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Research Article

3D-QSAR, DOCKING AND ADME STUDY ON FLAVONE DERIVATIVES AS HUMAN BREAST CANCER CELL LINE MCF-7 INHIBITORS

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ABSTRACT

The present study deals with atom based 3D-QSAR (quantitative structure-activity relationship)and docking (with HER2 receptor) analysis of flavones active against human breast cancer cell line (MCF-7). The atom based 3D-QSAR study showed a statistically significance model for both training set (R^2 = 0.9961, SD= 0.0558, F= 1202.7 and N= 24) and test set (Q^2 = 0.8129, Pearson R = 0.9570, N= 09, RMSE=0.30) ligands respectively. The model could be helpful in prediction of in-silico biological activity of non-tested molecules, virtual screening of database for new MCF-7 inhibitors. Moreover, docking information of highly active flavones could also be useful to design novel flavones derivatives as human breast cancer cell line inhibitors. The 3D-QSAR model, ADME study and docking information certainly reduce the number of MCF-7 inhibitory compounds to be synthesized, by making it possible to select the most promising compounds and provide guidance for the rational design of potential breast cancer inhibitors.

Keywords: Flavones, MCF-7 inhibitors, 3D-QSAR, Docking, ADME study.

INTRODUCTION

Breast cancer is the most common cancer in women all over the world. It is the number one cause of death from cancer every year among women.The frequency of breast cancer has been increasing globally, due to increase life expectancy, increase urbanization and taking up of western lifestyles[12].Flavonoids show wide range of activity such as anti-cancer, anti-ageing, antibacterial, anti-inflamatory etc.[3-5]. Phenolic compounds can be found in many fruits and vegetables including soya, turmeric, grapes, celery, apples, onions, parsley, capsicum, green tea, pepper, etc. and have been shown to possess anti-cancer activities[6].It is reported that some flavonoids, isoflavonoids, and lignans act as cancer protective agents in populations with low incidences of breast and prostate cancer[7]. Dai *et al* also suggested that flavonoids have potential role in breast cancer prevention[8]. Therefore flavonoids may be promising molecules as breast cancer inhibitor. Certain dietary flavonols and flavones targeting cell surface signal transduction enzymes, such as protein tyrosine and focal adhesion kinases, and the processes of angiogenesis appear to be promising candidates as anticancer agents[9].One of the important receptor for breast cancer is human epidermal growth factor receptor 2 (HER2)[10].These information indicates that human epidermal growth factor receptor 2 can be used as an therapeutic target for designing breast cancer inhibitor.

MATERIAL AND METHODS

Data set

For designing of potential breast cancer agents 33 flavonoid were collected from different literature having IC_{50} value against human breast cancer cell line MCF-7[11-16]. The IC_{50} values of the compounds were cited in the literature in µM, nM, and µgm/ml and then the values were converted into their corresponding pIC_{50} ranged from 6.903 to 2.83.

Ligprep

The structures of compounds were drawn in ChemBioDraw Ultra 11.0, and then converted into 3D and ligand preparation was done using OPLS_2005 force by keeping original chiralities allowing to generate one conformer per ligand. The prepared ligands with pIC_{50} values were imported and shape screening were performed to develop model panel of the PHASE with their respective biological activity values. The atom based 3D QSAR studies were performed using shape screened ligands using Phase module of Schrodinger 9.6[17]. The docking studies were carried out using GLIDE module of Schrodinger[18-21] installed in HP Z820 Workstation with CentOS 6.3.

Building 3D QSAR model

Phase module provides the building option of atom based 3D QSAR models. A set of 33 ligands with pIC_{50} values were aligned (**Fig.1**) by atom type macro model option under shape screen. In Build QSAR option random training set was kept as 70% and atom based model was generated by keeping 1Å grid spacing with maximum number of PLS factor 4.

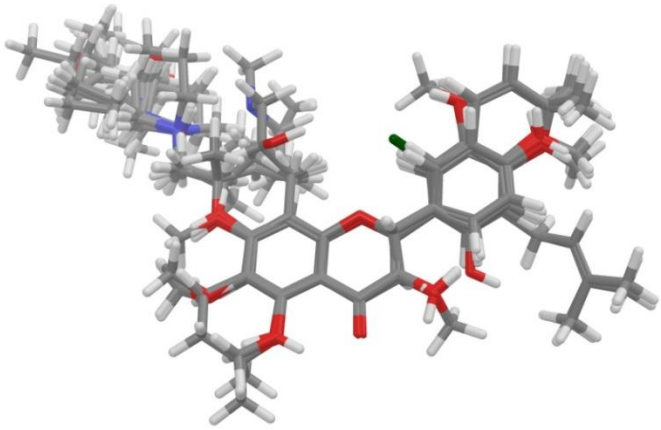


Fig. 1: Structural alignment use for atom based 3D-QSAR model generation

A statistically significant atom base 3D-QSAR model was generated with 0.0558 as standard deviation (SD) of the regression along with R-squared =0.9961, 1202.7as variance ratio. To avoid over-fitting of the results four PLS factors were used. A summary of statistical parameters is given in **Table 1**. The regression line for the observed and PHASE predicted activity is shown in **Fig 2** and the predicted and experimental activities of the training and test set molecules are listed in **Table 2**.

Table 1: Statistical parameters of the selected 3D-QSAR model with different PLS factor

PLS Factors	SD	R^2	R^2 CV	$R^2_{Scramble}$	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.494	0.6423	0.2045	0.5025	0.782	39.5	2.52E-06	0.51	0.4459	0.6987
2	0.1687	0.9602	0.2881	0.7813	0.335	253.2	2.00E-15	0.34	0.7619	0.9295
3	0.095	0.988	0.3354	0.9147	0.356	548.3	2.30E-19	0.3	0.8134	0.9505
4	0.0558	0.9961	0.5188	0.9703	0.337	1202.7	1.48E-22	0.3	0.8129	0.957

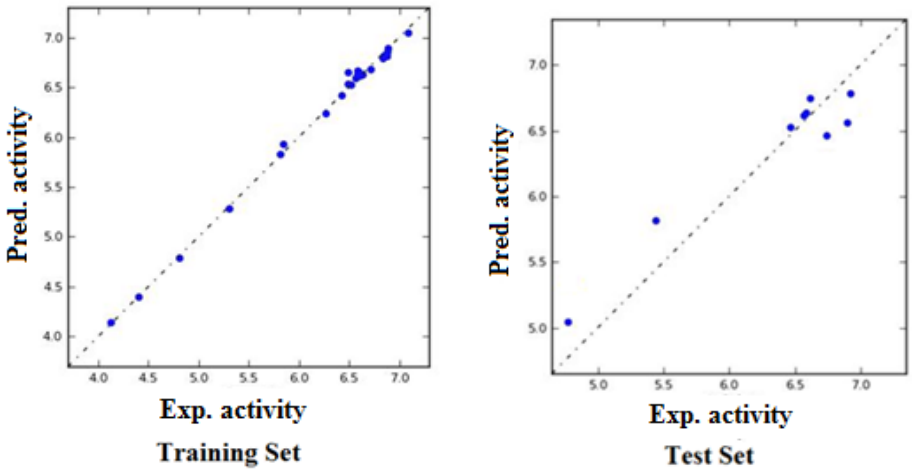


Fig. 2: Fitness graph of observed activity and PHASE predicted activity (pIC_{50}) for training and test set molecules

Molecular docking study

The molecular docking study was performed with HER2 (PDB ID: 3W32) retrieved from RCSB protein data bank complexes with an irreversible inhibitors[22]. The RMSD value (0.8765 Å) was calculated by superimposing best pose of co-ligand after docking on its initial co-crystallized pose and the value indicates close proximity between experimental and theoretical results. Docking study was carried out to ascertain the detailed interaction between flavones dataset under investigation and HER2 receptor. Protein was preprocessed, optimized and minimized with OPLS_2005 force field using the protein preparation wizard. A receptor grid was generated with 15Å length centering the co-ligand in protein inserted in workspace. The extra precision docking was carried out using Glide enabling "write XP descriptor information" option and keeping other factors as default options in glide module of Schrodinger.

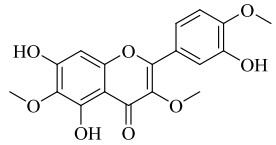
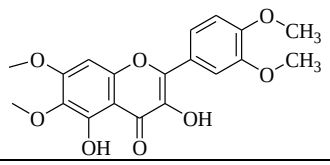
ADME study

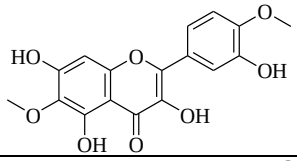
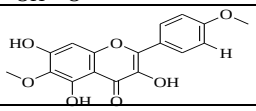
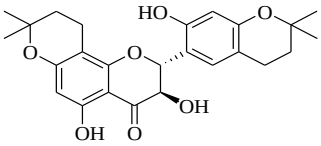
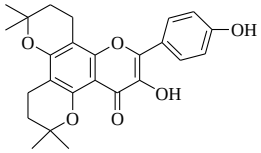
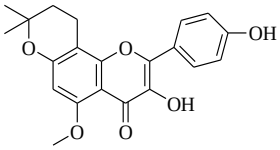
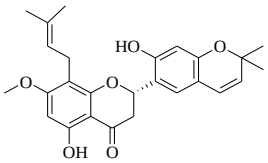
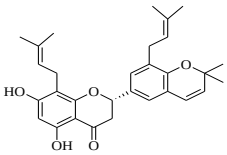
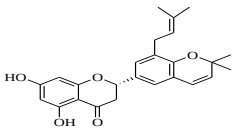
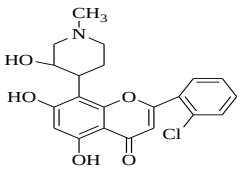
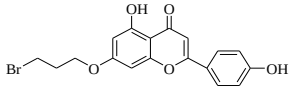
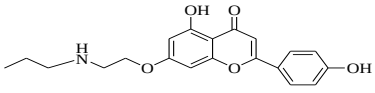
The ADME (adsorption, distribution, metabolism, and excretion) prediction programme provides ranges of values for comparing particular molecular properties with 95% of known drugs using Schrodinger module QikProp 3.5 [23].

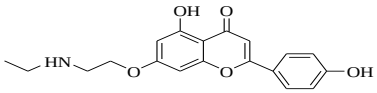
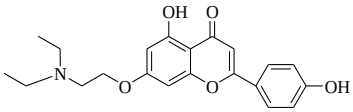
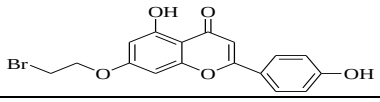
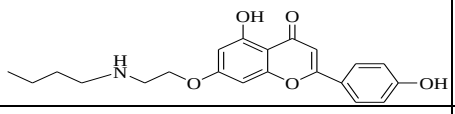
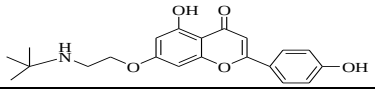
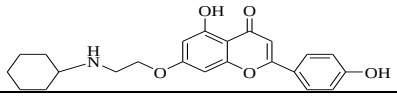
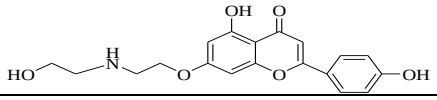
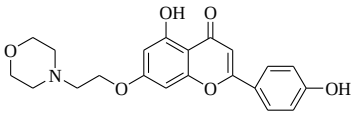
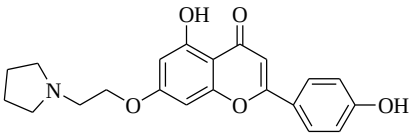
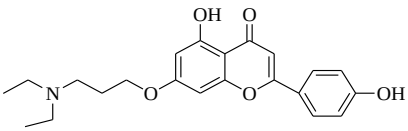
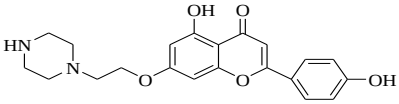
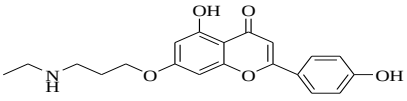
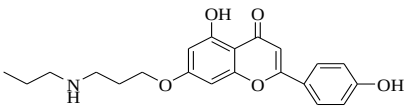
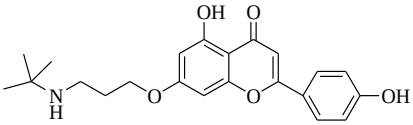
RESULT AND DISCUSSION

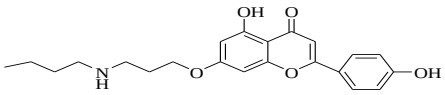
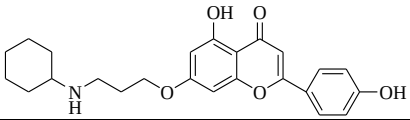
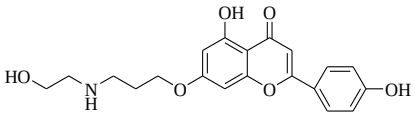
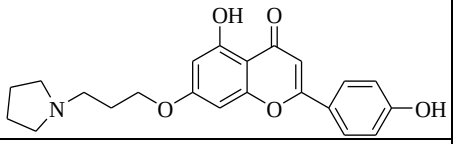
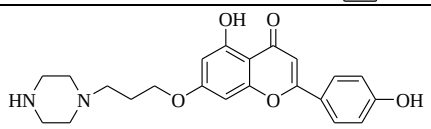
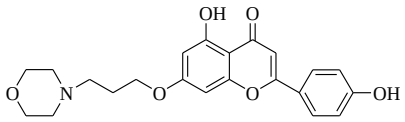
Atom based 3D-QSAR model were generated using a series of 33 flavonoid derivatives (**Table – 2**). These structurally diverse flavonoids displayed a broad range of inhibitory activity (pIC_{50}) ranging from 4.1295–7.0930 (**Table-2**). In this study 70% ligands were randomly selected for training set and remaining 30% in the test set to build QSAR model.

Table 2: Structure, Experimental original activity, predicted activity, docking interaction and extra precision glide docking score (XPGS) of flavone derivatives

Comp. No.	Structure of flavones	pIC_{50} (Exp)	pIC_{50} (Pred)	Interactions: interacting amino acid residues (atoms/groups of ligand), distance	XPGS
1*		6.9030	6.7587	HBD: MET-793 (7-OH),2.15 Å HBA: MET-793 (7-OH),1.79 Å	-10.687
2		5.8184	5.8244	HBD: ASN-842 (3-OH), 2.06 Å HBA: CYS-797 (6-OCH_3), 2.34 Å	-7.875

3		6.8860	6.8492	HBD: ASN-842 (3-OH), 2.28 Å	-8.528
4		6.4948	6.6456	HBD: MET-793 (7-OH), 2.16 Å HBA: MET-793 (7-OH),1.80 Å	-10.461
5		4.8124	4.7845	HBD: ASP-800 (3-OH),1.96 Å LEU-718 (2'-OH), 2.00 Å	-4.304
6		5.3098	5.2792	NA	-6.72
7*		5.4436	5.8136	HBA: MET-793 (4-CO),2.33 Å HBD: ASP-855 (4'-OH),1.99 Å	-7.32
8		4.4067	4.3938	HBD: MET-793 (5-OH),1.87 Å ARG-841(2'-OH),1.79 Å Π-cation: CYS-745	-8.43
9*		4.7746	5.1524	NA	-5.79
10		4.1295	4.1383	HBD: ALA-743 (7-OH),1.61 Å	-7.136
11		6.6020	6.6481	HBA: MET-793 (4-CO), 2.10 Å HBA: ARG-841 (8-substituent), 2.15 Å	-9.95
12		6.2722	6.2336	HBD: GLN-791(5-OH), 2.08 Å ASP-800 (4'-OH),1.95 Å HBA: MET-793 (5-OH), 2.14 Å PHR-844 (7-O), 2.15 Å	-9.80
13		5.8490	5.9258	HBD: MET-793(4-CO),2.08 Å HBA: ASP-855 (4'-OH),1.91 Å	-8.539

14		6.5246	6.5204	HBD: MET-793 (4'-OH),1.66 Å THR-854 (7-Substituent NH), 2.23 Å HBA: LYS-745 (5-OH),1.90Å	-8.915
15*		6.4706	6.5240	HBD: ASP-800 (4'-OH),2.09 Å GLN-791(5-OH), 2.21 Å HBA: MET-793 (4-CO), 2.50 Å GLN-791 (5-OH), 2.31 Å THR-854 (7-O), 2.15 Å	-8.375
16		6.4938	6.5290	HBD: GLN-791 (5-OH), 2.03 Å HBA: MET-793 (5-OH),1.97 Å THR-854 (7-O),1.91Å	-9.016
17		6.4307	6.4149	HBD: ASP-855 (5-OH),1.92 Å MET-793 (4'-OH),1.78 Å	-8.69
18*		6.5718	6.6133	HBA: MET-793 (5-OH),1.96 Å THR-854 (7-O), 2.18 Å HBD: GLN-791 (5-OH), 2.05 Å	-10.26
19*		6.7458	6.4098	HBD: GLN-791(5-OH), 2.03 Å LEU-718 (4'-OH), 2.18 Å HBA: MET-793 (5-OH),1.99 Å THR-854 (7-O),2.02 Å	-11.8
20		6.5893	6.6275	HBD: ASP-855 (5-OH),1.91 Å MET-793 (4'-OH),1.54 Å PHE-856 (7-Substituent OH),1.89 Å	-9.23
21		6.8512	6.8123	HBD: ASP-855 (5-OH),1.97 Å MET-793 (4'-OH),1.81 Å	-8.37
22		6.7200	6.6759	HBD: LYS-745 (5- OH),1.95 Å ASN-842 (5-OH), 2.24 Å HBA: MET-793 (4'-OH),1.51 Å	-8.11
23		6.5880	6.6282	HBD: MET-793 (4'-OH),1.80 Å ASP-855 (5-OH),1.88 Å	-8.563
24		6.8923	6.8867	HBD: LEU-718 (4'-OH), 2.19 Å, GLN-791 (5-OH), 2.11 Å HBA: MET-793 (5-OH), 2.27 Å THR-854 (7-O), 2.02 Å	-9.352
25		6.6111	6.6112	HBD: MET-793 (4'-OH),1.63 Å	-8.900
26*		6.5897	6.6339	HBD: MET-793 (4'-OH),1.68 Å, ASN-842 (5-OH), 2.23 Å, HBD: LYS-745 (5-OH),1.97 Å	-8.99
27		6.6392	6.6225	HBD: ASP-855 (5-OH),1.94 Å MET-793 (4'-OH),1.81 Å, HBA:ASP-855 (7-Substituent NH), 2.23 Å	-9.905

28		6.5708	6.5871	HBD: ASP-855 (5-OH),1.92 Å, MET-793 (4'-OH),1.82 Å	-9.492
29		6.8413	6.7866	HBD: GLN-791(5-OH), 2.14 Å ASP-800 (4'-OH),1.75 Å HBA: MET-793(4-CO), 2.36 Å MET-793 (5-OH), 2.36 Å THR-854 (7-O), 2.39 Å	-9.644
30*		6.6204	6.7445	HBD: ASP-855 (5-OH),1.87 Å MET-793 (4'-OH),1.76 Å CYS-775 (7-Substituent-OH),1.97 Å	-9.536
31		6.8824	6.8082	HBD: ASN-842 (5-OH),2.24 Å, MET-793 (4'-OH),1.79 Å HBA: LYS-745 (5- OH),1.84 Å	-9.307
32		7.0930	7.0420	HBD: LEU-718 (4-OH), 2.47 Å, GLN-791 (5-OH), 2.05 Å PHE-856 (7-Substituent NH),1.99 Å HBA: MET-793 (5-OH), 2.00 Å THR-854 (7-O), 2.19 Å	-11.553
33*		6.9271	6.6462	HBD: ASP-855 (5-OH),1.88 Å, MET-793 (4'-OH),1.79Å	-8.472

*Test set molecules, HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor , NA: No interactions

Hydrogen bond donor

The 3D-QSAR visualization of hydrogen bond donor (HBD) interactions generated by PHASE are represented (**Fig. 3**) on highest active compound **32** and lowest active compound **10** of the training set where the blue cubes indicates regions that are favorable for hydrogen bond donor and the orange cubes indicate regions that are unfavorable for hydrogen bond donor groups for better MCF-7 inhibitory activity. It could be emphasized from **Fig. 3** that the blue cubes near the position 4, 5, 7, 2' are favorable and orange cubes near 6, 8 positions are unfavorable for MCF-7 inhibitory activity.

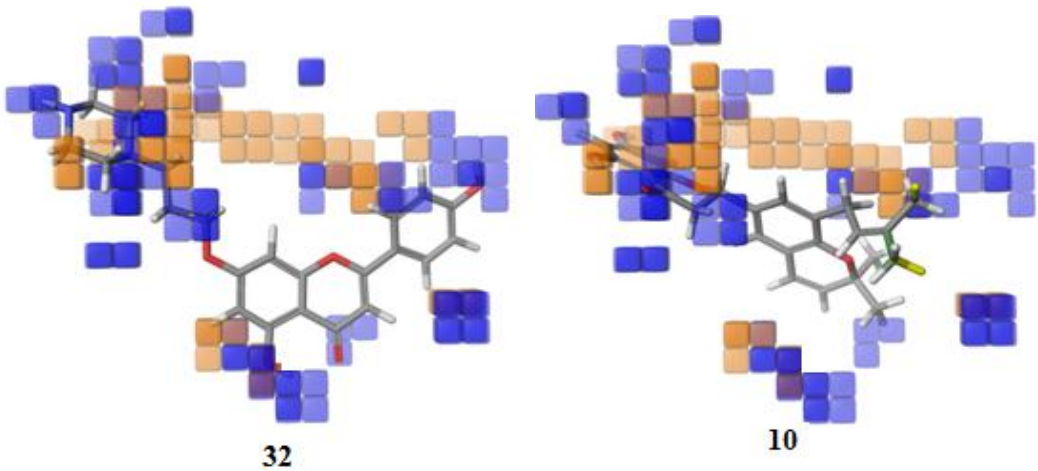


Fig. 3: Hydrogen bond donor visualization of 3D-QSAR model on the highest active compound 32 and least active compound 10 (Blue cubes indicate favorable regions while orange cubes indicate unfavorable region)

Effect of Hydrophobic

In the 3D QSAR visualization (**Fig. 4**) of hydrophobic interaction on both highest active (**32**) and lowest active (**10**) ligand generated by PHASE, the green cubes indicates favorable regions for hydrophobic interaction and the purple cubes indicate regions that are unfavorable for hydrophobic interaction in MCF-7 inhibition. It could be urged from **Fig. 4** that introduction of hydrophobic group at position 6, 4' and 5' is very much likely to favor the MCF-7 inhibitory activity while 3 and 8' position presence hydrophobic group would be detrimental in MCF-7 inhibitory activity.

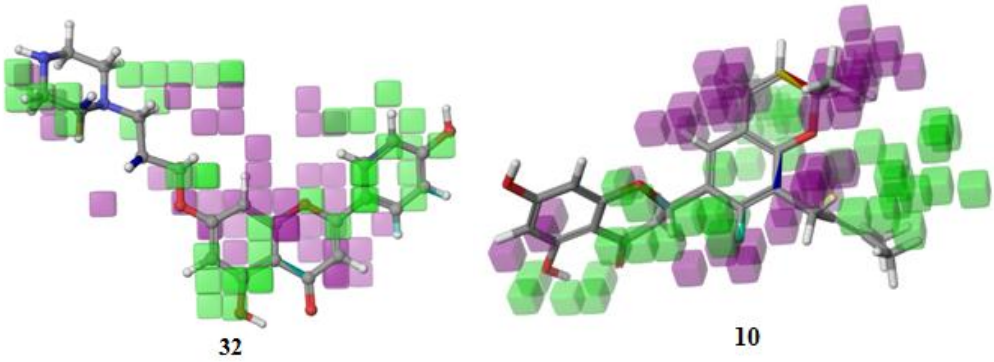


Fig. 4: Hydrophobic interaction visualization of 3D-QSAR model on highest active compound 32 and least active compound 10 (Green cubes indicate favorable regions while purple cubes indicate unfavorable region for activity)

Electron Withdrawing Effect

The blue regions appeared in pictorial presentation (**Fig. 5**) for electron withdrawing effect around the highest active ligand **32** and lowest active ligand **10** indicates that presence of electron withdrawing group in these region will favor the MCF-7 inhibitory activity and the orange coloured region around the ligands indicate that these regions are unfavorable for substitution with electron withdrawing groups. In the highest active ligand the electron withdrawing group at position 4 and 7 lies in the favorable region whereas in lowest active ligand the electron withdrawing groups lies in the unfavorable region.

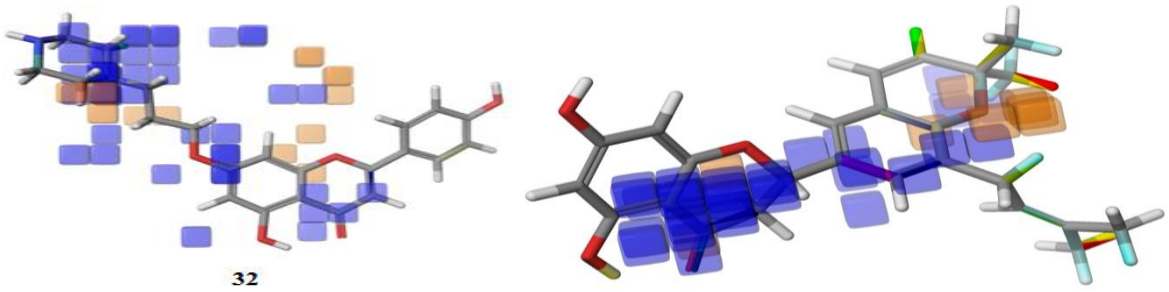


Fig. 5: Electron withdrawing visual representation of 3D-QSAR model of the most inactive compound 32 and lowest active compound 10(Blue cubes indicate favorable regions while orange cubes indicate unfavorable region for the activity)

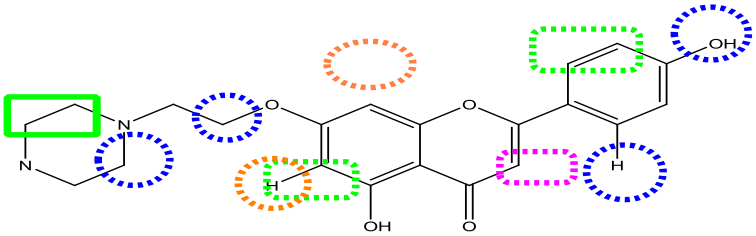


Fig 6

Therefore the visualization of the 3D-QSAR model shows (**Fig.6**) that substitution of hydrogen bond donor group at position dotted blue circle region favour the MCF-7 inhibitory activity, unfavourable region for hydrogen bond donor group at orange dotted circle for inhibitory activity. Introduction of hydrophobic group at green dotted rectangular region is favourable for MCF-7 inhibitory activity and introduction of hydrophobic group in the purple dotted rectangular region unfavorable for activity. Substitutions of electron withdrawing group in the green bold line rectangular region are important for MCF-7 inhibitory activity.

Docking

Docking results provides useful information for further structure optimization and designing of more potent inhibitors. In this study docking result shows that amino acid residues involved in hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) interactions in the active site of HER2 receptor (PDB: 3W32) is MET-793 and interacts with 4′-OH, 5-OH, 4-CO, 7-OH in thirteen, eight, five and four number of ligands respectively, in this dataset. In addition, significant number hydrogen bond donor and acceptor interactions occurs with amino acid residues (number of interactions)like ASP-855 (11), GLN-791 (9), THR-854 (8), ASN-842 (5) and four numbers of interactions occurs with each of ASP-800, LEU-718 residues in the active site . It is also observed that the five highest active (pIC_{50}) molecules **32** (7.093), **33** (6.927), **1** (6.903), **24** (6.892) and **3** (6.886) interacts mainly with MET-793, ASP-855, ASN-842, GLN-791, LEU-718. These docking interactions (HBD & HBA) corroborate the results obtained from previously discussed 3D-QSAR model.

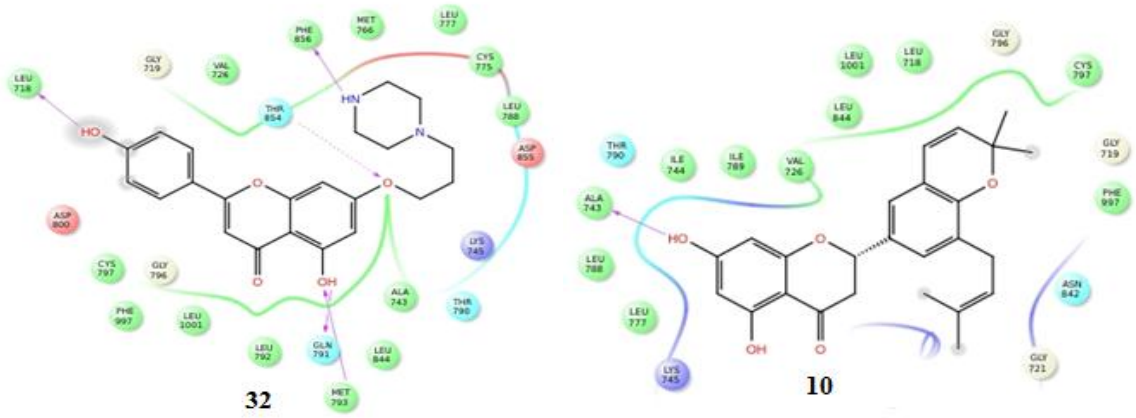


Fig. 8: 2D interaction diagram of most active ligand 32 and least active ligand 10

Table 3: Qikprop Property of MCF-7 inhibitors

Mol. No	ST	MW	SASA	volume	DHB	AHB	QPlogPw	QPlogPo/w	QPlogS	QPPCaco	QPPMDCK	PHOA	#RA
1	0	360.32	593.231	1037.584	2	6	10.965	2.178	-3.967	229.159	100.63	81.94	16
2	0	374.346	633.057	1109.453	1	6	9.212	3.076	-4.641	692.547	332.57	95.8	16
3	0	346.293	573.609	986.882	3	6	12.752	1.442	-3.575	92.049	37.54	70.54	16
4	0	330.293	557.531	962.869	2	5.25	10.621	2.162	-3.747	304.643	136.89	84.06	16
5	0	440.492	717.757	1314.219	2	6.45	11.873	3.804	-6.42	389.559	178.5	95.58	24
6	1	422.477	708.118	1296.405	2	5.5	11.412	4.265	-6.725	574.583	271.79	100	24
7	0	368.385	638.989	1128.96	2	5.5	11.247	3.204	-5.371	489.481	228.55	93.85	20
8	1	436.504	730.999	1362.659	1	4.75	8.493	5.162	-7.016	602.122	285.90	93.96	20
9	4	474.596	823.546	1553.787	1	4	7.77	6.662	-8.836	538.201	253.24	100	20
10	1	406.477	742.952	1330.559	1	4	8.518	5.234	-7.687	431.805	199.59	91.8	20
11	0	401.846	624.169	1144.971	2	6.7	12.916	2.257	-3.708	53.576	37.25	71.11	22
12	0	391.217	628.377	1063.536	1	3.75	7.976	3.97	-5.726	387.308	482.97	96.51	16
13	0	377.191	594.421	1001.909	1	3.75	8.115	3.584	-5.28	387.31	483.88	94.25	16
14	0	341.363	656.171	1110.69	2	5.25	10.841	2.548	-3.871	69.005	30.42	74.78	16
15	0	369.416	691.656	1205.409	1	5.75	9.614	3.181	-4.221	93.599	42.29	80.86	16
16	0	355.39	689.427	1171.532	2	5.25	10.699	2.917	-4.284	69.418	30.61	76.98	16
17	0	369.416	721.983	1231.83	2	5.25	10.556	3.294	-4.69	69.458	30.63	79.2	16
18	0	369.416	698.912	1209.728	2	4.75	10.399	3.415	-4.773	81.631	36.48	81.16	16
19	0	395.454	736.983	1281.693	2	5.25	11.001	3.644	-5.279	77.233	34.36	82.07	22
20	0	357.362	670.412	1135.849	3	6.95	13.955	1.49	-3.188	20.24	8.08	59.05	16
21	0	383.4	674.289	1178.706	1	7.45	11.723	2.292	-3.601	89.929	40.50	75.34	22
22	0	367.401	682.234	1175.445	1	5.75	10.078	3.139	-4.347	87.066	39.11	80.05	21
23	0	383.443	726.916	1266.975	1	5.75	9.502	3.57	-4.686	93.741	42.36	83.14	16
24	0	382.415	696.403	1205.346	2	7.25	13.247	1.693	-2.871	11.695	4.94	55.97	22
25	0	355.39	689.402	1171.547	2	5.25	10.699	2.916	-4.284	69.237	30.53	76.96	16
26	0	369.416	722.653	1232.385	2	5.25	10.557	3.299	-4.702	69.652	30.73	79.24	16
27	0	383.443	731.939	1270.359	2	4.75	10.257	3.792	-5.193	81.896	36.61	83.4	16
28	0	383.443	755.208	1292.683	2	5.25	10.415	3.672	-5.112	69.692	30.75	81.44	16
29	0	409.481	770.152	1342.492	2	5.25	10.859	4.023	-5.701	77.507	34.49	84.31	22
30	0	371.389	703.371	1196.428	3	6.95	13.813	1.849	-3.566	20.307	8.10	61.18	16
31	0	381.427	715.328	1235.979	1	5.75	9.939	3.405	-4.805	87.172	39.16	81.61	21
32	0	396.442	729.302	1265.497	2	7.25	13.107	2.056	-3.265	11.703	4.94	58.11	22
33	0	397.427	707.24	1238.888	1	7.45	11.584	2.662	-4.011	90.006	40.54	77.51	22
Recommended range for 95% known drugs ST: 0-5, MW: 130-725, SASA: 300.0-1000.0, Volume: 500.0-2000.0, DHB: 0.0-6.0, AHB: 2.0-20.0, QPlogPw: 4.0-45.0, QPlogPo/w: -2.0-6.5, QPlogS: -6.5-0.5, QPPCaco: <25 poor and >500 great, QPPMDCK : <25 poor and >500 great, PHOA : >80% is high and <25% is poor													
ST: #stars, DHB:donorHB, AHB: accptHB, PHOA: Percent HumanOralAbsorption													

ADME study

A large number of stars suggest that a molecule is less drug-likeness than molecules with few stars. The values of star for most of the molecules lie in the recommended range i.e. 0-5. The range of total solvent-accessible volume, total accessible surface area (SASA) in cubic angstroms using a probe with a 1.4 Å radius, the estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (donorHB), hydrogen bonds that would be accepted (accptHB) by solute from water for all the flavones are lies in the recommended range. For most of the flavones molecules the descriptors and properties like QPlogPw (predicted water/gas partition coefficient), QPlogPo/w (octanol/water partition coefficient), QPlogS (predicted aqueous solubility), QPPCaco (cell permeability in nm/sec), QPPMDCK (MDCK cell permeability in nm/sec), and PHOA (percentage of human oral absorption) lies in the recommended range. The value QPPCaco and QPPMDCK for high active molecules **32** and **24** is poor compare to **1** and **3**. Therefore compound **1** and **3** may be developed further as MCF-7 inhibitor.

CONCLUSION

An atom based 3D-QSAR model with good statistical significance and good predictive ability has been developed with r^2 = 0.9961, q^2 = 0.8129, Pearson R = 0.9633, RSME = 0.30 and R^2_{CV} = 0.5188. 3D-QSAR visualization indicates the favourable positions of substitution for HBD and HBA groups in flavonoid skeleton. These pictorial presentations also highlighted the positions of substitution for hydrophobic and electron withdrawing groups crucial for better MCF-7 inhibition. Docking results being in good agreement with this 3D-QSAR outcome indicates the robustness of the model. This atom based 3D-QSAR model could be very useful for predicting the in silico activity of non-tested molecules while docking results would be helpful for development and optimization of new lead as MCF-7 inhibitor.So this 3D-QSAR model, docking and ADME informations may be likely to reduce, time and effective cost, the number of MCF-7 inhibitor to be synthesized.

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