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Design, Synthesis, Characterization, Molecular Docking Studies of Novel Quinazolinone Derivatives as Potential EGFR Inhibitors

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Abstract
A series of some novel quinazolinone derivatives III-3(a-j) were synthesized by a conventional method via cyclization and Schiff's base mechanism. All the synthesized compounds gave a good yield between 78-86%. Final structure was confirmed by FT-IR, LC-MASS and ^{1}H NMR analytical data. The novel Quinazolinone derivatives (III-3a-3j) are screened for anticancer activity against MCF-7, SKVO3 Cell lines by MTT assay method. From the resulting data, the compound **III-3i** (IC_{50} value of **0.035 µM** against MCF-7 and **0.1 µM** against SKVO3) exhibited good anticancer activity compared with Doxorubicin as standard. The molecular docking studies of these novel Qunazolinone showed good agreement with the biological results their binding pattern and affinity towards the active site of EGFR was examination.

Keywords
Quinazoline, Molecular Docking, Anti-cancer activity, MCF-7 and SKVO3 Cell lines, Doxorubicin.

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INTRODUCTION:
In synthetic chemistry conventional method plays a vital role in the progress of chemical science. Hybridization of bioactive natural and synthetic compounds is one of the most promising novel approaches for the design of hit and lead compounds with new molecular structures. Design of new drug-like small molecules based on the pharmacologically active scaffolds is a rational and a promising direction in modern medicinal chemistry. A number of compounds have been synthesized by the combination of biologically active pharmacophores and utilized by medicinal chemists to develop novel therapeutics agents with a broad range of pharmacological activities (1-5). Some Qunazolinone conjugates showed remarkable anticancer activity with 50% growth inhibition (GI50) values of 0.02 µM and 0.49 µM against central nervous system (SNB-75) and leukemia (K-562) cell lines, respectively (6). The heterocyclic compounds with five-membered rings bearing both sulphur and nitrogen atoms are privileged essential organic structural scaffolds in compounds used as medicinal drugs[7-9]. Due to their high potency and efficacy towards therapeutic properties, tremendous efforts have been to novel quinazolinone bearing derivatives. All these structural motifs are having numerous therapeutic properties such as anti-inflammatory, antihypertensive α-blocking, anti-leishmanial, neuroprotective agents in Parkinson's and Alzheimer's disease [10-12]. The qinazolinone ring systems is a beneficial structural element in medicinal chemistry and has wide-ranging application in the drug development process. Among the different Schiff's basses linked with other hetero nucleus compounds known in the literature for their potent biological active compounds with a very wide range of therapeutic properties

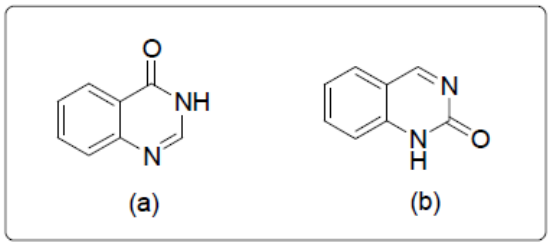


Fig.2-Quinazolinone and 4-Quinazolinone

In view of these research, great significance of these quinazolinone hybrids in continuation of our work on biologically active molecules [13-15], here in the present work an attempt has been made to synthesize newly novel quinazolinone hybrids, with the expectation to procure new molecules with strengthen biological activity.

EXPERIMENTAL SECTION

Material and Methods: All the chemicals used in the synthesis of the final and intermediates were of A.R grade and procured from the Merck and LOBA chemicals. All the synthesized quinazolinone derivatives(III-3a-3j) were characterized by melting point determination using Veergo digital melting point apparatus in open capillary tubes and were uncorrected. The IR spectra were recorded using Perkin Elmer FTIR spectrophotometer using KBr pellets techniques, and ^{1}HNMR spectra of the synthesized compounds in deuterated DMSO were recorded on BRUKER AVANCE II 400MHz NMR Spectrometer instrument using TMS as the internal standard. Mass spectra were recorded using LC-MSD-Tranp- SL2010A SHIMADZU using Dimethyl-sulphoxide (DMSO) as a solvent. TLC was performed using silica gel GF254 coated plates of 0.25 mm thickness. Ethyl acetate and n-Hexane (3:7).

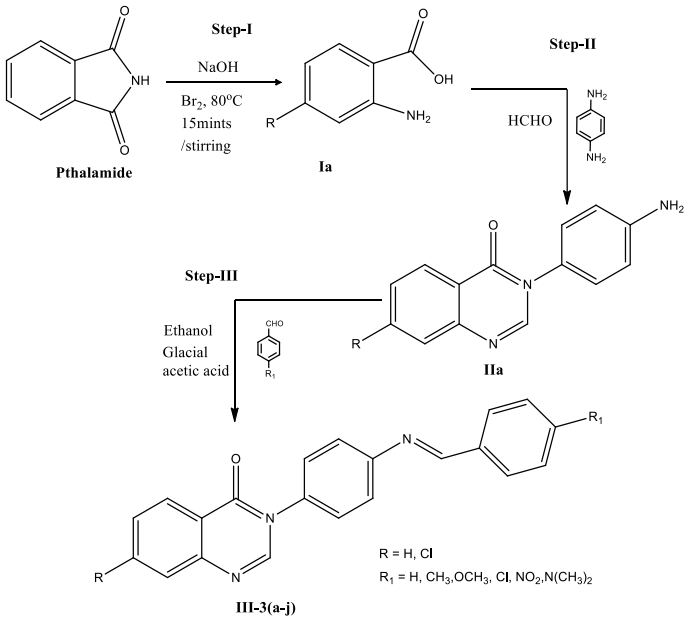
GENERAL PROCEDURES:

Step-1: Synthesis of Antranilic acid: To take Bromine (4.2ml, 0.082M) is added in one lot to a cooled solution of NaOH(15gm). The mixture is shaken till all the bromine has reacted. The temperature is maintained below 0^{O}c and finally powdered phthalamide (12g, 0.082 M) is added in one lot, the mixture is shaken vigorously and cooled. Then add cooled solution of NaOH (11g NaOH in 40ml water) and the reaction mixture shaken and temp rises to about 70^{o}c, the reaction mixture is warmed to 80^{o}c for 5min. then add 30ml of con.HCl to the clear solution with constant stirring until the solution is just neutral, then add glacial acetic acid(10-12ml) to get the antranilic acid. The separated acid is filtered, washed with cold water and recrystallized by using hot water.

Step-2: Synthesis of 3-(4-aminophenyl)-7-substitutedquinazolin-4(3H)-one: The equimolar amounts 0.01 moles of Antranilic acid, formaldehyde and p-Phenylenediamine were mixed together and dissolved in 25ml of ethanol in round bottomed flask. The reaction mixture was stirred for 10mints and refluxed for 5-7hrs. The progress of the reaction was monitored by TLC. After the completion of the reaction of the flask content was poured into in 100ml of cold water to get corresponding compound **2**.

Step-3: Synthesis of 7-substituted-3-(4-((4-substituted benzylidene) amino) phenyl) quinazolin-4(3H)-one. Substituted benzaldehydes (0.01 mol) were taken in a mixture of compound **2** (0.01 mol) and glacial acetic acid (5 mL) and Ethanol 30ml, then the reaction mixture was refluxing for 3hrs. The progress of the reaction was monitored by TLC (Hexane: EtoAc 7:3). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off and washed with hexane and recrystallized from methanol to give crystalline solid.

Compound.III-3a: 3-(4-(benzylideneamino) phenyl) quinazolin-4(3H)-one. IR(ν cm^{-1}): 3058(C-H *Str*, Ar), 2973, 2826(C-H Str, Aliphatic), 1705(C=O *Str,* quinolone),1536(C=H, Ar), 1344(C=C *Str*), 1070(C-C *Str*).^{1}H-NMR(DMSO) $\delta\delta$ ppm:9.5373(CH=N *Str,* benzyl Proton), 8.3734(d, 2H, Ar-H), 7.9005-7.8854(d, 2H, Ar-H), 7.8643-7.7634(d, 2H, Ar-H), 7.6903-7.6821(d, 2H, Ar-H), 7.6754-7.5463(d, 2H, Ar-H), 7.4894-7.4703(t, 2H, Ar-H).Mass (LC-MS): m/z 325.12(M), 326.21(M+1, 100%).



Scheme-I

Compound.III-3b: 3-(4-((4-methylbenzylidene) amino)phenyl) quinazolin-4(3H)-one: IR(ν cm^{-1}): 3073(C-H *Str*, Ar), 2984, 2897(C-H Str, Aliphatic), 1708(C=O *Str,* quinazolin),1548(C=H, Ar), 1372(C=C *Str*), 1024(C-C *Str*).^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.8234(CH=N *Str,* benzyl Proton), 8.3898-8.2763(d, 2H, Ar-H), 8.1098(s, 1H, Ar-H), 7.8973-7.8034(t, 2H, Ar-H), 7.6902-7.6489(d, 2H, Ar-H), 7.5452-7.5372(d, 2H, Ar-H), 7.5298-7.5192(d, 2H, Ar-H), 7.1018-7.1002(d, 2H, Ar-H), 2.0272(s, 3H, Ar-CH_3). Mass (LC-MS): m/z 339.14(M), 340.31(M+1, 100%).

Compound.III-3c: 3-(4-((4-chlorobenzylidene) amino) phenyl) quinazolin-4(3H)-one:

IR(ν cm^{-1}): 3018(C-H *Str*, Ar), 2937(C-H Str, Aliphatic), 1700(C=O *Str,* quinazolin),1529(C=H, Ar), 1444(C=C *Str*), 1153(C-C *Str*), 860(C-Cl *Str*, Ar-Cl). ^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.6739(CH=N *Str,* immine proton), 8.0674(s, 1H, Ar-H), 7.9093-7.9003(d, 2H, Ar-H), 7.7873-7.6900(d, 2H, Ar-H), 7.5954-7.5673(d, 2H, Ar-H), 7.5253-7.5000(d, 2H, Ar-H), 7.4893-7.4783(d, 2H, Ar-H), 7.4689-7.4563(d, 2H, Ar-H). Mass (LC-MS): m/z 359.08(M), 360.32(M+1, 100%), 361.04(M+2, 30%).

Compound.III-3d: 3-(4-((4-(dimethylamino) benzylidene) amino) phenyl) quinazolin-4(3H)-one. IR(ν cm^{-1}):

3023(C-H *Str*, Ar), 2942, 2823(C-H Str, Aliphatic), 1703(C=O *Str,* quinazolin),1538(C=H, Ar), 1383(C=C *Str*), 1225(C-C *Str*). ^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.7843(CH=N *Str,* immine proton), 8.4984-8.3873(d, 2H, Ar-H), 7.9023-7.8673(d, 2H, Ar-H), 7.7884-7.7802(d, 2H, Ar-H), 7.6923-7.6899(d, 2H, Ar-H), 7.6763-7.5880(d, 2H, Ar-H), 7.5792-7.4834(t, 2H, Ar-H), 7.1564(s, 1H, Ar-H), 3.1174(s, 6H, Ar-$N(CH_3)_2$). Mass (LC-MS): m/z 368.16(M), 369.30(M+1, 100%).

Compound.III-3e: 3-(4-((4-methoxybenzylidene) amino) phenyl) quinazolin-4(3H)-one: IR (ν cm^{-1}): 3067(C-H *Str*, Ar), 2954, 2876(C-H Str, Aliphatic), 1712(C=O *Str,* quinazolin),1545(C=H, Ar), 1329(C=C *Str*), 1198(C-C *Str*). ^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.6543(CH=N *Str,* immine proton), 8.3862-8.2343(d, 2H, Ar-H), 8.1392-8.1003(d, 2H, Ar-H), 7.9832-7.8032(d, 2H, Ar-H), 7.7632-7.6032(d, 2H, Ar-H), 7.5773-7.4983(d, 2H, Ar-H), 7.3784-7.2983(t, 2H, Ar-H), 7.2903(s, 1H, Ar-H), 3-7654(s, 3H, Ar-OCH_3). Mass (LC-MS): m/z 355.13(M), 356.21(M+1, 100%).

Compound.III-3f: 3-(4-(benzylideneamino) phenyl)-7-chloroquinazolin-4(3H)-one: IR(ν cm^{-1}): 3034(C-H *Str*, Ar), 2939(C-H Str, Aliphatic), 1707(C=O *Str,* quinazolin),1538(C=H, Ar), 1376(C=C *Str*), 1049(C-C *Str*), 873(C-Cl *Str*, Ar-Cl). ^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.6909(CH=N *Str,* immine proton), 7.9093-7.9003(s, 1H, Ar-H), 7.7873-7.5892(d, 2H, Ar-H), 7.5783-7.5109(d, 2H, Ar-H), 7.5012-7.5000(d, 2H, Ar-H), 7.4893-7.4563(d, 2H, Ar-H), 7.4402-7.3890(t, 3H, Ar-H). Mass (LC-MS): m/z 359.08(M), 360.32(M+1, 100%), 361.04(M+2, 30%).

Compund.III-3g: 7-chloro-3-(4-((4-methylbenzylidene) amino) phenyl) quinazolin-4(3H)-one:

IR(ν cm^{-1}): 3067(C-H *Str*, Ar), 2956(C-H Str, Aliphatic), 1710(C=O *Str,* quinazolin),1554(C=H, Ar), 1321(C=C *Str*), 1109(C-C *Str*), 799(C-Cl *Str*, Ar-Cl). ^{1}H-NMR(DMSO) $\delta\delta$ ppm: 9.5876(CH=N *Str,* immine proton), 7.7894(s, 1H, Ar-H), 7.6732-7.6003(d, 2H, Ar-H), 7.5983-7.5293(d, 2H, Ar-H), 7.4873-7.4021(d, 2H, Ar-H), 7.3894-7.3092(d, 2H, Ar-H), 7.2192-7.2002(s, 1H, Ar-H), 2.0324(s, 3H, Ar-CH_3). Mass (LC-MS): m/z 373.10(M), 374.51(M+1, 100%), 375.20(M+2, 30%).

Compound.III-3h: 7-chloro-3-(4-((4-methoxybenzylidene) amino) phenyl) quinazolin-4(3H)-one: IR (ν cm^{-1}): 3098(C-H *Str*, Ar), 2923, 28973(C-H Str, Aliphatic), 1704(C=O *Str,* quinazolin),1498(C=H, Ar), 1302(C=C *Str*), 1112(C-C *Str*), 803(C-Cl *Str*, Ar-Cl). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 9.6873(CH=N *Str,* immine proton), 7.9873(s, 1H, Ar-H), 7.8796-7.8032(d, 2H, Ar-H), 7.7932-7.6843(d, 2H, Ar-H), 7.5098-7.4213(d, 2H, Ar-H), 7.4873-7.3129(d, 2H, Ar-H), 7.1023-7.0342(s, 1H, Ar-H), 3.6533-3.5093(s, 3H, Ar-OCH_3). Mass (LC-MS): m/z 389.09(M), 390.32(M+1, 100%), 391.36(M+2, 30%).

Comound.III-3i: 7-chloro-3-(4-((4-(dimethylamino) benzylidene) amino) phenyl) quinazolin-4(3H)-one: IR(ν cm^{-1}): 3065(C-H *Str*, Ar), 2956, 2865(C-H Str, Aliphatic), 1712(C=O *Str,* quinazolin), 1487(C=H, Ar), 1315(C=C *Str*), 1205(C-C *Str*), 812(C-Cl *Str*, Ar-Cl). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 9.4532(CH=N *Str,* immine proton), 7.8892(s, 1H, Ar-H), 7.7834-7.7001(d, 2H, Ar-H), 7.6743-7.5984(d, 2H, Ar-H), 7.4673-7.4032(d, 2H, Ar-H), 7.2873-7.1209(d, 2H, Ar-H), 6.9876-6.8933(s, 1H, Ar-H), 3.4232-3.2123(s, 6H, Ar-$N(CH_3)_2$). Mass (LC-MS): m/z 405.12(M), 406.21(M+1, 100%), 407.12(M+2, 30%).

Table. 1. Physical properties(III-3a-3j)

S.NO	R	R_1	Mol.For	Mol.Wt	M.P(^{O}C)	%Yield	Rf
III-3a	H	H	$C_{21}H_{15}N_3O$	325.12	177-179	84	0.67
III-3b	H	CH_3	$C_{22}H_{17}N_3O$	339.14	203-205	78	0.59
III-3c	H	Cl	$C_{21}H_{14}N_3OCl$	359.08	233-235	86	0.78
III-3d	H	$N(CH_3)_2$	$C_{23}H_{20}N_4O$	368.16	201-203	80	0.66
III-3e	H	OCH_3	$C_{23}H_{17}N_3O$	355.13	196-198	76	0.53
III-3f	Cl	H	$C_{21}H_{14}N_3OCl$	359.08	219-221	83	0.81
III-3g	Cl	CH_3	$C_{21}H_{15}N_3OCl$	373.10	183-185	85	0.71
III-3h	Cl	OCH_3	$C_{22}H_{16}N_3O_2Cl$	389.09	167-169	81	0.65
III-3i	Cl	$N(CH_3)_2$	$C_{23}H_{19}N_4OCl$	402.12	189-191	74	0.72
III-3j	Cl	Cl	$C_{21}H_{13}N_3OCl_2$	393.04	211-213	82	0.62

Compound.III-3j:
7-chloro-3-(4-((4-chloro benzylidene) amino) phenyl) quinazolin-4(3H)-one: IR (ν cm^{-1}): 3087(C-H *Str*, Ar), 2945, 2877(C-H Str, Aliphatic), 1709(C=O *Str,* quinazolin), 1498(C=H, Ar), 1321(C=C *Str*), 1223(C-C *Str*), 799(C-Cl *Str*, Ar-Cl). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 9.6764(CH=N *Str,* immine proton), 7.9806(s, 1H, Ar-H), 7.8234-7.8032(d, 2H, Ar-H), 7.7843-7.6809(d, 2H, Ar-H), 7.5674-7.5098(d, 2H, Ar-H), 7.4321-7.3409(d, 2H, Ar-H), 6.9231-6.7896(s, 1H, Ar-H). Mass (LC-MS): m/z 393.21(M), 394.32(M+1, 100%), 395.02(M+2, 30%).

Pharmacological activity: Anticancer activity [16-18]: MTT Assay is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol- 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The assay depends both on the number of cells present and, on the assumption, that dead cells or their products do not reduce tetrazolium. Cell viability was evaluated by the MTT Assay with three independent experiments with six concentrations of compounds in triplicates. Cells were trypsinized and preform the trypan blue assay to know viable cells in cell suspension. Cells were counted by haemocytometer and seeded at density of 5.0 X 10^3 cells / well in 100 µl media in 96 well plate culture medium and incubated overnight at 37 ^{0} C. After incubation, take off the old media and add fresh media 100 µl with different concentrations of test compound in represented wells in 96 plates. After 48 hrs., Discard the drug solution and add the fresh medic with MTT solution (0.5 mg / $Ml^{-1)}$ was added to each well and plates were incubated at 37 ^{0} C for 3 hrs. At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula.

$$\% \text{ Inhibition} = \frac{100\ (\text{Control} - \text{Treatment})}{\text{Control}}$$

The Ic50 value was determined by using linear regression equation i.e. y =mx+c. Here,
y = 50, m and c values were derived from the viability graph.

Molecular Docking Studies [19-20]. The 2D structures of 8 compounds were generated from the ACD/Chemsketch Software. The generated ligands cleaned and performed 3D optimization then saved in the MDL Molfile format. The ligands were then converted to a PDBQT file format using the Open Babel chemistry toolbox. The three-dimensional (3D) structure of Epidermal Growth Factor Receptor tyrosine kinase (PDB ID: 1M17) was downloaded from Brook Heaven Protein Data Bank

(https://www.rcsb.org) and saved as a Brookhaven protein data bank file and the structure was optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using AUTODOCK suite of MGL Tools.

Auto dock Vina was used for molecular docking studies. A grid was generated around the co-crystallized ligand. The co-ordinates (x = 20.671, y = -0.422, z = 53.244) were generated with the help of MGL Tools & Pharmit: interactive exploration of chemical space (http://pharmit.csb.pitt.edu/). Prepared pdbqt files for both target & ligands. and docking performed in the absence of water molecules for all 8 molecules. The molecules were analysed after docking and visualized in the discovery studio for the interactions with the active site amino acids. Binding interactions and efficiency of the binding were calculated in terms of dock Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Vander Waals energy, freezing rotatable bonds and polar interactions with receptor.

RESULTS AND DISCUSSION:

Chemistry: A series of some novel quinazolinone derivatives III-3(a-j) were synthesized by a conventional method via cyclization and Schiff's base mechanism. All the synthesized compounds gave a good yield between 78-86%. Final structure was confirmed by FT-IR, LC-MASS and ^{1}H NMR analytical data. Synthesis method was involved cyclisation and Schiff's bases mechanism between substituted anthranilic acid with 4-amino aniline to form IIa compound. Then IIa compound we're undergone by the Schiff's base mechanism with substituted Benzaldehyde to give final novel Quinazolinone derivatives (III3a-3j). Finally, all the synthesized compounds were characterized by the physical data **(Table.1)** and spectral properties.

Anticancer activity: The novel Quinazolinone derivatives was tested for their anticancer activity against two cancer cell lines like MCF-7 and SKVO3 by using MTT assay method and doxorubicin as a standard drug. The results of anticancer screening of novel quinazolinone derivatives were expressed as IC_{50} values are summarized in **Table 2**.

Table.2. Anticancer activity of novel Quinzolinone derivatives (III-3a-3j) on MCF-7 and SKVO3 Cell lines.

S. No	SAMPLE NAME	IC_{50} (µg) MCF -7	IC_{50} (µg) SKVO3
1	III-3b	44.8	40.48
2	III-3c	45.16	56.49
3	III-3e	41.21	46.21
4	III-3g	54.51	60.14
5	III-3h	26.53	55.95
6	III-3i	14.42	41.25
13	Doxorubicin	12.23	15.21

From resulting data (Table 2), it is observed that compound the IC_{50} values in the range of 14.42µg(0.035µM) to 45.16µg(0.13µM) against MCF7 cell line and 40.48µg(0.11µM) to 60.14µg(0.2µM) against SKVO3 cell line. The compound **III-3i** (IC_{50} value of **14.42µg(0.035µM)** against MCF-7 and **41.25µg(0.1µM)** against SKVO3) exhibited good anticancer activity compared with Doxorubicin as standard, whereas remaining are moderated activity.

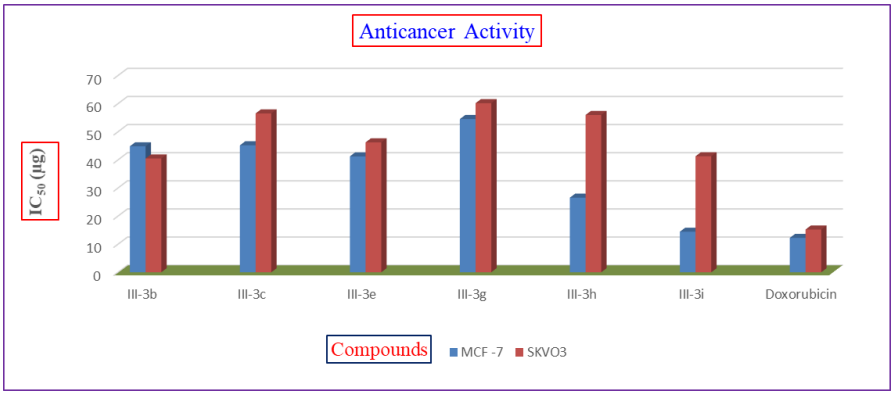


Figure 1: Graphical representation of Anticancer activity of Novel Quinazolinones on MCF-7 and SKVO3 Cell lines.

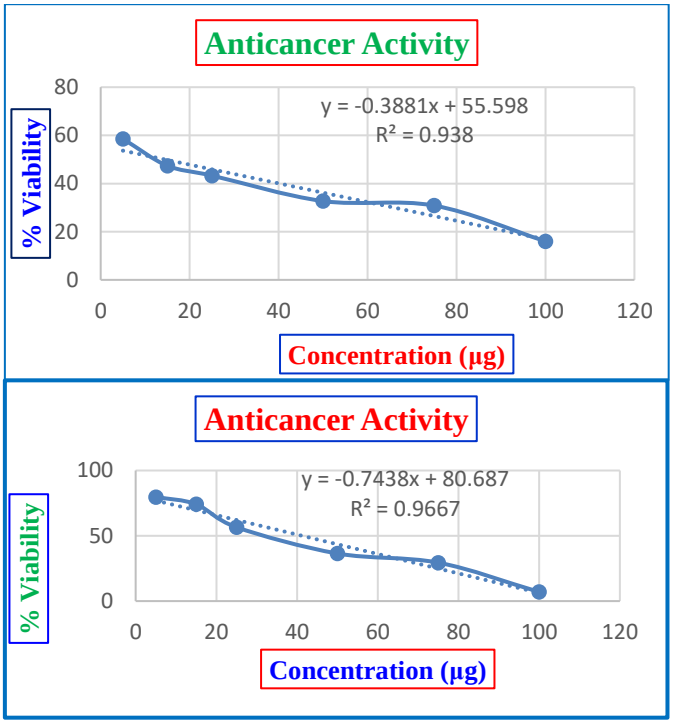


Figure.2. Graphical representation of novel Quinazolinones (III-3i)-IC_{50} values

Molecular Docking Studies: Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. The potential active site amino acids of 1M17 complex were predicted using CASTp. The target protein and inhibitors were geometrically optimized. All the 8 compounds were docked against active site of target protein using AUTODOCK VINA. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About 100 different protein-ligand complex conformations for each docked complex were generated through AUTODOCK suite of MGL Tools, the confirmation with lowest binding energy was displayed as the best binding energy. Binding energy of the dataset ligands were shown in Table 1 along with the interaction amino acids and number of amino acids.

Table.No.3: Insilico EGFR inhibition of Novel Quinazolinone derivatives (III-3a-3j)-Glide dock scores of the dataset ligands.

Compound No	Binding Energy (Kcal/mol)	No of H-bonds	Interacting amino acids	H-bond lengths (Å)
3a	**-8.6**	Nil	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, LEU:820	Nil
3b	**-8.7**	Nil	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, LEU:820	Nil
3c	**-8.8**	Nil	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, LEU:820	Nil
3d	**-8.5**	Nil	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, LEU:820	Nil
3e	-8.4	Nil	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, LEU:820	Nil
3g	**-8.5**	1	LEU:694, VAL:702, ALA:719, LYS:721, MET:742, LEU:764, CYS:773, LEU:820	2.05
3h	-8.3	1	PHE:699, VAL:702, ALA:719, LEU:820, ASP:831, LYS:851	3.28
3i	**-8.8**	1	PHE:699, LEU:694, VAL:702, LYS:721. LEU:820, ASP:831	2.96

Among the docked ligands, compound 3a, 3b, 3c, 3d, 3g & 3i reported lowest binding energy between -8.8 to -8.5 Kcal/mol. Binding energy of all the compounds ranged from -8.8 to -8.3 Kcal/mol. Compounds 3g, 3h & 3i possess one hydrogen bond each with CYS:773, ASP:831, LYS:721 amino acids. Compounds 3a, 3b, 3c, 3d, 3e had no hydrogen bond interaction. 3c & 3i possess lowest binding energy than all designed compounds.

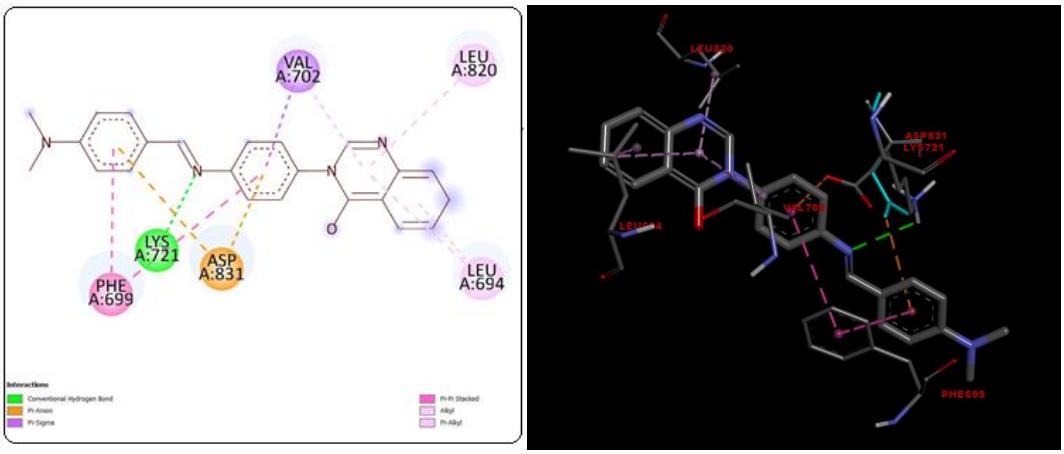


Figure.3. Docking Pose between the Ligand and the Protein (Dock1 and Dock-2)-Compound III-3i

CONCLUSION:

The novel Quinazolinone derivatives were synthesized by conventional method and characterized by spectral analysis. The main focus of this research work was to synthesize novel series of quinazolinone derivatives (III-3a-3j), purify, characterize and evaluate their anti-cancer activity and Molecular docking studies. From the results, it can be concluded that the modified quinazolinone shows significant biological evaluation as anti-cancer agents (III-3i,3h and 3e). However, further evaluation of quinazolinone will be undertaken concerning the structural arrangements in ring for anti-cancer activity.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Yihenew Simegniew B, Adnan Ahmed B and Ariaya H: *In-vivo* antimalarial evaluation of some 2, 3-disubstituted-4(3H)-quinazolinone derivatives. BMC Research Notes 2015; 8: 01-06.
2. Panda S and Tripathy UP: Quinazoline a molecule of significant pharmacological and biological activity. Research Journal of Pharmacy and Technology 2013; 6(8): 849-55.
3. Kumar A, Sharma P, Kumari P and Kalal BL: Exploration of antimicrobial and antioxidant potential of newly synthesized 2, 3-disubstituted quinazoline-4(3H)-ones. Bioorganic and Medi Chem Letters 2011; 21: 4353-57.
4. Rasha SG and Mohsen MK: Synthesis and reactions of some new quinazoline derivatives for *In-vitro* evaluation as anticancer and antimicrobial agents. Journal of Heterocyclic Chemistry 2018; 000: 1-8.
5. Krishnan SK, Ganguly S, Veerasamy R and Clercq ED: Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3H)-ones. European Jour of Medicinal Chemistry 2010; 45: 5474-79.
6. Reddy PSN, Mittapelli V and Reddy VD: Antibacterial, antifungal and antifeedant activity of quinazolinonyl-β-lactams/quinazolinones and bis (quinazolinonyl-β-lactams). Rasayan Journal of Chemistry 2010; 03(04): 635-40.
7. Alagarsamy V, Chitra K, Saravanan G, Solomon VR, Sulthana MT and Narendhar B: An overview of quinazolines: pharmacological significance and recent evelopments. European Journal of Medicinal Chemistry 2018; 151: 628-85.
8. Ahmed K, Pogula PK, Mohammed NA, Bobburi NS, Olepu S. Hybrid pharmacophore design and synthesis of naphthalimide– benzimidazole conjugates as

potential anticancer agents. Lett Drug Des Discov 2015; 12:374-384.
9. Sashidhara KV, Rao KB, Kushwaha P, Modukuri RK, Singh P, Soni I, *et al.* Novel chalcone-thiazole hybrids as potentinhibitors of drug resistant staphylococcus aureus. ACS Med Chem Lett 2015; 6:809-813.
10. Yang XD, Wan WC, Deng XY, Li Y, Yang LJ, Li L, *et al.* Design, synthesis and cytotoxic activities of novel hybrid compounds between 2-phenylbenzofuran and imidazole. Bioorg Med Chem Lett 2012; 22:2726-2729.
11. Sharma PC, Kaur1 G, Pahwa R, Sharma A, Rajak H. Quinazolinone analogs as potential therapeutic agents. Curr Med Chem 2011; 18:4786-4812.
12. Mohammadi MA, Askari S, Rohi H, Soorki AA. Design, synthesis and antibacterial evaluation of same novel 3'-(phenylamino)-1'h-spiro [indoline-3,2'-quinazoline] -2,4'(3'h)-dione derivatives. Synth Commun 2014; 44:457-467.
13. Modh RP, Clercq ED, Pannecouque C, Chikhalia KH. Design, synthesis, antimicrobial activity and anti-HIV activity evaluationof novel hybrid quinazoline–triazine derivatives. J Enzyme Inhib Med Chem 2014; 29:100-108.
14. Faraj FL, Zahedifard M, Paydar M, Looi CY, Abdul Majid N, Ali HM, et al. Synthesis, characterization, and anticancer activity of new quinazoline derivatives against MCF-7 cells. Sci World J. 2014; 2014:1–15.
15. Kamal A, Bharathi EV, Ramaiah MJ, Dastagiri D, Reddy JS, Viswanath A, et al. Quinazolinone linked pyrrolo [2, 1-c] [1, 4] benzodiazepine (PBD) conjugates: design, synthesis and biological evaluation as potential anticancer agents. Bioorg Med Chem. 2010;18(2):526–42.
16. Lee S, Kim J, Duggirala KB, Go A, Shin I, Cho BC, et al. Allosteric inhibitor TREA-0236 containing non-hydrolysable quinazoline-4-one for EGFR T790M/C797S mutants' inhibition. Bull Korean Chem Soc.2018;39(7):895–8.
17. Park H, Jung HY, Mah S, Hong S. Discovery of EGF receptor inhibitors that are selective for the d746–750/T790M/C797S mutant through structurebased de novo design. Angew Chem Int Ed. 2017;56(26):7634–8.
18. Noolvi MN, Patel HM, Bhardwaj V, Chauhan A. Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: Search for anticancer agent. Eur J Med Chem 2011; 46:2327-2346.
19. Khodarahmi GA, Rahmani Khajouei M, Hakimelahi GH, Abedi D, Jafari E, Hassanzadeh F. Antibacterial, antifungal and cytotoxic evaluation of some new 2,3-disubstituted 4(3H)-quinazolinone derivatives. Res Pharm Sci 2012; 7:151-158.
20. Van de Loosdrecht AA, Beelen RHJ, Ossenkoppele GJ, Broekhoven MG, Langenhuijsen MMAC. A tetrazolium based colorimetric MTT assay to quantitate human monocyte mediated cytotoxicity against leukemic cells from cell lines and patients with acute myeloid leukemia. J Immun Methods 1994; 174:311-320.