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Design, synthesis of a series of 6-substituted- 4-hydroxy-1-[(-4-substitutedphenyl)sulfonyl]quinolin-2(1*H*)-thiones derivatives and evaluation of their *in vitro* anticancer activity

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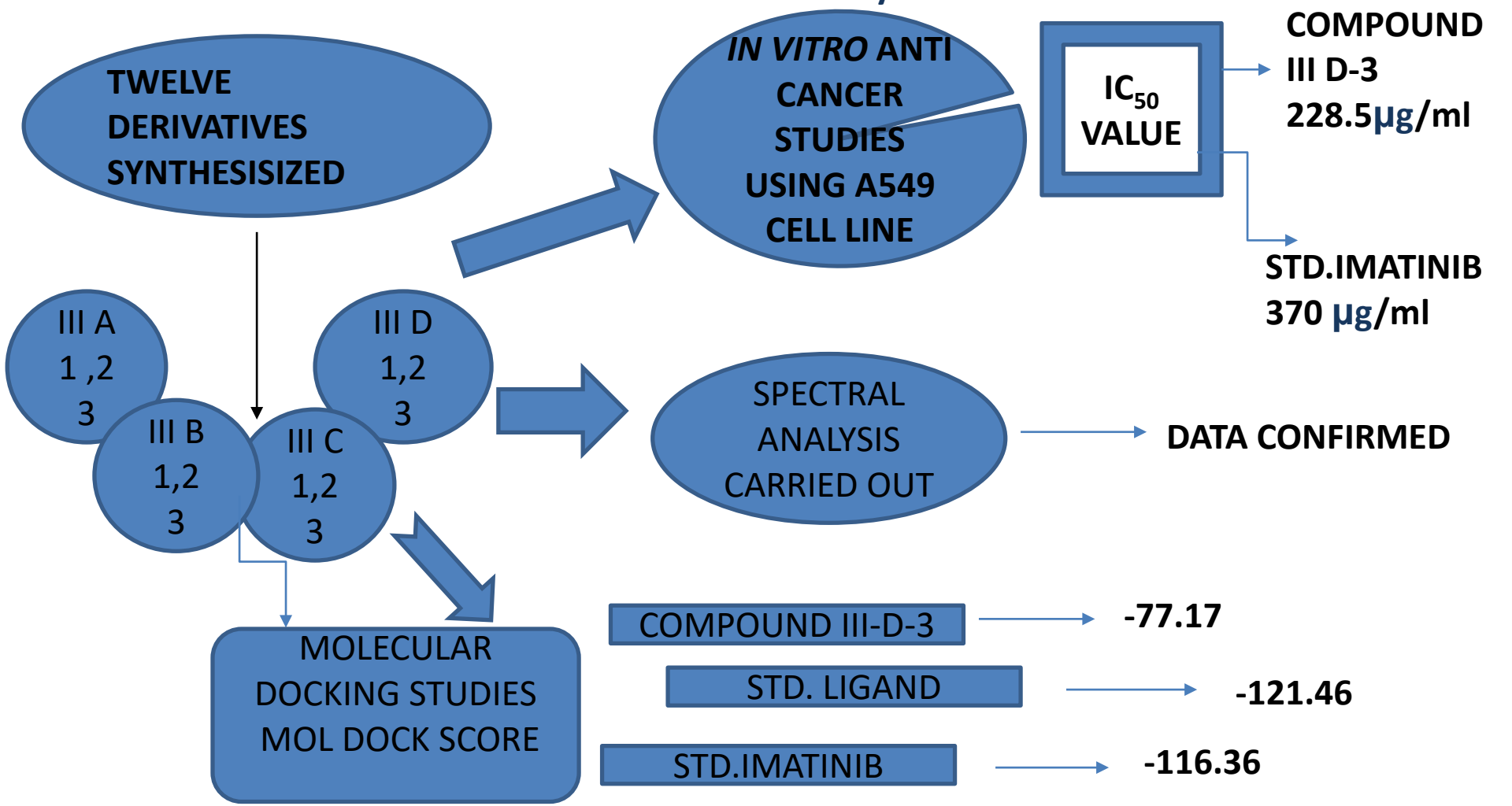

Abstract: The current research work deals with the design, synthesis of a series of 6-substituted- 4-hydroxy-1-(-4-substitutedphenyl)sulfonyl)quinolin-2(1*H*)-thiones [III A (1-3), III B (1-3), III C (1-3), III D (1-3)]derivatives and evaluation of their *in vitro* anticancer activity. Molecular docking studies of the title compounds 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). The MolDock Score of compound (III D-3) was (-77.1739) which is comparable to that of the standard ligand(-121.469) and imatinib (-116.362). 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. The compounds were synthesized using appropriate synthetic route and all the synthesized compounds were characterized by IR, NMR spectral data. Twelve derivatives were tested for their *in vitro* anticancer activity using A549 cell line. Compound (III D-3) was found to be the most cytotoxic as compared to the other synthesized derivatives, with IC_{50} values of 228.51 µg/ml against A549 cell line was more potent than standard drug Imatinib with IC_{50} value of 370µg/ml.

Keywords:anti-cancer ;docking ;Quinoline-2-one.

Introduction

Cancer or Neoplasm is the appearance of a tumor. A tumour is a growth of unwanted mass of a tissue, whose growth is extreme and uncoordinated and persists even after removal of stimulus that causes such change.According to Cancer Research UK (2013), Over 325,000 new cases were reported in 2010 and mortality was in excess of 157,000 (global figure, 7.4 million).

Compared with that of bacterial diseases, cancer chemotherapy presents a difficult conceptual problem. In biochemical terms, microorganisms are different from human cells, but oncogenic cells and non-oncogenic cells are so similar in most respects that it is more difficult to find general, exploitable differences between them. Cells undergoing carcinogenic changes usually exhibit antigens on surface of cells that might be normally life killing type, may show other signs of non-maturity, including various translocations and the exhibiting of amplified gene sequences.

Conventional cytotoxic drugs act on all cell lines and rely on small margin of selectivity to be useful as anticancer agents, but the scope of cancer therapy has now broadened to include drugs that affect either the hormonal regulation of tumour growth, or the defective cell cycle controls that underlie malignancy.

Lung Cancer

Lung cancer is the leading health problem and cause of morbidity. Lung cancer is also known as lung carcinoma, is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung. The most common symptoms are coughing (including coughing up blood), weight loss, shortness of breath, and chest pains. The vast majority (85%) of cases of lung cancer are due to long-term tobacco smoking. About 10–15% of cases occur in people who have never smoked. These cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos, second-hand smoke, or other forms of air pollution.

Worldwide in 2012, lung cancer occurred in 1.8 million people and resulted in 1.6 million deaths. This makes it the most common cause of cancer-related death in men and second most common in women after breast cancer. The most common age at diagnosis is 70 years. Overall, 17.4% of people in the United States diagnosed with lung cancer survive five years after the diagnosis, while outcomes on average are worse in the developing world.

Predisposing Factors:

I. Cigarette Smoking

II. Radon gas

III. Asbestos

IV. Air pollution

The usage of chemotherapeutic agents has decreased mortality and morbidity rate in cancer patients. The major setback of these anticancer drugs is its unoriented targeting and toxic effects. Although chemotherapy is a most basic approach for the treatment of disease. Also, resistance to this chemotherapeutic agent is a biggest challenge in the treatment of cancer, so discovery of anticancer agents with high potency and minimal toxicity is need of hour.

Quinolones have become an important class of drugs and have led to a keen interest of various synthetic and clinical investigators as these derivatives have potential for use in clinical medicine as anticancer and antibacterial agents. There are large number of heterocyclic compounds that have already been reported to exhibit anticancer properties. Research on 2-quinolone, lead to discovery of 4-hydroxy-2(1*H*)-quinolone which is one of the most important class of heterocycles possessing wide spectrum of biological activities.

Many researchers identified linomide, quinolone derivative as a lead molecule for development of various anticancer and antibacterial agents. Thus, various research workers identified linomide analogues as a lead molecule having higher potency and with lesser side effects and number of quinoline derivatives have been reported till date for their anticancer activity.

In the view of above preamble, considering linomide as the lead molecule, we thought of synthesizing the substituted thiazole derivatives of quinolin-2(1*H*)-one, and making modifications at the 3rd and 1st position on same and evaluating them for anticancer activity.

Results and discussion

The sequence of reactions consists of the initial synthesis of 6-substituted 4-hydroxyquinolin-2(1*H*)-ones (Ia/Ib/Ic/Id) from dianilide formed with polyphosphoric acid. Then thionation was carried out on resultant compound using P_4S_{10}/Al_2O_3 reagent to give 6-substituted-4-hydroxyquinolin-2(1*H*)-thione (II A /II B/II C/II D), further the formed compound is treated with substituted aromatic sulfonyl chloride to give 12 derivatives of 6-substituted-4-hydroxy-1-(4-substitutedphenyl) sulfonyl)quinolin-2(1*H*)-thiones. [IIIa (1-3), IIIb (1-3), IIIc (1-3), IIId (1-3)]. Physical data of all synthesized compounds are given in Table A. All the synthesized compounds were characterized by UV, IR, ^{1}H-NMR and ^{13}C-NMR spectral data.

The *in vitro* anticancer activity of 6-substituted-4-hydroxy-1-(4-substitutedphenyl) sulfonyl) quinoline-2(1*H*)-thiones. [IIIa (1-3), IIIb (1-3), IIIc (1-3), IIId (1-3)] derivatives were performed by MTT assay on A-549 (lung cancer) cell lines as given in Table B.1. From the obtained results, the synthesized compounds (III D-3), (III C-3), (III C-1) showed IC_{50} values of 228.51,243.3, 245.33µg/mL respectively against A549 (Lung Cancer) cell and compound 6-Fluoro- 4-hydroxy-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (**III D-3**) was the most potent compound with IC_{50} value of 228.51µg/mL against A549 cell line as given Table B.2.

The spectral data of 4-Hydroxy -1-(phenylsulfonyl)quinolin-2-(1*H*)-thione (III A-1):

IR data (KBr,cm^{-1}): 3603.03 (-OH) ,1390.68 (-S=O stretch),3053.32 (aromatic-C-H-stretch),1211.30 (-C=S stretch)

The spectral data of 6-Chloro-4-hydroxy -1-(phenylsulfonyl) quinolin-2-(1*H*)-thione (III B-1):

IR data (KBr,cm^{-1}): 3570.24 (-OH), 1213.23 (-C=S-stretch), 1340.53 (-S=O stretch), 815.89 (-C-Cl stretch), 3078.39 (aromatic-C-H stretch)

The spectral data of 6-Fluoro-4-hydroxy -1-(phenylsulfonyl)quinolin-2-(1*H*)-thione (III C-1):

IR data (KBr,cm^{-1}): 3570.24 (-O-H), 1253.73 (-C=S stretch), 1340.53 (-S=O stretch),1022.27 (-C-F stretch), 3032.10 (aromatic-C-H stretch)

The spectral data of 4-Hydroxy-6-methyl-1-(phenylsulfonyl)quinolin-2-(1*H*)-thione (III D-1):

IR data (KBr,cm^{-1}): 3589.53 (-O-H), 3022.45 (aromatic-C-H stretch), 2852.72 (-C-H-stretch), 1205.51 (-C=S stretch), 1338.60 (-S=O stretch)

The spectral data of 4-Hydroxy-1-tosylquinolin-2-(1*H*)-thione (III A-2):

IR data (KBr,cm^{-1}): 3502.73 (-OH), 13650.60 (-S=OStretch), 3053.32 (aromatic-C-H Stretch), 2916.37,2848.86 (-C-H Stretch), 1209.37 (-C=S Stretch)

The spectral data of 6-Chloro-4-hydroxy-1-tosylquinolin-2-(1*H*)-thione (III B-2):

IR data (KBr,cm^{-1}): 3639.68 (-O-H), 1236.37 (-C=S Stretch), 1348.24 (-S=O Stretch), 817.82 (-C-Cl Stretch), 3072.60 (aromatic-C-H Stretch), 2848.86 (-C-H Stretch)

The spectral data of 6-Fluoro-4-hydroxy-1-tosylquinolin-2(1*H*)-thione (III C-2):

IR data (KBr,cm^{-1}): 3570.24 (-O-H), 1253.73 (-C=S Stretch), 1379.10 (-S=O Stretch), 1016.49 (-C-F Stretch), 3109.25 (aromatic-C-H Stretch), 2918.30 (-C-H Stretch)

The spectral data of 4-Hydroxy-6-methyl-1-tosylquinolin-2-(1*H*)-thione (III D-2):

IR data (KBr,cm^{-1}): 3523.95 (O-H), 3049.46 (aromatic-C-H Stretch), 2848.86 (-C-H Stretch), 1355.96 (-C=S Stretch), 1207.44 (-S=O Stretch)

^{1}H NMR data (δ ppm,DMSO-*d*6): 6.967-7.784 (m, 7H ,Ar-H); 12.128 (s,1H , -O-H); 2.508 (s, 3H ,-CH_3)

^{13}C NMR data (δ ppm, DMSO-*d*6):39.82(-CH_3 attached phenyl),39.99(-CH_3 attached quinoline),118.25-14.77(11 Aromatic -C),173.42(-C-OH),154.6 (-C=S).

The spectral data of 4-Hydroxy-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III A-3):

IR data (KBr,cm^{-1}): 3523.95 (-O-H) , 1334.74 (-S=O Stretch) , 3059.10 (aromatic-C-H Stretch), 1215.15 (-C=S Stretch)

^{1}H NMR data (δ ppm,DMSO-*d*6): 6.762-8.212 (m, 8H ,Ar-H) ;11.799 (s,1H ,-O-H)

The spectral data of 6-Chloro- 4-hydroxy-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III B-3):

IR data (KBr,cm^{-1}): 3529.73 (-O-H), 821.68 (-C-Cl Stretch), 1232.51 (-C=S Stretch), 3091.89 (aromatic--C-H Stretch), 1377.17 (-S=O Stretch)

The spectral data of 6-Fluoro- 4-hydroxy-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III C-3):

IR data (KBr,cm^{-1}): 3541.31 (-O-H), 1315.45 (-C=S Stretch), 1338.60 (-S=O Stretch), 1253.73 (-C-F Stretch), 3143.97 (aromatic-C-H Stretch)

^{1}H NMR data (δ ppm,DMSO-*d*6): 6.981-8.260 (m, 7H ,A-H);12.325(s, 1H ,-O-H)

^{1}H NMR data (δ ppm,DMSO-*d*6): 6.981-8.260 (m, 7H ,A-H);12.325(s, 1H ,-O-H)

The spectral data of 4-Hydroxy-6-methyl-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III D-3):

IR data (KBr,cm^{-1}): 3682.11 (-O-H), 3053.32 (aromatic-C-H Stretch), 2848.86 (-C-H-Stretch), 1355.96 (-C=S Stretch), 1207.44 (-S=O stretch)

Molecular Docking Studies:

Molecular docking studies of the synthesized compounds {6-substituted-4-hydroxy-1-(4-substitutedphenyl)sulfonyl) quinolin-2(1H)-thiones. [IIIa (1-3), IIIb (1-3), IIIc (1-3), IIId (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-aminoquinazoline inhibitor (PDB ID: 1m17) for anticancer docking study. The results are given in Table No.C

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 -77.17 to -98.17. Imatinib was used as the reference standard for comparison of efficiency and exhibited MolDock score of -116.362. Compound 4-hydroxy-6-methyl-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III D-3) having a MolDock score of -77.1739. The best poses of compounds exhibiting the most promising hydrogen bonding are shown in the Figure A.4

Compound	Mol.Formula	M.W	M.P(°C)	% Yield	Rf value	Solubility
IIIa-1	$C_{15}H_{11}NO_3S_2$	317.38	>300	70	0.67	DMSO
IIIa-2	$C_{16}H_{13}NO_3S_2$	331.41	>300	72	0.75	DMSO
IIIa-3	$C_{15}H_{11}N_2O_5S_2$	362.38	>300	58	0.78	DMSO
IIIb-1	$C_{15}H_{10}ClNO_3S_2$	351.83	>300	74	0.6	DMSO
IIIb-2	$C_{16}H_{12}ClNO_3S_2$	365.85	>300	54	0.77	DMSO
IIIb-3	$C_{15}H_9ClN_2O_5S_2$	396.83	>300	68	0.88	DMSO
IIIc-1	$C_{15}H_{10}FNO_3S_2$	335.37	>300	75	0.7	DMSO
IIIc-2	$C_{16}H_{12}FNO_3S_2$	349.40	>300	55	0.78	DMSO
IIIc-3	$C_{15}H_9FN_2O_5S_2$	380.37	>300	78	0.88	DMSO
IIId-1	$C_{16}H_{13}NO_3S_2$	331.41	>300	74	0.72	DMSO
IIId-2	$C_{17}H_{15}NO_3S_2$	345.44	>300	72	0.98	DMSO
IIId-3	$C_{16}H_{12}N_2O_5S_2$	376.41	>300	78	0.82	DMSO

Table A: Physical data of synthesized compounds.

Concentration µg/ml	% Cell Viability (A549 cell line)					
	IIIa-1	IIIa-2	IIIa-3	IIIb-1	IIIb-2	IIIb-3
500	60.3	59.3	57.5	64.11	71	70.4
250	65.8	61.4	59.3	68.22	65.27	70
125	64.9	61.07	61.58	65.18	70.1	69.12
62.5	57.11	72.1	64.8	70.1	70.9	68.29
31.25	55.2	74.29	67	75	73	65.4

Concentration µg/ml	% Cell Viability (A549 cell line)					
	IIIc-1	IIIc-2	IIIc-3	IIId-1	IIId-2	IIId-3
500	63.14	65.03	71	70.12	62.1	75.5
250	64	65.3	71.5	65.19	63.9	74.8
125	69.115	70.1	69.99	61.52	66.8	79.54
62.5	70.12	64.2	68.21	64.8	62.1	66.7
31.25	65.19	63.74	65.1	61	69.5	74

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

Compounds	IC_{50} (µg/ml)
IIIa-1	277.78
IIIa-2	280.42
IIIa-3	290.02
IIIb-1	292.74
IIIb-2	247.40
IIIb-3	246.06
IIIc-1	245.33
IIIc-2	261.78
IIIc-3	243.3
IIId-1	256.14
IIId-2	271
IIId-3	228.51
Imatinib	370

Table B.2: IC_{50} values of synthesised compounds on A549 cell line

Compound	MolDock Score	Rerank Score	H-Bond
IIIa-1	-89.8189	-68.1888	-4.18534
IIIa-2	-81.9143	-56.0226	-0.189769
IIIa-3	-95.5887	-71.393	-12.2059
IIIb-1	-91.1866	-67.4568	-5.48286
IIIb-2	-88.5872	-66.7812	-5.0
IIIb-3	-93.899	-80.3234	-11.6815
IIIc-1	-97.6693	-65.3484	-6.49989
IIIc-2	-77.9319	-40.0192	-5.90417
IIIc-3	-98.7178	-60.6418	-7.90587
IIId-1	-86.7488	-66.6841	-3.15993
IIId-2	-89.7229	-67.7032	-5.0
IIId-3	-77.1739	-60.6418	-7.90587
Imatinib	-116.362	-73.7364	-4.8365
1m17	-121.469	-73.4548	-6.04189

Table C: MolDock Scores of synthesized compounds of 6-substituted- 4-hydroxy-1-(-4-substitutedphenyl)sulfonyl)quinolin-2(1H)-thiones [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.

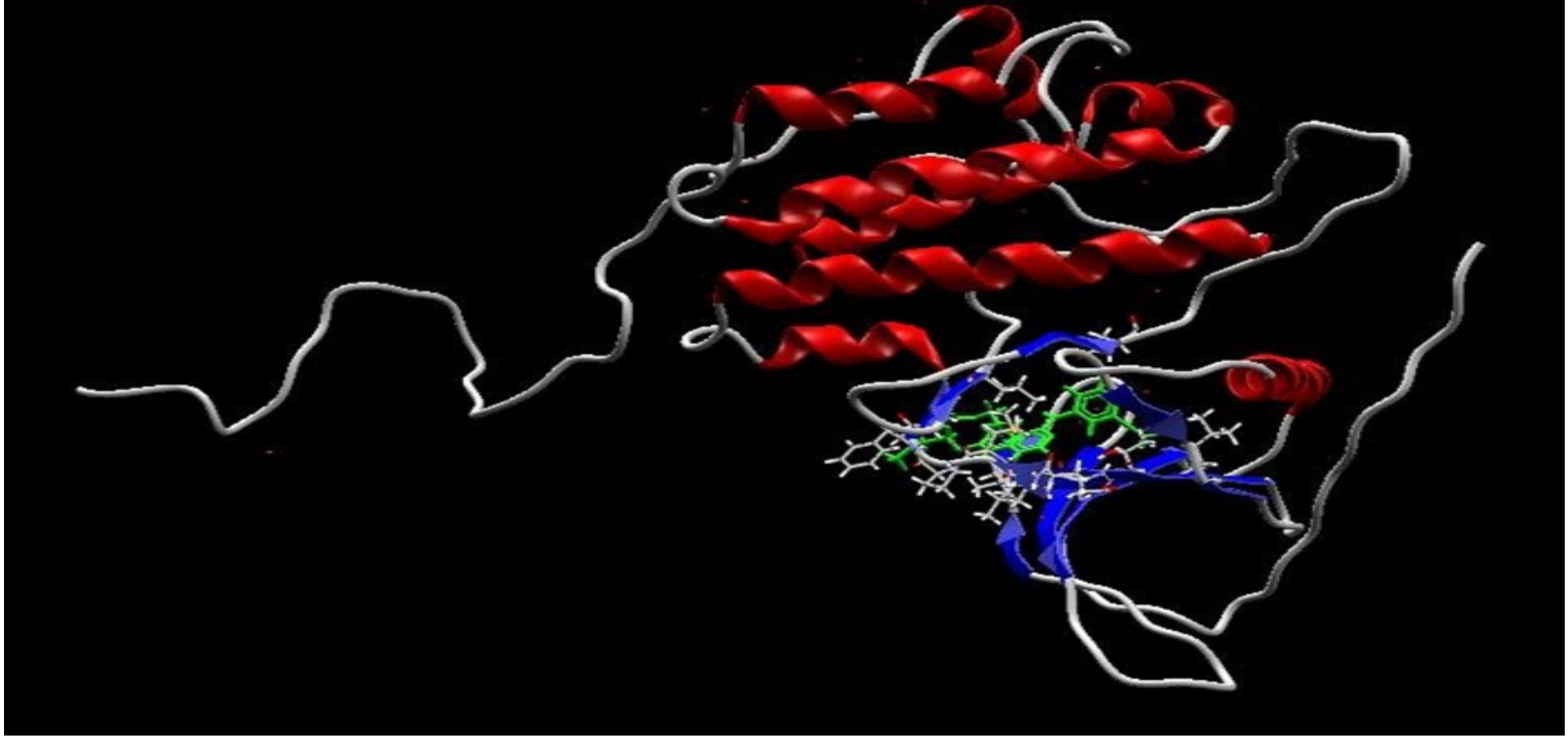

Fig. A.1: Structure of EGFR-tyrosine kinase domain complexedwith 4-anilinoquinazoline inhibitor (PDB ID: 1m17)

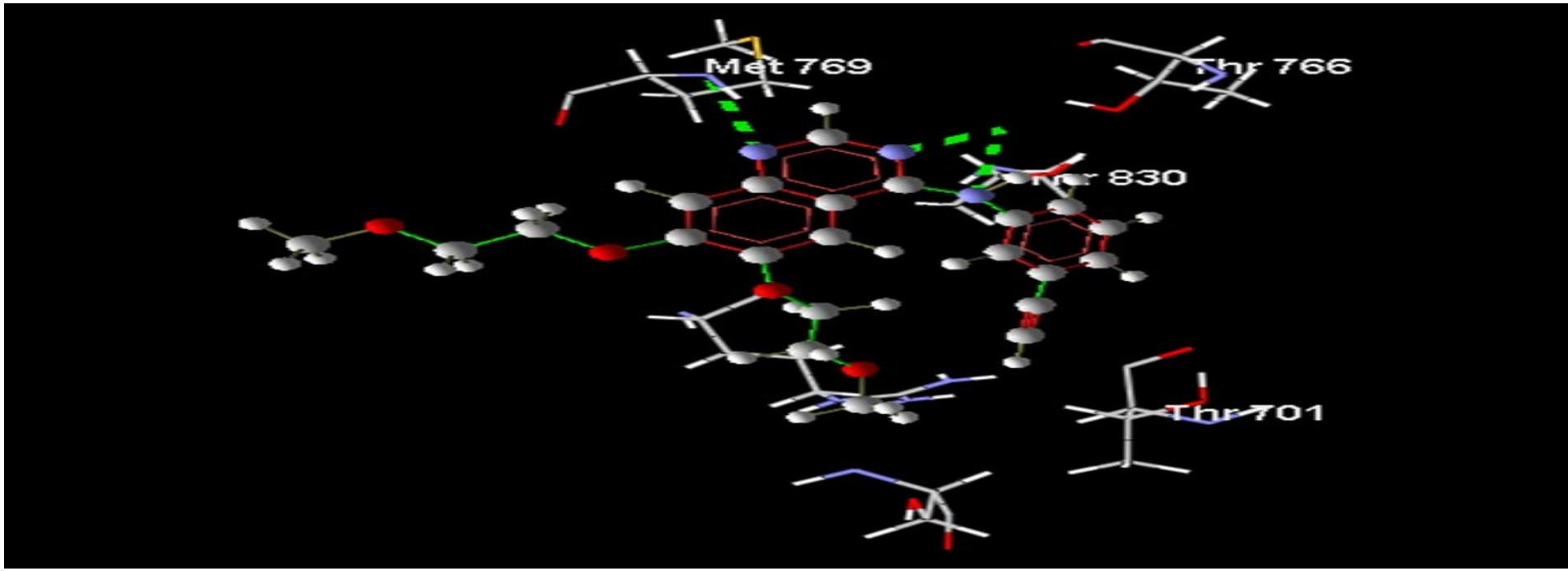

Fig. A.2: Ligand 4-anilinoquinazoline docked in best of its conformation (pose) into the binding site of 1m17

- The -N at 1st position of quinazoline moiety forms hydrogen bond with –NH 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.

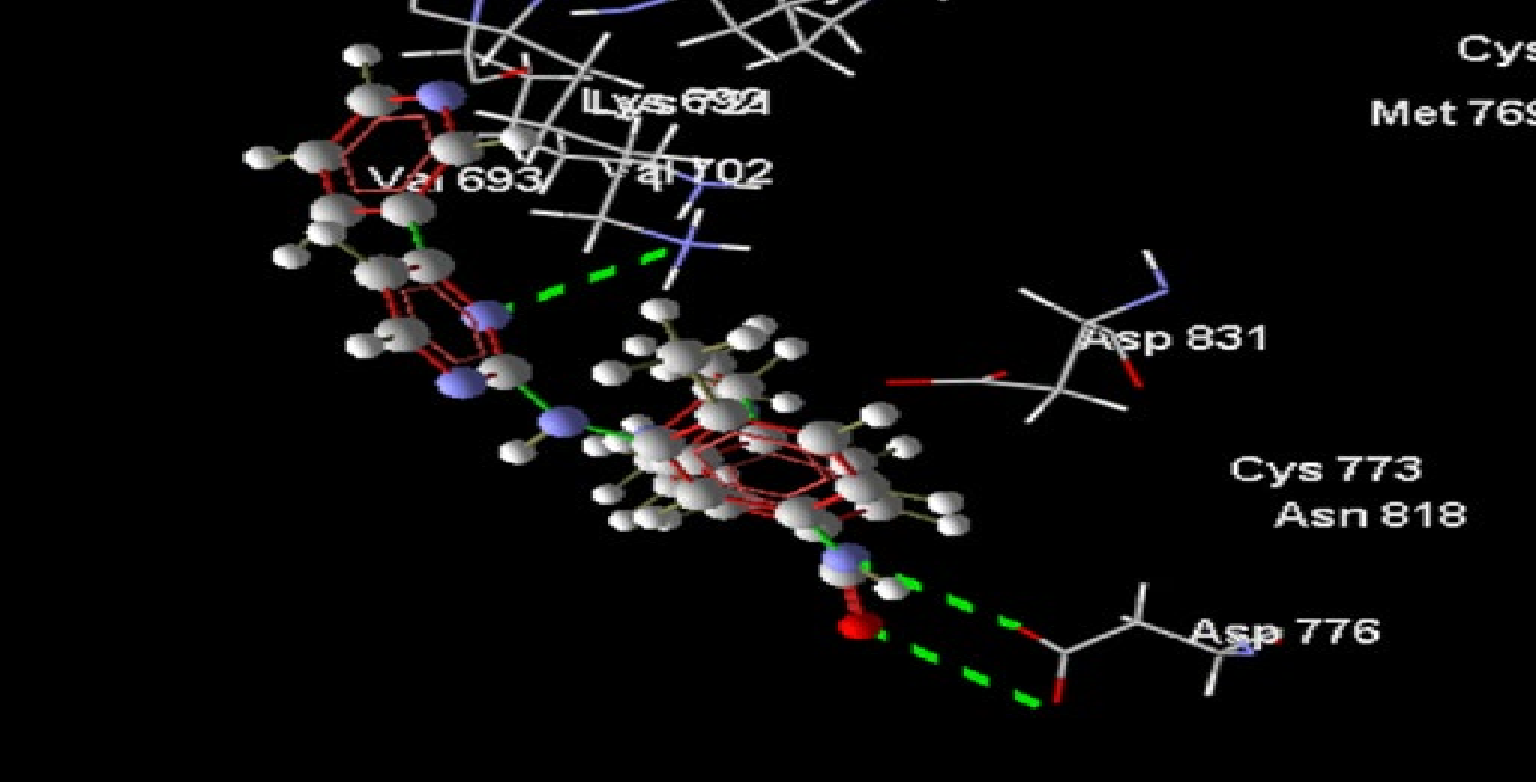

Fig.A.3: Imatinib docked in best of its conformation (pose) into the binding site of 1m17

- 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.

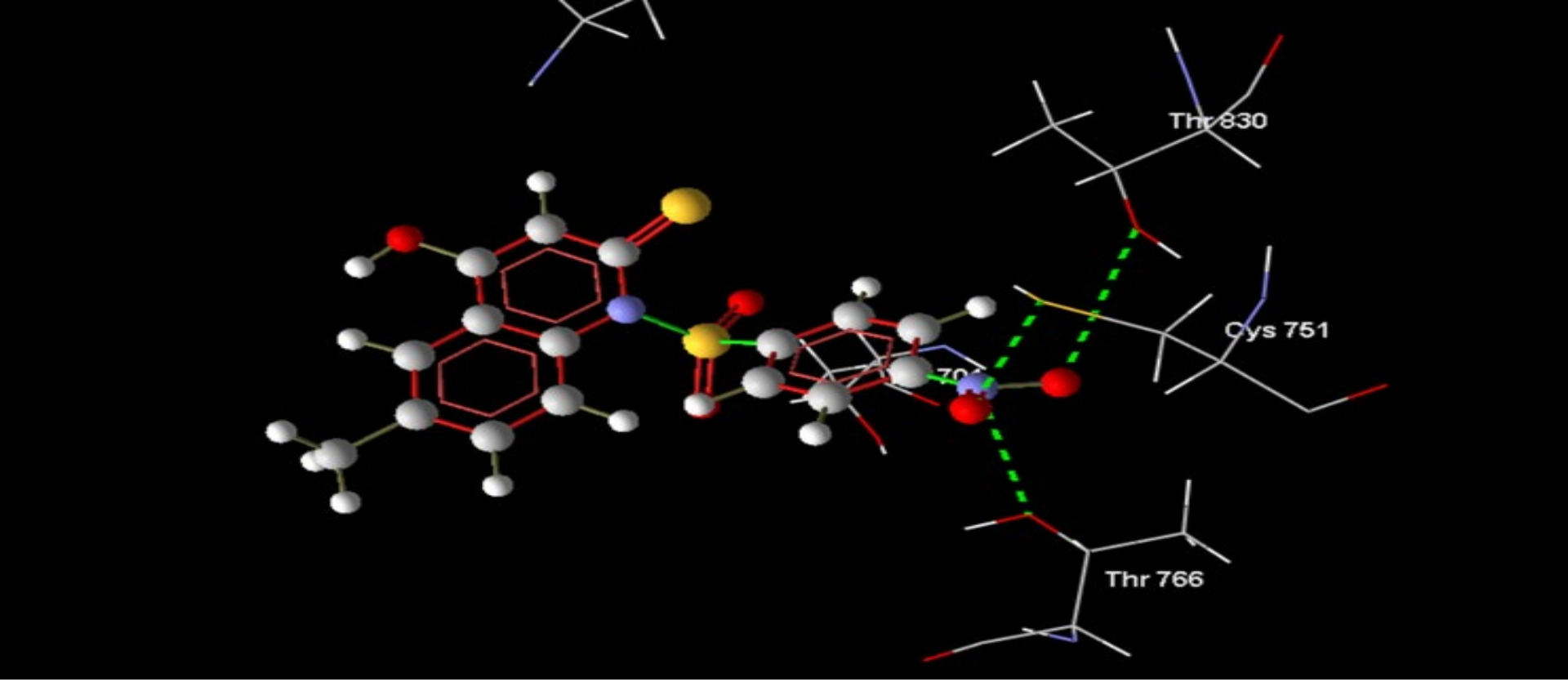

Fig. A.4: Compound 4-Hydroxy-6-methyl-1-((4-nitrophenyl)sulfonyl)quinolin-2(1H)-thione (III D-3) docked in best of its conformation(pose) into the binding site of 1m17

- The -N of Nitro group forms hydrogen bond with -OH of Thr 766
- The -O from N-O of Nitro group forms hydrogen bond with -OH of Thr 830
- The -O from N=O of Nitro group forms hydrogen bond with -SH of Cys 751

Conclusions

Twelve derivatives of 6-substituted-4-hydroxy-1-(4-substitutedphenyl)sulfonyl) quinolin-2(1*H*)-thiones [IIIa (1-3), IIIb (1-3), IIIc (1-3), IIId (1-3)] derivatives designed, synthesized and characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Selected compounds were evaluated for their *in vitro* anticancer activity. A549 (Lung cancer) cell lines based upon MTT assay were used for anticancer activity. 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 standard imatinib.Compound 4-hydroxy-6-methyl-1-((4-nitrophenyl)sulfonyl)quinolin-2(1*H*)-thione (III D-3) exhibited highest MolDock score of (-77.1739) which was comparable to that shown by the standard Imatinib ligand (-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 228.51µg/ml and as comparable to standard imatinib with IC_{50} value of 370 µg/ml against A549 (Lung cancer) cell line . This was probably observed may be because of the presence of nitro group at 4th position of phenyl ring and methyl group at 6th position of thionated quinoline moiety. This molecule was found to possess promising anticancer activity and could be used for future research work.

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