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In-silico Interaction studies of curcumin and structurally related commercial drug afatinib and bicalutamide with probable anticancer targets

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Abstract: Computational studies have become an important strategy in discovering and developing new drug candidates in terms of both money and time. Curcumin, a biologically active ingredient of the natural product turmeric is reported to possess a variety of pharmacological activities such as antibacterial, anti-inflammatory; immunoregulator makes it a molecule of choice as a probable anticancer drug. In the present work, we have compared the potential of curcumin as an anti-cancer agent virtually with two structurally related commercial drugs (Afatinib and Bicalutamide). 7 anticancer targets I-CDK2, II-PI3K, III- NF-KB, IV-PSA, V- MMP-2, VI-MMP-9, and VII- VEGF-Amainly involved in four major cancer types namely-lung, breast, prostate, and colorectal cancer were selected. Computational tools include CHEM 3D, free online web server molinspiration, vNNADMET, SWISS ADME, admetSAR, OPEN BABEL, AUTODOCK 4. O mgl tools, AUTODOCK Vina, and DS-Visualizer were used. In-silico analysis of curcumin against various anticancer targets validate the anticancer activities of curcumin.

Keywords: ADMETox; Anticancer; Natural product; Computational; Docking

1. Introduction

The second leading fatal disease is cancer. According to the National Cancer Registry Programme of the India Council of Medical Research (ICMR), more than 1300 Indians die every day due to cancer. Cancer treatment cells include the use of chemotherapeutic drugs such as alkylating agents, anti-metabolites, spindle toxins, and DNA binders and cutters. Repeated therapy with these agents adversely affects the body and also results in drug resistance. Besides, chemotherapy-induced side effects like bone marrow Suppression, neuropathy, stomach problems, baldness, exhaustion, depression, and skin disorders were also reported [1].Thus there is a need to explore natural products as the future anticancer drug that treats cancerous cells with the least toxicity and side effects [2, 3]. One such bioactive natural compound as reported in the literature is curcumin [4-17]. To

evaluate the potential of curcumin to interact with anticancer targets the present work was undertaken. Seven anticancer targets I-CDK2 [18], II-PI3K [19], III- NF-KB [20], IV-PSA [21], V- MMP-2[22], VI-MMP-9[22], and VII- VEGF-A [22] were selected to carry out the studies. These reported anticancer targets are mainly involved in four major cancer types namelylung, breast, prostate, and colorectal cancer. The results have been compared with two commercially available drugs Afatinib and Bicalutamide which happen to be structurally analogs to curcumin. The study directs the target-oriented research of curcumin as an anticancer drug [23]. Computational outcome reduces a load of chemicals on the environment, biological systems and helps in identifications of potential targets for curcumin in cancer studies. In new of the above, first of all, we used CHEM 3D for molecular modeling studies to select structurally similar commercial drugs, free online web server molinspiration to evaluate bioactivity score, drug-likeness properties, vNADMET, admetSAR, and SWISS ADME to predict the properties of absorption, distribution, digestion, and toxicity [24] of curcumin and selected drugs, OPEN BABEL to convert downloaded files in the required format, AUTODOCK 4. O mgl tools and AUTODOCK Vina to compare their affinity for target proteins via molecular docking, and to visualize final docking results i.e. interaction between ligand-target complexes DS-Visualizer was used.

2. Method

2.1. Selection of commercial drugs

Molecular structure viewer chem3D is used to access the Overlay of the molecular structure of various commercially available anticancer drugs as analogous to curcumin. Out of several compounds, only two compounds Afatinib and Bicalutamide were selected for further study based on their structural similarity with curcumin (Fig1).

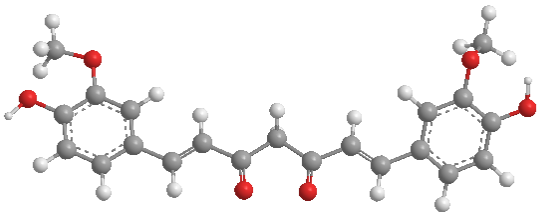


Fig: 1 3D structure of curcumin

Molecular modeling studies were carried out using Perkin Elmer (https://perkinelmer.flexnetoperations.com/). A Series of overlays and alignments were processed between Curcumin and Afatinib, Bicalutamide as per methodology mentioned in the Chem 3D 18.0 User Guide (https://library.columbia.edu).

2.2 Mechanistically similarity

The bioactivity score of curcumin, afatinib, and bicalutamide against many receptors, such as GPCR (G-protein coupled receptor) ligand, ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitor, and other enzyme inhibitors, were also calculated using server molinspiration along with drug-likeness properties to verify and compare theprobable mechanism of action.

2.3 Correlation of the probable drug properties of curcumin with Afatinib and Bicalutamide To correlate the drug properties as per Lipinski's rule of five have been calculated by using free online web server molinspiration (accessible at http://www.molinspiration.com/) either by using the SMILES code or manually drawing the structure of each compound.

For a compound to be a potent drug its parameters ranges partition coefficient(LogP) ≤5, molecular weight (M.W.)≤500, the no. of hydrogen bond acceptors ≤10, and the no. of hydrogen bond donors ≤5, and no. of rotatable

bonds should be ≤10 were considered[25].

2.4 Determination of ADMEproperties

To predict ADME ligand properties of curcumin and free online web server vNADMET (https://vnnadmet.bhsai.org/vnnadmet/home.xhtml),admetSAR(http://lmmd.ecust.edu.cn/admetsar2/), andSWISS ADME (http://www.swissadme.ch/) were used.These servers deliver the possible pharmacological profile of compounds with quick access to properties like bioavailability score, solubility, overall prescribed medicinal dosage (MRTD), human liver microsomal stability, etc.

2.5 Determination of toxicity profile

To compare the toxicity profile of curcumin, afatinib, and bicalutamide toxicity properties were determined by using the admetSAR server.

2.4 protein-drug interaction

2.4.1 Preparation of ligand

PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used to collect SDF format files of our compound i.e. curcumin, afatinib, and bicalutamide. SDF format has been modified to PDB format using OPEN BABEL (http://openbabel.org/wiki/Main_Page) which was used to prepare these compounds as a ligand in AUTODOCK 4. O MGL tools (http://mgltools.sripps.edu/downloads) by adding Gasteiger charges and saved in PDBQT format (required for docking against protein targets).

2.4.2 Preparation of protein

Several anticancer targets for curcumin are reported in the literature, some of which have been selected to perform molecular docking studies. The structure of selected target proteins was downloaded from the protein data bank in PDB format. For this PDB id (table1) of each target was obtained from the literature. The target proteins were then prepared for docking in AUTODOCK 4. O mgl tools by following some steps like removal of water molecules (to avoid their interference), adding polar hydrogen, adding Kollmann charge, and removal of ligand already present at their site. Further, the file for each target was saved in pdbqt format for docking.

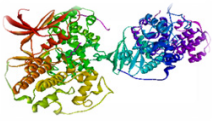
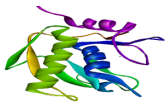
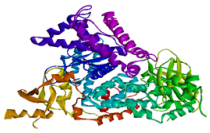
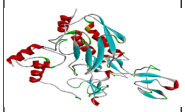
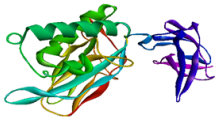
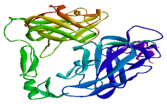
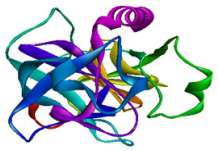
Table1: PDB ID of protein target from literature

S.NO	Target Protein	PDB ID	Reference
1	CDK2	2CCI	26
2	PI3K	1E8X	27
3	NF-KB	1SVC	28
4	PSA	1GVZ	29
5	MMP-2	3AYU	30
6	MMP-9	1L6J	28
7	VEGF-A	4DEQ	31

2.4.3 Molecular docking

In the present work, AUTODOCK VINA (http:/vina.scripps.edu/), an interactive molecular graphics applicationusing a gradient optimization algorithm was used to dock curcumin, afatinib and bicalutamide selected drugs against selected anticancer targets for better insight of protein-ligand interactions [32]. To obtain all possible poses the ligand was in fluid shape while the protein target was kept acquired rigid form. The grid box of dimension 30x30x30 was prepared for each target with coordinates corresponding to ligand present in them is compiled in table 2. Among various poses obtained, the best pose with maximum release of energy [33] was analyzed in discovery studio visualizer(https://discover.3ds.com/discovery-studio-visualizer-download) In addition; binding affinity, the best pose selected for curcumin and the selected

Table2: 3D structures and grid parameters of each protein.

S.NO	Target Protein	3D Structure	Grid parameter Centrex, y, z	S.NO	Target Protein	3D Structure	Grid parameter Centrex, y, z
1	CDK2		center_x =21.975774 center_y =37.814661 center_z =28.154823	5	MMP-2		center_ x=9.988000 center_y =13.861903 center_z= -10.662430
2	PI3K		center_x=23.1415 center_y=64.401762 center_z =20.773595	6	MMP-9		center_x =30.187000 center_y =40.981333 center_z = 42.464333
3	NF-KB		center_x =28.037026 center_y =30.707541 center_z =27.623566	7	VEGF-A		center_x= -0.850892 center_y = 67.133054 center_z =-17.276811
4	PSA		center_x =11.389731 center_y =34.386115 center_z =20.599538				

commercial drug was redocked with targets to confirm our results.

3. Results and discussion

3.1. Selection of drugs

From several commercially available anticancer drugs Afatinib, Afinitor, Fentanyl, and Bicalutamide were selected based on some common structural features with curcumin. Molecular modeling studies with Chemdraw3D showed that curcumin shows great similarity with afatinib and bicalutamide (fig 2, table3)

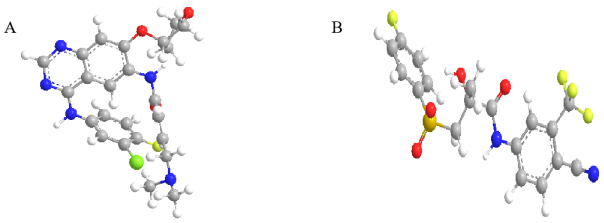
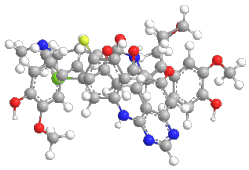
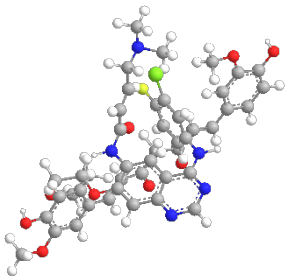
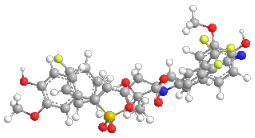
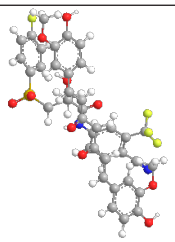


Fig2: 3D structure of A- Afatinib drug, B- Bicalutamide drug.

3.2Mechanistically similarity

Afatinib is a second-generation

Table3: Molecular modeling studies of Afatinib and Bicalutamide with Curcumin.

Curcumin and Afatinib		**Curcumin and Bicalutamide**	
Overlay	Alignment	Overlay	Alignment
			
Atoms	**Actual(Å)**	**Atoms**	**Actual(Å)**
C(13)-C(48)	4.711	C(11)-C(48)	4.554
C(14)-C(49)	5.286	C(17)-C(49)	5.306
C(15)-C(50)	5.462	C(18)-C(50)	5.522
C(16)-C(51)	5.113	C(19)-C(51)	5.991
C(10)-C(52)	5.010	C(20)-C(52)	5.538
C(12)-C(53)	4.789	C(21)-C(53)	4.226
C(11)-C(59)	4.812	C(1)-C(55)	2.644
C(17)-C(60)	5.523	C(2)-C(56)	4.395
C(18)-C(61)	6.476	C(12)-C(61)	4.680
C(19)-C(62)	6.383	C(13)-C(62)	5.790
C(20)-C(63)	5.166	C(14)-C(63)	5.596
C(21)-C(64)	4.532	C(15)-C(64)	5.133
O(23)-O(67)	4.839	C(16)-C(65)	5.253
C(24)-C(68)	5.554	C(10)-C(66)	4.576
C(2)-C(70)	4.062	C(4)-C(70)	5.189
C(1)-C(71)	3.765	C(9)-C(72)	5.372
O(5)-O(72)	4.097	O(5)-O(76)	6.125
C(3)-C(73)	5.247		
C(7)-C(74)	6.703		

anilinoquinazoline that inhibits members of the ErbB receptor family by binding irreversibly to an intracellular tyrosine kinase domain [34]. Bicalutamide competes with androgen for the binding of androgen receptors, preventing androgens from the adrenal and testicles from stimulating natural and malignant prostatic tissue development. Curcumin is a highly reactive molecule that has been reported as a multi-target compound because of the presence of structural features. For its biological potential different targets needs to be explored. In the present work, we have related the bioactivity score of curcumin with afatinib and bicalutamide. The results reported in table4 shows that all the three compounds under study show moderate bioactivity scores in form of receptors, such as GPCR (G-protein coupled receptor), ion channel modulator, a kinase inhibitor, nuclear receptor, protease inhibitor, and other enzyme inhibitors.

3.3 Probable drug properties of curcumin withAfatinib and Bicalutamide

To compare the potential of curcumin as an anticancer drug,its drug-likeness properties were compared with Afatinib and Bicalutamide. Molinspiration, an online web server gave quick access to properties like TPSA, no of H-bond donors, No. of H-bond acceptors, volume, no. of rotatable bonds, and partition coefficient. Results compiled in table5 shows that curcumin like Afatinib and Bicalutamide also follow Lipinski's rule of five. Curcumin shows most of the parameters in-between the range of these two drugs and cleared the first level of screening to be an anticancer drug.

3.4 ADME properties of Curcumin, Afatinib, and Bicalutamide

The pharmacokinetic profile of any compound is an important factor for consideration as a probable drug candidate.The profile of curcumin, afatinib, and bicalutamide was obtained from vNADMET, admetSAR, and SWISS ADME free online servers in terms of their ADMEproperties is compiled in table6. The results show that despite the problems related to curcumin bioavailability reported in several reports [35, 36], curcumin showed a

Table 4: Bioactivity score of curcumin and selected commercial drugs

Compounds	GPCR	Ion channel modulator	Kinase inhibitor	Nuclear receptor	Protease inhibitor	Enzyme inhibitor
Curcumin	-0.09	-0.39	-0.13	-0.02	-0.09	0.12
Afatinib	-0.05	-0.07	0.05	0.56	0.25	0.00
Bicalutamide	0.21	-0.11	0.73	-0.38	-0.07	0.21

Table5: Drug-likeness Physico-chemical properties of curcumin and selected drugs by Molinspiration

Compound	miLogP	TPSA(A◦)	MW(kDa)	nON	nOHNH	nrotb	Volume(g/mol)	Violation
Curcumin	3.05	96.22	368.38	6	3	7	331.83	0
Afatinib	4.21	88.61	485.95	8	2	8	417.87	0
Bicalutamide	2.15	107.26	430.38	6	2	6	329.24	0

better bioavailability index over afatinib and bicalutamide. Its solubility is also marginally superior to afatinib. The results suggested that the issues related to curcumin solubility [37] are not significantly affecting its bioavailability. As observed the bioavailability score of all the three compounds under investigation was found to be almost similar ~0.55 despite the difference in solubility of curcumin with bicalutamide. Like commercial drugs, curcumin shows promising prediction towards human intestinal absorption, oral bioavailability, and comparable topological polar surface area suggesting good absorption. A very interesting outcome of the study was the MRTD value. Afatinib was found ~4 times more acceptable than bicalutamide. Curcumin was found 13 and 3.25 times acceptable than bicalutamide and afatinib respectively. A higher MRTD value reflects that natural product curcumin has lower toxicity to the living system with this data one of the aspects to explore the natural product, curcumin as the anticancer drug has been achieved. The simultaneously available literature on antibacterial [38, 39], anti-inflammatory [40], immunoregulator [41, 42] activities reported for curcumin in addition to anticancer drugs make it a molecule of choice because the mentioned bioactivitiesare usually required in synergism with anti-cancer drugs. Therefore curcumin displays multi-target specificity and its categorization as a panacea [43] in cancer chemotherapy is justified.

* Cyp1A2=Cytochrome p450 1A2, Cyp3A4=Cytochrome p450 3A4, Cyp2D6= Cytochrome p450 2D6, Cyp2C9= Cytochrome p450 2C9, Cyp2C19= Cytochrome p450 2C19, Inhb. =inhibitor, BBB=blood brain barrier, Bio. Score= bioavailability score, MRTD= maximum recommended therapeutic dose.

3.5 Toxicity profileof Curcumin, Afatinib, and Bicalutamide

Table 6: ADMEpredictions of curcumin and selected drugs

Name of ligand	Human Intestinal Absorption	Caco-2 Permeability	%Ab=109-(0.345*TPSA)	Human oral bioavailability	Plasma protein binding	BBB	P-glycoprotein inhibitors	Cyp1A2 Inhb	Cyp3A4 Inhb	Cyp2D6 Inhb	Cyp2C9 Inhb	Cyp2C19 Inhb	Bio. Score	Solubility(mg/ml)	MRTD (mg/day)
Curcumin	+	-	75.80	+	0.89	-	+	-	-	-	+	+	0.56	0.158	650
Afatinib	+	-	78.42	+	1.214	-	+	+	+	-	-	-	0.55	0.156	191
Bicalutamide	+	-	71.99	+	1.364	-	-	-	-	-	-	-	0.55	0.244	51

Every bioactive molecule with strong pharmacokinetic properties must have a high level of human and environmental safety. Since determining the toxicity of substancesexperimentally is expensive andtime-consuming, the use of statistical models has been seen as a complementary solution because it can reduce the expense of experimental toxicity evaluation.The results of screening for organ, genomic, and eco-toxicity, for selected commercial drugs and curcumin, are complied in Table7 shows that curcumin shows 4 positive predictions among 10 toxicities tested. Both commercial drugs show Hepatotoxicity but curcumin possesses a negative prediction for the same. Like both selected drugs curcumin is also safe towards carcinogenicity. Thus lie in the line of an effective drug.

3.6. Protein-Drug Interaction

After studying similar drug-likeness and ADMET properties of curcumin with afatinib and bicalutamide docking studies were performed against 7 anticancer targets (PSA, NF-kβ, CDK2, PI3K, MMP-2, MMP-9, and VEGF-A) to compare their interaction and affinity for these targets. Docking was executed by AUTODOCK VINA and DS visualizer was used to analyze interactions for the best docking pose (Fig3). Table8 includes affinity in Kcal/mol, total no. of interactions between protein and ligand, no. of hydrogen bonds, no. of hydrophobic interactions and amino acids involved in interactions shows that curcumin has a higher affinity with selected anticancer targets as compared to afatinib and bicalutamide.2D pose of curcumin shows that curcumin aligns and interacts well with these targets with its enolic form. Enolic H of curcumin is involved in H-bonding interactions only whereas benzene ring, the hydroxyl group on benzene and methoxy group are observed to be involved in both hydrogen and hydrophobic interactions. Furlan et al [44]have also used Inverse Molecular Docking as a Novel Approach to Study Anticarcinogenic and Anti-Neuroinflammatory Effects of Curcumin. In the present work, we have incorporated molecular docking studies using two different software for evaluating the interactions between curcumin, afatinib, and bicalutamide with seven selected

Table 7: Toxicity Profile

Type of toxicity	**Organ toxicity**					**Genomic toxicity**			**Eco-toxicity**			
Name of ligand	**Human either-a-go-go inhibition**	**Hepatotoxicity**	**Acute Oral Toxicity (c)**	**Eye corrosion**	**Eye irritation**	**Ames mutagenesis**	**Carcinogenicity (binary)**	**Carcinogenicity (trinary)**	**crustacea aquatic toxicity**	**Avian toxicity**	**Fish aquatic toxicity**	**Honey bee toxicity**
Curcumin	+	-	III	-	+	-	-	Non-req.	-	-	+	+
Afatinib	+	+	III	-	-	-	-	Non-req.	+	-	+	-
Bicalutamide	+	+	III	-	-	-	-	Non-req.	-	-	+	-

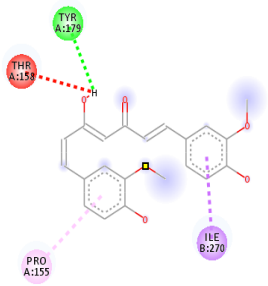
anticancer targets.

Our multidimensional drug screening approaches demonstrated the use of computational parameters for estimation and comparison of a bioactive natural product, curcumin with commercial drugs afatinib and bicalutamide research. The results confirm that computational tools can provide a comprehensive approach to the explorer for natural products as an anticancer drug, with a higher affinity for targets than commercial drugs with both, in terms of money and time. However, our methods can not completely explain the complex metabolism of drugs that takes place in the body. We, therefore, propose future studies on curcumin as an anticancer in animal cell lines.

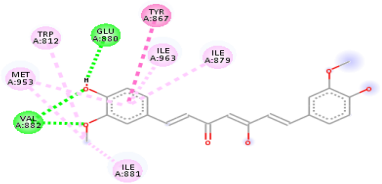
4. Conclusion

In the present work, we have reported curcumin as a probable anticancer drug after comparing it with twostructurally similar drugs Afatinib and Bicalutamide. The conclusion has been drawnin terms of drug-likeness and ADMET-

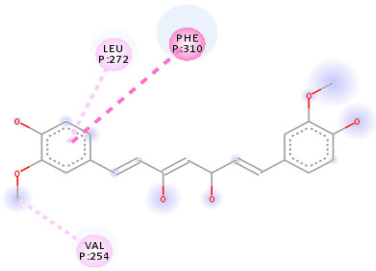
Fig.3. Interactions, Cur-I to Cur-VII (Curcumin-Targets complexes), Afa-I to Afa-VII (Afatinib-Targets complexes), and Bic-I to Bic-VII (Bicalutamide-targets complexes) and I- CDK2, II-PI3K, III- NF-KB, IV-PSA, V- MMP-2, VI-MMP-9, VII- VEGF-A.



(Cur I)



(Cur II)



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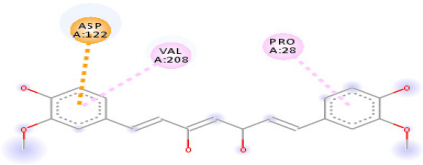

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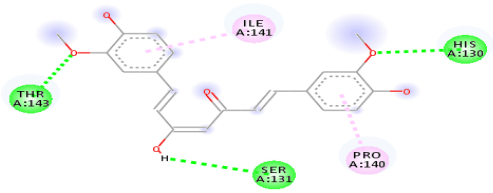

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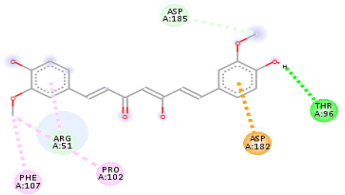

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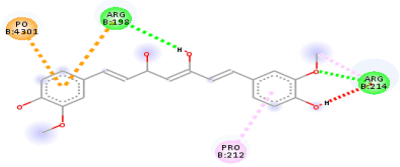
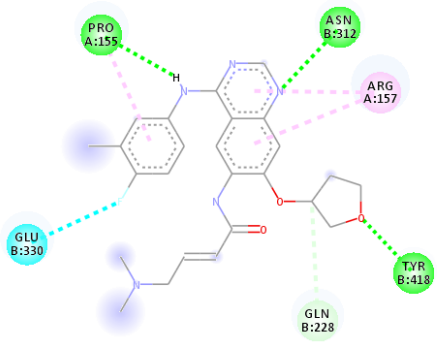


(Cur VII)



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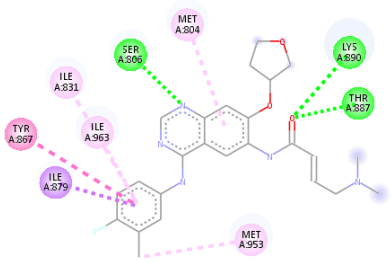

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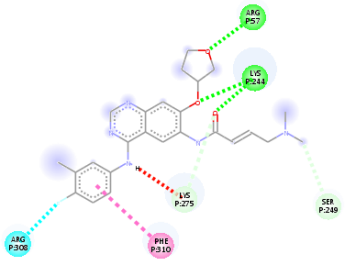

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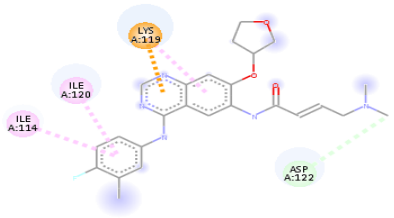

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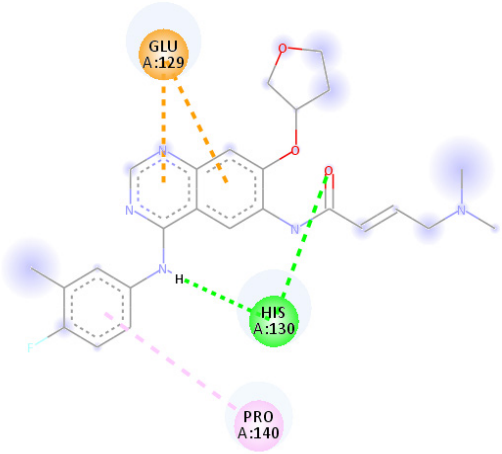

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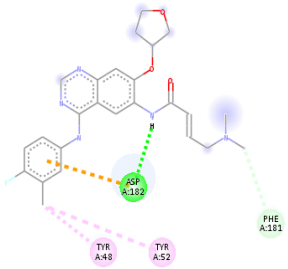

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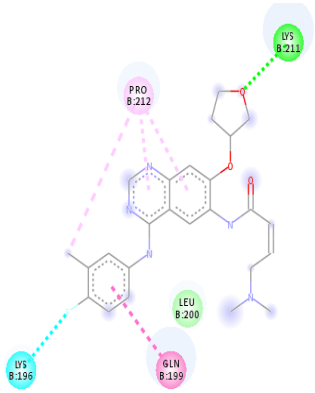

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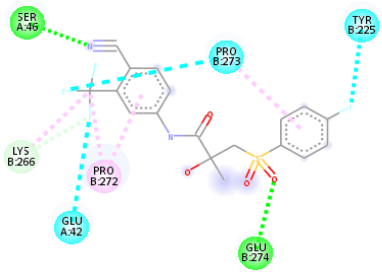

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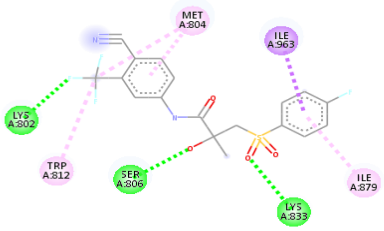

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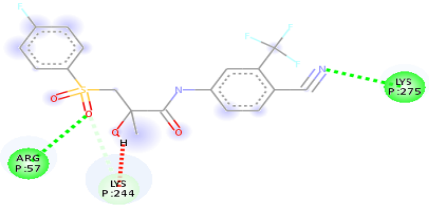

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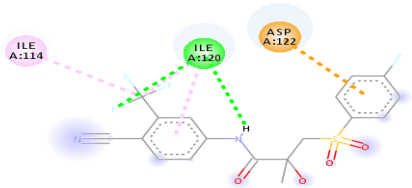

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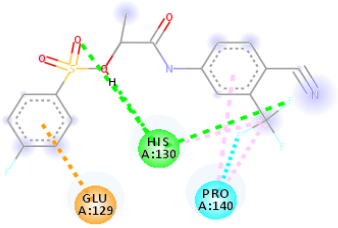

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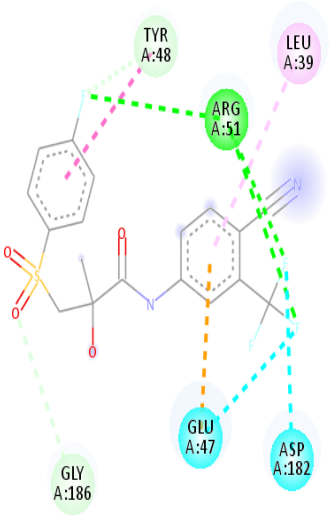

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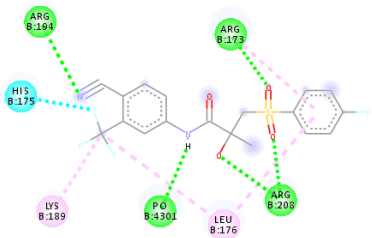

(Bic VII)

Table 8: Molecular Docking Results of curcumin, afatinib, and bicalutamide against selected anticancer targets.

Target protein	Compound/ligand	Affinity(Kcal/mol)		Total no. ofinteractions	H-bondinginteractions	Hydrophobicinteractions	Amino acids involved in interactions (H:-Hydrogen bonding interactions, HP:- hydrophobic interactions)
		Docking score	Redocking score				
CDK2	Curcumin	-8.4	-8.4	04	01	03	TYR179(H),THR158(HP),PRO155(HP),ILE270(HP)
	Afatinib	-7.2	-6.6	08	04	04	ASN312(H),TYR418(H),GLN228(H),PRO155(H,HP), GLU330(HP), ARG157(HP-2),
	Bicalutamide	-7.5	-7.5	10	03	07	GLU274(H),SER46(H),LYS266(H,HP-2),PRO272(HP-2), PRO273(HP-2),TYR225(HP),
PI3K	Curcumin	-9.3	-9.3	09	03	06	VAL882(H-2),GLU880(H),MET953(HP-2),TRP812(HP), TYR867(HP),ILE963(HP),ILE879(HP)
	Afatinib	-8.8	-8.9	08	03	05	SER806(H),THR887(H),LYS890(H),MET804(HP),ILE879(HP), TYR867(HP),ILE963(HP),ILE831(HP)
	Bicalutamide	-8.4	-8.4	08	03	05	LYS833(H),SER806(H),LYS802(H),TRP812(HP),MET804(HP-2),ILE963(HP),ILE879(HP)
NF-KB	Curcumin	-7.7	-7.8	02	00	02	LEU272(HP),PHE310(HP)
	Afatinib	-6.8	-6.7	08	05	03	ARG57(H),LYS244(H-2),SER249(H),LYS275(H,HP),PHE310(HP), ARG306(HP)
	Bicalutamide	-6.8	-6.9	04	03	01	ARG57(H),LYS275(H),LYS244(H,HP),
PSA	Curcumin	-7.9	-7.7	03	00	03	ASP122(HP),VAL208(HP),PRO28(HP)
	Afatinib	-6.3	-6.2	05	01	04	ASP122(H),ILE114(HP),ILE120(HP),LYS119(HP-2)
	Bicalutamide	-6.5	-6.4	06	02	04	ILE120(H-2,HP-2),ILE114(HP),ASP122(HP)

MMP-2	Curcumin	-7.5	-7.5	05	03	02	THR143(H),SER131(H),HIS130(H),PRO140(HP),ILE141(HP)
	Afatinib	-6.1	-6.1	05	02	03	HIS130(H-2),PRO140(H),GLU129(HP)
	Bicalutamide	-6.1	-6.1	8	3	5	HIS130(H-3,HP),PRO140(HP-3),GLU129(HP)
MMP-9	Curcumin	-8.6	-8.6	06	02	04	THR96(H),ASP185(H),ASP182(HP),PHE107(HP),PRO102(HP), ARG51(HP)
	Afatinib	-6.8	-7.2	05	02	03	PHE181(H),ASP182(H,HP), TYR48(HP),TYR52(HP)
	Bicalutamide	-7.3	-7.1	10	5	5	ARG51(H-3), GLY186(H),TYR48(H,HP),LEU39(HP),ASP182(HP), GLU47(HP-2),
VEGF-A	Curcumin	-6.4	-6.6	06	02	04	ARG214(H,HP-2),ARG198(H,HP),PO4301(HP)
	Afatinib	-5.4	-5.4	07	01	06	LYS211(H),GLN199(HP),LYS196(HP),LEU200(HP), PRO212(HP-3)
	Bicalutamide	-5.6	-5.6	10	5	5	ARG194(H), ARG208(H-2),PO4301(H),ARG173(H,HP),LEU176(HP-2),LYS189(HP),HIS175(HP)

ox properties followed by affinity through molecular docking.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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