-OH stretch), 3093.82 (Aromatic –CH stretch), 2951.09 (Aliphatic -CH stretch), 1668.43 (-C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.20 (s, 1H, -OH), 7.89–7.21 (m, 10H, Ar-H), 5.04 (s, 1H, -CH thiazole), 3.09 (s, 3H, N)

The spectral data of 4-(6-chloro-4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-aminium iodide (IIIb-1):

IR data (KBr,cm^{-1}): 3441.19 (-OH stretch), 3089.96 (Aromatic –CH stretch), 2927.94 (Aliphatic -CH stretch), 1658.78 (-C=O stretch), 817.82 (C-Cl stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 16.60 (s, 1H, -OH), 7.13–7.01 (m, 4H, Ar-H), 5.68 (s, 1H, -CH thiazole), 3.95 (s, 3H, N)

^{13}C NMR data (δ ppm, DMSO-*d6*): 167.51 (1C, -C=O), 161.78 (1C, -C-OH), 159.89 (1C, -C=N of thiazole ring), 140.56 (1C, -C=N of thiazole ring), 128.67 (1C, -C=C of thiazole ring), 127.61–120.96 (5C,-C-Ar), 98.54 (1C, 3rd C of Quinolin-2-one)

The spectral data of 2-(4-(6-chloro-4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-yl)hydrazin-1-ium iodide (IIIb-2):

IR data (KBr,cm^{-1}): 3463.8 (-OH stretch), 3088.03 (Aromatic –CH stretch), 2991.59 (Aliphatic -CH stretch), 1658.78 (-C=O stretch), 817.82 (C-Cl stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.34 (s, 1H, -OH), 8.09 (d, 3H, NH_3), 7.86–7.38 (m, 4H, Ar-H), 5.68 (s, 1H, -CH thiazole), 3.95 (s, 1H, N-H)

The spectral data of 6-chloro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1H)-one (IIIb-3):

IR data (KBr,cm^{-1}): 3443.8 (-OH stretch), 3091.89 (Aromatic –CH stretch), 2937.59 (Aliphatic -CH stretch), 1658.78 (-C=O stretch), 817.82 (C-Cl stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 16.31 (s, 1H, -OH), 7.97-7.12 (m, 9H, Ar-H), 4.89 (s, 1H, -CH of thiazole ring)

^{13}C NMR data (δ ppm, DMSO-*d6*): 180.94 (2C, -C=O), 168.87 (1C, -C-OH), 163.34 (1C, -C-Cl), 161.64 (1C, -C=N of thiazole ring), 161.61 (1C, -C=N of thiazole ring), 157.88–107.49 (11C, C-Ar), 120.11 (1C, -C=C of thiazole ring), 99.01 (1C, 3rd C of Quinolin-2-one)

The spectral data of 4-(6-fluoro-4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-aminium iodide (IIIc-1):

IR data (KBr,cm^{-1}): 3409.56 (-O-H stretch), 3089.96 (Aromatic –CH stretch), 2949.16 (Aliphatic –CHstretch), 1658.78(-C=O stretch), 1197.79 (C-F stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.98 (s, 1H, -OH), 7.48-7.21 (m, 4H, Ar-H), 5.68 (s, 1H, -CH thiazole), 3.95 (s, 3H, N)

^{13}C NMR data (δ ppm, DMSO-*d6*): 168.45 (1C, -C=O), 162.54 (1C, -C-OH), 159.94 (1C, C-F) 156.45 (1C, -C=N of thiazole ring), 143.67 (1C, -C=N of thiazole ring), 128.67 (1C, -C=C of thiazole ring), 124.51–119.96 (5C,-C-Ar), 99.08 (1C, 3rd C of Quinolin-2-one)

The spectral data of 2-(4-(6-fluoro-4-hydroxy-2-oxoquinolin-1(2H)-yl)thiazol-2-yl)hydrazin-1-ium iodide (IIIc-2):

IR data (KBr,cm^{-1}): 3469.64 (-NH stretch), 3093.82 (Aromatic –CH stretch), 2997.08 (Aliphatic -CH stretch), 1643.35 (-C=O stretch), 1197.79 (C-F stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.14 (s, 1H, -OH), 7.98 (d, 3H, NH_3), 7.89–7.58 (m, 4H, Ar-H), 5.95 (s, 1H, -CH thiazole), 3.34 (s, 1H, N-H)

The spectral data of 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1H)-one (IIIc-3):

IR data (KBr,cm^{-1}): 3498.57 (-OH stretch), 3091.89 (Aromatic –CH stretch), 2947.23 (Aliphatic -CH stretch), 1658.78 (-C=O stretch), 1197.79 (C-F stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 16.20 (s, 1H, -OH), 7.86–7.09 (m, 9H, Ar-H), 3.79 (s, 1H, -CH of thiazole ring)

The spectral data of 4-(4-hydroxy-6-methyl-2-oxoquinolin-1(2H)-yl)thiazol-2-aminium iodide (IIId-1):

IR data (KBr,cm^{-1}): 3409.45 (O-H stretch), 3016.97(Aromatic –CH stretch), 2974.23 (Aliphatic -CH stretch), 1652.64(-C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 11.34 (s, 1H, -OH), 7.59-7.19 (m, 4H, Ar-H), 5.74 (s, 1H, -CH of thiazole ring), 3.56 (s, 3H, $-NH_3$), 2.33 (s, 3H, $-CH_3$)

^{13}C NMR data (δ ppm, DMSO-*d6*): 162.26 (1C, -C=O), 160.46 (1C, -C-OH), 137.14 (1C, -C=N of thiazole ring), 131.98 (1C, -C=C of thiazole ring),130.45 1C (-C=N of thiazole ring) 129.95–114.84 (5C, -C-Ar), 98.18 (1C, 3rd C of Quinolin-2-one), 20.47 (1C, $-CH_3$)

The spectral data of 2-(4-(4-hydroxy-6-methyl-2-oxoquinolin-1(2H)-yl)thiazol-2-yl)hydrazin-1-ium iodide (IIId-2):

IR data (KBr,cm^{-1}): 3469.64 (-OH stretch), 3076.76 (Aromatic -CH stretch), 2968.45 (Aliphatic -CH stretch), 1653.35 (-C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 15.17 (s, 1H, -OH), 8.65 (d, 3H, NH_3), 7.55–7.14 (m, 4H, Ar-H), 4.52 (s, 1H, -CH thiazole), 2.51 (s, 1H, -NH), 2.31 (s, 3H, $-CH_3$)

The spectral data of 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1H)-one (IIId-3):

IR data (KBr,cm^{-1}): 0456.98 (-OH stetch), 3091.89 (Aromatic –CH stretch), 2972.31, (Aliphatic -CH stretch), 1650.71 (-C=O stretch)

^{1}H NMR data (δ ppm, DMSO-*d6*): 16.20 (s, 1H, -OH), 7.76–7.17 (m, 9H, Ar-H), 6.86 (s, 1H, -CH thiazole) 2.76 (s, 3H, $-CH_3$)

6. Molecular Docking Studies

Molecular docking studies of the title compounds 6-substituted-4-hydroxy-1-(2-substituted thiazol-5-yl) quinolin-2(1*H*)-one derivatives [IV(a–d)(1–3)] were carried out using Molegro Virtual Docker (MVD-2013, 6.0) carried on Epidermal Growth Factor Receptor tyrosine kinase domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) for anticancer docking study and on *S. aureus* DNA Gyrase domain complexed with a Ciprofloxacin inhibitor (PDB ID: 2XCT) for antibacterial docking study and the results are given in Tables 8 and 9 respectively.

Table 8. MolDock Scores of synthesized compounds 6-substituted-4-hydroxy-1-(2-substituted thiazol-5-yl) quinolin-2(1*H*)-one derivatives [IIIa (1–3)/IIIb (1–3)/IIIc (1–3)/IIId (1–3)] on Epidermal Growth Factor Receptor tyrosine kinase domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) for anticancer docking study.

Compound	MolDock Score	Rerank Score	H-Bond
IIIa-1	−84.9181	−49.7949	−9.77059
IIIa-2	−81.5187	−50.9204	−7.20758
IIIa-3	−93.7	−70.4611	−4.06774
IIIb-1	−85.7083	−68.6253	−11.963
IIIb-2	−87.6417	−70.2548	−8.14117
IIIb-3	−94.4958	−63.5041	−1.06333
IIIc-1	−85.5101	−50.2843	−8.09707
IIIc-2	−89.2279	−72.9138	−5.34053

IIIc-3	**−102.53**	**−76.6081**	**−2.56136**
IIId-1	−85.4127	−68.6809	−11.8601
IIId-2	−88.3794	−31.5497	−9.90744
IIId-3	−95.435	−77.5096	−2.82161
Imatinib	−116.362	−73.7364	−4.8365
Linomide	−76.3611	−56.9182	−6.58355
1m17	−112.993	−78.2784	−6.00021

Table 9. MolDock Scores of synthesized compounds 6-substituted-4-hydroxy-1-(2-substituted thiazol-5-yl) quinolin-2(1*H*)-one derivatives [IIIa (1–3)/IIIb (1–3)/IIIc (1–3)/IIId (1–3)] on *S. aureus* DNA Gyrase domain complexed with a Ciprofloxacin inhibitor (PDB ID: 2XCT)for antibacterial docking study.

Compound	MolDock Score	Rereank Score	H-Bond
IIIa-1	−93.555	−72.3784	−11.0466
IIIa-2	−97.8265	−79.223	−8.12065
IIIa-3	−91.0571	−68.1721	−1.30233
IIIb-1	−103.624	−75.6611	−13.6909
IIIb-2	−105.667	−82.0175	−7.70513
IIIb-3	−93.1406	−58.7972	−5.23331
IIIc-1	−104.584	−75.8215	−14.1072
IIIc-2	−105.228	−81.333	−7.64975
IIIc-3	−100.326	−58.5921	−10.463
IIId-1	−95.5846	−70.0187	−10.0994
IIId-2	−96.2145	−63.0514	−8.05509
IIId-3	**−114.722**	**−82.9237**	**−6.13317**
Ciprofloxacin Ligand	−71.706	−47.8567	−3.17295
Norfloxacin	−96.7747	−70.3299	−5.51208

(a). Anticancer Docking study:

Docking of the synthesized compounds for anticancer activity with EGFR-tyrosine kinase domain exhibited well conserved hydrogen bonding with the amino acid residues at the active site. The MolDock scores of the test compounds ranged from −81.5187 to −102.53 while that of linomide was −76.3611. Ligand 4-anilinoquinazoline exhibited MolDock score of −112.993. Imatinib was used as the reference standard for comparison of efficiency and exhibited MolDock score of −116.362. The twelve designed molecules exhibited MolDock score higher than that exhibited by linomide; with compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one **(IIIc-3)** having a highest MolDock score of −102.535. The best poses of compound exhibiting the most promising hydrogen bonding are shown in the Figure 3. These results show that the novel quinoline-2-one derivatives possess higher affinity than linomide towards the active site of the target protein EGFRK.

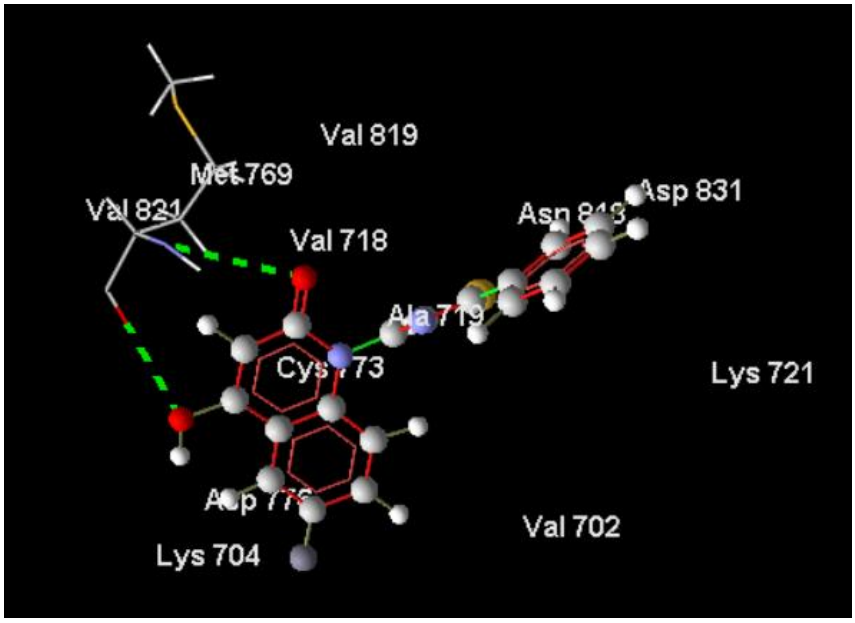


Figure 3. Compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIIc-3) docked in best of its conformation (pose) into the binding site of 1m17. The –O from –C=O at 2nd position of quinolin-2-one moiety forms hydrogen bond -NH of Met 769. The -O of -OH at 4th position of quinolin-2-one moiety forms hydrogen bond -OH of Met 769.

(b). Antibacterial Docking Study:

Docking of synthesised compounds for antibacterial activity with the DNA Gyrase enzyme exhibited well conserved hydrogen bonds with one or more amino acid residues in the active pocket. The MolDock scores of the test compounds 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl) quinolin-2(1*H*)-one derivatives [III(a–d)(1–3)] ranged from −91.0571 to −114.722. Norfloxacin was used as the reference standard for comparison of efficiency and exhibited MolDock score of −96.7747 while Ciprofloxacin ligand exhibited MolDock score of −71.706. The twelve designed molecules exhibited MolDock score higher than that exhibited by ciprofloxacin ligand; with compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one **(IIId-3)** having a highest MolDock score of −114.722. The best poses of compound exhibiting the most promising hydrogen bonding are shown in the Figure 4. These results show that the novel quinoline-2-one derivatives possess higher affinity than ciprofloxacin ligand and standard norfloxacin towards the active site of DNA Gyrase enzyme.

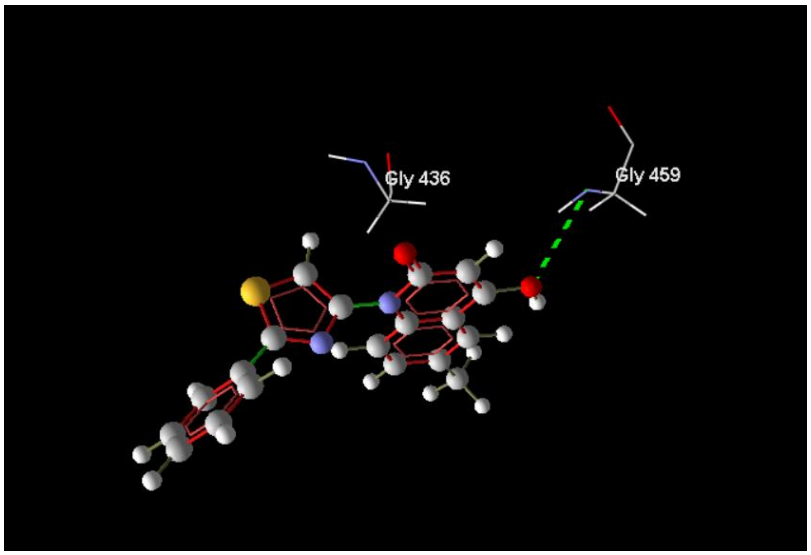


Figure 4. Compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) docked in best of its conformation (pose) into the binding site of 2XCT. The -O of -OH at 4th position of quinoline moiety forms H-bond with -NH of Gly 459.

7. Conclusions

Twelve derivatives of 6-substituted-4-hydroxy-1-(2-substitued thiazol-4-yl)quinolin-2(1*H*)-one **[III(a-d)(1-3)]** were designed, synthesized and characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Selected compounds were evaluated for their in vitro anticancer and antibacterial activity. MDA-MB (Breast cancer) and A549 (Lung cancer) cell lines based upon MTT assay were used for anticancer activity. In vitro antibacterial were determined by the measurement of zone of inhibition and determining the Minimum Inhibitory Concentration (MIC). Further the novel compounds were subjected to in silico docking studies using Molegro Virtual Docker (MVD-2013, 6.0) software.

From the obtained results of the research project, it can be concluded that all synthesized derivatives were found to be more potent against A549 (Lung cancer) cell line as compared to MDA-MB (Breast cancer) cell line. Compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIIc-3) exhibited highest MolDock score (−102.535) which was comparable to that shown by the standard Imatinib (−116.362) for anticancer docking and was found to be the most cytotoxic as compared to the other synthesized derivatives, with IC_{50} values of 397.56 μg/mL against A549 (Lung cancer) cell line whereas the MolDock score of compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) was (−114.722) which was higher to that shown by Ciprofloxacin ligand (−71.706) and standard Norfloxacin (−96.774) for antibacterial docking and was found to be most potent antibacterial agent as compared to other synthesized compounds. However, all synthesized derivatives were found to be a poor antibacterial agent when compared with standard norfloxacin.

Thus, the synthesized derivatives possessed a potential to bind with some of the residues of the active site and can be further developed into potential pharmacological agents.

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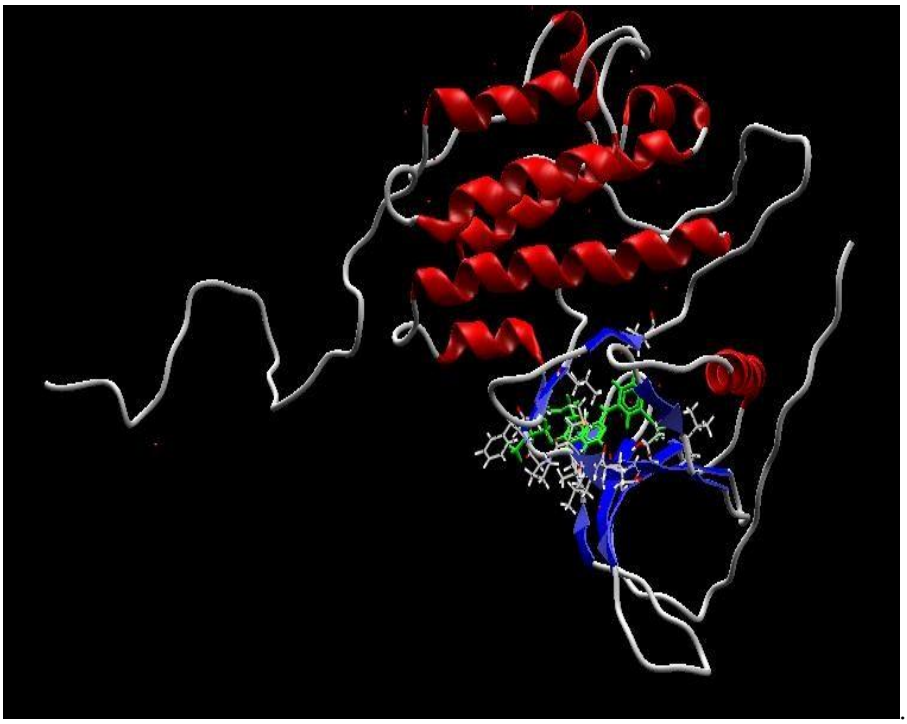

Figure B.1: Structure of EGFR-tyrosine kinase domain complexed. with 4-anilinoquinazoline inhibitor (PDB ID: 1m17).

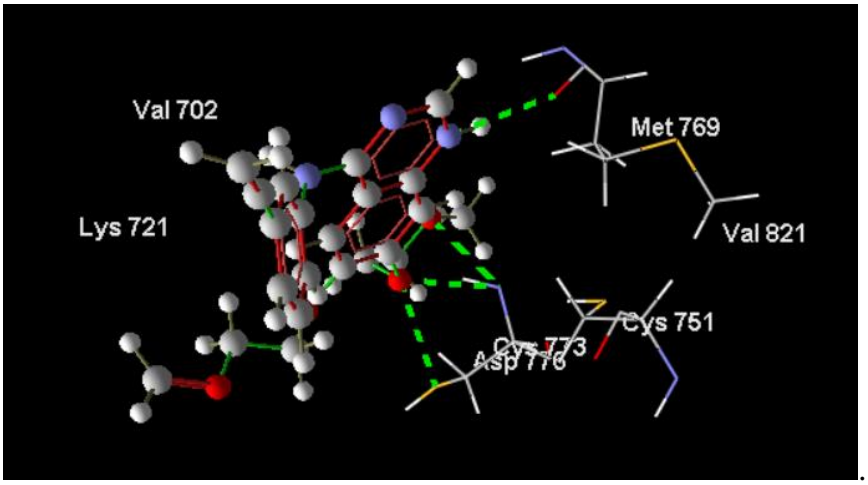

Figure B.2: Ligand 4-anilinoquinazoline docked in best of its conformation (pose) into the binding site of 1m17.
The –N at 1st position of the quinazoline moiety forms hydrogen bonds with –OH of Met 769.
1st and 2nd Etherial oxygen of side chain forms hydrogen bond with -NH of Cys 773.
1st Etherial oxygen of side chain forms hydrogen bond with -SH of Cys 773.
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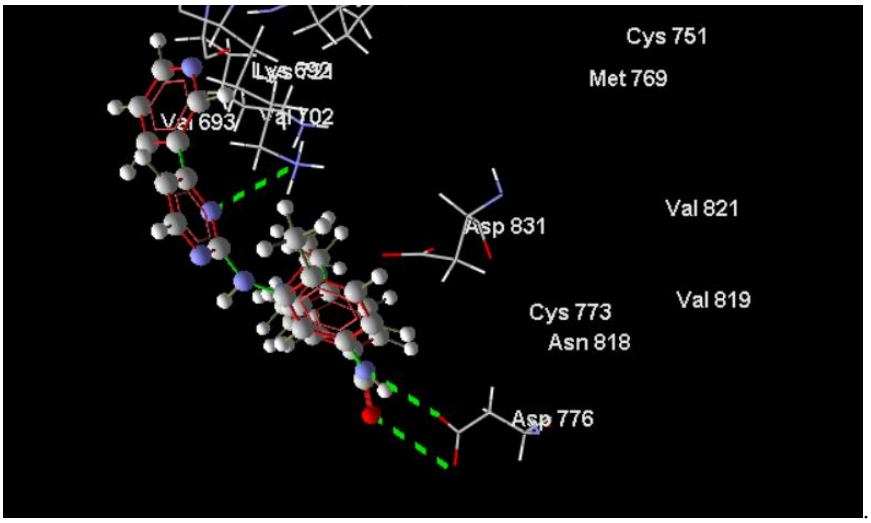

Fig.B.3: Imatinib docked in best of its conformation (pose) into the binding site of 1m17.
The -O and -N of -CONH forms H-bond with -OH of Asp 776.
The -N at 2nd position of pyrimidine ring forms H-bond with -NH of Lys 721.

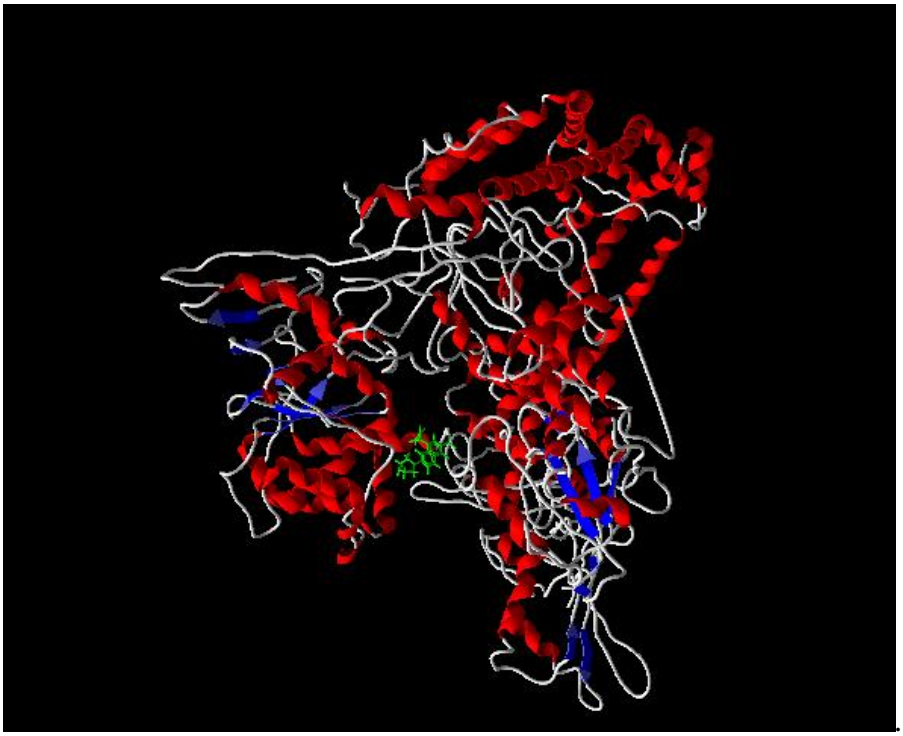

Fig C.1: Shows the binding of the Ciprofloxacin ligand with the DNA Gyrase domain.

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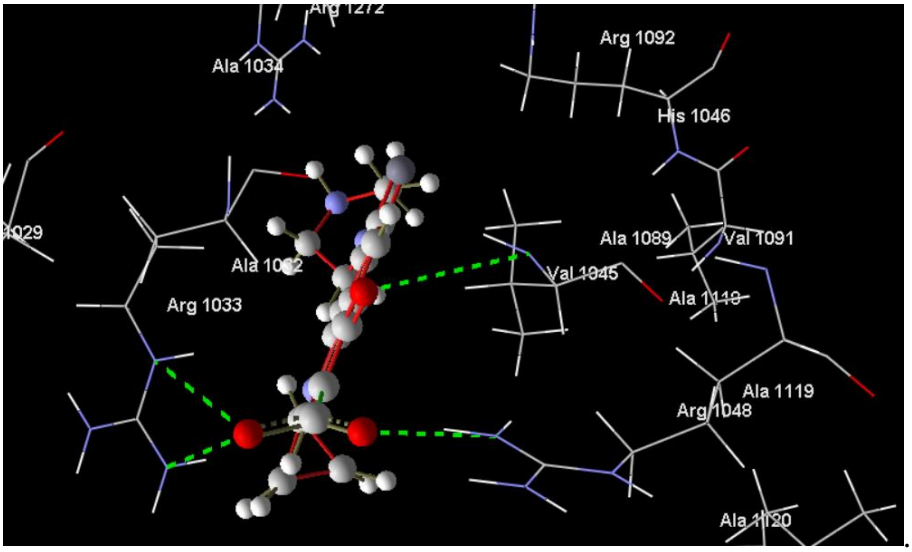

Fig C.2: Ciprofloxacin ligand docked in best of its conformation (pose) into the binding site of 2XCT.
The -O of -C=O at 4th position of quinoline moiety forms H-bond with -NH of Val 1045.
The -Carbonyl oxygen at 3rd position of quinoline moiety forms H-bond with -NH of Arg 1048.
The -O of -COOH at 3rd position of quinoline moiety forms H-bond with -NH of Arg 1033.

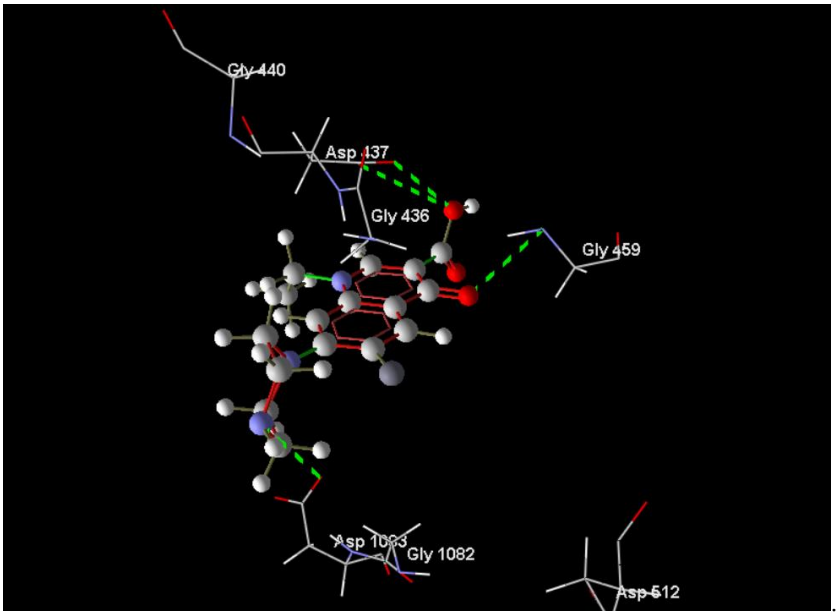

Fig.C.3: Norfloxacin docked in best of its conformation (pose) into the binding site of 2XCT.
The -O of -C=O at 2nd position of quinoline moiety forms H-bond with -NH of Gly 459.
The -O of -OH at 4th position of quinoline moiety forms H-bond with -OH of Asp 437.
The -N at 4th position of piperazine ring forms H-bond with -OH of Asp 1083.