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NOVEL RESVERATROL DITHIOCARBAMATEDERIVATIVES AS POTENTIAL NEW LEADS TARGETTING 2L98 & 4YHJ FOR CARDIOVASCULAR DISEASE

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ABSTRACT:

Phytochemicals are an attractive sourcetodiscover new leadsfor the development of novel compounds for various diseases. Cardiovascular diseases are the principal cause of morbidity and mortality worldwide. Resveratrol is a stilbene, which is a type of natural polyphenolic compound, used for cancer therapy, and it has shown useful effects against cardiovascular diseases. Otherside Dithiocarbamates obtained from phytoalexins exhibited diverse pharmacological profiles.So, we thought its worthwhile to combine two natural compounds resveratrol and dithiocarbamate as a single entity to develop novel cardiovascular agents. All the designed compounds were subjected to various pharmacokinetics and pharmacodynamic properties by using Insilco tools. Further Molecular docking studies were performed to know the suitable target for the cardiovascular disease. All the compounds obeyed Lipinski rule of five and among the series, compound 26 and 30 are more potent when compared to dock score of the standard drug resveratrol against selected targets, G protein-coupled receptor kinase 4 (**2L98)**, Cardiac troponin (**4YHJ)** of cardiovascular disease. The present investigations concluded that the designed resveratrol dithio derivatives are the effective and bioavailable molecules.

Keywords: Resveratrol,Dithiocarbamate, Drug likeness, AutodockVina, Discovery studio.

1.INTRODUCTION:

Most of the current drugs were derived from microbial or plant origins. Photochemical are an attractive.An agent with low cost, biocompatibility, effectiveness, makes photochemical a striking cause for lead development for identifying compounds that give support to the biological activity of existing drugs.

Cardiovascular diseases are the leading cause of morbidity and mortalityworldwide. It is group of diseasesthat affect the heart and blood vessels of the body including stroke, heart failure, hypertension, coronary artery diseases, heart arrhythmia, peripheral artery disease, and atherosclerosis[1].

Now, phyto antioxidants and a stilbene such as quercetin, curcumin, sulforaphane, and resveratrol are extensively used to treat many kinds of cardiovascular disease.Resveratrol is a stilbene, which is a type of natural polyphenolic compound. It is abundantly found in grape skins, peanuts, mulberries, and red wine[2,3,4].For of ADMET properties identification of target Insilicomethodologies plays a crucial role in recognition of new molecule beforehand[5,6].Resveratrol used for cancer therapy, and it has shown useful effects againstcardiovasculardiseases from atherosclerosis, hypertension, ischemia/reperfusion, and heart failure to diabetes, obesity,stress. Resveratrol's shows good interaction with multiple molecular targets of diverse intracellular pathways[7,8].

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Dithiocarbamateare measured as a significant theme owing to its widespread biological applications in medicinal chemistry. Dithiocarbamates linked to heterocyclic moieties exhibited diverse pharmacological profiles includinganticancer, antibacterial, antifungal, antitubercular, anti-Alzheimer activities and many more[9]To treat individual cardiovascular diseases huge number of drugs are available.

G protein-coupled receptor kinase 4 (GRK4) (PDB ID: 4yhj) represent the largest family of membrane receptors and are responsible for regulating a wide variety of physiological processes[10].As changes in GRK expression have featured prominently in many cardiovascular pathologies, including heart failure, myocardial infarction, hypertension, and cardiac hypertrophy[11,12].It has been reported to play an important role in hypertension, but little is known about its role in cardiomyocytes and myocardial infarction (MI) [13].

Cardiac troponin (PDB ID: 2L98) is a cardiac regulatory protein that controls heart contraction, it signifies an attractive target for the advancement of drugs for treating heart disease[14].

Even though suitable medicines are abundant in developing countries to fight CVDs, it is critically significant to identify new therapeutic targets in order to develop new, active drugs. The discovery and development of novel therapeutic targets, improved drugs directed to considerable perfections in the treatment of hypertension and other cardiovascular diseases[15]. Opportunely, several natural cures are available that appear to uphold cardiovascular health. For example, maintaining a healthy lifestyle, daily exercise, and choosing proper diets certainly help maintain a healthy heart[16].

2. Materials and Experimental Methodology

2.1 InsilicoADMET predictions and Evaluation of drug-likeness:

In this study we designed 31 novel resveratrol with various aliphatic, alicyclic, aralkyl and heterocyclic moieties on dithiocarbamates.

During the process drug discovery,ADMET (absorption, distribution, metabolism, and excretion), and toxicity profile prediction andevaluation of drug-likeness makes a rational decision on further development of potent ResveratrolDithiocarbamate derivatives.To estimate the pharmacokinetic and pharmacodynamic properties some web-based Insilcotools were used such asSwissADMET (http://www.swissadme.ch/index.php), Molinspiration (https://www.Molinspiration.com/cgi-bin/properties),Molsoft(https://molsoft.comprop/),PkCSM(http://biosig.unimelb.edu.au/pkcsm/prediction). Chemsketchsoftware was used to design compounds.(https://www.acdlabs.com/resources/freeware/chem sketch/download.php).

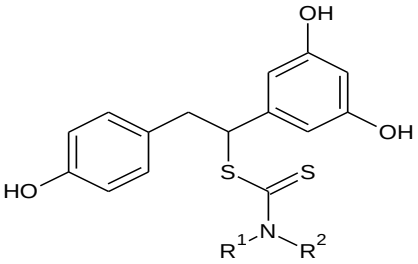

Figure 1: Resveratrol derivatives with Dithiocarbamate as a side chain.

Compound No	$R^1$and R^2	Compound No	$R^1$and R^2
1	methyl	18	methylpiperazine

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2	ethyl	19	ethylpiperazine
3	ethyl	20	marpholine
4	propyl	21	methylamine
5	propyl	22	4-hydroxy pyridine
6	butyl	23	4-methylphenylpropylamine
7	2-methylbutane	24	4-(2-aminoethyl)phenol
8	butyl	25	2-(4-methoxyphenylethanalamine
9	phenyl	26	1,2,3,4-tetrahydroisoquinone
10	4-methylphenyl	27	4-nitro-1H-pyrazole
11	4-methoxyphenyl	28	1H-pyrazole4-carbaldehyde
12	4-ethylphenyl	29	1H-benzimidazole
13	4-isopropylphenyl	30	5-methyl 1H-benzimidazole
14	pyrrolidine	31	Thiomorpholine
15	pyrrole	32	Reservetrol
16	piperidine		
17	piperazine		

2.2 Molecular Docking study:

Molecular Docking is the reliable method for preliminary evaluation of binding affinity and prediction of intermolecular interactions of novel compounds with receptors. AUTO DOCK Vina software was used for molecular docking. Software installed on a single machine running on an Intel Core i5-3317U CPU @ 1.70 GHz Processor with 6 GB RAM and Windows7 with 64-bit Operating System. Target and ligand were generated with the help of MGL Tools &Pharmit (http://pharmit.csb.pitt.edu/) [17]. Prepared pdbqt files for both target & ligands.

2.2.1 Ligand structure: The designed Novel Resveratrol derivatives were drawn and cleaned using ChemSketch software and saved in. mol format. Later the structures are converted to .pdb format by Open Babel software. For all the structures the geometry optimization was done by using Argus lab. At the end these structures converted to .pdbqt format by Open Babel software. The optimized inhibitor structure was used as input file for docking. we selected Resveratrol as standard ligand and some of the designed inhibitors for the docking studies against selected targets.

2.2.2 Protein structure: In the current study, two protein targets named G protein-coupled receptor kinase 4 (GRK4) (PDB ID: 4yhj)[10] and a heterotrimeric protein complex Cardiac troponin (PDB ID: 2L98) were selected [14]. The protein 3DX-ray crystal structure was retrieved from the RCSBProtein Data Bank and was used as the receptor starting structure. The enzyme structure contained a co-crystallized inhibitor and water molecules. The co-crystallized inhibitor was detached for the docking studies[17],we applied AutodockVina, in order to set up the docking runs and predict the inhibitors binding free energy[18].

2.2.3 Docking Protocol: AutoDock Vina was employed to docking process of inhibitors to the targets. Initially, water molecules were deleted, all of the polar hydrogens were added and Gasteiger atomic partial charges were set. Saved the macromolecule in. pdbqt format. The final ligand structures were saved in. pdbqt format are used for docking studies. Grid box was generated with 40 × 40 × 40 points in x, y and z directions and center of box was positioned on the active site according to co-crystallized inhibitor coordination. Active site was found with the help of MGL Tools & Pharmit (http://pharmit.csb.pitt.edu/). The molecules were analyzed after docking and visualized in thediscovery studio for the interactions with the active site amino acids.

3.Result And Discussion:

3.1ADMET properties prediction and drug-likeness assessment: The ADMET properties prediction and assessmentof drug-likeness concept offers valuable guidelines for the early stage in drug discovery to reduce cost and time by dropping mismatched compounds through the drug discovery process. The designed ResveratrolDithiocarbamate derivatives obeys Lipinski rule of five statesthat, Molecular weight ≤ 500, Log P

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(Octanol-water partition coefficient) value≤ 5, H-bond acceptors ≤ 10, H-bond donors≤ 5 and the values are exhibited in Table **3.1.1**. The designed compounds have good synthetic accessibility and bioavailability Scores were presented inTable **3.1.2**

All the designed compounds were predicted for ADMET properties and compared with the standard drug Resveratrol are shown in Table **3.1.3**.and Table **3.1.4**. Gastrointestinal absorptionand Blood-brain barrier penetrationare the key parameters for the distribution of drugs.The ADMET results indicating the compound numbers 1, 2, 14-20 and 26 are having high GIT absorption and none of the compoundsarepermeable to blood brain barrier. The compound numbers 7,13,17,20 and 26 are P-glycoprotein substrates, whereas remaining are P-glycoprotein inhibitors. Estimation of drug metabolism based on cytochrome P450major isoforms(CYP) (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) the designedcompounds are the inhibitors of CYP2C9, and compound no 4-8,22,27,28 are non-inhibitors of CYP2D6. Compounds 12, 17, 24,25,27,28 are considered as hepatotoxic. Ames test indicates that the compound 1,27,29,30 and standard Resveratrol are mutagenic and act as carcinogenic only compound no 22 showing skin sensitization.

Compound	**MW**	**Rotatable bonds**	**H-bond acceptors**	**H-bond donors**	**MR**	**XLOGP3**	**WLOGP**	**MLOGP**	**Silicos-IT LogP**	**Ali Log S**
1	349.47	6	3	3	99.47	3.69	3.34	2.15	3.59	-5.93
2	377.52	8	3	3	109.08	4.42	4.12	2.62	4.38	-6.69
3	391.55	9	3	3	113.89	4.95	4.51	2.85	4.79	-7.24
4	405.57	10	3	3	118.7	5.47	4.9	3.08	5.19	-7.78
5	419.6	10	3	3	123.5	5.91	5.15	3.29	5.43	-8.23
6	433.63	11	3	3	128.31	6.27	5.54	3.51	5.84	-8.61
7	447.65	11	3	3	133.12	6.7	5.79	3.72	6.08	-9.05
8	433.63	12	3	3	128.31	6.19	5.68	3.51	6.01	-8.52
9	397.51	7	3	4	115.79	5.06	4.7	3.12	4.76	-7.53
10	411.54	7	3	4	120.75	5.43	5.01	3.33	5.28	-7.92
11	427.54	8	4	4	122.28	5.03	4.71	2.77	4.83	-7.7
12	425.56	8	3	4	125.56	5.86	5.26	3.55	5.68	-8.36
13	439.59	8	3	4	130.37	6.19	5.83	3.76	5.91	-8.71
14	375.5	6	3	3	110.88	4.17	3.5	2.23	4.28	-6.43
15	371.47	6	3	3	105.73	4.51	4.13	2.31	4	-6.81

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16	389.53	6	3	3	115.69	4.53	3.89	2.46	4.52	-6.8
17	390.52	6	4	4	117.6	3.03	1.92	1.4	3.57	-5.5
18	404.55	6	4	3	122.5	3.5	2.27	1.63	3.51	-5.8
19	418.57	7	4	3	127.31	3.86	2.66	1.85	3.9	-6.17
20	391.5	6	4	3	111.97	3.31	2.73	1.4	3.89	-5.73
21	335.44	6	3	4	94.57	3.5	3	1.91	3.65	-5.92
22	400.49	6	4	4	112.16	4.47	4.12	1.94	3.63	-7.2
23	439.59	9	3	4	128.83	5.82	4.92	3.49	6.08	-8.32
24	441.56	9	4	5	125.89	5.1	4.32	2.72	5.08	-8
25	455.59	10	4	4	130.35	5.43	4.62	2.93	5.63	-8.11
26	437.57	6	3	3	130.72	5.21	4.31	3.1	5.38	-7.51
27	417.46	7	6	3	112.35	4.24	3.43	1.95	1.3	-7.77
28	400.47	7	5	3	108.92	3.87	3.34	1.41	3.66	-6.78
29	422.52	6	4	3	121.03	5.28	4.68	2.91	4.47	-7.88
30	436.55	6	4	3	126	5.65	4.99	3.13	5	-8.27
31	407.57	6	3	3	118.48	4.11	3.45	2.23	4.45	-6.9
Resveratrol.	228.24	2	3	3	67.88	3.13	2.76	2.26	2.57	-4.07

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Table **3.1.1**Physicochemical and pharmacokinetic properties of ResveratrolDithiocarbamate derivative.

Compound	**Synthetic Accessibility**	**Lipinski violations**	**Ghose violations**	**Veber violations**	**Egan violations**	**Muegge violations**	**Bioavailability Score**
1	3.46	0	0	0	0	0	0.55
2	3.67	0	0	0	0	0	0.55
3	3.82	0	0	0	0	0	0.55
4	3.93	0	0	0	0	1	0.55
5	4.05	0	0	0	0	1	0.55
6	4.17	0	0	1	0	1	0.55
7	4.29	0	2	1	0	1	0.55
8	4.17	0	1	1	0	1	0.55
9	3.63	0	0	0	0	1	0.55
10	3.73	0	0	0	0	1	0.55
11	3.74	0	0	0	1	1	0.55
12	3.85	0	0	0	0	1	0.55
13	3.96	0	2	0	0	1	0.55
14	3.64	0	0	0	0	0	0.55
15	3.5	0	0	0	0	0	0.55
16	3.72	0	0	0	0	0	0.55
17	3.73	0	0	0	1	0	0.55
18	3.84	0	0	0	0	0	0.55
19	3.96	0	0	0	0	0	0.55
20	3.66	0	0	0	0	0	0.55
21	3.35	0	0	0	0	0	0.55
22	3.62	0	0	1	1	0	0.55
23	3.95	0	0	0	0	1	0.55
24	3.9	0	0	1	1	2	0.55
25	3.96	0	1	0	1	1	0.55
26	3.94	0	1	0	0	1	0.55
27	4.05	0	0	1	1	1	0.55
28	3.82	0	0	1	1	1	0.55
29	3.81	0	0	0	1	1	0.55
30	3.93	0	0	0	1	1	0.55
31	3.85	0	0	1	1	0	0.55
Resevetrol.	2.02	0	0	0	0	0	0.55

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Table **3.1.2**Synthetic Accessibility, Bioavailability Score of ResveratrolDithiocarbamate derivative.

Compound	**GI absorption**	**BBB permeant**	**Pgp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**
1	**High**	No	No	Yes	Yes	Yes	Yes	Yes
2	**High**	No	No	Yes	Yes	Yes	Yes	Yes
3	Low	No	No	Yes	Yes	Yes	Yes	Yes
4	Low	No	No	Yes	Yes	Yes	No	Yes
5	Low	No	No	Yes	Yes	Yes	No	Yes
6	Low	No	No	Yes	Yes	Yes	No	Yes
7	Low	No	Yes	Yes	No	Yes	No	Yes
8	Low	No	No	Yes	Yes	Yes	No	Yes
9	Low	No	No	Yes	Yes	Yes	Yes	Yes
10	Low	No	No	Yes	Yes	Yes	Yes	Yes
11	Low	No	No	Yes	Yes	Yes	Yes	Yes
12	Low	No	No	Yes	Yes	Yes	Yes	Yes
13	Low	No	Yes	Yes	Yes	Yes	Yes	Yes
14	**High**	No	No	Yes	Yes	Yes	Yes	Yes
15	**High**	No	No	Yes	Yes	Yes	Yes	Yes
16	**High**	No	No	Yes	No	Yes	Yes	Yes
17	**High**	No	Yes	No	No	Yes	Yes	No
18	**High**	No	No	No	No	Yes	Yes	No
19	**High**	No	No	No	No	Yes	Yes	No
20	**High**	No	Yes	No	Yes	Yes	Yes	No
21	**High**	No	No	Yes	Yes	Yes	Yes	Yes
22	Low	No	No	No	Yes	Yes	No	No
23	Low	No	No	Yes	Yes	Yes	Yes	Yes
24	Low	No	No	No	Yes	Yes	Yes	Yes
25	Low	No	No	No	Yes	Yes	Yes	Yes
26	**High**	No	Yes	Yes	Yes	Yes	Yes	Yes
27	Low	No	No	No	No	Yes	No	No
28	Low	No	No	No	Yes	Yes	No	No
29	Low	No	No	No	Yes	Yes	Yes	Yes
30	Low	No	No	No	Yes	Yes	Yes	Yes
31	Low	No	No	Yes	Yes	Yes	Yes	Yes
Reservetrol.	**High**	Yes	No	Yes	No	Yes	No	Yes

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Table **3.1.3** Absorption, distribution, metabolism, Resveratrol Dithiocarbamate derivative

Compound	**AMES toxicity**	**Max. tolerated dose (human) <_0.477log (mg/kg/day**	**hERG I inhibitor**	**hERG II inhibitor**	**Oral Rat Acute Toxicity (LD50)**	**Oral Rat Chronic Toxicity (LOAEL)**	**Hepatotoxicity**	**Skin Sensitisation**	**T.Pyriformis toxicity**	**Minnow toxicity**
1	YES	0.839	NO	YES	2.356	2.268	No	No	0.654	0.764
2	NO	0.131	NO	YES	2.489	0.786	No	No	0.405	1.822
3	NO	0.154	NO	YES	2.489	0.789	No	No	0.392	1.583
4	NO	0.208	NO	YES	2.451	0.783	No	No	0.353	1.157
5	NO	0.261	NO	YES	2.363	0.884	No	No	0.326	1.222
6	NO	0.274	NO	YES	2.349	0.879	No	No	0.317	1.055
7	NO	0.303	NO	YES	2.315	1.027	No	No	0.305	1.036
8	NO	0.265	NO	YES	2.396	0.764	No	No	0.324	0.866
9	NO	0.358	NO	YES	2.339	1.512	No	No	0.295	1.657
10	NO	0.357	NO	YES	2.34	1.394	No	No	0.294	1.561
11	NO	0.365	NO	YES	2.274	2.605	No	No	0.291	1.079
12	NO	0.395	NO	YES	2.354	2.559	Yes	No	0.294	1.466
13	NO	0.3	NO	YES	2.255	1.657	No	No	0.286	2.113
14	NO	0.609	NO	YES	2.452	2.005	No	No	0.579	0.625
15	NO	0.39	NO	YES	2.386	1.27	No	No	0.653	1.331
16	NO	-0.029	NO	YES	2.592	1.072	No	No	0.725	1.252
17	NO	0.079	NO	YES	2.645	1.804	Yes	No	0.541	2.901
18	NO	0.041	NO	YES	2.653	0.883	No	No	0.342	5.188
19	NO	0.05	NO	YES	2.674	0.745	No	No	0.337	5.022
20	NO	-0.116	NO	YES	2.42	1.299	No	No	0.677	1.197
21	NO	0.121	NO	YES	2.412	1.179	No	No	0.426	2.265
22	NO	-0.005	NO	YES	2.443	0.88	No	Yes	0.358	2.424
23	NO	0.359	NO	YES	1.995	2.055	No	No	0.321	0.755
24	NO	0.367	NO	YES	2.314	2.671	Yes	No	0.292	0.976
25	NO	0.279	NO	YES	2.191	2.48	Yes	No	0.289	0.205
26	NO	0.235	NO	YES	2.44	1.805	No	No	0.354	0.773
27	YES	-0.101	NO	YES	3.412	2.268	Yes	No	0.351	1.406

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28	NO	0.226	NO	YES	2.392	1.612	Yes	No	0.321	-0.115
29	YES	0.205	NO	YES	2.443	2.179	No	No	0.285	0.964
30	YES	0.07	YES	YES	2.444	2.247	No	No	0.285	0.136
31	NO	-0.03	NO	YES	2.57	1.239	No	No	0.706	1.237
Reservetrol	**YES**	**0.648**	**NO**	**NO**	**2.062**	**1.93**	**No**	**No**	**0.977**	**1.174**

Table **3.1.4** Toxicity Parameters of the compounds

3.2 Molecular docking interactions:

The Docking simulations in the active site of G protein-coupled receptor kinase 4 **(2L98)**and Cardiac troponin **(4YHJ)** were performed by AutoDock Vina program, which has been shown in Table **3.2** The results revealed that all the designed resveratrol dithiocarbamate derivatives showed better binding affinities when compared to standard drug resveratrol. Against target 2L98 compound 26 and 30 has two hydrogen bond interactions and six hydrophobic interactions,whereas standard resveratrol has three hydrogen bond interactions and one hydrophobic interaction. So, the above results indicates that the hydrophobic interactions are more favorable for the cardiovascular activity.

Against target 4YHJ compound 26 and 30 has five hydrogen bond interactions and 2 to 4 hydrophobic interactions, whereas standard resveratrol has two hydrogen bond interactions and three hydrophobic interactions. A close view of binding interactions of target 4YHJ indicating hydrogen bond interactions are more favorable for the cardiovascular activity.

Compound Id	**2L98 Dock score (Kcal/mol)**	**Hydrogen Bond Interactions**	**Hydrophobic interactions**	**4YHJ Dock score (Kcal/mol)**	**Hydrogen Bond Interactions**	**Hydrophobic interactions**
1	-5.7	LEUA:121, LEUA:117, LEUA:136, GLUA:161	PHEA:104	-6.8	CYSA:475, GLYA:270, THRA:265	VALA:201, ALAA:214, LEUA:319, LEUA:193
2	-5.9	LEUA:121, LEUA:117, LEUA:136, VALA:160, PHEA:153	LEUA:100, META:120, PHEA:104	-7	ASNA:317, LEUA:193, META:267, THRA:265	VALA:201, ALAA:214, LEUA:319
3	-6.2		LEUA:100, META:120, PHEA:156, ILEA:148, LEUA:117, VALA:160, LEUA:121, PHEA:104, PHEA:153	-7	ASPA:330, ASNA:317,META:267, THRA:265	LEUA:319, VALA:201, ALAA:214

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4	-5.7	PHEA:156, PHEA:153, LEUA:100, ILEA:112, LEUA:117	LEUA:136	-7	ASNA:317, META:267,THRA:265	LEUA:319, VALA:201, ALAA:214
5	-6.2	META:90, META:120, THRA:124	PHEA:153, ILEA:112, LEUA:117, PHEA:156	-7.4	GLYA:270, GLYA:194, META:267, LEUA:193, ILEA:266,THRA:265, SERA:329, LEUA:264, ASNA:317, GLUA:316, ASPA:330	LEUA:319, VALA:201, ALAA:214
6	-6.6	LEUA:136, THRA:124, LEUA:121, LEUA:100, GLUA:161	PHEA:156, ILEA:112, LEUA:117, META:120, PHEA:104	-7.1	LEUA:193, META:267, THRA:265	CYSA:475, ALAA:214, LEUA:319, VALA:201
7	-6.7	PHEA:104, META:120, GLUA:161	LEUA:100	-7.2	META:267, SERA:329, GLUA:316	LEUA:319, VALA:201, ALAA:214, CYSA:475, LEUA:193
8	-6.5	THRA:124, META:90, LEUA:136	LEUA:121, LEUA:117, ILEA:148, PHEA:156	-6.7	ASPA:271, LYSA:195, VALA:248, LEUA:264, META:267, LEUA:193	CYSA:475, LEUA:319, ALAA:214, VALA:201
9	-6.6	PHEA:156, LEUA:100, LEUA:117, LEUA:121	PHEA:104, META:120	-7.1	GLYA:194, LYSA:195, GLUA:316, LEUA:264, VALA:248, THRA:265, ILEA:266, ASNA:268, META:267, SERA:329, ASNA:317	ASPA:271, VALA:201, ALAA:214, LEUA:319
10	-6.8	LEUA:100, META:120, LEUA:117, PHEA:156, PHEA:153, ILEA:112	LEUA:121, PHEA:104, META:157	-7.1	CYSA:475, ASPA:330, LYSA:216, META:267	LEUA:319, VALA:201, ALAA:214
11	-6.6	LEUA:117, LEUA:121, ALAA:123	LEUA:100, PHEA:104, META:120	-7.6	LEUA:193, ASPA:271, ASPA:330, THRA:265	ALAA:214, VALA:201

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12	-7	PHEA:156, VALA:160, PHEA:153, LEUA:117, LEUA:136	META:120, PHEA:104, LEUA:100	-7.1	ASPA:271, THRA:265, ASPA:330	LEUA:319, VALA:201, LEUA:193, ALAA:214, LYSA:216
13	-7.3	LEUA:121, VALA:160, PHEA:156	META:157, LEUA:100	-7.3	LYSA:195, META:267, LYSA:476	VALA:201, LEUA:319, CYSA:475, ASPA:271
14	-6.2	GLUA:161, PHEA:156, LEUA:100, META:120	VALA:160, PHEA:104, LEUA:117	-7.1	GLYA:270, ASNA:268,	CYSA:475, LEUA:319, LEUA:193, VALA:201,ALAA: 214
15	-6.6		LEUA:117, ILEA:148, PHEA:156, META:120, PHEA:104, LEUA:121, LEUA:100, VALA:160, GLUA:161	-7.1	GLYSA:270, CYSA:475, META:267, THRA:265,	ALAA:214, VALA:201, LEUA:319, LEUA:193
16	-7	LEUA:121, PHEA:153, META:120, LEUA:136	PHEA:104, VALA:160, LEUA:117	-7.3	LYSA:476, ASPA:271, GLYA:194, LYSA:195, CYSA:475, ILEA:266, META:267, VALA:248, LEUA:264,AS NA:268, TYRA:474, ASPA:330, GLYA:270, LYSA:216, SERA:329,	LEUA:193,ALAA: 214, LEUA:319,VALA: 201, THRA:265
17	-6.3	GLUA:161, LEUA:100, META:120, PHEA:156	PHEA:104, LEUA:117	-7.6	GLUA:316, GLYA:270, ASNA:268	CYSA:475, LEUA:193, ALAA:214, VALA:201, LEUA:319
18	-6.4	LEUA:121, LEUA:117	META:120, PHEA:104, LEUA:100	-7.5	ASNA:268, ASPA:330, THRA:265, META:267	LEUA:319, VALA:201, ALAA:214
19	-6.7	LEUA:121, LEUA:117	META:120, PHEA:104, LEUA:100	-7.5	ASNA:268, THRA:265, META:267, ASPA:330, ASNA:317	VALA:201, LEUA:319, ALAA:214

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20	-6	GLUA:161	PHEA:156, META:120, PHEA:104, LEUA:100	-7.4	THRA:265, ASNA:268, CYSA:475, ASPA:271	VALA:201, ALAA:214, LEUA:319, LEUA:193,
21	-7.1	PHEA:104, LEUA:136	PHEA:153, LEUA:100, ILEA:148, LEUA:117,PHEA:156, GLYA:140	-6.9	SERA:329, LYSA:216, ASPA:271, META:267	VALA:201, ALAA:214, LEUA:319, LEUA:193
22	-6.6	LEUA:100, PHEA:156, GLUA:161	PHEA:104, META:120	-7.8	ASPA:330, META:267, VALA:248, LEUA:264	LEUA:193, LEUA:319, ALAA:214, VALA:201
23	-7.1	GLUA:161, LEUA:117	META:157, PHEA:156, LEUA:100, LEUA:97, META:120	-7	SERA:329, META:267	VALA:201, LEUA:193, ALAA:214
24	-7.3	PHEA:156, META:157, LEUA:97	PHEA:104, LEUA:100	-7.1	LYSA:216, META:267, ASNA:317	VALA:201, LEUA:193, ALAA:214, LEUA:319, GLUA:316
25	-7	ILEA:133, GLYA:140	PHEA:104, LEUA:136, LEUA:121, LEUA:117, PHEA:156, ILEA:148, VALA:160, GLUA:126	-7.6	LYSA:195, ASPA:271, META:267	ALAA:214, VALA:248, LEUA:264, VALA:201, LEUA:319, LEUA:193, CYSA:475
26	-7.6	GLUA:96, META:90	META:157, GLUA:161, LEUA:97, LEUA:100	-8	CYSA:475, SERA:329, ASPA:330, ASPA:271, LYSA:216	LEUA:319, VALA:201
27	-6.7	LEUA:100	PHEA:156, META:120, PHEA:104	-7.9	LYSA:216, SERA:329, META:267, ASNA:317, GLUA:316, ASPA:271	LEUA:264, VALA:201, CYSA:475, LEUA:319
28	-6.4	GLUA:161	PHEA:156, LEUA:100, META:120, LEUA:121, PHEA:104, LEUA:117, META:157	-7.7	ASNA:268, CYSA:475, GLUA:316	LEUA:193, ALAA:214, VALA:201, LEUA:319, META:267
29	-7.2	GLUA:161, META:90	PHEA:156, LEUA:100, META:120, LEUA:121, PHEA:104	-7.3	META:267, TYRA:474	CYSA:475, ALAA:214, VALA:201, VALA:248, LEUA:319

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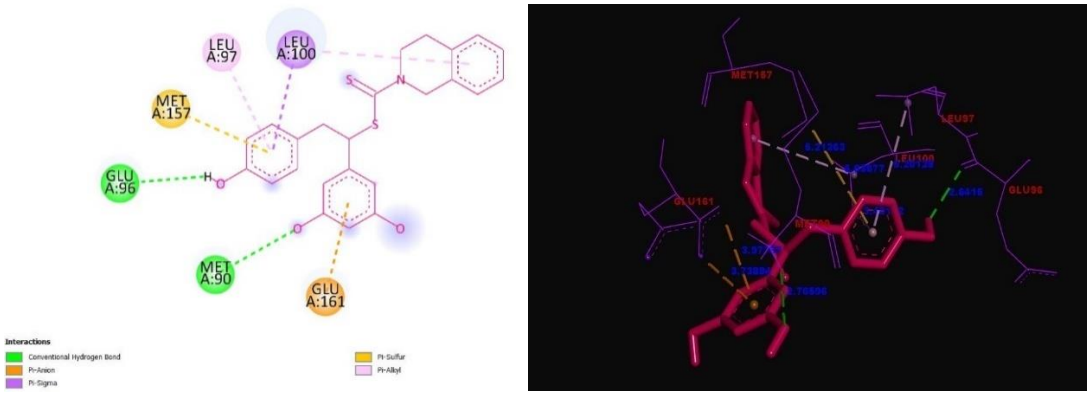
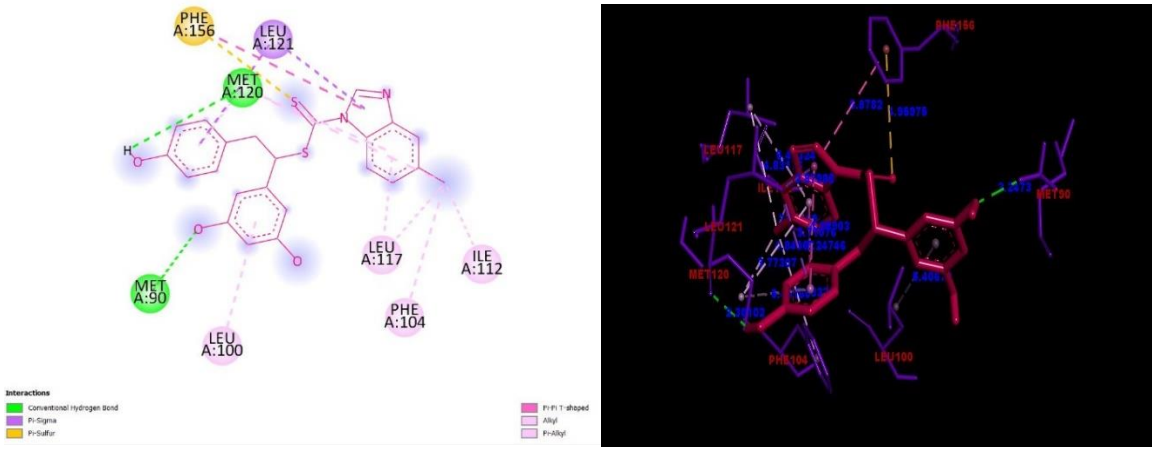
30	-7.5	META:90, META:120	LEUA:121, LEUA:100, LEUA:117, PHEA:104, ILEA:112, PHEA:156	-8	CYSA:475, ASNA:317, ILEA:266, GLYA:196	LEUA:193, LEUA:319, VALA:201, ALAA:214
31	-6.1	LEUA:136, LEUA:117, LEUA:121	META:120, PHEA:104	-7.4	THRA:265, GLYA:270, CYSA:475, META:267, LEUA:193, LYSA:195	LEUA:319, VALA:201, ALAA:214
Reservetrol	**-6**	**GLUA:161, VALA:160, LEUA:117**	**META:120**	**-7**	**LEUA:319, ALAA:214**	**LEUA:193, VALA:201, CYSA:475**

Table **3.2** Molecular docking interactions of Novel ResveratrolDithiocarbamate derivative with targets2L98 and 4YHJ.

.



Compound 26



Compound 30

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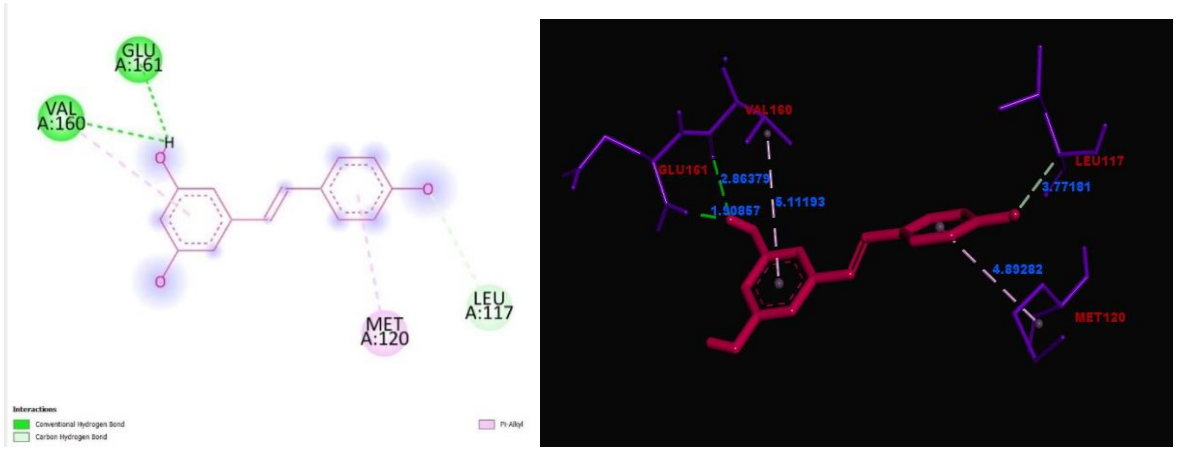
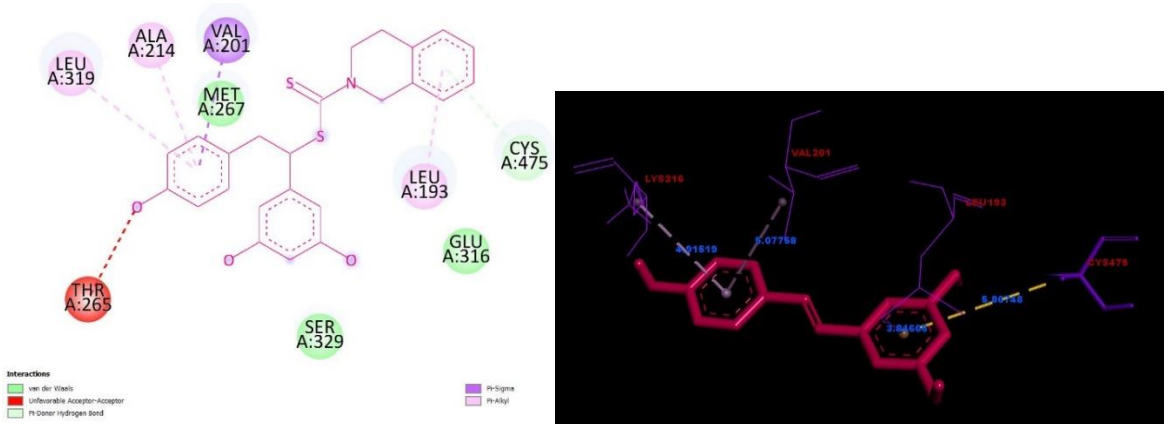


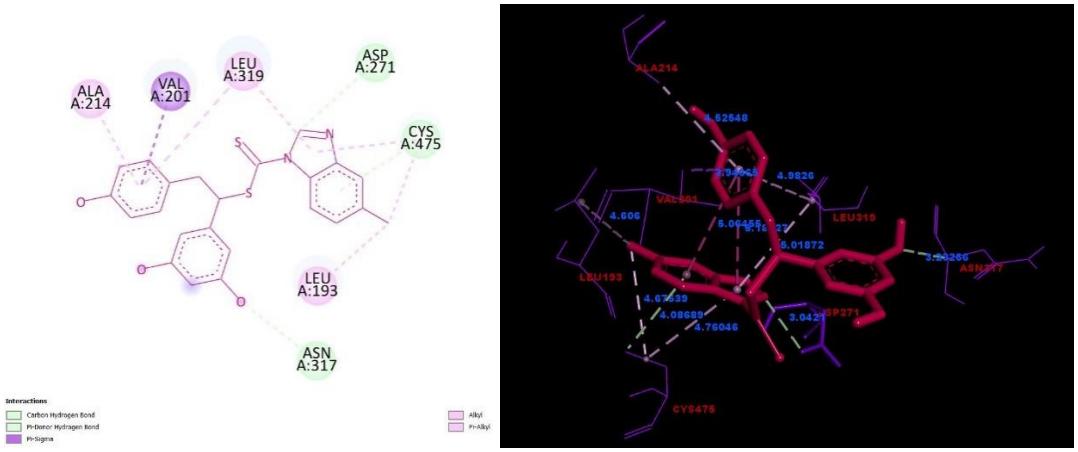
Standard Resveratrol

Figure **3.2.1** D and 3D visualization of Compound 26, 30 and Standard Reservetrolwith target active site 2L98

.



Compound 26



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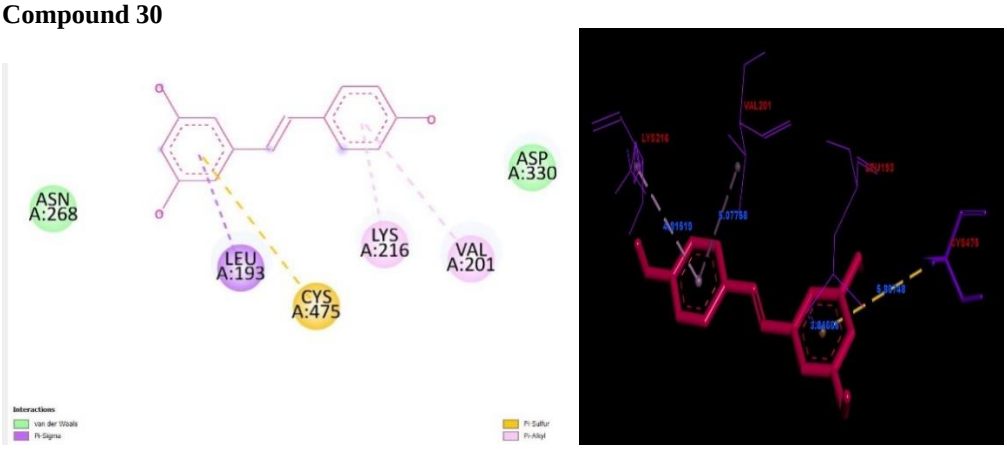
Compound 30



Standard Reservetrol

Figure **32.2** D and 3D visualization of Compound 26, 30 and Standard Reservetrol with target active site 4YHJ

4.Conclusion:

For the present investigation we designed 31 novel resveratrol with various aliphatic, alicyclic, aralkyl and heterocyclic moieties ondithiocarbamates. Studies like ADMET property prediction, Bioactivity, toxicity risk assessment and molecular descriptors were performed by insilico methods. As all the Compounds has druglike properties, further subjected to molecular docking studies with two different cardiovascular targets such as G protein-coupled receptor kinase 4 (2L98) and Cardiac troponin (4YHJ).The docking results revealed that all 31 compounds have good binding interactions when compared to standard resveratrol. Specifically compound 26 and 30 identified as potential lead inhibitors of both the targets (2L98 & 4YHJ) of cardiovascular disease.

A deep investigation of invitro activity supported by insilico ADMET and docking assessment clearly suggested that these molecules would be of use as therapeutics in medicine to treat the cardiovascular disease.

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