Design, Synthesis and Evaluation of New Compounds Potent Anticancer Agent

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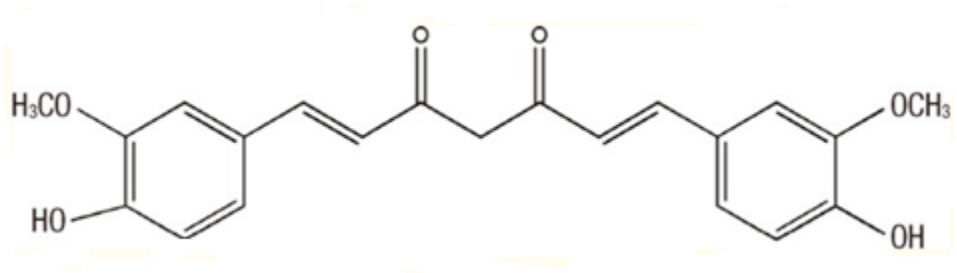
Abstract:
Aim of the present study is design, synthesis and evaluation of potent anticancer activity of the Curcumin. But in these studies main focus on the breast cancer. Anticancer agent such as Tamoxifen, raloxifene, Toremifene and Fulvestrant but they have some limitation to treat for breast cancer. So we hypothesized that tamoxifen can be used as standard drugs and it may be helpful to develop antiestrogens should not only have good binding affinity with particular receptor but it also must have selective activation for that receptor which expressed in breast cancer progression. Therefore, selective ER α antagonists may be helpful for the breast cancer treatment. Curcumin's antiproliferative effects are estrogen dependent in ER (estrogen receptor)-positive MCF-7 cells, being more pronounced in estrogen-containing media and in the presence of exogenous 17- estradiol.

Keywords: molecular docking, Compounds, Anticancer Agent, Ligands Preparation, Validation of Docking Method, Molecular Docking Analysis

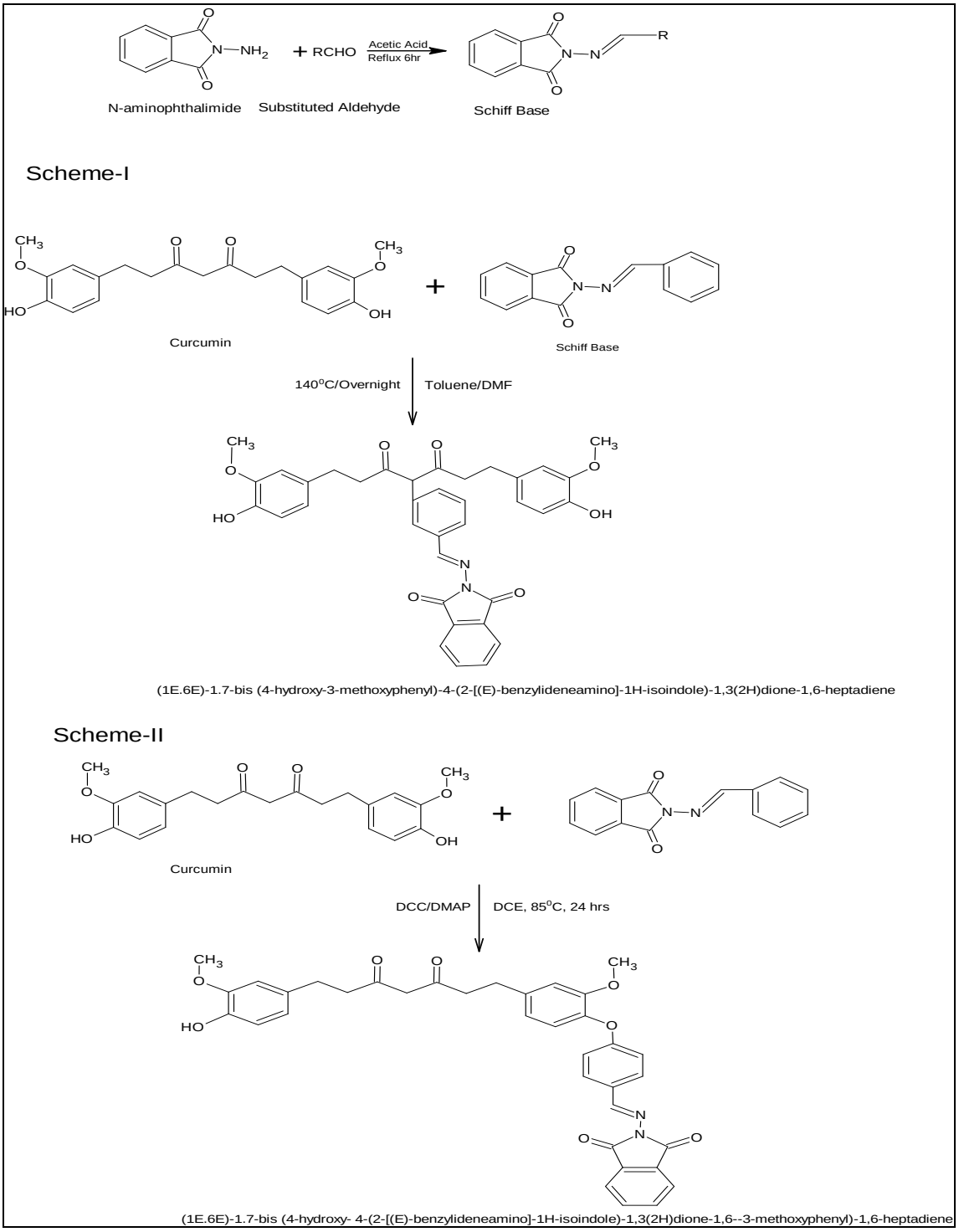
Introduction:

Curcumin derivative were designed and studied with respect to docking with ERα inhibitor.

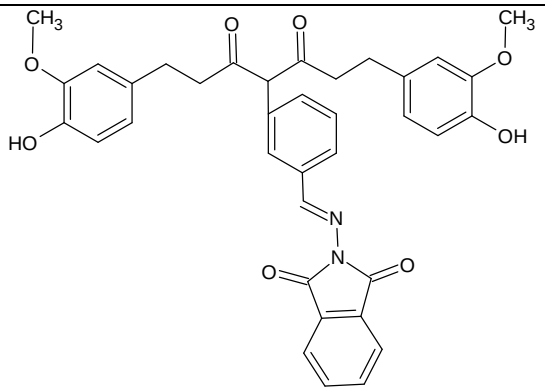
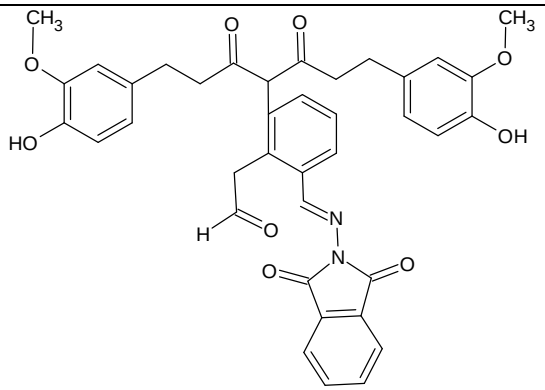
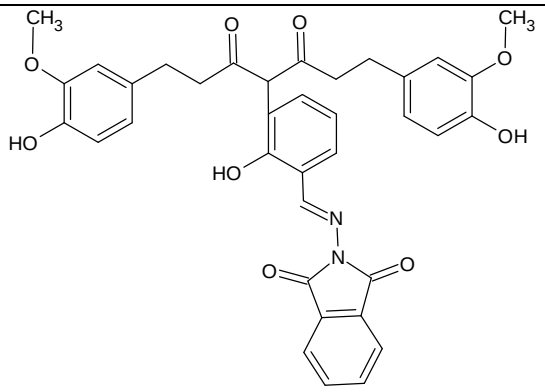
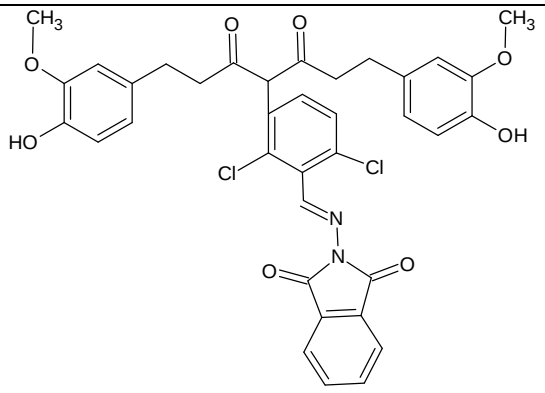


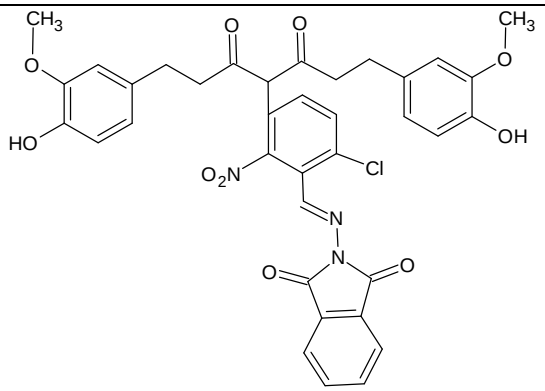
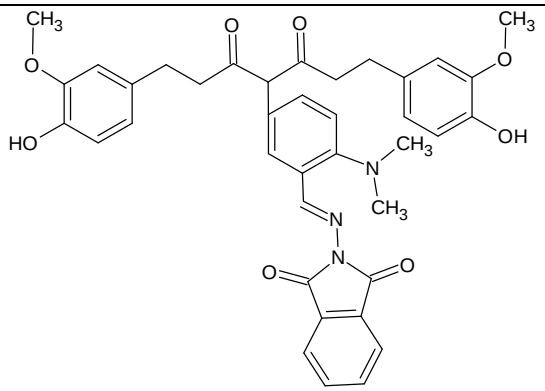
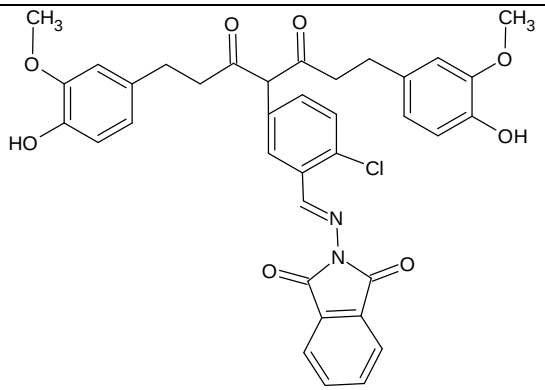
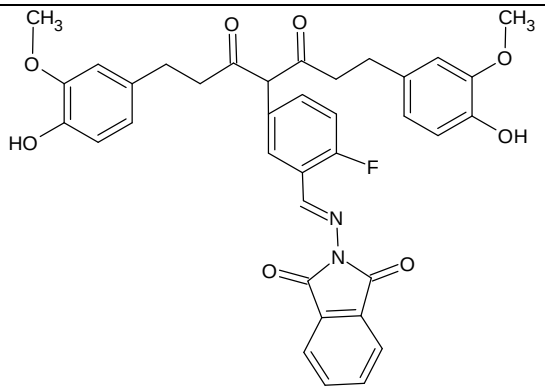
Molecular Docking Study:

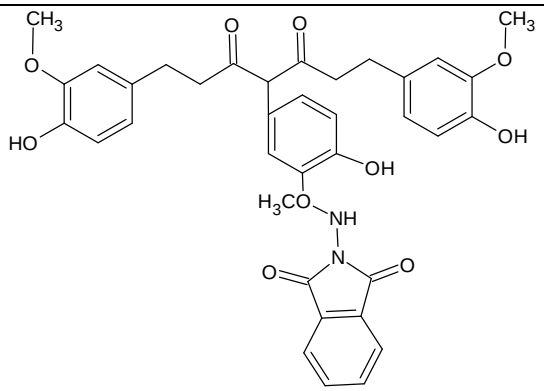
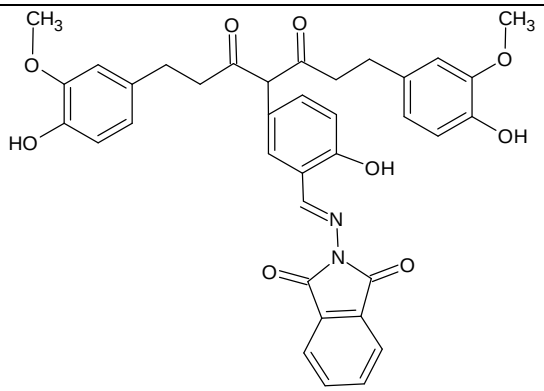
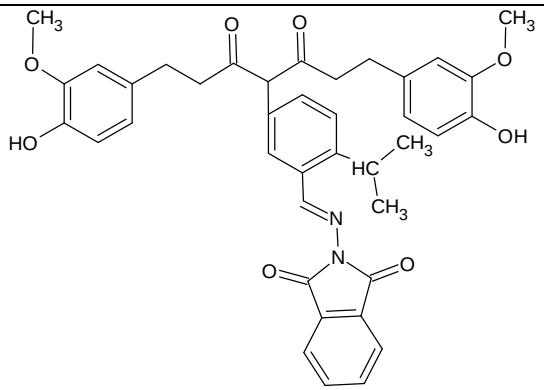
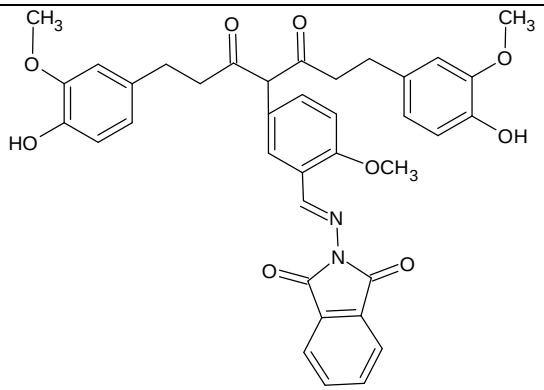
Scheme:

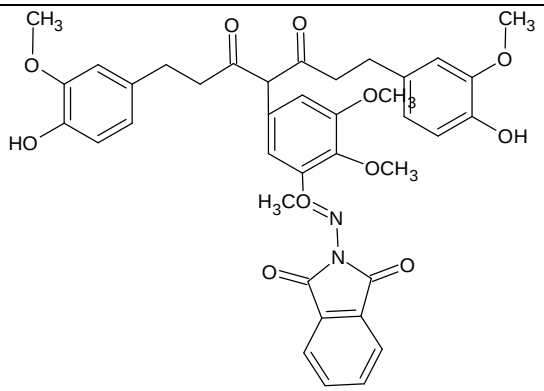


Substitutions: Scheme-I

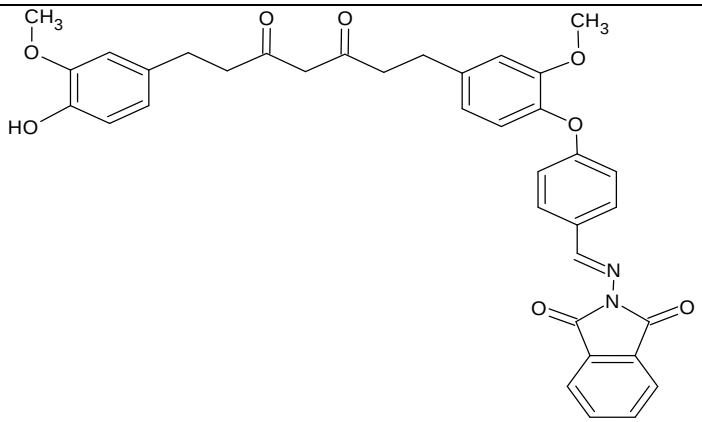
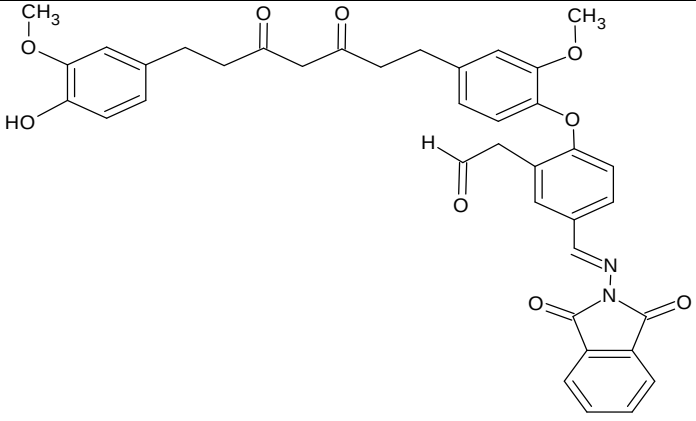
Sr.No	Molecule Name	Structure
1.	Benzaldehyde	
2.	Cinnamaldehyde	
3.	2- Hydroxy Benzaldehyde	
4.	2,4-Dichloro Benzaldehyde	

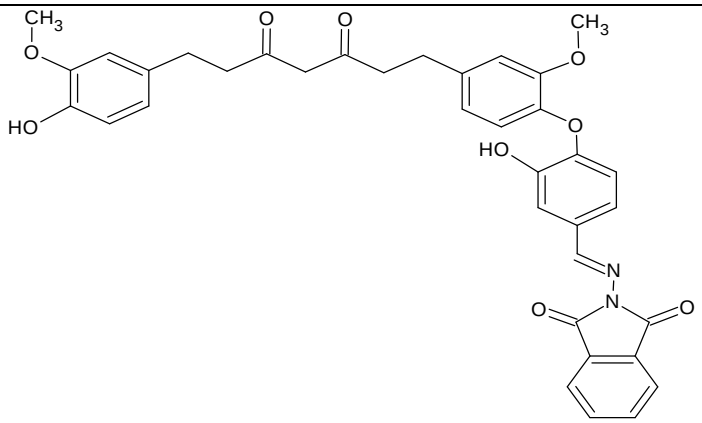
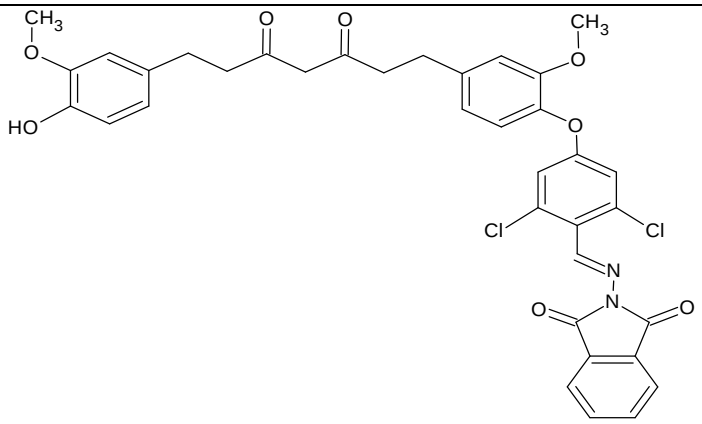
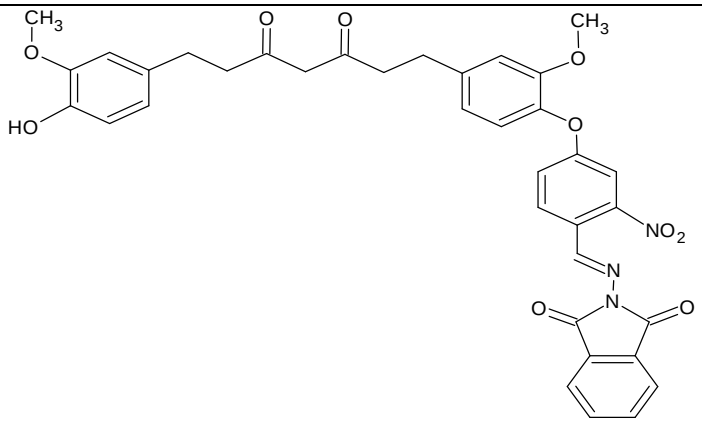
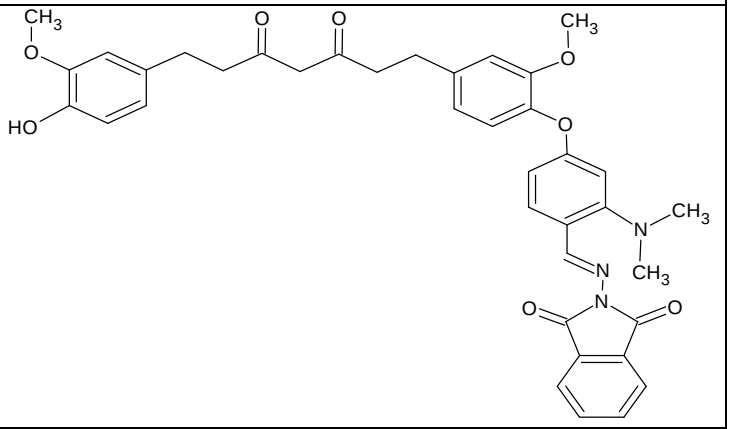
5.	2-Nitro Benzaldehyde	
6.	4-(N,N-Dimethylamine) Benzaldehyde	
7.	4-Chlorobenzaldehyde	
8.	4-Fluorobenzaldehyde	

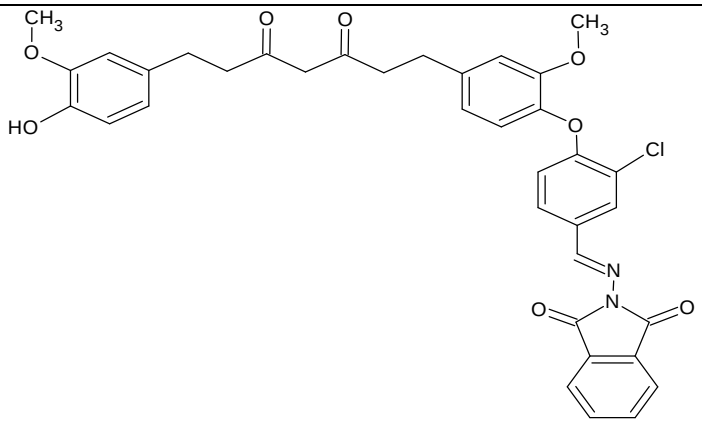
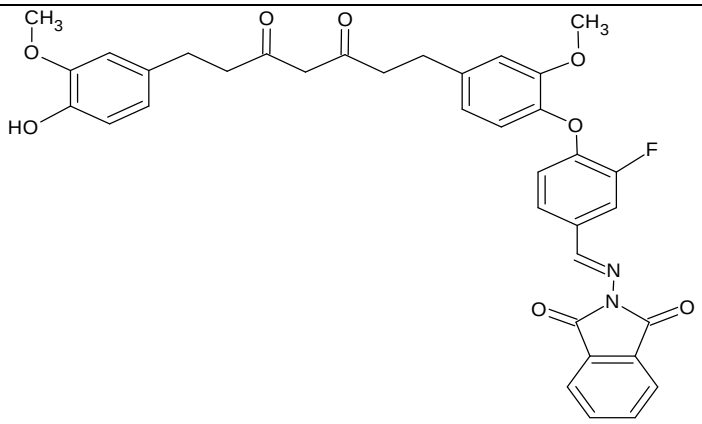
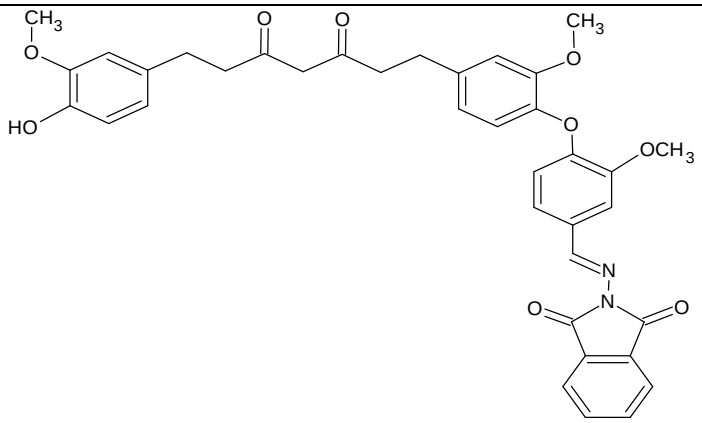
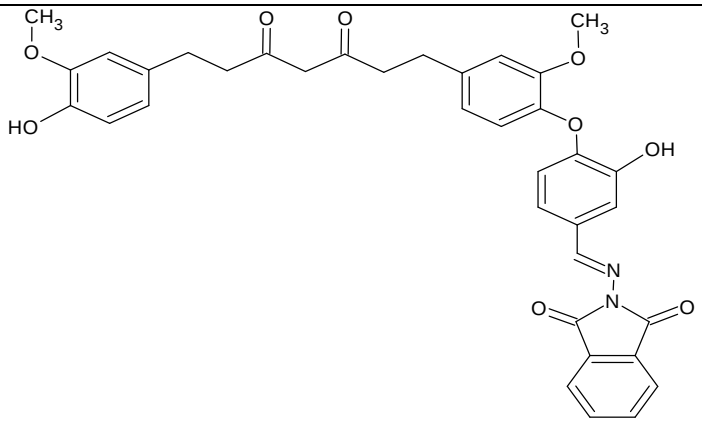
9.	4-Hydroxy 3- Methoxy Benzaldehyde	
10.	4-Hydroxy Benzaldehyde	
11.	4-Isopropyl Benzaldehyde	
12.	4-Methoxy Benzaldehyde	

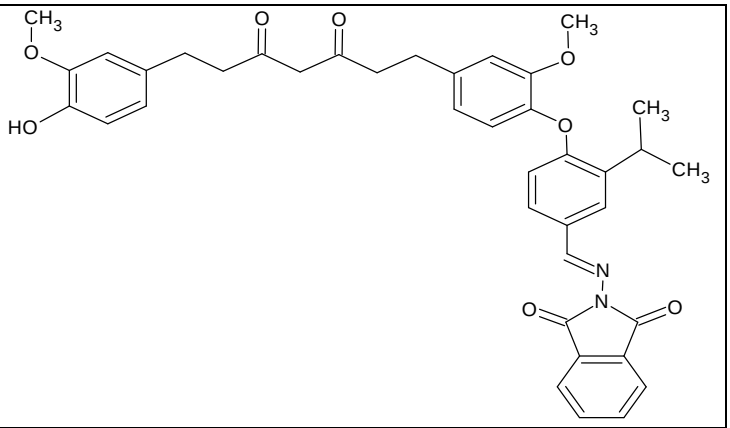
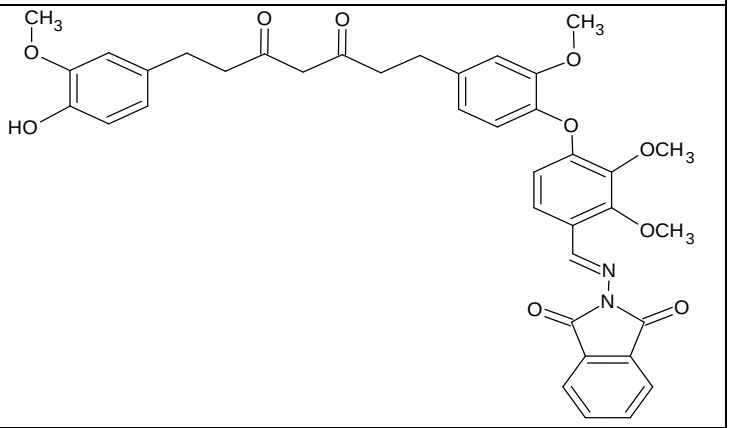
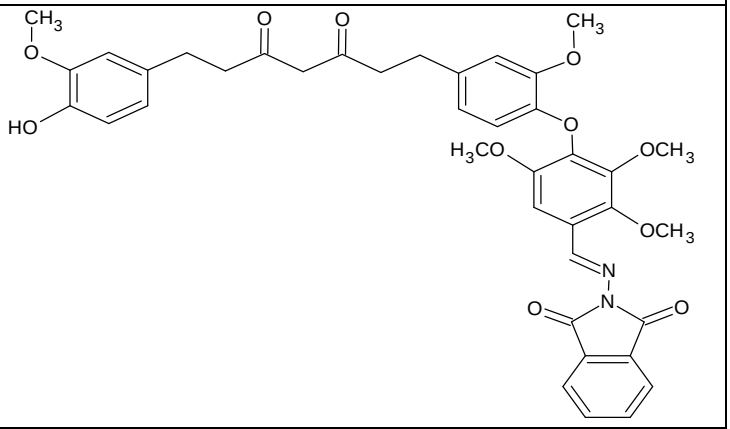
13.	3,4,5-Trimethoxy Benzaldehyde	

Substitutions: Scheme-II

Sr.No	**Molecule Name**	**Structure**
1.	Benzaldehyde	
2.	Cinnamaldehyde	

3.	2- Hydroxy Benzaldehyde	
4.	2,6-Dichloro Benzaldehyde	
5.	2-Nitro Benzaldehyde	
6.	4-(N,N-Dimethylamine) Benzaldehyde	

7.	3-Chlorobenzaldehyde	
8.	3-Fluorobenzaldehyde	
9.	3- Methoxy Benzaldehyde	
10.	3-Hydroxy Benzaldehyde	

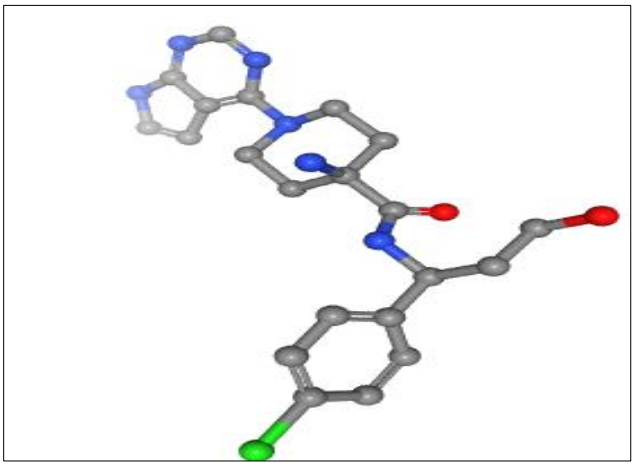
11.	3-Isopropyl Benzaldehyde	
12.	2,3-dimethoxy Benzaldehyde	
13.	2,3,5-Trimethoxy Benzaldehyde	

Structure Feasibility:

Structural feasibility has been checked using ACD Chemsketch software (License Version). All structures found stereospecific and with optimized bond length and angles.

Target PDB: 0XZ

4-amino-N-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidine-4-carboxamide



Ligands Preparation

The twelve structures of chemical constituents of curcumin with schiff base were studied, the two-dimensional (2D) chemical structures of the ligands were sketched using ACD Chemsketch, and the energy minimizations of the prepared ligands were carried out with Chem3D Ultra and were saved in pdb format.

Target Preparation and Validation of Docking Method

The three dimensional structure of glycogen phosphorylase was obtained from Brookhaven protein databank (PDB ID: 0XZ). The docking study was started with the definition of a binding site, in general a restricted region of the protein. The size and location of this binding site was visualized in PyMOL. The protein target were further validated with AutoDock Vina in PyRx 0.8 by RMSD value determination.

Molecular Docking Analysis

Binding mode and interaction of transferase inhibitor with individual chemical constituent was performed using AutoDock Vina software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. The protein was loaded in Pyrex software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues. All bonds of ligands were set to be rotatable. All calculations for protein-fixed ligand-flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method. The docking site on protein target was defined by establishing a grid box with the dimensions of X: 38.0729 Y: 33.3208 Z: 25.0000 Å, with a grid spacing of 0.375 Å, centered on X: 20.2892 Y: 10.3219 Z: 32.3218 Å. The best conformation was chosen with the lowest docked energy, after the docking search was completed. Ten runs with AutoDock Vina were performed in all cases per each ligand structure, and for each run the best pose was saved. The average affinity for best poses was taken as the final affinity value. The interactions of complex transferase inhibitor

protein-ligand conformations, including hydrogen bonds and the bond lengths were analyzed using PyMol.

Results and Discussion

Docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure based drug design process. AutoDock Vina is a open-source program for drug discovery, molecular docking and virtual screening, offering multicore capability, high performance and enhanced accuracy and ease touse. The parameters chosen for the docking can be judged by the docking tool's ability to reproduce the binding mode of a ligand to protein, when the structure of the ligand–protein complex is known. The criterion usually used is the all atom root mean square deviation (RMSD) between the docked position and the crystallographically observed binding position of the ligand, and success is typically regarded as being less than 2Å9 . In this study, the native ligand was (1E.6E)-1.7-bis (4-hydroxy-3-methoxyphenyl)-4-(2-[(E)-benzylideneamino]-1H-isoindole)-1,3(2H)dione-1,6-heptadiene. This compound has been identified as a potent inhibitor of transferase inhibitor. Figure 1 showed the model of interaction between I-1 and binding site of transferase inhibitor. Amino acids residues of transferase inhibitorwhich involved in interaction with I-1 were Glu234A, Ala230A, Thr 160A, Lys179A. A hydrogen bond was occurred between carbonyl group of Glu234A as hydrogen bond acceptor and –NH of indole ring as hydrogen bond donor. Between cationic center of Ala230A and anionic center of I-1, an electrostatic interaction was formed.

Binding energy of interactions were calculated as per software format and mentioned in table 3.

Figure 1:

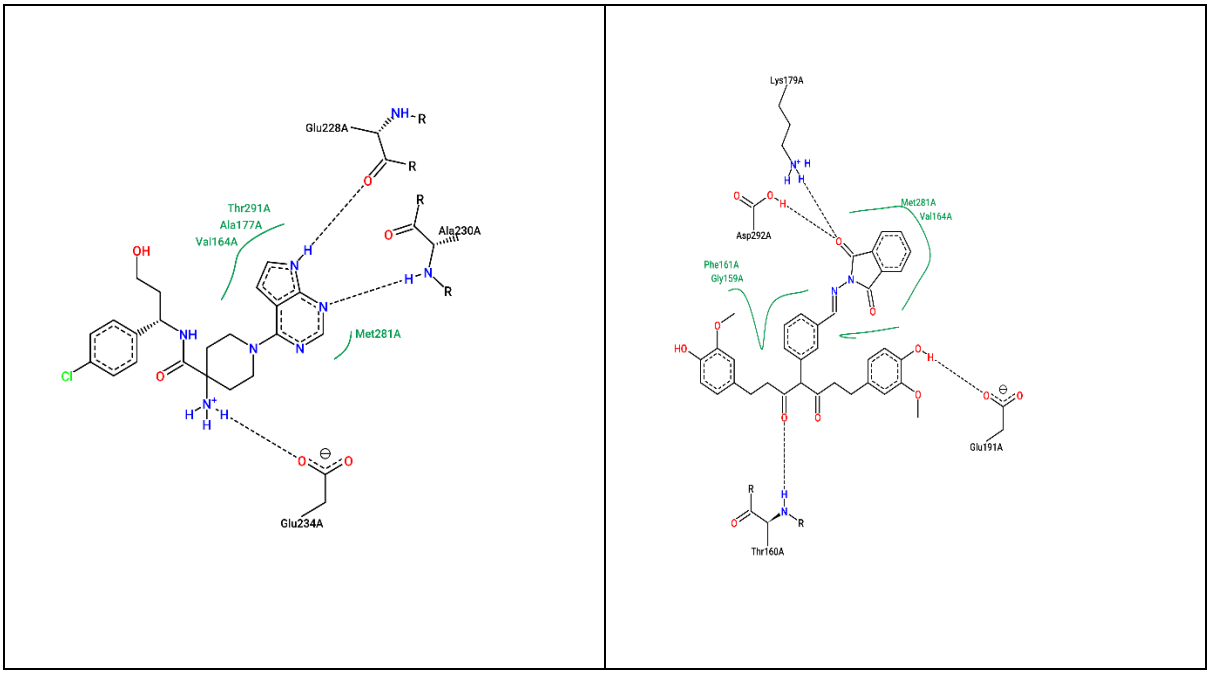


Table-1 Actual and Predicted activities as per 3D models (Training set)

Compound	(R)	Actual IC50	Predicted IC50	Fitness Score
A	2,4-Dichloro Benzaldehyde	1.65	2.03	-0.38
B	2-Hydroxy Benzaldehyde	2.48	2.22	0.26
C	2-Nitro Benzaldehyde	8.13	3.17	4.96
D	3,4,5-Trimethoxy Benzaldehyde	1.3	1.31	-0.01
E	4-(N,N dimethylamino) Benzaldehyde	1.31	1.30	0.01
F	4-Chloro Benzaldehyde	1.07	1.80	-0.73

Table-2 Actual and Predicted activities as per 3D models (Test set)

Compound	(R)	Actual IC50	Predicted IC50	Fitness Score
G	4-Fluro Benzaldehyde	1.40	1.79	0.39
H	4-Hydroxy 3-methoxy Benzaldehyde	3.92	2.46	1.46
I	4-Hydroxy Benzaldehyde	8.93	1.69	7.24
J	4-Isopropyl Benzaldehyde	1.96	1.67	0.29
K	4-Methoxy Benzaldehyde	0.51	1.69	-1.1
L	Cinnamaldehyde	0.49	1.30	-0.81

Table-3Binding Energy

Sr.No	**Molecule Name**	**Dock Score**
1.	Cinnamaldehyde_3D.mol2	-9.976
2.	2- Hydroxy Benzaldehyde._3D.mol2	-10.054
3.	2,4-Dichloro Benzaldehyde._3D.mol2	-10.412
4.	2-Nitro Benzaldehyde._3D.mol2	-10.382
5.	4-(N,N-Dimethylamine) Benzaldehyde_3D.mol2	-10.021
6.	4-Chlorobenzaldehyde._3D.mol2	-9.676
7.	4-Fluorobenzaldehyde._3D.mol2	-10.165
8.	4-Hydroxy 3- Methoxy Benzaldehyde._3D.mol2	-10.551
9.	4-Hydroxy Benzaldehyde._3D.mol2	-9.755
10.	4-Isopropyl Benzaldehyde._3D.mol2	-9.807
11.	4-Methoxy Benzaldehyde._3D.mol2	-10.025
12.	3,4,5-Trimethoxy Benzaldehyde._3D.mol2	-9.967

Table-4 Statistical parameters for 3D QSAR (kNN Method (Simulated Annealing))

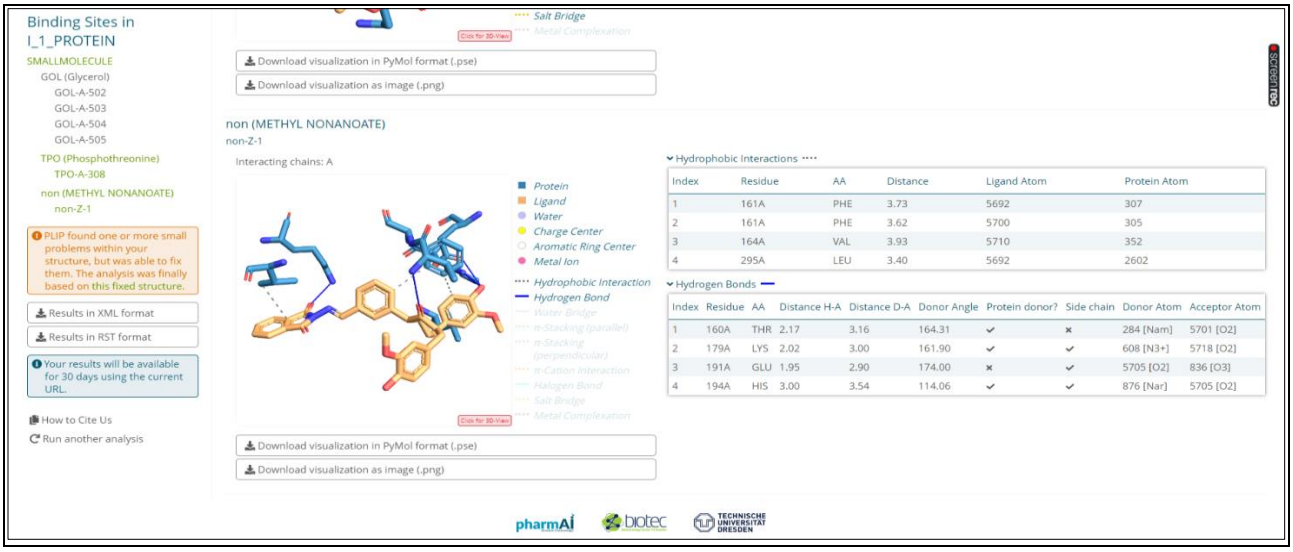
Parameter	Reading
k Nearest Neighbour (kNN)	2
n	12
Degree of freedom	-5
q2	0.5141
q2_se	0.6931
Predr2	0.1109
pred_r2se	3.9922

Table-5 Descriptors

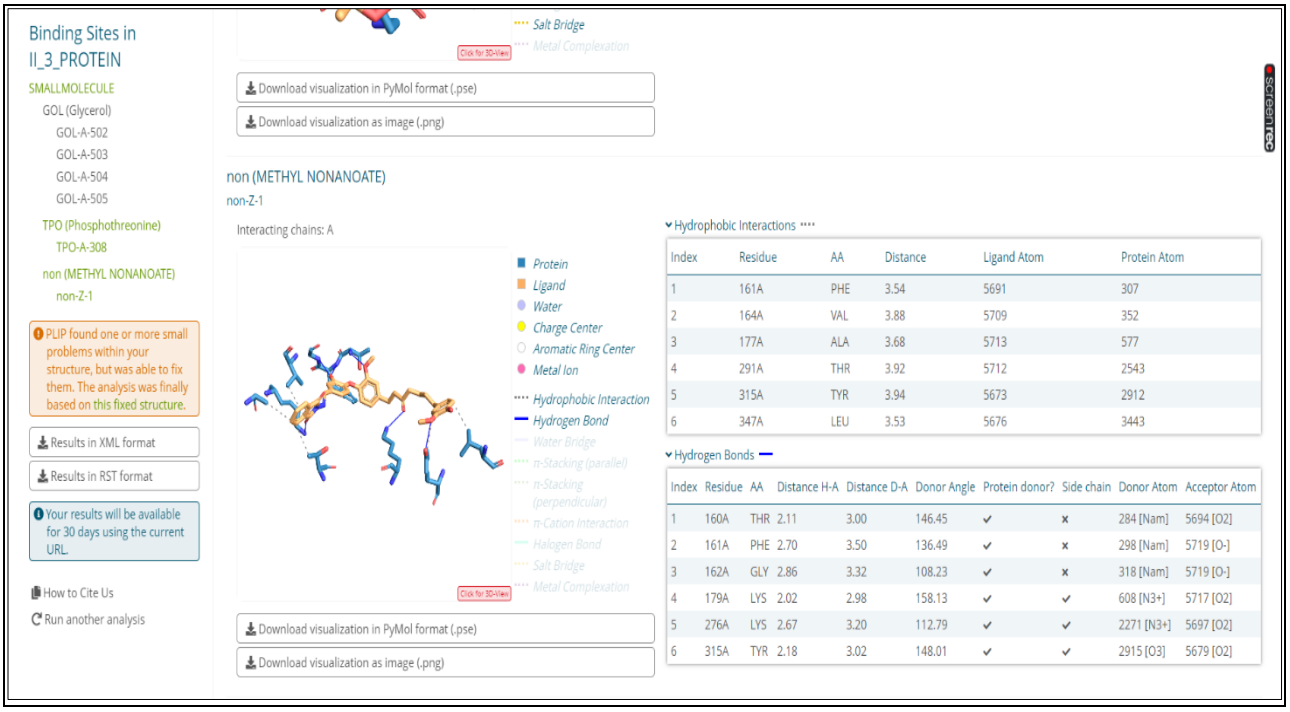
Descriptors	Range	
E_945	0.0566	0.0475
S_764	0.3492	2.2903
S_897	0.0220	0.0134
E_774	3.8370	0.3605
E_898	0.2903	0.2839
S_973	0.1085	0.0279
E_383	0.0802	0.2196
E_319	0.0764	0.3860
S_832	0.0178	0.0107
E_546	0.6775	0.4462

Hydrophobic Interaction:

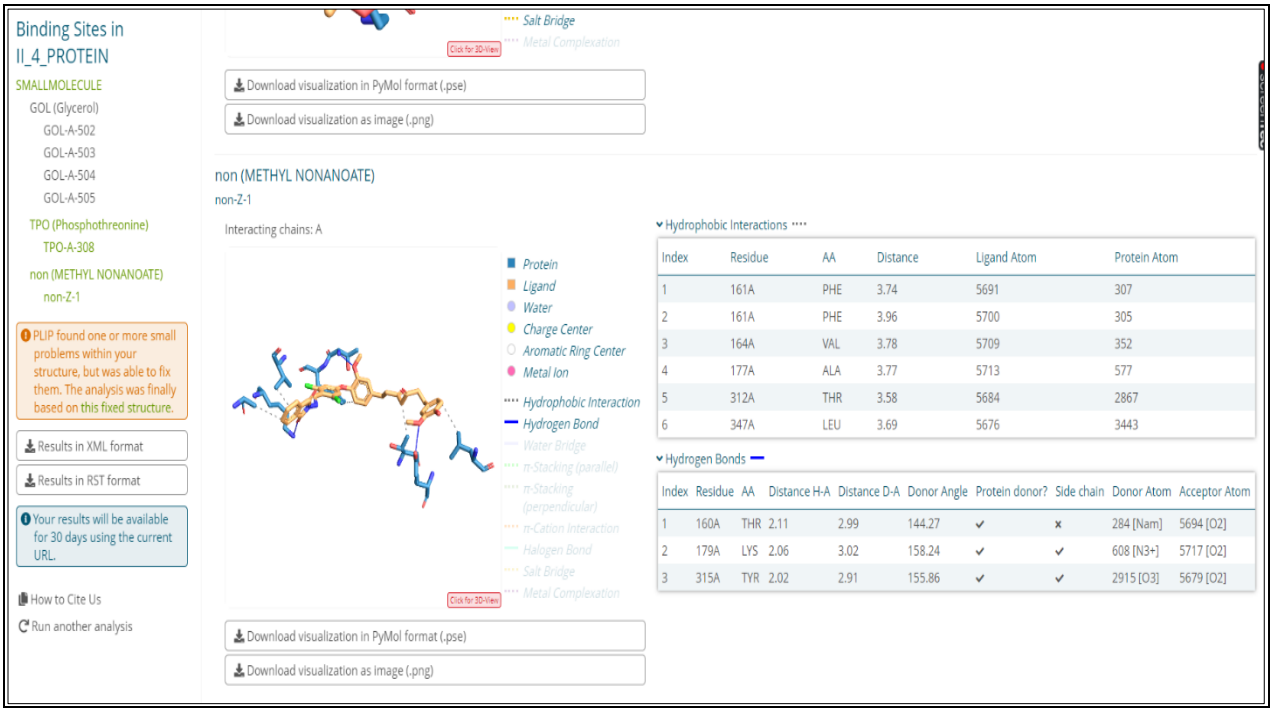
Compound I-1



Compound II-3



Compound II-4



Conclusion:

The current work, the design, synthesis, and in vitro and in silico evaluation of a series of thiazolyl hydrazone derivatives as potential antitumor agents targeting Akt were described. Compound **1,3,4** was identified as the most potent and selective anticancer agent on A549 and C6 cells in this series. Moreover, compound **1,3,4** induced early and late apoptosis in C6 cell line more than cisplatin and showed significant Akt inhibitory activity. According to in vitro and in silico studies, compound **6** stands out as a potential orally bioavailable anticancer agent for further in vivo studies.

References:

1. Ansari, J.; Shackelford, R.E.; El-Osta, H. Epigenetics in Non-Small Cell Lung Cancer: From Basics to Therapeutics. Transl. Lung Cancer Res. **2016**, 5, 155–171.
2. Gyoba, J.; Shan, S.; Roa, W.; Bédard, E.L.R. Diagnosing Lung Cancers through Examination of Micro-RNA Biomarkers in Blood, Plasma, Serum and Sputum: A Review and Summary of Current Literature. Int. J. Mol. Sci. **2016**, 17, 494.
3. Patil, S.A.; Hosni-Ahmed, A.; Jones, T.S.; Patil, R.; Pfeffer, L.M.; Miller, D.D. Novel Approaches to Glioma Drug Design and Drug Screening. Expert Opin. Drug Discov. **2013**, 8, 1135–1151.
4. Roy, N.K.; Bordoloi, D.; Monisha, J.; Padmavathi, G.; Kotoky, J.; Golla, R.; Kunnumakkara, A.B. Specific Targeting of Akt Kinase Isoforms: Taking the Precise Path for Prevention and Treatment of Cancer. Curr. Drug Targets **2017**, 18, 421–435
5. Das, D.; Sikdar, P.; Bairagi, M. Recent Developments of 2-Aminothiazoles in Medicinal Chemistry. Eur. J. Med. Chem. **2016**, 109, 89–98.
6. Mathew, B.; Suresh, J.; Ahsan, M.J.; Mathew, G.E.; Usman, D.; Subramanyan, P.N.S.; Safna, K.F.; Maddela, S. Hydrazones as A Privileged Structural Linker in Antitubercular Agents: A Review. Infect. Disord. Drug Targets **2015**, 15, 76–88.
7. Kumar, P.; Narasimhan, B. Hydrazides/Hydrazones as Antimicrobial and Anticancer Agents in the New Millennium. Mini-Rev. Med. Chem. **2013**, 13, 971–987.
8. Ashwell, M.A.; Lapierre, J.M.; Brassard, C.; Bresciano, K.; Bull, C.; Cornell-Kennon, S.; Eathiraj, S.; France, D.S.; Hall, T.; Hill, J.; et al. Discovery and Optimization of a Series of 3-(3-Phenyl-3**H**-imidazo[4,5-**b**]pyridin-2-yl)pyridin-2-amines: Orally Bioavailable, Selective, and Potent ATP-Independent Akt Inhibitors. J. Med. Chem. **2012**, 55, 5291–5310