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"DESIGN, SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED THIAZOLE DERIVATIVES OF LINOMIDE ANALOGUES FOR ANTICANCER AND ANTIBACTERIAL ACTIVITY"

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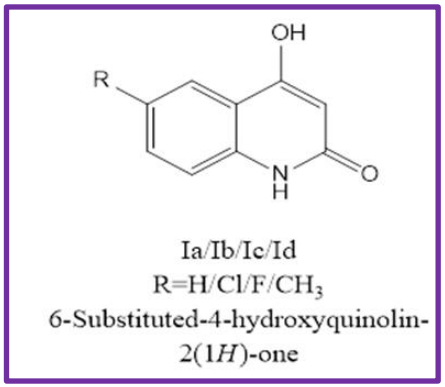
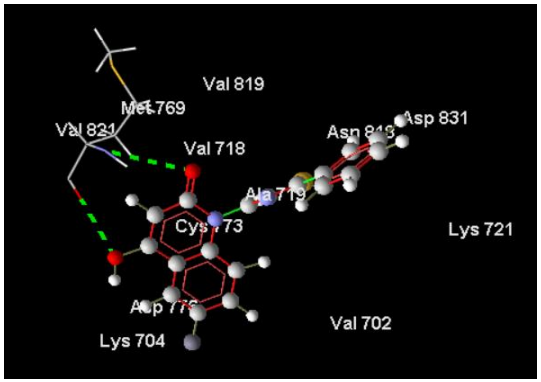
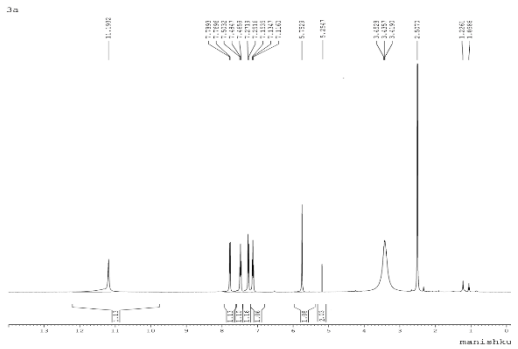
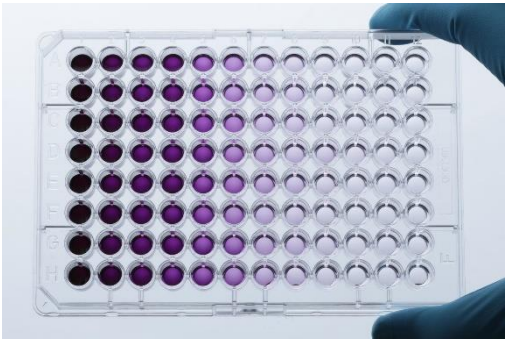
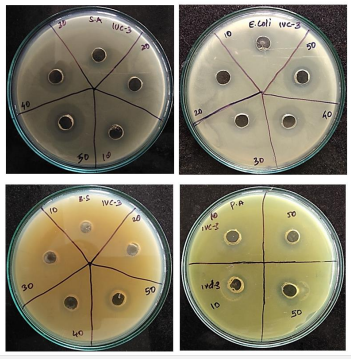


Ia/Ib/Ic/Id
R=H/Cl/F/CH_3
6-Substituted-4-hydroxyquinolin-2(1*H*)-one









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 derivatives were capable of binding with some of the amino acid residues at the active site and thus can be further developed into new therapeutic agents.

Keywords: Anticancer; Antibacterial; DNA Gyrase protein; EGFRK protein; Molegro Virtual Docker; Quinolin-2-one.

Introduction:

Cancer is characterized by an abnormal and uncontrolled, division of cells, which produces tumours and invades adjacent normal tissues.

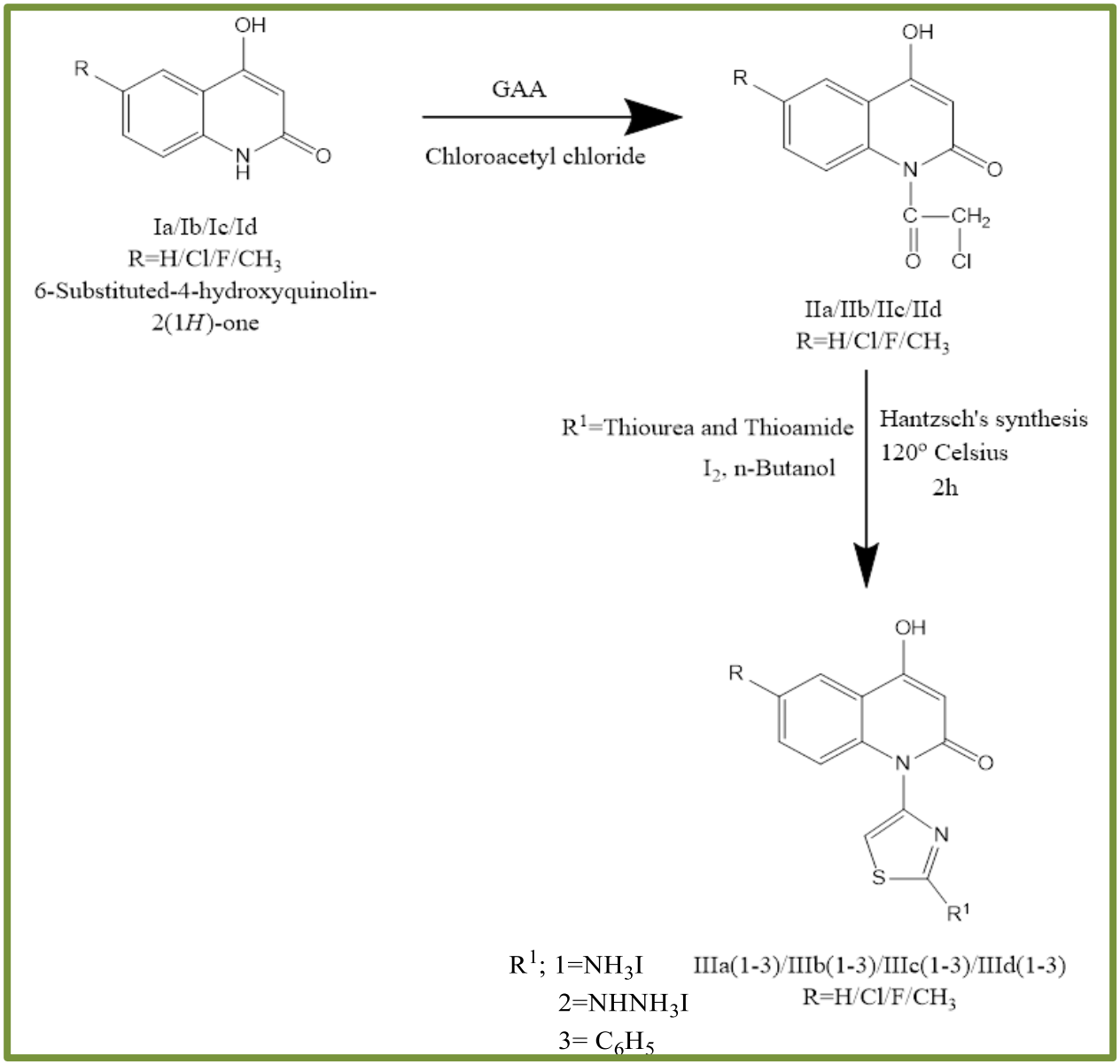
Cancer is the second leading cause of death globally. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and thyroid cancer are the most common among women.

Antimicrobials are probably one of the most successful forms of chemotherapy in the history of medicine.

In recent decades the activity of conventional antibiotics against pathogenic bacteria has decreased due to the expansion of bacterial resistance. Overuse and misuse of antibiotics has led to a rise in antibiotic resistance.

Therefore, antibiotic resistance problem demand 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.

Experimental section:



SCHEME:

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

Docking studies

- Molecular docking studies of the title were carried out using Molegro Virtual Docker (MVD-2013, 6.0).
- The coordinate file and crystal structure of Epidermal Growth Factor Receptor tyrosine kinase domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) for anticancer activity
- *S.aureus* DNA Gyrase domain complexed with a ciprofloxacin inhibitor (PDB ID: 2XCT) were obtained from the RCSB-PDB website for antibacterial activity.

Biological activity

Anticancer activity: *In vitro* anticancer activity of 6-substituted-4-hydroxy-1-(2-substituted thiazol-4-yl)quinolin-2(1*H*)-one derivatives [III(a-d)(1-3)] was performed by MTT assay on MDA-MB (Breast cancer) and A549 (Lung cancer) cell lines. Erlotinib was used as reference standard drug.

MTT (Cytotoxicity) Assay:

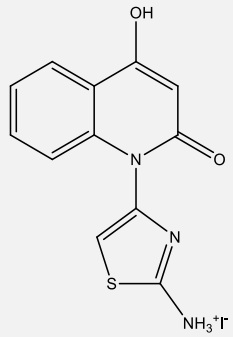
In vitro growth inhibition effect of test compound was examined by MTT assay which is a colorimetric or spectrophotometric method that measures reduction of MTT into "Formazan blue" by living cells.

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).

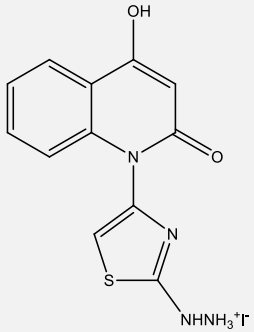
- For Zone of Inhibition, drug solution was used at five different concentrations of 10, 20, 30, 40 and 50mg in gram positive and gram negative strains and compared with the reference standard drug Norfloxacin.
- MIC of the synthesized derivatives were determined in the range of concentrations from 1-50mg/mL.

Results and discussion:

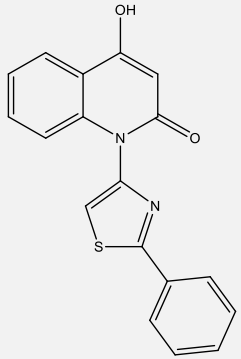
IIIa-1



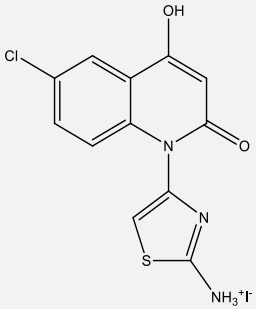
IIIa-2



IIIa-3



IIIb-1



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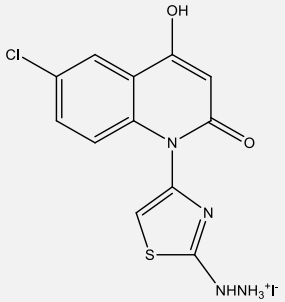
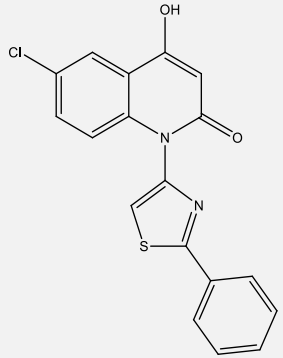


IIIb-3



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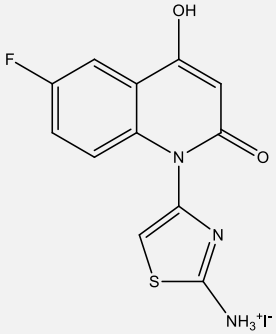

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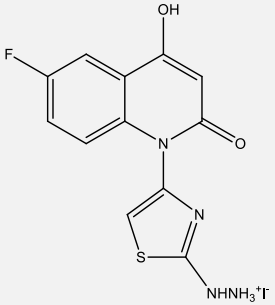
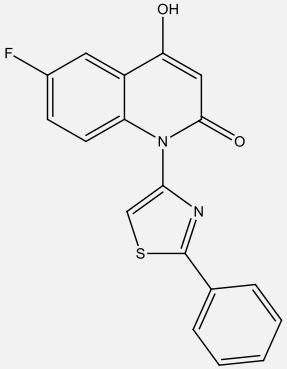
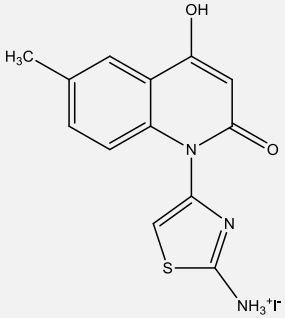


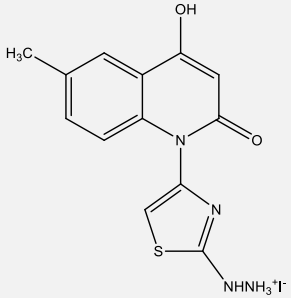
IIIc-3



IIId-1



IIId-2



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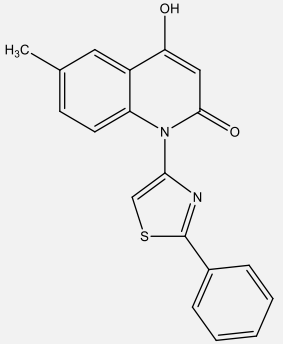
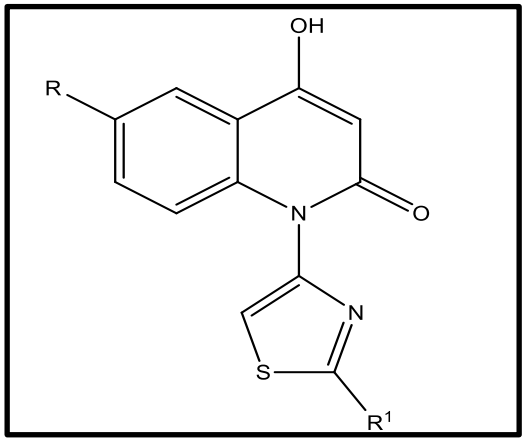
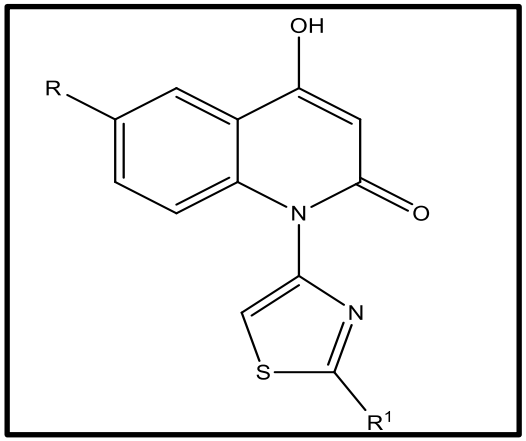


The physical data of 6-substituted- 4-hydroxy-1-(2-substitued thiazol-4- yl)quinolin-2(1*H*)-one {III(a-d)(1-3)}:



Compound	R	R^1	Mol. Formula	M.W	M.P(°C)	% Yield	Rf value	λ_{max}(nm)
IIIa-1	H	NH_3I	$C_{12}H_{10}N_3O_2SI$	387	>300	71	0.74	231.8
IIIa-2	H	$NHNH_3I$	$C_{12}H_{11}N_4O_2SI$	402	>300	89	0.77	216.8
IIIa-3	H	Ph	$C_{18}H_{12}N_2O_2S$	320	>300	74	0.72	231.8
IIIb-1	Cl	NH_3I	$C_{12}H_9ClN_3O_2SI$	421.5	>300	68	0.75	223.0
IIIb-2	Cl	$NHNH_3I$	$C_{12}H_{10}ClN_4O_2SI$	436.5	>300	90	0.69	226.8
IIIb-3	Cl	Ph	$C_{18}H_{11}ClN_2O_2S$	354.5	>300	76	0.71	232.8

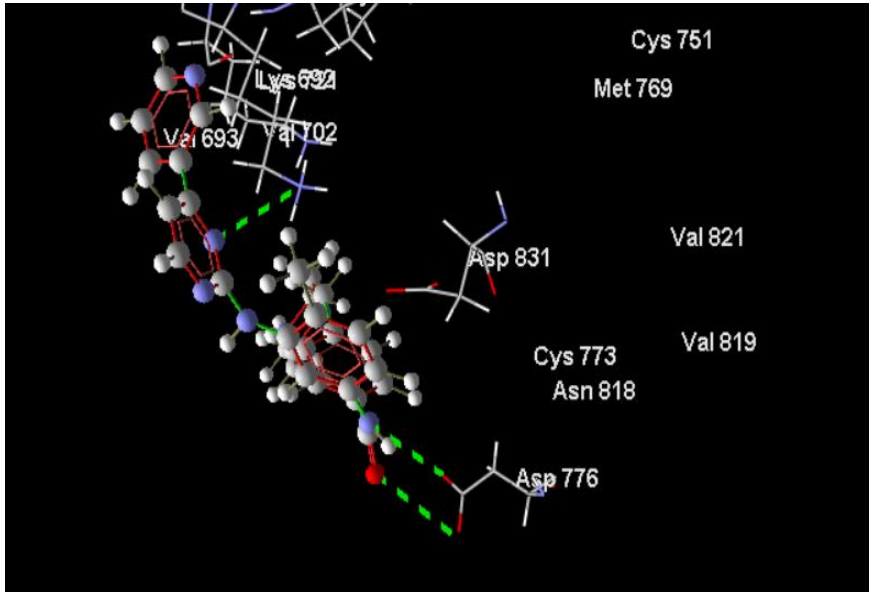
The physical data of 6-substituted- 4-hydroxy-1-(2-substitued thiazol-4- yl)quinolin-2(1*H*)-one {III(a-d)(1-3)}:



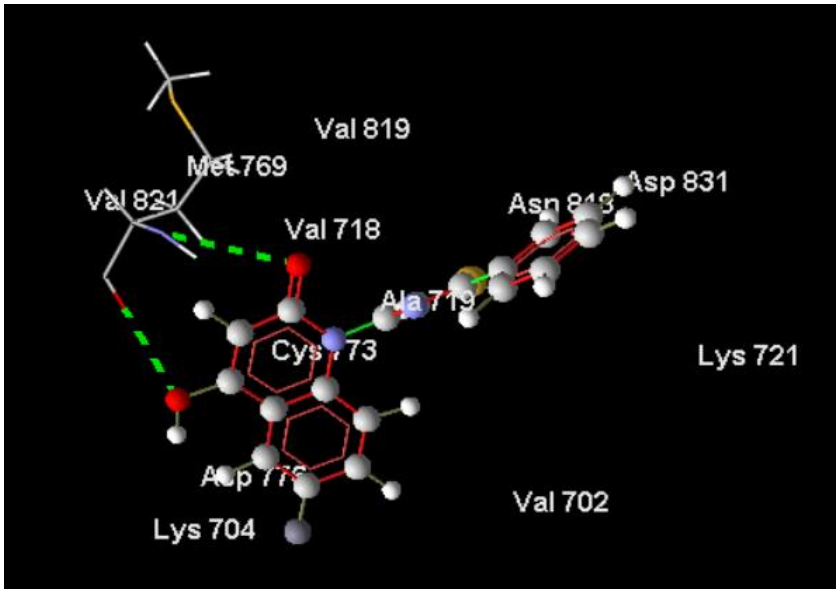
Compound	R	R^1	Mol. Formula	M. W	M.P(°C)	% Yield	Rf value	λ_{max}(nm)
IIIc-1	F	NH_3I	$C_{12}H_9FN_3O_2SI$	405	>300	65	0.77	225.0
IIIc-2	F	$NHNH_3I$	$C_{12}H_{10}FN_4O_2SI$	420	>300	95	0.70	230.0
IIIc-3	F	Ph	$C_{12}H_{10}FN_4O_2S$	293	>300	75	0.73	229.8
IIId-1	CH_3	NH_3I	$C_{13}H_{12}N_3O_2SI$	401	>300	63	0.73	234.8
IIId-2	CH_3	$NHNH_3I$	$C_{13}H_{13}N_4O_2SI$	416	>300	88	0.71	218.6
IIId-3	CH_3	Ph	$C_{19}H_{14}N_2O_2S$	334	>300	66	0.68	232.4

Fig No 01: Docking of standard Imatinib and compound IIIc-3 in best of its conformation with binding site of 1m17

Imatinib



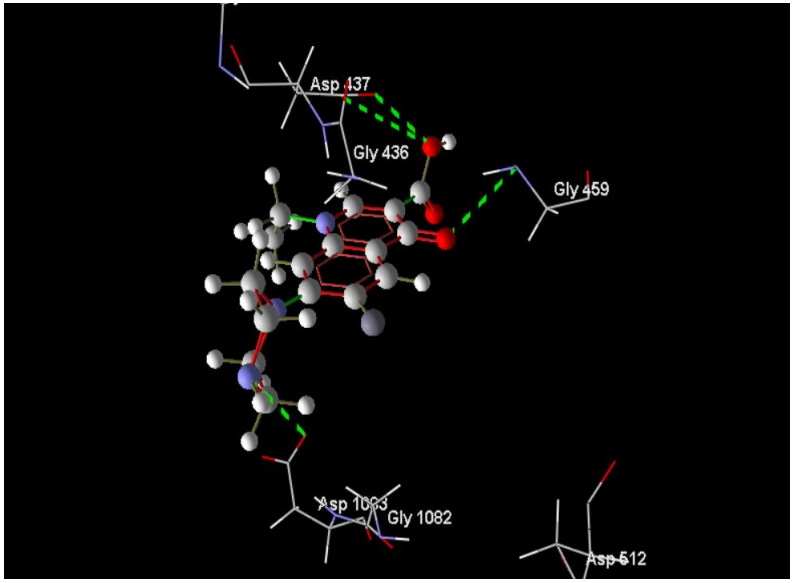
IIIc-3



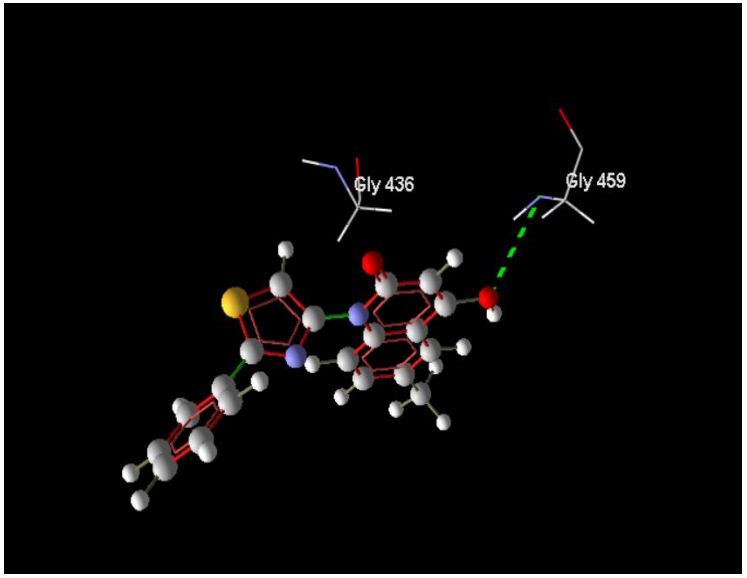
Compound 6-fluoro-4-hydroxy-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIIc-3) exhibited highest MolDock score (-102.535) on EGFR tyrosine kinase domain complexed with a 4-anilinoquinazoline inhibitor (PDB ID: 1m17) for anticancer docking study and was comparable with that of standard Imatinib which exhibited MolDock score of -116.362.

Fig No 02: Docking of standard Norfloxacin and compound IIId-3 in best of its conformation with binding site of 2XCT

Norfloxacin



IIId-3



Compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) was having highest MolDock score of (-114.722) on *S.aureus* DNA Gyrase domain complexed with a Ciprofloxacin inhibitor (PDB ID: 2XCT) for antibacterial docking study and was higher than the MolDock score of standard Norfloxacin which exhibited MolDock score of -96.7747.

TABLE NO 1: **IC_{50} VALUES OF SYNTHESISED COMPOUNDS ON A549 CELL LINE**

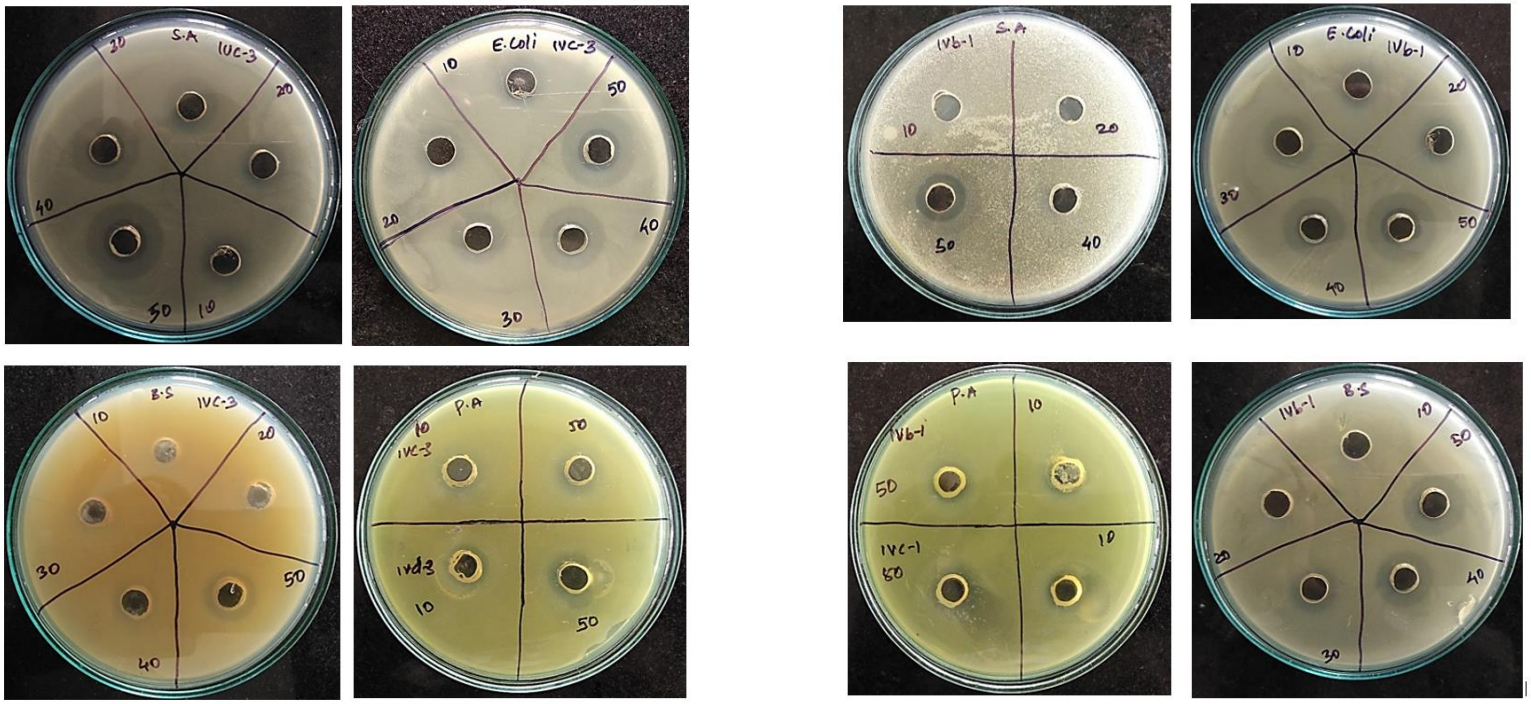
Compound	IC_{50} (µg/ml)
IIIa-1	353.87
IIIa-2	377.32
IIIc-3	397.56
IIId-1	346.12
Imatinib	337.61

TABLE NO 2: **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

Fig No 03: ANTIBACTERIAL ACTIVITY BY ZONE OF INHIBITION

(IIId-3) **(IIIb-1)**



Antibacterial activity of compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) and 4-(6-chloro-4-hydroxy-2-oxoquinolin-1(2*H*)-yl)thiazol-2-aminium iodide (IIIb-1) respectively against *S.aureus*, *B.subtilus*, *E.coli*, *P.aeruginosa*

TABLE NO 3: ANTIBACTERIAL ACTIVITY BY 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

Conclusions:

- 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 and was found to be the most cytotoxic as compared to the other synthesized derivatives against A549 (Lung cancer) cell line.
- MolDock score of compound 4-hydroxy-6-methyl-1-(2-phenylthiazol-4-yl)quinolin-2(1*H*)-one (IIId-3) exhibited highest MolDock score 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.

Acknowledgments:

- ✓ I also take this opportunity to express a deep sense of gratitude to the Director, SAIF, Panjab University Chandigarh for providing necessary spectra and analysis on the desired time.
- ✓ I wish to acknowledge the authorities of **Dr. Prabhakar Kore Basic Science Research Centre (BSRC), Belgavi** for providing the biological activity facility to carry out the anti-cancer activity.