



# ***In-silico* Drug Design, ADMET Screening, MM-GBSA Binding Free Energy of Some Chalcone Substituted 9-Anilinoacridines as HER2 Inhibitors for Breast Cancer**

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**Abstract:** Due to their DNA-intercalating agents 9-anilinoacridines play an important role as antitumor agents. A Series of some Chalcone substituted 9-anilinoacridines 1a-x were designed for their anti-breast cancer activity. Molecular docking studies were performed by Glide module of Schrodinger suite-2016, targeted against Human epidermal growth factor receptor HER2 (PDB id-3PP0). *In-silico* ADMET screening by qikprop module and binding free energy by Prime-MMGBSA module also performed. Based on the binding affinity of the designed molecules with HER2 on the basis of GLIDE score and interaction patterns. Most of the compounds 1a-x have significant Glide scores when compared with standard anticancer drugs ledacrine and tamoxifen. Most of the Chalcone substituted 9-anilinoacridine derivatives 1a-x have good binding affinity with Glide score in the range of -5.32 to -9.37 compared with the standard ledacrine (-5.23) and tamoxifen (-3.78). The results reveals that, Chalcone substituted 9-amino acridines as HER2 inhibitor and the compounds, 1g, f, b, h, t, u with good Glide score may produce significant anti-breast cancer activity for further refinement.

**Keywords:** Docking Studies, Acridine, Chalcone, MM-GBSA, Antibreast Cancer, HER2

## **1. Introduction**

Many chemotherapeutic agents still plays an important role in the fight against cancer. Especially, about 1 in 5 women affected by breast cancer. Human epidermal growth factor receptor HER2 overexpression is present in 20–30% of the breast cancer. HER2 overexpression is associated with a more aggressive disease, higher recurrence rate, and shortened survival [1]. These type of breast cancers, grow and spread more aggressively. The benefit of anti-HER2 therapies are one of the most promising molecules for targeted therapy [2]. Human epidermal growth factor receptor-2 is membrane tyrosine kinase was over expressed and gene amplified in human breast cancers. So it is an important tumor cell proliferation and survival pathways [3]. Breast cancers have up to 25–50 copies of the HER2 gene, and up to 40–100 fold increase in HER2 protein resulting in

more than 2 million receptors expressed at the tumor cell surface (ERBB2 amplification in breast cancer analysed by fluorescence in situ hybridization [4].

In general, 9-aminoacridine derivatives are inhibiting DNA due to the ability of acridine nucleus to intercalate into DNA base pair. Presently available 9-aminoacridine derivatives like amsacrine and CI-921 a well-known anti-proliferative agent used in the treatment of acute leukaemia. They are biologically unstable because of the Amsacrine (m-AMSA) and CI-921 possess a methane sulfonyl and a methoxy function at C-1' and C-3' of the 9-anilino ring and readily undergo reversible oxidation either chemically or microsomally converted in to quinonediimine. More than 50% of the dose is excreted as the glutathione conjugate. To address these drawbacks of 9-aminoacridines, the effective strategy is to design some modified drugs to overcome these above problems.

Acridines are more importance for their various pharmacological activities like antimicrobial [5], antimicrobial [6], anticancer [7-11], antimalarial [12, 13], anti-inflammatory [14], analgesic [15], antileishmanial [16], antinociceptive [17], acetyl cholinesterase inhibitors [17] and antiherpes [19] etc. The structural modification of acridines by the introduction of different substitutions were allowed expansion of research on the structure activity relationship to afford new insight into molecular interactions at the receptor level [20]. Similarly, chalcones are also be an important class of compounds with a wide range of biological activities [21-23] like antimicrobial, anticancer etc.

The present research work by *in-silico* drug design gives knowledge about the new drug discovery by modifying the structure of the compounds for breast cancer activity and save time and money spending by wet lab. So after *in-silico* drug design, we will synthesize selected compounds with good docking score.

As part of our ongoing research on searching novel antitumor agents [24-27], we have designed some novel 9-aminoacridine analogues bearing the chalcone residue on 9-aminoacridine rings by molecular docking studies by using Schrodinger suit-2016. The results revealed that the newly designed chalcone substituted 9-anilinoacridines exhibited significant inhibition with HER2 exhibit anti-breast cancer activity.

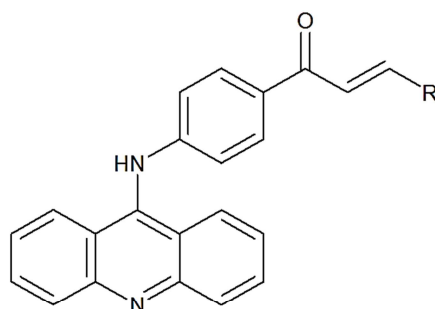
## 2. Materials and Methods

### 2.1. Protein Preparation

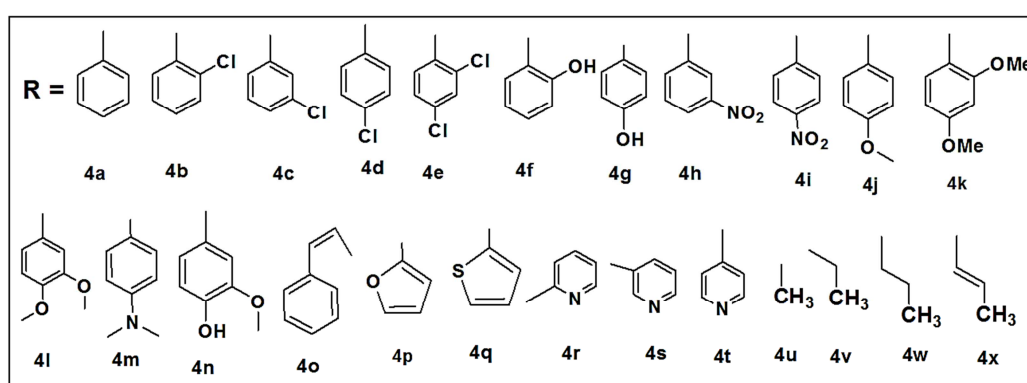
The Human epidermal growth factor receptor 2 (HER2) with co crystallized ligand (PDB ID: 3PP0, resolution 2.25 Å) was retrieved from protein data bank. protein preparation was performed by Protein preparation wizard module of Schrödinger suite 2016-2. Missing chain atoms are added by using prime module of Schrödinger suite 2016-2. Energy minimization of the protein structure was carried out using OPLS3 force field. A grid box was generated to defined the centroid of the active site for docking studies [28]

### 2.2. Ligand Preparation

The designed ligands (1a-x) were prepared by LigPrep module of Schrodinger suite 2016-2. 2D structures were converted to 3D structures, as well as energy minimization and optimized for their geometry, desalted and corrected for their chirality. The ionization and tautomeric states were generated between pH of 6.8 to 7.2 by using Epik module. The compounds 1a-x were minimized using Optimized Potentials for Liquid Simulations-3 (OPLS-3) force field in Schrodinger suit until a root mean square deviation of 2.0 Å was achieved. A single low energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis.



**Chalcone substituted 9-anilinoacridine derivatives (1a-x)**



**Figure 1.** Structure of designed compounds (1a-x).

### 2.3. Glide Ligand Docking

The designed chalcone substituted 9-aminoacridines (1a-x) were docked in to catalytic pocket of HER2 protein (PDB ID:

3PP0) by Glide module of Schrödinger suite 2016-2. The favourable interactions between the receptor and ligands were scored by using Glide ligand docking module. Docking calculations were performed using extra precision (XP) mode

and OPLS-3 force field. The flexible docking was performed for docking process in which automatically generates conformations for each ligand. This algorithm recognizes favourable hydrogen-bonding, hydrophobic, and electrostatic interactions, and penalizes steric clashes. Finally, the minimized poses were re-scored using Glide Score scoring function [29]. The XP-Glide score of the compounds were summarized and compared with the standard compound containing acridine ring ledacrine and the anti-breast cancer drug tamoxifen.

The *in-silico* ADMET properties of the proposed molecules were determined by qikprop module of Schrödinger suite-2016.

#### 2.4. Binding Free Energy Calculation by Using Prime/MM-GBSA Approach

The binding free energies of ligand and receptor complex were computed by Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) using the Prime module of Schrödinger suite 2016-2 which incorporates the OPLS3 force field and VSGB solvent model to search algorithms.

### 3. Results and Discussion

#### 3.1. Docking Studies

The docking studies of the designed molecules (1a-x) to the protein active sites were performed by Glide module of Schrödinger suite-2016-2 for determining the binding affinities of the ligands. The designed compounds are docked towards the HER2 (3PP0) in order to ascertain their HER2 inhibition activity against breast cancer. The compounds 1a-x were exhibited good affinity to the receptor when compared with standard acridine derivative with anticancer activity ledacrine and anti-breast cancer agent tamoxifen. The Glide scores of docking studies against HER2 inhibitor (PDB id 3PP0) are shown in the Table 1. From the docking results, the interactions are mainly lipophilic factors due to the presence of aromatic rings of acridine and heterocyclic rings. The ligand interactions of the compound 1g with high Glide score (-9.374) are mainly dominated in the region of LEU726 to PHE 864 residues which are the active site region (Figure 2). The compound 1g is exhibited hydrogen bonding with LEU 807 (H-bond length 1.92) residues (Figure 3). The best docked poses of the compounds 1g and 1f with high Glide score were shown in the Figure 4.

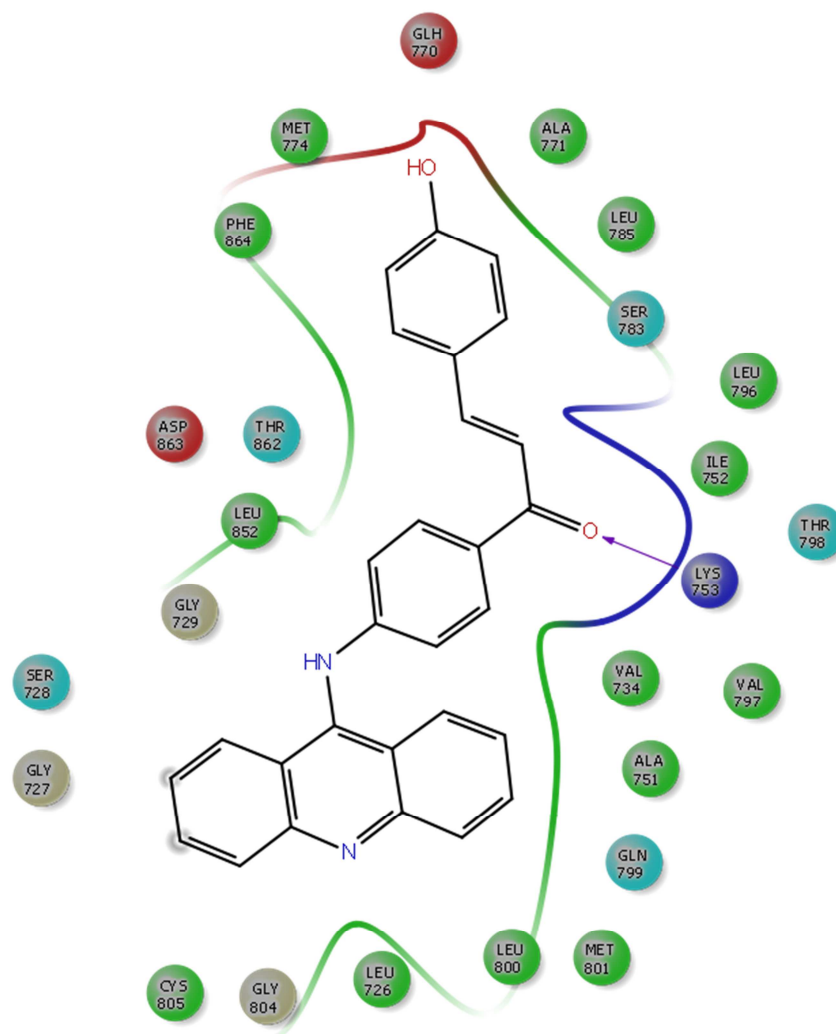


Figure 2. Ligand interaction of compound 1g with HER2 (3PP0).

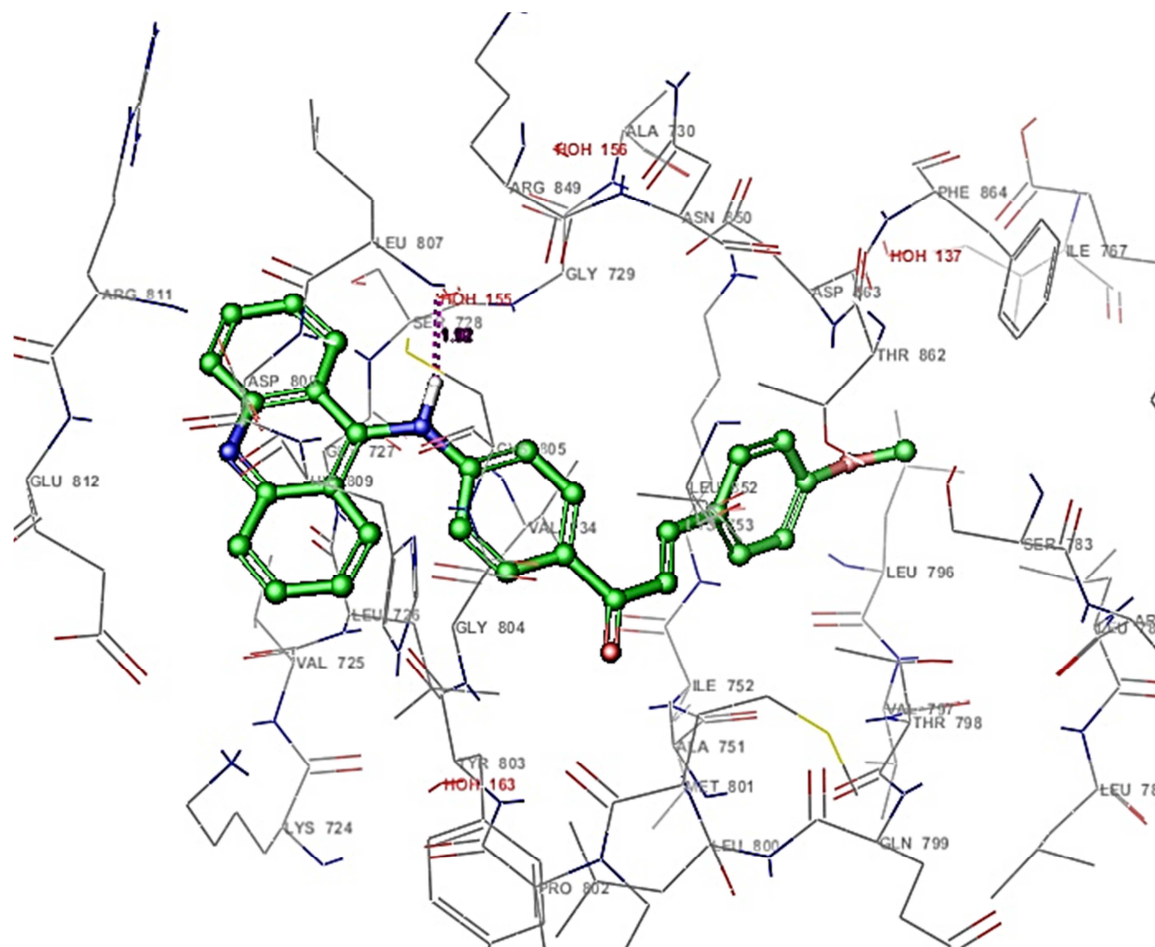


Figure 3. Hydrogen bonding affinity of docked compounds 1g with HER2 (3PP0).

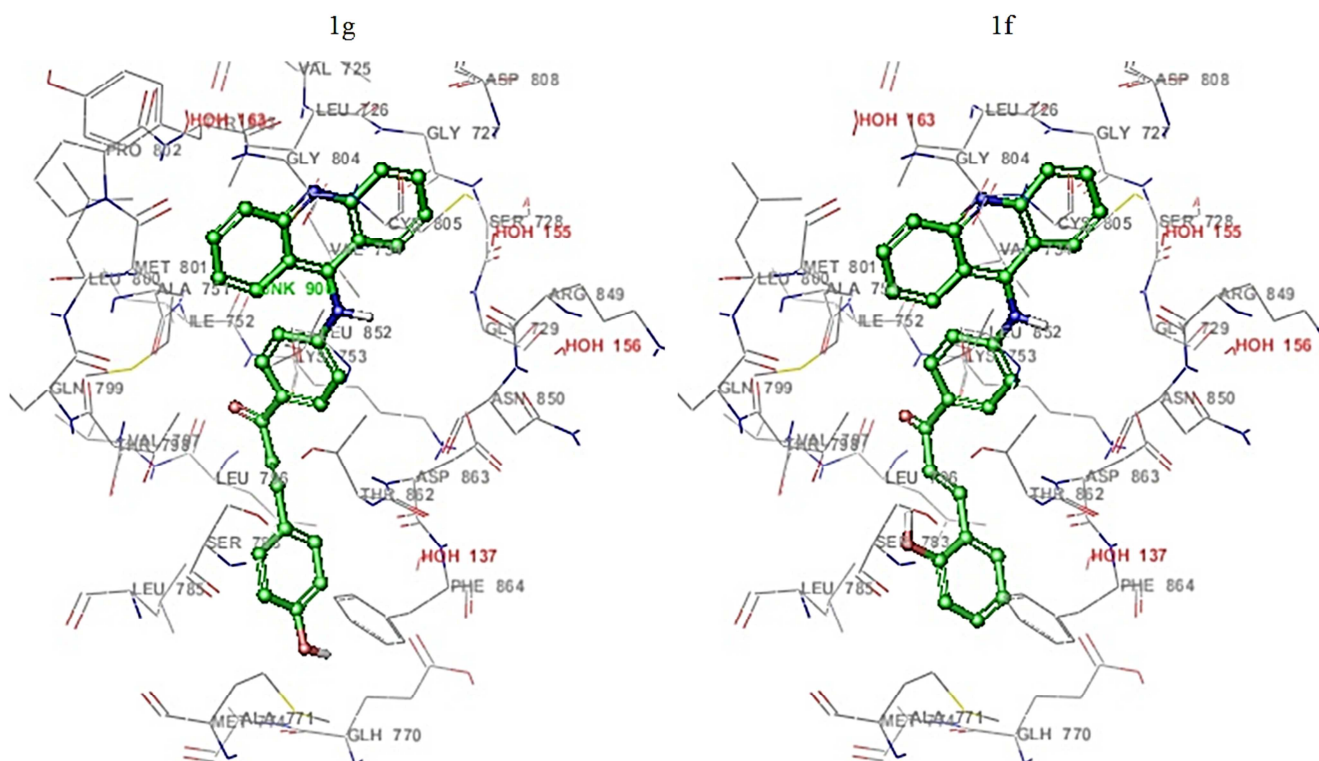


Figure 4. Best affinity mode of docked compounds 1g and 1f with HER2 (3PP0).

**Table 1.** Docking results for Chalcone substituted 9-anilinoacridines (1a-x) with HER2 (3PP0).

Compounds	GScore	Lipophilic EvdW	HBond	Electro	Low MW	Penalties	Rot Penal
1g	-9.374	-9.128	-0.032	0.053	-0.112	0	0.244
1f	-9.358	-9.127	0	0.037	-0.112	0	0.244
1b	-8.586	-9.277	-0.112	0.072	-0.05	1	0.181
1h	-8.558	-9.159	0	0.05	-0.015	1	0.216
1t	-8.2	-8.359	0	-0.075	-0.162	1	0.209
1u	-8.108	-7.656	0	0.037	-0.372	0	0.283
1s	-7.977	-8.676	0	0.052	-0.162	1	0.209
1p	-7.471	-8.849	0	-0.068	-0.199	2.5	0.219
1v	-7.459	-8.097	0	0.033	-0.325	1	0.329
1w	-7.429	-8.43	0	0.058	-0.278	1.5	0.307
1c	-7.005	-9.743	-0.32	0.003	-0.05	4	0.181
1a	-6.648	-9.632	0	0.002	-0.165	4	0.21
1x	-6.5	-8.474	0	0.074	-0.285	2.5	0.31
1n	-6.433	-6.327	-0.48	0.17	-0.012	0	0.215
1e	-6.357	-9.77	-0.157	0.031	0	4	0.157
1q	-6.161	-9.148	0	-0.072	-0.145	4	0.204
1j	-6.13	-6.103	-0.7	-0.101	-0.065	0	0.23
1d	-6.044	-6.687	0	-0.03	-0.05	0	0.181
1i	-5.929	-5.496	-0.547	0.049	-0.015	0	0.216
1m	-5.693	-5.997	-0.427	-0.053	-0.022	0	0.218
1o	-5.515	-5.562	-0.404	-0.067	-0.078	0	0.234
1k	-5.324	-5.871	0	-0.129	0	0	0.203
1r	-3.797	-9.151	0	-0.043	-0.162	6.4	0.209
1l	-2.539	-5.752	-0.7	-0.11	0	4	0.203
Lidacrine (std)	-5.23	-3.95	-0.83	-0.12	-0.15	0	0.1
Tamoxifen (std)	-3.787	-4.179	0	-0.262	0.42	-0.023	0

### 3.2. *In-silico* ADMET Screening

The ADMET properties of the designed ligands (1a-x) were determined *in-silico* by qikprop module of Schrödinger suite 2016-2. Molecular weight of the designed compounds between 352 to 460. Estimated no. of hydrogen bonds donors are in the range of 1-2. Estimated no. of hydrogen bonds acceptors are in the range of 3.5- 5. Predicted octanol/water partition coefficient are in the range of 4.9 to 7.2. Predicted brain/blood partition coefficient are in the range of -3.3 to -1.6. Number of likely metabolic reactions of the compounds are in the range of 1-4. Prediction of binding to human serum albumin for the compounds are in the range of -0.8 to -1.4. Number of violations of Lipinski's rule of five is 0-1. All the compounds have 90 to 100% Human Oral Absorption. So almost all the properties of the compounds

are within the recommended values. The details of the ADMET properties for the compounds 1a-x are shown in the Table 2.

Binding free energy calculation using Prime/MM-GBSA

The stability of docking was also evaluated with MM-GBSA free binding energy [30] which is related to post scoring approach for HER2 (PDB ID: 3PP0) target. The accuracy of docking is confirmed by the lowest energy poses predict by scoring function. The Glide scores are almost resembling to the experimental binding mode as determined by the X-ray crystallography. The Glide score and MM-GBSA free energy values are obtained by the docking of ligands in to the binding pocket. The details of the MM-GBSA free binding energy for the ligands 1a-x are shown in the Table 3.

**Table 2.** *In-silico* ADMET screening for compounds 1a-x.

Compounds	mol MW	Donor HB	Accept HB	QLogP o/w	QP log BB	# metab	QLog Khsa	%Human Oral Absorption	Rule of Five
1a	400.479	1	3.5	6.302	-0.498	2	1.224	100	1
1b	434.924	1	3.5	6.751	-0.357	2	1.333	100	1
1c	434.924	1	3.5	6.8	-0.336	1	1.345	100	1
1d	434.924	1	3.5	6.801	-0.337	2	1.346	100	1
1e	469.369	1	3.5	7.238	-0.192	1	1.452	100	1
1f	416.478	2	4.25	5.552	-1.06	3	0.996	100	1
1g	416.478	2	4.25	5.505	-1.164	3	1.005	100	1
1h	445.476	1	4.5	5.595	-1.667	2	1.172	90.76	1
1i	445.476	1	4.5	5.607	-1.676	2	1.175	90.831	1
1j	430.505	1	4.25	6.404	-0.576	3	1.235	100	1



Compounds	mol MW	Donor HB	Accept HB	QLogP o/w	QP log BB	# metab	QLogKhsa	%Human Oral Absorption	Rule of Five
1k	460.531	1	5	6.532	-0.659	4	1.252	100	1
1l	460.531	1	5	6.582	-0.661	4	1.268	100	1
1m	443.547	1	4.5	6.722	-0.635	3	1.387	100	1
1n	446.504	2	5	5.742	-1.044	4	1.015	100	1
1o	426.517	1	3.5	7.011	-0.659	2	1.429	100	1
1p	390.44	1	4	5.673	-0.49	3	0.959	100	1
1q	406.501	1	3.5	6.213	-0.391	3	1.145	100	1
1r	401.467	1	4.5	5.633	-0.718	3	0.985	100	1
1s	401.467	1	5	5.354	-0.802	3	0.878	100	1
1t	401.467	1	5	5.35	-0.802	3	0.877	100	1
1u	338.408	1	3.5	4.956	-0.335	3	0.827	100	0
1v	352.435	1	3.5	5.342	-0.416	3	0.954	100	1
1w	366.462	1	3.5	5.729	-0.496	3	1.078	100	1
1x	364.446	1	3.5	5.651	-0.492	3	1.027	100	1
Recommended values	130-725	0-6	2-20	2-6.5	-3-1.2	1-8	-1.5-1.5	7-200	0-4

MW- Molecular weight of the molecule,

donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.

acptHB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution

QLogPo/w - Predicted octanol/water partition coefficient.

QP log BB Predicted brain/blood partition coefficient

#metab- Number of likely metabolic reactions.

QLogKhsa- Prediction of binding to human serum albumin.

RuleOfFive Number of violations of Lipinski's rule of five.

%Human- Oral absorption- Predicted human oral absorption on 0 to 100% scale.

**Table 3.** Binding free energy calculation for compounds 1a-x using Prime/MM-GBSA approach.

Compounds	$\Delta G_{bind}$ (Kcal/mol)	$\Delta G_{bind}$ Coulomb	$\Delta G_{bind}$ Vander	$\Delta G_{bind}$ HBond	$\Delta G_{bind}$ covalent	$\Delta G_{bind}$ Lipophilic
1a	-63.2916	-35.6655	-37.2151	-2.94571	-5.15878	-26.9411
1b	-64.4452	-26.1298	-39.7237	-0.43671	-8.03151	-28.5308
1c	-40.3856	20.71722	-35.1217	5.732459	-17.1177	-26.4266
1d	-64.1664	-3.75509	-42.1457	-0.53399	-5.19287	-25.9174
1e	-68.0454	9.404431	-53.6695	1.296063	-12.0695	-26.2351
1f	-60.9029	-20.1311	-30.3334	-0.66922	-2.12714	-20.1654
1g	-64.5958	-10.3487	-39.6925	3.270054	-17.5304	-26.6284
1h	-67.3007	-26.1181	-39.2795	-1.0628	-9.15781	-25.5037
1i	-72.0653	-10.1229	-46.8267	-0.95492	-6.14237	-22.722
1j	-65.5068	-11.8431	-46.2886	-1.38587	-7.0343	-25.0214
1k	-73.6077	-13.0051	-39.0165	1.70326	-17.0842	-29.4083
1l	-79.4697	-27.2758	-50.7698	-0.4232	-4.23311	-31.2384
1m	-68.871	-10.5547	-38.6772	1.026628	-16.6679	-24.607
1n	-43.6982	-6.83597	-43.4849	2.434836	13.21079	-26.1138
1o	-73.6327	-18.4178	-45.0856	1.502527	-11.9557	-33.0445
1p	-74.1282	-18.4891	-51.5734	-1.35663	-7.11058	-28.6394
1q	-37.5453	1.922893	-36.9764	0.10371	-13.3517	-17.0213
1r	-48.314	-34.3285	-35.7612	-0.3345	-4.86448	-19.2435
1s	-61.6737	-39.0154	-56.924	-5.6718	16.7104	-21.567
1t	-55.7057	-39.2176	-41.3566	-1.44176	-6.81391	-21.022
1u	-72.5252	-19.4196	-53.6654	0.046481	3.02907	-31.5128
1v	-46.7637	-22.3516	-35.7654	1.073849	-3.88373	-17.5289
1w	-70.0558	-4.41536	-50.4707	0.266061	-8.52899	-29.1382
1x	-63.193	-8.45533	-47.8544	0.845721	3.264462	-26.7074

## 4. Conclusion

9-Aminoacridines are exhibited various biological activities. The molecular docking study revealed that chalcone

substituted 9-aminoacridines were showed better alignment at active site by interacting with many amino acid residues. The *in-silico* method adopted in the present study helped to identify the lead molecules. On this basis, we are recently demonstrated that diverse compounds of the chalcone substituted 9-

anilinoacridine series exerted HER2 inhibition as anti-breast cancer activity. The present study clearly demonstrated that many derivatives of the chalcone substituted 9-anilinoacridine family may exert interesting antitumour activity. The compounds 1g, f, b, h, t, u may have significant anti-breast cancer activity with therapeutic potentials and are likely to be useful as drugs after further refinement.

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