**IJPSR (2022), Volume 13, Issue 11** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 February 2022; received in revised form, 26 April 2022; accepted, 04 May 2022; published 01 November 2022

# PREDICTION OF POTENTIAL DIETARY COMPOUNDS AGAINST HER2: AN *IN-SILICO* ASSESSMENT

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**Keywords:**

Breast cancer, HER2, Phytochemicals, *In-silico* inhibition, Computational tools

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**ABSTRACT:** Presently, *in-silico* approaches have been introduced as alternative methods for the process of drug invention. The current investigation aimed to explore expectations and the examination of the chemotherapeutic potential dietary phytochemicals as effective anti-cancer agents against *HER2*. This receptor plays a pivotal role in the development of breast cancer. Here, protein-ligand virtual screening was established as a coherent strategy for the identification of new inhibitors. The primary screening was performed with a molecular approach using iGEM DOCKv2.1 software. Bioinformatics & system analytical techniques were used for the extrapolation of adverse assessments. Lastly, the best compounds with a good outfit score, non-toxic and better drug-likeness esteems were scrutinized for interactions with the key residues and were escalated to final screening. The final re-docking simulation was performed using AD Vina in pyrx 0.8 software. Finally, the top Phytoconstituents as the best binders to the active site of protein structures and muscularly agree with massive experimental consequences. The results confirmed that (2R, 3R)-2-(3, 4-dihydroxyphenyl)-3, 4-dihydro-2H-chromene-3, 5, 7-triol and 2-(3, 4-dihydroxyphenyl)-3, 7-dihydroxychromen-4-one can be ascribed as promising compounds that exhibited reliable consequences with fewer side effects and more efficient for the target protein. Hence, we propose the best two-hit scaffolds as virtual candidates for *HER2* inhibitors. Further, wet lab exploration and experimental validation justify the utmost attention.

**INTRODUCTION:** Some studies strongly assist in the connection between nutrition and breast cancer progression. It is a kind of hormonal disease observed in women around the world [1, 2]. According to cancer statistics, the ACS appraised that there will be an expected 281,550 cases of invasive and 43,600 cases of breast cancer demises among women in the US for the year 2021[3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(11).4577-85

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(11).4577-85

Therefore, it is essential to develop new anti-cancer agents that can reduce the progression of BC. The cancer is mostly due to environmental, western diet, lifestyle factors and hereditary reasons such as gender, over-fatness and exercise [4, 5]. The other well-known risk factors include the existence of benign tumors in the breast, Lack of exposure to sunlight, hormone replacement therapy, or a long menstrual cycle that increases the progression of breast cancer.

At present, there has been an explosion of life-saving action advances against BC to bring expectations and excitement. Several types of treatments are available for patients suffering from breast cancer.

They are surgical exclusion, followed by radiation therapy and hormone therapy [6]. HER2 is a member of the ERBB family comprising of four specific receptors: ErbB-1/HER1, HER2/ErbB-2, HER3/ErbB-3 and HER4/ErbB-4. The over-expression of the *HER2* oncogene plays a significant role in breast cancer progression. The receptor is over-expressed in 20-30% of breast cancer tumors. The clinical action of breast cancer related to this gene was primarily demonstrated in 1987 [7, 8, 9]. Radiotherapy with synthetic drugs used in treating breast cancer evokes serious side effects such as infectious diseases and organ failure, which causes the death of a patient after recovering from cancer. Therefore, from this point of view, the induction of programmed cell death in a neoplastic cell line without detrimental to the body's healthy cells with the natural compounds as chemopreventive agents seems to be the best approach in the therapy of breast cancer[10].

Phytochemicals are naturally active non-nutritive chemical compositions that occur naturally in plants. Nowadays, natural products are frequently investigated for modern medicine. These products play a prominent role in cancer therapy. Presently, most efficacious anti-cancer drugs are derivatives from traditional compounds or their analogs. Recent reports strongly suggested that a high dietary intake of raw and leafy vegetables along with the related lifestyle is a potential strategy for significantly decreasing the risk of chronic disease. Plant-derived compounds are substantiated to be very productive in diminishing various human malignancies. Breast cancer risk can be decreased by consuming the richest basis of bioactive phytochemicals like flavones, polyphenols, *etc*. Their primary sources are apples, vegetables, berries, coffee, cocoa, onions, green tea, and wine. Natural ingredients are regularly investigated in modern biology, and these compounds serve as major factors in the synthesis of many therapeutic agents. According to recent scientific reports, nearly 75-80% of the composites used in human cancer treatments are natural products. In recent years, enormous work has been done on these phytochemicals, which play an imperative role in routine healthcare systems. These natural health products can be reported to show many encouraging activities against human cancers [11, 12, 13, 14, 15].

Computational approaches are used extensively in the drug innovation process. Auto Dock Vina and iGem Dock is the most modern versions extensively used for Virtual Screening because of enhanced docking speed. Structure-based screening is one of the key components in computer-aided drug design [16]. This study explained the Log S and Log *P* properties of efficient phytocompounds, which are essential for drug-likeness examinations. The toxicity endpoints like carcinogenicity, mutagen city, developmental toxicity, and skin sensitization evinced fingerprints were carefully assessed with CAESAR models. The toxicological etiologies and pharmacokinetics assets of selected phytochemicals were considered using computational and analytical tactics against the *HER2* (PDB ID: 4GFU) ligand-binding domain to potentiate the probably predictable drug scaffolds for future *HER2* mitigators for breast cancer treatment. So, in this investigation, an attempt was made to identify the plausible potential drug candidates that can inhibit breast cancer progression. Predicting new molecular targets for an individual molecule using experimental and wet biology approaches for these examinations has ethical considerations, captivates a lot of time, and is a more expensive process.

The selected natural compounds: (-)-Epicatechin (Pubchem CID: 72276); Fisetin (CID:5281614); Epigallo Catechin 3-gallate (CID: 65064); Ellagic acid (CID:5281855); Rosmanol(CID:13966122); and Flavanone (CID:10251) has outstanding anti-cancer activity, better PK parameters, and low toxic effects. These plant-derived compounds were chosen for the current investigation based on their properties.The alternative approach for the use of bioinformatics and computational system biology techniques. Virtual screening is the best one among the computational methodologies in such a scenario.

## MATERIALS AND METHODS:

### Computational Analysis:

**Selection of Molecular Targets and Retrieval of Ligands from the Database:** The crystallographic structure of the following breast cancer target was availed from the Brookhaven protein data bank (www.rcsb.org/pdb) with the PDB ID: 4GFU as shown in **Fig. 1**. Removing attached ligands, Gesteiger partial charges, and amino acid side

chain hydrogen atoms were added to the receptor structure using UCSF Chimera 1.10.2, which is very important for molecular docking studies. The three-dimensional structures of the natural ingredients used in this study were downloaded in SDF format using the Pubchem compound database (http://pubchem.ncbi.nlm.nih.gov/).

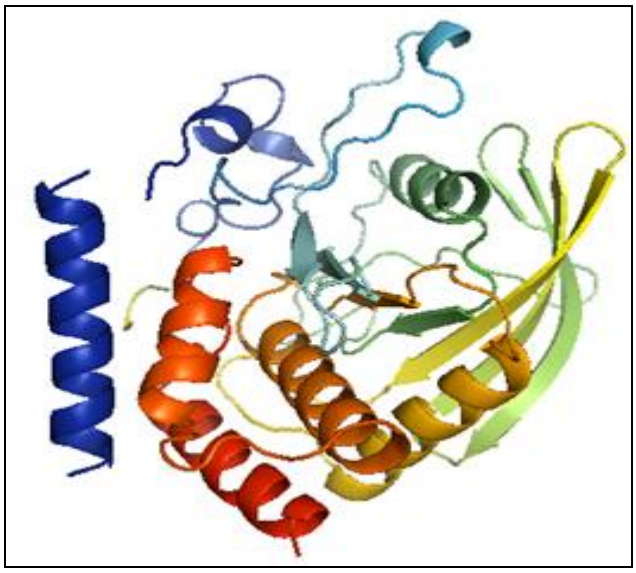


**FIG. 1: HER2 PROTEIN IN CARTOON MODEL**

**Receptor-ligand Docking:**

**Primary Screening:** Molecular docking is a computational approach and also an efficient tool for *in-silico* screening. It is one of the most significant methods in structure-based drug design. The primary screening was performed with a molecular docking approach using I GEMDOCK v2.1 module software [17].

**Final Screening:** In the step of final screening, the compounds, which showed good binding energy values to the target *HER2* in primary screening as well as have good physicochemical and pharmacokinetic properties without toxicity potential, were selected for further analysis.

For this, final docking was performed using Auto Dock Vina in PyRx Virtual screening software. These procedures attempt to efficiently predict the non-covalent binding of macromolecule and a small molecule (ligand). AD Vina in PyRx 0.8 is a new program for virtual screening and docking that has been widely used. Afterward, the active site was selected as a grid for docking, generating respective grid maps. Grid with 48×58×48Å grid spacing was placed at the center- x=15.818, center - y =-308.8151, center- z=10.4975 with 0.375Å spacing value between each point to generate docking input files.

**Drug Scan and screening of Chemicals on the Premise of Lipinski's Rule of Five:** *In-silico* pharmacokinetics, drug-likeness esteems, different molecular attributes, synthetic accessibility, lead-likeness, medicinal chemistry properties, and SAR-based ADMET (absorption, distribution, metabolism, elimination, and toxicity) analysis of the screened scaffolds were envisaged using robust Swiss ADME online server tool [18]. DruLiTo and ADMETSAR programs, respectively. Drug-likeness esteems were evaluated by Pfizer's rule of five principles.

Therefore, physicochemical properties like molecular weight (≤500 Daltons), hydrogen bond donors (≤5), hydrogen bond acceptors (≤10) and other versatile features were predicted and analyzed with the macromolecule. Additionally, drug likeness was measured with molecular properties using the DruLiTo server (http://www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_index.html). The bioactive properties of phytochemical compounds were envisaged using an online Chemoinformatics tool Molinspiration (http://www.molinspiration.com/).

The SMILES (simplified molecular-input line-entry system) of regarded data set phytochemicals were retrieved from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/search.cgi). The filtered Potentlead scaffolds were utilized for further screening and molecular docking approaches from the above promising consequences.

**Analysis and Screening of QSAR-based Adverse Effects:** In this investigation, the QSAR-based endpoint analysis was implemented to estimate the adverse effects of selected leads using a proficient VEGA-*NIC* program package.

The mutagenicity, carcinogenicity, developmental toxicity and skin sensitization potentials of selected Phytoconstituents were predicted by applying QSAR models established by the CAESAR project. CAESAR developed simulations for various toxic endpoints considering REACH guidelines.

## RESULTS AND DISCUSSIONS:

**Binding Mode Analysis of Top Complexes with the Macromolecule:** In this regard, we identified the three best hits *i.e.,* CID:72276, CID:5281614, and CID: 5281855, might be chosen as new inhibitors for the human epidermal growth factor receptor 2 and these compounds have good anti-cancer properties and also have high *HER2* binding capacity.

The molecular screening protocol was validated by docking natural compounds into the binding pocket of protein structure conducted by virtual screening with Auto Dock Vina in Pyrx interface. The preliminary docking (IGEMDOCK) screening scores in **Table 1** and final screening (AD Vina) compounds are shown in **Table 2**.

The binding mode analysis of the best hits is shown in **Fig. 2**. Among them, compound CID: 72276 is the most potential, with a binding affinity value of-.1 kcal/mol.

The hydrogen atoms in the side chain amino group Arg268 and Gln34 are involved in the formation of two hydrogen bonds with an oxygen atom in the hydroxyl group of the ligand. The oxygen atom in the carboxyl group of Gln34, Ser37, Asp 64, and Leu66 are involved in forming four hydrogen bonds with hydrogen atoms of hydroxyl groups in the ligand presented on CID: 72276 **Fig. 2A**. CID: 5281614 has a binding affinity value of -7.9 kcal/mol. It is bound to the selected Protein by forming a hydrogen bond. A hydrogen bond is formed between the amino group of Gly1250 and the oxygen atom of the ligand. Two hydrogen bonds are formed between the oxygen atom of the ligand and the main chain Amino group of Ala231 and Ser230. The oxygen atom of the hydroxyl group present in the ligand forms a hydrogen bond with the hydrogen atom of the side chain amino group present in Arg235. Another hydrogen bond is formed between the oxygen atom of the main chain carboxyl group of Gln276 and the hydrogen of the hydroxyl group presented in CID: 5281614 **Fig. 2B**.

The third compound, CID: 5281855, also showed better binding energy of -7.9kcal/mol. The oxygen atom of the hydroxyl group in the ligand was involved in the formation of a hydrogen bond with the hydrogen atoms of the main chain amine groups of Leu 1251 and Ala231 in **Fig. 2C**.

**TABLE 1: RESULTS OF PRIMARY SCREENING OF THE PHYTOCHEMICALS FOR INTRODUCING EFFECTIVE HER2 INHIBITORS**

| CID | TE (Kcal/mol) | VDW (Kcal/mol) | H-BOND (Kcal/mol) | EI (Kcal/mol) |
|---|---|---|---|---|
| 72276* | -113.53 | -77.45 | -36.08 | 0 |
| 5281614 | -111.62 | -71.84 | -39.78 | 0 |
| 5281855 | -100.2 | -56.28 | -43.92 | 0 |
| 65064 | -98.34 | -71.97 | -26.37 | 0 |
| 13966122 | -95.03 | -70.55 | -24.48 | 0 |
| 10251 | -77.68 | -68.3 | -9.38 | 0 |

VDW: Van der Waals force; H Bond: Hydrogen bond; EI: Electrostatic interaction; TE: Total energy.

**TABLE 2: THE RESULTS OF THE FINAL MOLECULAR DOCKING STUDY**

| Molecule's ID | Compound Name (IUPAC) | Chemical formula | AutoDock Binding energy ΔGB(Kcal/mol) |
|---|---|---|---|
| 72276* | (2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol. | $C_{15}H_{14}O_6$ | -8.1 |
| 5281614 | 2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one. | $C_{15}H_{10}O_6$ | -7.9 |
| 5281855 | 6,7,13,14-tetrahydroxy-2,9-dioxatetracyclo[6.6.2.04,16.011,15]hexadeca-1(15),4,6,8(16),11,13-hexaene-3,10-dione. | $C_{14}H_6O_8$ | -7.9 |
| 13966122 | (1R,8S,9S,10S)-3,4,8-trihydroxy-11,11-dimethyl-5-propan-2-yl-16-oxatetracyclo[7.5.2.01,10.02,7]hexadeca-2,4,6-trien-15-one. | $C_{20}H_{26}O_5$ | -7.5 |
| 10251 | 2-phenyl-2,3-dihydrochromen-4-one | $C_{15}H_{12}O_2$ | -7.3 |

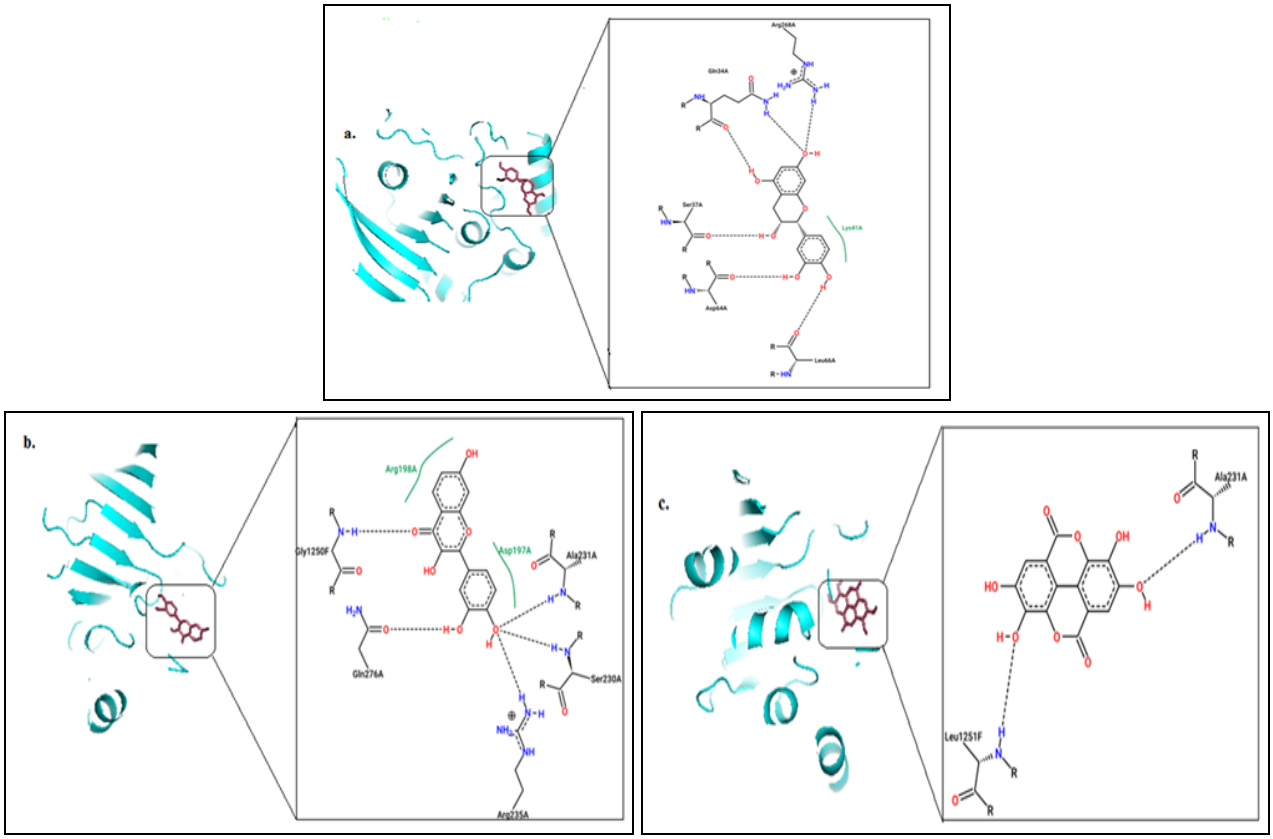



**FIG. 2: VISUALIZATION OF TOP DOCKING COMPLEXES**

**Drug-likeness Assessment of the Docked Complexes:** Analysis of pharmacological and pharmacokinetic profiles of chemical molecules is imperative assortment before going for preclinical and clinical evaluations, and they provide pinpoints to potentiate them as auspicious drug gable chemicals towards therapy for various disorders. These consequences shall delineate what the evident functionalities associated with their structures and how the predicted ligands act as drug gable candidates.

Hence, auspicious pharmacokinetics and drug-likeness parameters of chemicals were precisely assessed with respective robust Swiss ADME, ADMET SAR and DruLiTo programs, respectively. According to **Tables 3 & 4**, all virtual leads are espoused din the range of Lipinski's principles. Atomic and knowledge-based techniques were used to foresee partition coefficient (Log P) for measuring the lipophilicity of compounds and illustrate all leads ranging between 0.79 and 2.50 (log P), which indicates all chemical molecules are easily soluble and permeable. Pharmacokinetic assets of ligands are informative observable values, including all competitors to restrain the higher gastrointestinal absorption (GI), BBB permeant, and metabolize through cyp450 family genes, and probable skin permeations were identified. Furthermore, the medicinal chemistry properties ensued that the molecules do not violate Lipinski's principles but contain reliable bioavailability scores, and in future perspectives, they have potential synthetic accessibilities.

Further, drug-like acceptances were assessed with comparable Physico-chemical parameters of docked hits through the quantitative estimation, informed that all have predictable drug-likeness properties **Table 4** and the structures of chemical scaffolds and the pictorial representations of bioavailability radars are shown in **Fig. 3**.

The ADME/Toxicity profiles of chemical ligands are depicted in **Fig. 4**. Overall analysis potentially says that hits have adequate biological features with low toxic effects; therefore they may be used as hopeful drug gable candidates for *HER2* towards moderating the breast cancer and other malignant disorders associated with *HER2* and their biological significant pathways.

**TABLE 3: PHARMACOLOGICAL PROFILES AND LEAD-LIKENESS PARAMETERS OF PREDICTED MOLECULAR CANDIDATES**

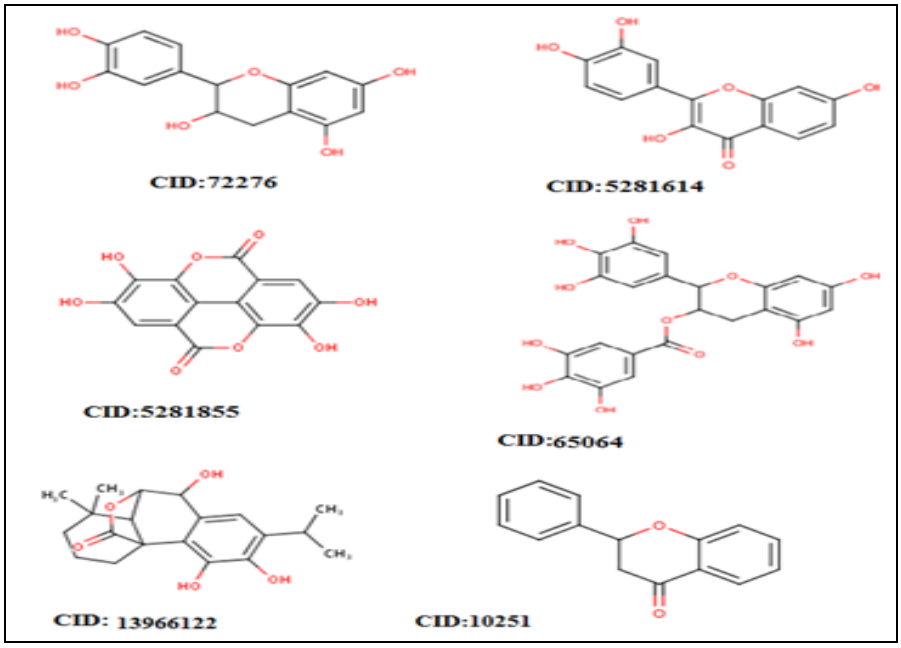
| Molecular descriptors | 72276 | 5281614 | 5281855 | 13966122 | 10251 |
|---|---|---|---|---|---|
| **Physicochemical properties** | | | | | |
| MW (g/mol) | 290.27 | 286.24 | 302.19 | 346.42 | 224.25 |
| Fraction Csp3 | 0.20 | 0.00 | 0.00 | 0.65 | 0.13 |
| RB | 1 | 1 | 0 | 1 | 1 |
| HBA | 6 | 6 | 8 | 5 | 2 |
| HBD | 5 | 4 | 4 | 3 | 0 |
| MR | 74.33 | 76.01 | 75.31 | 93.99 | 65.50 |
| TPSA (Å2) | 110 | 107.22 | 141.34 | 86.99 | 26.20 |
| Log P | 1.47 | 1.50 | 0.79 | 2.50 | 2.41 |
| **Pharmacokinetics properties** | | | | | |
| Pgp substrate | Yes | No | No | Yes | No |
| CYP1A2 inhibitor | No | Yes | Yes | No | Yes |
| CYP2C19 inhibitor | No | No | No | No | No |
| CYP2C9 inhibitor | No | No | No | No | No |
| CYP2D6 inhibitor | No | Yes | No | Yes | No |
| CYP3A4 inhibitor | No | Yes | No | No | No |
| log Kp (cm/s) | -7.82 | -6.65 | -7.36 | -5.99 | -5.44 |
| **Drug-likeness** | | | | | |
| Lipinski violations | 0 | 0 | 0 | 0 | 0 |
| Bioavailability score | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 |
| Medicinal chemistry properties | | | | | |
| Synthetic accessibility | 3.50 | 3.16 | 3.17 | 5.07 | 2.77 |

MW: molecular weight; RB: rotatable bonds; HBA: H-bond acceptors; HBD: H-bond donors; MR: Molar refractivity; TPSA: topological polar surface area; log P: Octanol–water partition coefficient; GI absorption: gastrointestinal absorption; BBB permeant: blood-brain barrier permeant; Pgp substrate: a p-glycoprotein substrate; CYP: cytochrome P450 (isoforms); log Kp: skin permeation.

**TABLE 4: ESTIMATED DRUG-LIKENESS PARAMETERS OF LEAD COMPOUNDS**

| ID | MW | HBA | HBD | Log *P* | TPSA (Å2) | AROM | uw-QED | w-QED | DL score |
|---|---|---|---|---|---|---|---|---|---|
| 72276* | 290.08 | 6 | 5 | 0.852 | 110.38 | 2 | 0.545 | 0.524 | 0.92 |
| 5281614 | 286.05 | 6 | 4 | 1.915 | 107.22 | 2 | 0.594 | 0.554 | 0.76 |
| 5281855 | 302.01 | 8 | 4 | 1.366 | 133.52 | 2 | 0.416 | 0.398 | -0.98 |
| 13966122 | 346.18 | 5 | 3 | 3.867 | 86.99 | 1 | 0.646 | 0.532 | 0.35 |
| 10251 | 224.08 | 2 | 0 | 1.877 | 26.3 | 2 | 0.723 | 0.739 | 1.02 |

DL: Drug-likeness score; TPSA: topological polar surface area; AROM: aromatic ring structures.



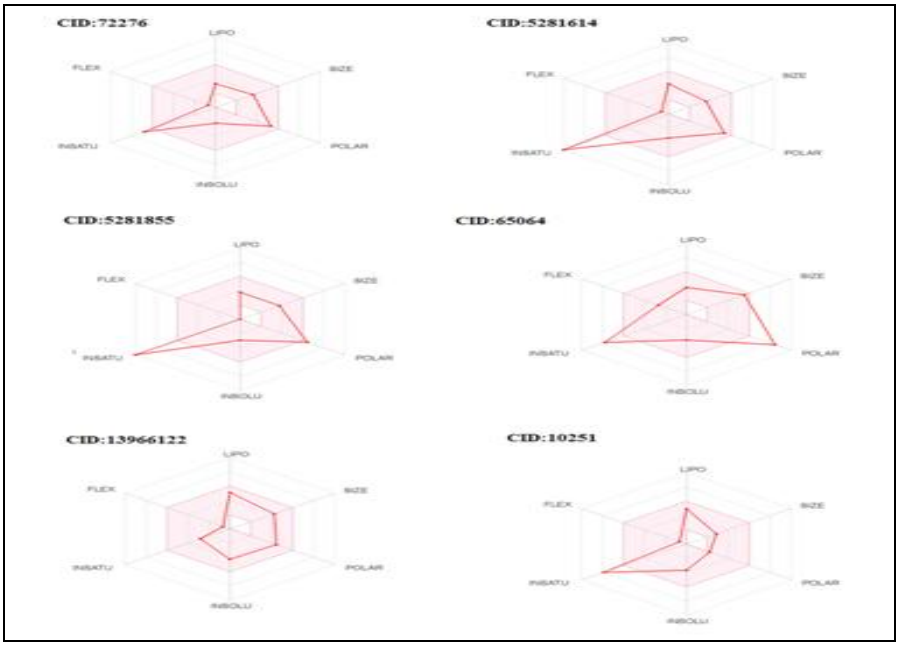



**FIG. 3: PICTORIAL REPRESENTATION OF CHEMICAL SCAFFOLDS AND BIOAVAILABILITY RADARS**

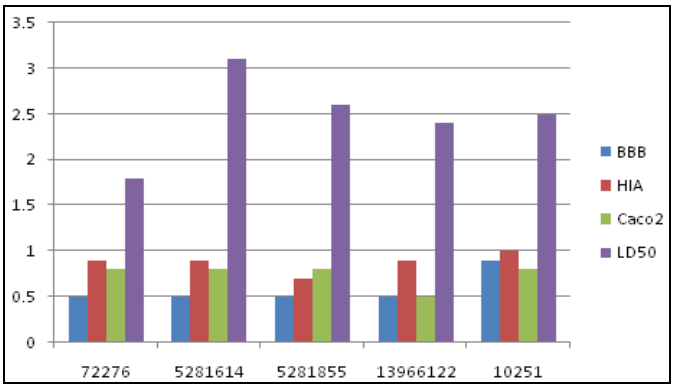



**FIG. 4: ADMET PROFILES OF THE LIGANDS**

## Docking Simulations:

**I GEM DOCK:** I GEM DOCK V 2.1 is a graphical, automated software for integrated docking, screening, and post-analysis. It uses a generic evolutionary method (GA) to compute a ligand conformation and orientation relative to the binding site of the protein target.

The selected GA parameters were as follows: population size = 200, generations = 70, No. of solutions = 2 and docking function as 'slow docking'. The experimental scoring function is given by:

Fitness = Vdw.+ H bond+ Elec.

Moreover, the I GEMDOCK v2.1 suite was found to execute flexible docking for eachlig and by generating protein-ligand interaction profiles of electrostatic (E), hydrogen-bonding (H), and Vander Waal's (V) interactions based on the LIE model.

**Auto Dock Vina:** AutoDock Vina is again a freeware designed to be approximately two orders of magnitude faster than Auto Dock 4, at the same time, more accurate in binding model predictions[19].

**Toxicity Potential Assessment:** The toxicity prediction of chemical compounds is a crucial step in the drug innovation process. The mutagenic, carcinogenicity, toxicity, and skin sensitization of selected molecules were assessed by using the *VEGANIC* platform, and the predicted values are illustrated in **Table 5**.

**TABLE 5: PREDICTED ADVERSE EFFECTS OF BEST HITS**

| Compound ID | SMILES | Mut. | | Car. | | | Dev. | | Ski. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ass. | Pre. | Ass. | Pre. | Pre. Pos. | Ass. | Pre. | Ass. | Pre. | Pre. Pos. |
| 72276* | C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O. | $0^{g}$ | 0 | $0^{m}$ | 0 | 0.693 | 1 | 1 | $1^{l}$ | 1 | 0.56 |
| 5281614 | C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O) | $1^{m}$ | 1 | $0^{m}$ | 0 | 0.693 | 1 | 1 | $1^{l}$ | 1 | 0.54 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5281855 | O. C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O. | 0 | 0 | 0 | 0 | 0.76 | 1[g] | 1 | 1[l] | 1 | 0 |
| 13966122 | CC(C)C1=C(C(=C2C(=C1)C(C3C4C2(CCCC4(C)C)C(=O)O3)O)O)O. | 0[l] | 0 | 0[g] | 0 | 0.75 | 1 | 1 | 1[l] | 1 | 1 |
| 10251 | C1C(OC2=CC=CC=C2C1=O)C3=CC=CC=C3 | 1[m] | 1 | 0[m] | 0 | 0.721 | 1[g] | 1 | 1[l] | 1 | 0.91 |

**Bioactivity Score Prediction:** The bioactivity of the drug can be checked by computing the activity scores of the GPCR ligand, ion channel modulator, a nuclear receptor legend, a kinase inhibitor, protease inhibitor, and enzyme inhibitor. All the properties were verified with the assistance of Mol inspiration software as shown in **Table 6**.

The calculated drug-likeness score of each ligand was associated with the certain activity of other chemical molecules. For organic molecules, the probability of the score is (>0), then it is active; if (-5.0-0.0), then slightly active, if (< -5.0), then inactive.

**TABLE 6: PARAMETERS OF BIOACTIVITY SCORE**

| Compound CID | GPCR ligand | Ion channel modulator | Kinase inhibitor | Nuclear receptor ligand | Protease inhibitor | Enzyme inhibitor |
|---|---|---|---|---|---|---|
| 72276 | 0.41 | 0.14 | 0.09 | 0.60 | 0.26 | 0.47 |
| 5281614 | -0.11 | -0.27 | 0.18 | 0.20 | -0.36 | 0.20 |
| 5281855 | -0.29 | -0.27 | -0.01 | 0.11 | -0.18 | 0.17 |
| 13966122 | 0.36 | 0.11 | -0.19 | 0.54 | -0.04 | 0.32 |
| 10251 | -0.14 | -0.43 | -0.63 | 0.01 | -0.38 | 0.04 |

**CONCLUSION:** In this analysis, we had chosen a rational approach for the identification of new inhibitors for the macromolecule by using molecular screening, computational, and analytical toxicity studies.

Results showed that two chemical compounds have better binding affinity values, in silico pharmacokinetics and drug-likeness esteems. Therefore, it was determined that bioinformatics methods could recognize novel scaffolds that may act as good inhibitors against HER2 for human breast cancer therapy. Further chemical analysis, wet lab examination, and experimental substantiation deserve extreme attention.

**ACKNOWLEDGMENT:** Y. Suneetha is thankful to Human Resource Development for Health Research, New Delhi (F.No.V.25011/542-HRD/2016-HR).

**CONFLICTS OF INTEREST:** No conflict of interest is associated with this work

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**How to cite this article:**
Megana KSNM and Suneetha Y: Prediction of potential dietary compounds against HER2: an *in-silico* assessment. Int J Pharm Sci & Res 2022; 13(11): 4577-85. doi: 10.13040/IJPSR.0975-8232.13(11).4577-85.