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ORIGINAL STUDY

In silico Examination of Peptides Containing Selenium and Ebselen Backbone to Assess Their Tumoricidal Potential

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Abstract

Introduction: **Cancer has been one of the highest causes of morbidity and mortality in the world for decades. Owing to improved therapeutics along with detection, breast cancer mortality has been slowly reducing. The incidence of breast cancer, on the other hand, has increased gradually. More than 100 types of cancer have been identified with a wide range of treatment protocols comprising of chemotherapy, radiation therapy, hormone therapy, etc. In an attempt to curb the serious deleterious effects caused by the chemotherapeutic drugs, numerous peptide molecules are currently popular as alternatives to the standard chemotherapeutic drugs.**

Methods: **In this study, we have carried out *in silico* investigations to ascertain the anti-proliferative potential of novel peptides based on selenium and ebselen, i.e. Eb-Trp-Asp, 13, Eb-Trp-Glu, 14, and Eb-Trp-Lys, 15. Analysis of protein-ligand interactions, resulting in protein-ligand complex formation, has been carried out using the AutoDockVina in PyRx aided molecular docking technique, which may be an essential indication of druggability of the test peptides.**

Results: **The molecular docking results revealed that the screened ligands had extraordinarily strong binding interactions and affinity for the target.**

Conclusion: **Findings suggested that novel peptide molecule Eb-Trp-Glu, 14 may be a potent anti-cancer agent.**

Keywords: Cancer, EGRR/HER3, Selenium. Ebselen, Molecular docking

1. Introduction

Cancer has been a major public health concern and cause of death throughout the world. More than 100 types of cancers have been identified throughout the human body, and therefore, new methods or effective cancer therapies are continuously explored [1]. The most recent treatment regimen for cancer includes chemotherapy, radiation therapy, hormone therapy, immunotherapy, and nutritional supplement treatment [2]. Cancer therapy is constantly evolving with new drugs continuously being developed; however, this process is complex. For instance, in addition to destruction of tumour cells with their cytotoxicity, chemotherapeutic medication has also been observed to harm surrounding healthy cells [3].

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Even though early detection and diagnosis can improve results, breast cancer continues to be one of the leading causes of mortality in women. Several developed countries have mammography screening on massive scales for early identification and cure. According to many healthcare professionals, it is important for women between the ages of 40–50 to be screened regularly for breast cancer [4].

Owing to improved therapeutics along with detection, breast cancer mortality has been slowly reducing. The incidence of breast cancer, on the other hand, has increased gradually. Though the utilization of mammographic techniques has been raised in screening, there is a failure in the breast cancer prevention techniques. Statistics reports that, breast cancer affects one in eight women in high-income nations by the age of 85 with a prediction of being the primary cancer type in women. Only prevention may be the most significant cancer-control technique and it would lessen the global impact of breast cancer [5].

Tumours that are overlooked during screening may not be identified until they're progressed and may become uncurable [4]. Breast cancer is greatly affected by both hereditary and non-genetic adverse outcomes. Clinical subtypes of breast cancer maybe identified by Histopathological appearance and expression of hormone receptors and growth factors including the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2; also known as ERBB2). The most common type has been identified as the ER-positive breast cancer [5]. The American Cancer Society projects breast cancer for the United States in 2021 to be:

- About 281,550 new cases of invasive breast cancer [6].
- About 49,290 new cases of ductal carcinoma in situ (DCIS) [6].
- About 43,600 deaths.

An upward trend (by 0.5%) in the incidence of breast cancer has been observed in recent years, the chances of death from breast cancer is estimated to be around 2.6% [6].

Selenium (Se) is a fundamental element with exceptional physiological and pharmacological features. Present in the same group as oxygen and sulphur in the periodic table, selenium is a semimetallic element [1]. Numerous examinations have shown, that the retention of Se has diminished the risk of a few diseases, including cancer, muscle issues, type 2 diabetes and heart disease. Additionally, Se plays a major role in selenoenzyme inception [3]. Being present in large quantities in the thyroid glands, this element is essential in hormone metabolism [5]. It plays a major role in the functioning of the innate and adaptive immune system [7]. Almost all forms of this micronutrient, have also been known to have anti-cancer properties with a varied mechanism. Despite this, due to dose-related adverse effects, most selenium compounds are yet to be developed as chemotherapeutic agents [8].

2-phenyl-1,2-benzisoselenazol-3 (2H)- one ebselen is a seleno-organic atom which acts as an extremist scavenger and may be effective in the treatment of oxidative stress in cells [9]. Derivatives of ebselen have various biological functions like cytostatic and cytotoxic potential which play a major role in fighting tumour cells [10]. Multiple medicinal properties of this compound include anti-atherosclerotic, anti-thrombotic, anti-inflammatory, cytoprotective effects and anti-proliferative effects. It has been known to fight cancers of the pancreas and kidneys, the liver, breast, and lung, as well as cervical adenocarcinoma [11].

The conventional drug Ebselen has also been identified as a novel inhibitor of 6-phosphogluconate dehydrogenase enzyme via the oxidative pentose phosphate pathway both *in vitro* and *in vivo* mice models [12]. (Feng et al.) ebselen derivatives have also demonstrated strong cytotoxic efficiency towards prostate cancer cells via increase in the level of reactive oxygen species *in vitro* [11].

The Epidermal growth factor and its receptors were identified by Stanley Cohen of Vanderbilt University in the United States. Stanley Cohen and Rita Levi Montalcini were granted the Nobel Prize in Medicine in 1986 the discovery of growth factors [13]. In several malignancies, the epidermal development factor receptor (EGFR) group of receptor tyrosine kinases take the lead in proliferative signalling. Other than EGFR (also known as ErbB1), the group also includes an abandoned receptor HER2 (ErbB2), variants of protein kinase HER3 (ErbB3) and HER4 (also known as ErbB4). HER2 is an oncogenic driver in approximately 20% breast tumours [14].

Several essential catalytic residues are missing from the kinase area of HER3/ErbB3. It is because the catalytic activity of the EGFR ancestry turned on through inducible connection within kinase areas in a deviated space dimer, HER3 may be specific to go about as an activator to other relatives. The gem construction of HER3 was resolved and uncovered, it is secured in a dormant compliance like that of EGFR and HER4. These go through ligand-independent homo and heterodimerization which leads to phosphorylation and as a result, the hiring of different flagging proteins to the receptor enactment site. HER3 is unique because it has a less kinase domain of certain residue that is well acknowledged and necessary in catalytic

activity of other kinases. Even though the HER3 kinase domain binds ATP in the crystal structure, it has been confirmed to be chemically inert yet working as an activator of the EGFR kinase space [15].

With increasing resistance of tumors to standard existing chemotherapeutic drugs, as well as their severe side effects, it becomes important to identify new and effect anti-cancer drugs. Hence, this *in-silico* study aims to look into the anti-cancer activity of the peptides based on selenium with ebselen as a basic backbone. Our research group has evaluated the anti-breast cancer effect of selenium with ebselen as a basic backbone via computational methods. Further validation of these results with molecular docking simulations, *in vitro* cytotoxicity and *in vivo* studies, peptides based on selenium with ebselen as a basic backbone could be developed into potent anti-breast cancer drugs.

2. Methods and materials

2.1. Macromolecule preparation and validation

Cancer is one of the deadliest diseases worldwide. Thus, keeping cancer as a target in this study, we used peptides based on selenium with ebselen backbone to look for anti-cancer activity and to reduce the side effects of the therapies like radiotherapy, chemotherapy, etc.

In this regard, the crystal structure of EGFR kinase domain with compound4 (PDB ID- 3W2S) was considered and downloaded from Protein Data Bank (PDB) i.e., the biological structural database of proteins. The protein 3D structure was inspected for the presence of any previous ligands and water particles were erased and the final 3D figure was saved in .pdb format for additional assessment. The active binding sites of the protein were selected utilizing an online instrument CASTp.

2.2. Ligand optimization

EGFR kinase domain with compound4 (PDB ID-3W2S) docking required 3-dimensional files of peptides based on selenium with ebselen backbone. Hence, the preliminary 2-dimensional structure required was sketched and the geometry was cleaned utilizing the chemsketch freeware computer programming by ACD labs, Canada. The final 2-dimensional construction was saved in .mol format and later the .mol file was converted to .pdb using a free software open babel. It was further cleaned again for the second time in Arguslab software before continuing with the docking studies.

2.3. Molecular docking studies

Docking investigation of arranged protein and ligand records were docked utilizing AutoDock Vina in PyRx (https://pyrx.soueceforge.io/), an open hotspot for virtual screening.

At first, the prepared protein and ligand file was loaded, .pdbqt files were generated for the ligand and protein files with .pdb to confirm the addition of hydrogen and charges required. At this point, the active sites were chosen and a lattice box was generated around the active sites in such a way that the active pockets fit into the lattice box. Eventually, using the genetic algorithm, the virtual screening was run, results were presented with RMSD values and their binding affinity along with the eight different conformations. The interaction was inspected against the protein and the pose docked at its best was saved in .pdb format [16–18].

3. Results

3.1. Macromolecule preparation and validation

The EGFR kinase domain with compound4 protein (PDB ID - 3W2S) was envisioned utilizing UCSF Chimera, a representation programming, addressed in Fig. 1. The chosen proteins were altered as referenced above and their approval was finished utilizing PROCHECK web apparatus to acquire the Ramachandran Plot favoured, allowed and disallowed regions of the proteins as displayed in Fig. 2. The active pocket deposits of the proteins answerable for the protein-ligand binding were acquired utilizing CASTp 3.0. Fig. 3a displays the protein pockets and the featured piece of Fig. 3b depicts the amino acid sequence.

3.2. Ligand optimization

The structure of the peptides screened are displayed in Fig. 4.

3.3. Molecular docking studies

The binding interactions of the screened ligands with the identified cancer target proteins were investigated using molecular docking interaction studies. One of the nine poses of each ligand was chosen as having the least binding energy and was visualised using PyMOL 2.4 to assess its binding affinity and interaction with target proteins. The higher the number of hydrogen bonds and hydrophobic interactions created with the chosen amino

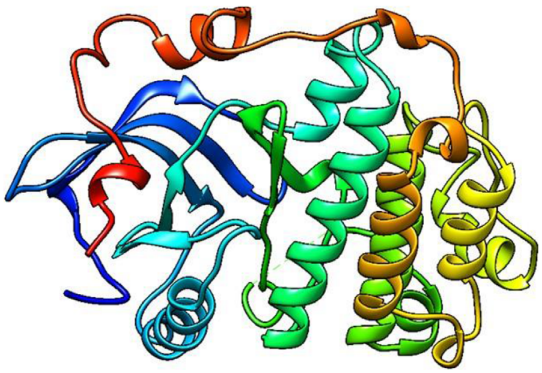

Fig. 1. The 3D structure of 3W2S.

acid residues during the docking cycle, Table 1 assures higher the binding affinity between the protein-ligand interaction. All of the screened ligands had good binding affinity with the specified binding site residues of the individual proteins in this investigation. The small molecule Eb-Trp-Glu, 14 had the least binding affinity of −9.3 kcal/mol, which has almost nearer binding affinity to the standard drug. When compared to the standard drug, it has the maximum binding affinity and interactions with the target. The 2D interactions, which included amino acid residues generating both bonded and non-bonded interactions, were captured using the BIOVIA discovery studio visualizer in various hues (Fig. 5).

4. Discussion

This examination uncovers the properties of the peptide containing selenium with ebselen backbone using a progression of bioinformatics tools, which could prompt the utilization of such mixtures to build insusceptible reactions and lessen the side effects during anti-cancer action and treatments. The protein used in this study was retrieved from PDB. The obtained protein was examined for the presence of any ligands or water molecules before being erased in the protein using UCSF chimera software for visualization followed by validations of the protein using an online tool Procheck (https://servicesn.mbi.ucla.edu/PROCHECK/). Ligands were sketched with the software ChemSketch and the standard molecule was obtained from PubChem. The saved ligands were converted into .pdb files using OpenBabel, then followed by molecular docking using AutoDock Vina in PyRx [5]. Molecular Docking techniques were used to investigate the likely binding patterns of all the ligands chosen for the study, as well as interactions between the selected compounds. The three ligands employed in PyRx with the drug were examined based on the acquired binding affinity and number of binding interactions with the protein. The data was analyzed depending on the interaction within those active sites of the protein that were chosen.

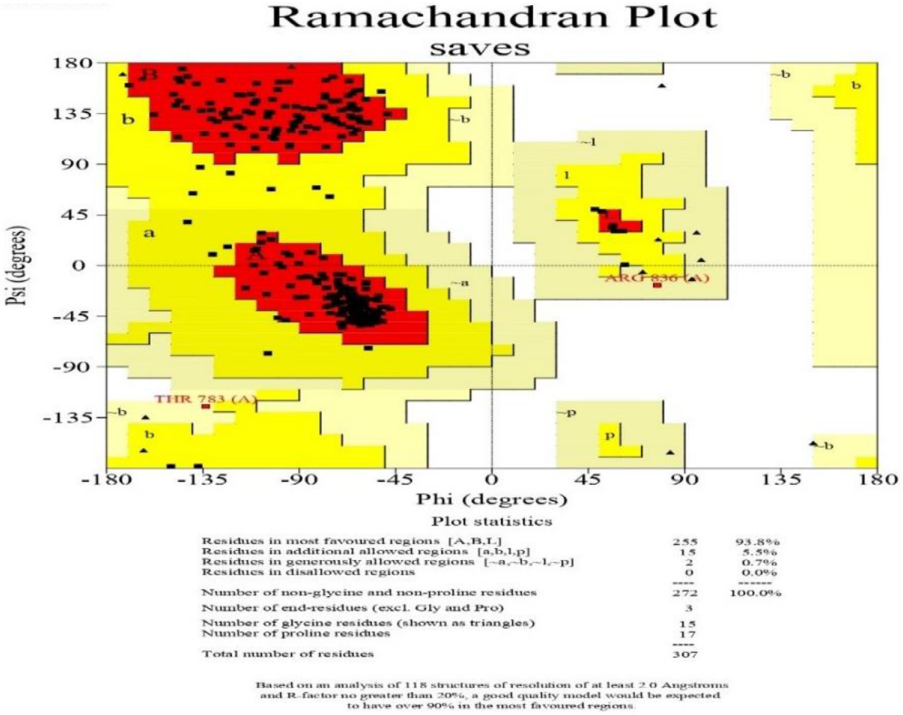

Fig. 2. Ramachandran plot of psi and phi angles.

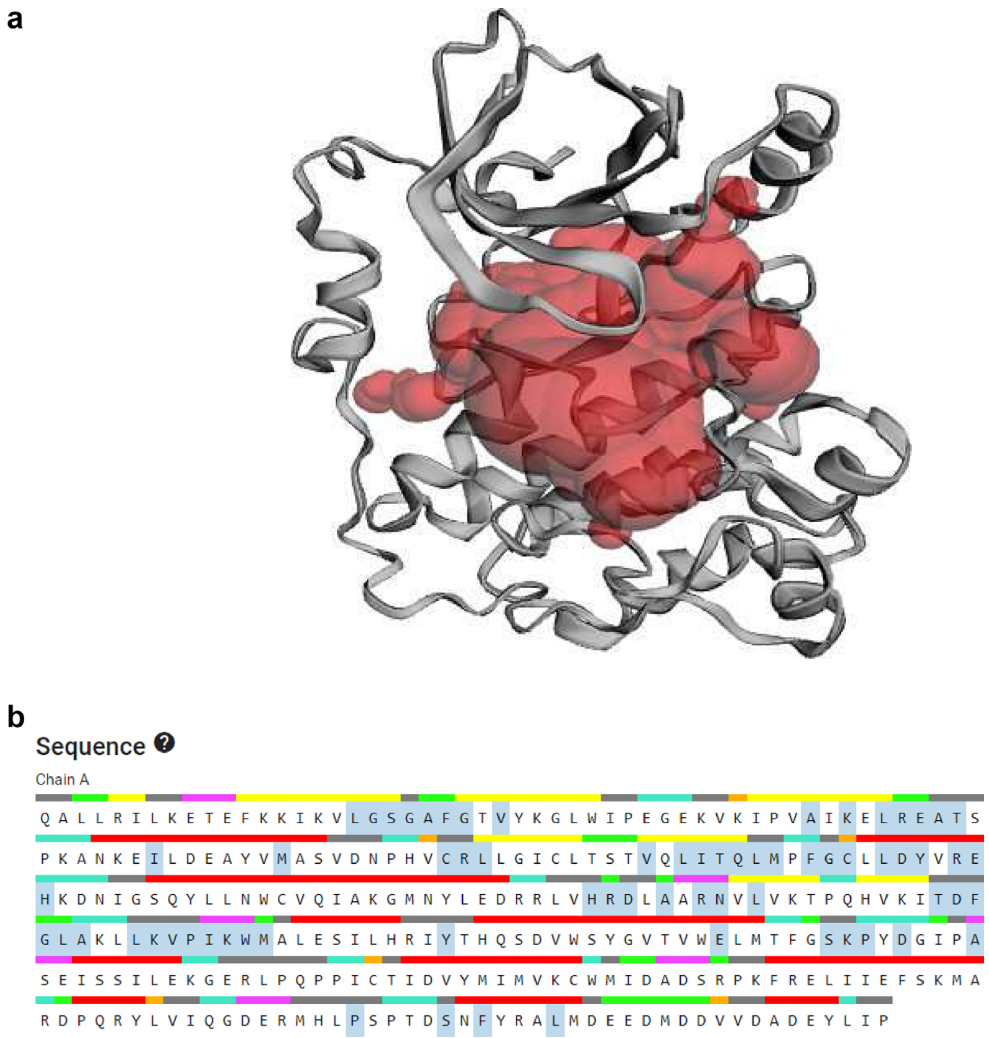

Fig. 3. a. The hued part (Red tone) demonstrating the active sites of 3W2S. b. Featured succession addresses the amino acid residue forming the binding pocket in the protein 3W2S.

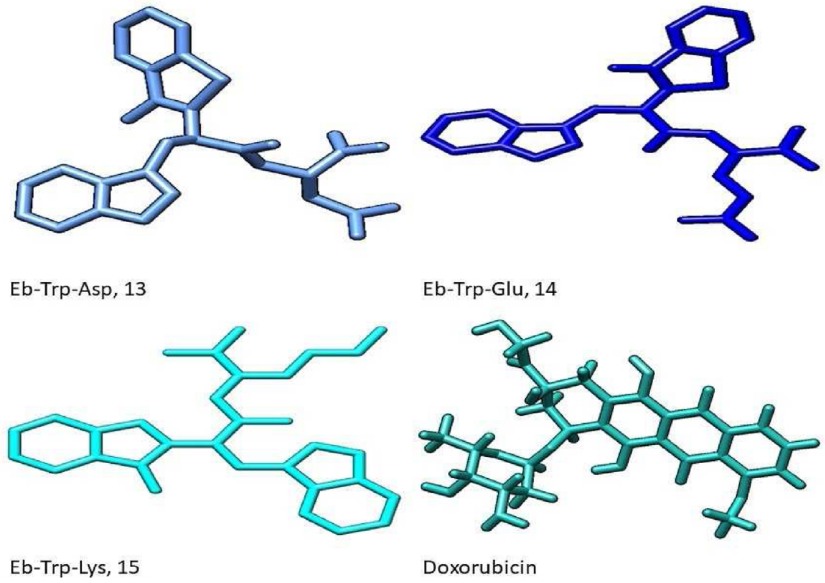

Fig. 4. The structure of the screened peptides and the standard drug.

Table 1. The detailed description of bonded (hydrogen bonds) and non-bonded (hydrophobic interactions) between the respective protein-ligand complex.

Sl No	Ligand name	Protein ID	Binding affinity	No. of H- bonds	Amino acid residue forming H- bond	Amino acid residue forming hydrophobic interactions
1.	(Standard Ligand) Doxorubicin		−9.5	4	ASP-855 GLY-724 PHE-723 ASP-800	ALA-722, GLY-721, LEU-799, CYS-797, SER-720, GLY-719, ARG-841, GLY-796, PHE-997, MET-793, VAL-726, ALA-743, LEU-1001, LEU-718, LEU-792, LEU-844, THR-854, LYS-745
2.	Eb-Trp-Asp, 13		−8.7	3	ASP-855 CYS-797 ASP-800	LEU-844,VAL 726,ALA-743, LEU-718, THR-790, GLY-796, THR-854, MET-793, LEU-792, GLY-719, GLY-721, ALA-722, GLY- 724, PHE-723, LYS-745, ARG-841
3.	Eb-Trp-Glu, 14	**3W2S**	−9.3	2	GLY-724 PHE-723	GLY-721, ALA-722, THR-854, ASP-855, LEU-788, LEU-777, THR-790, LYS-745, ILE-744, ALA-743, VAL-726, LEU-792, MET-793, LEU-1001, GLY-796, PHE-997, LEU-718, LEU-844, CYS-797, ASN-842
4.	Eb-Trp-Lys, 15		−8.2	7	ASN-842 PHE-723 ALA-722 GLY-724	SER-720, LEU-799, GLY-719, GLY-721, ASP-855, ASP-837, LYS-745, THR-854, THR-790, GLN-791, VAL-726, ALA-743, MET-793, LEU-718, LEU-844, LEU-792, ARG-841, CYS-797

Each of the three ligands was viewed as interacting very well with the protein by framing binding energies inside the scope of −9.3 to −8.7 kcal/mol, the standard drug molecule determined the binding affinity of −9.5 kcal/mol towards the protein 3W2S. The ligand Eb-Trp-Glu, 14 showed the highest binding affinity of −9.3 kcal/mol, which is almost nearer to the standard drug whereas Eb-Trp-Lys, 15 showed the lowest binding affinity −8.2 kcal/mol. To evaluate the outcomes, PyMol was used to open the best-docked posture of the ligand and protein and the consolidated protein-ligand structures were stored in a. pdb file to create a protein-ligand complex. Identical procedure was done for each of the three ligands including the standard Doxorubicin drug. The development of bonded and non-bonded interactions of the ligands with responsible active site amino acids of the protein was obtained utilizing Discovery Studio. As the small molecule Eb-Trp-Glu, 14 exhibits the highest binding affinity −9.3 kcal/mol, along with protein's binding pocket establishing two H-bonds GLY-724, PHE-723, and hydrophobic bonds GLY-721, ALA-722, THR-854, ASP- 855, LEU-788, LEU-777, THR-790, LYS-745, ILE-744, ALA-743, VAL-726, LEU-792, MET- 793, LEU-1001, GLY-796, PHE-997, LEU-718, LEU-844, CYS-797, ASN-842. The cumulative interaction and binding affinity of Eb-Trp-Glu, 14 was found to be close to the standard drug [19].

In this *in silico* study, three peptide small molecules were screened against EGFR kinase protein (The EGFR kinase domain with compound4, PDB ID 3W2S). The molecular docking results revealed that the screened ligands had extraordinarily strong binding interactions and affinity for the target.

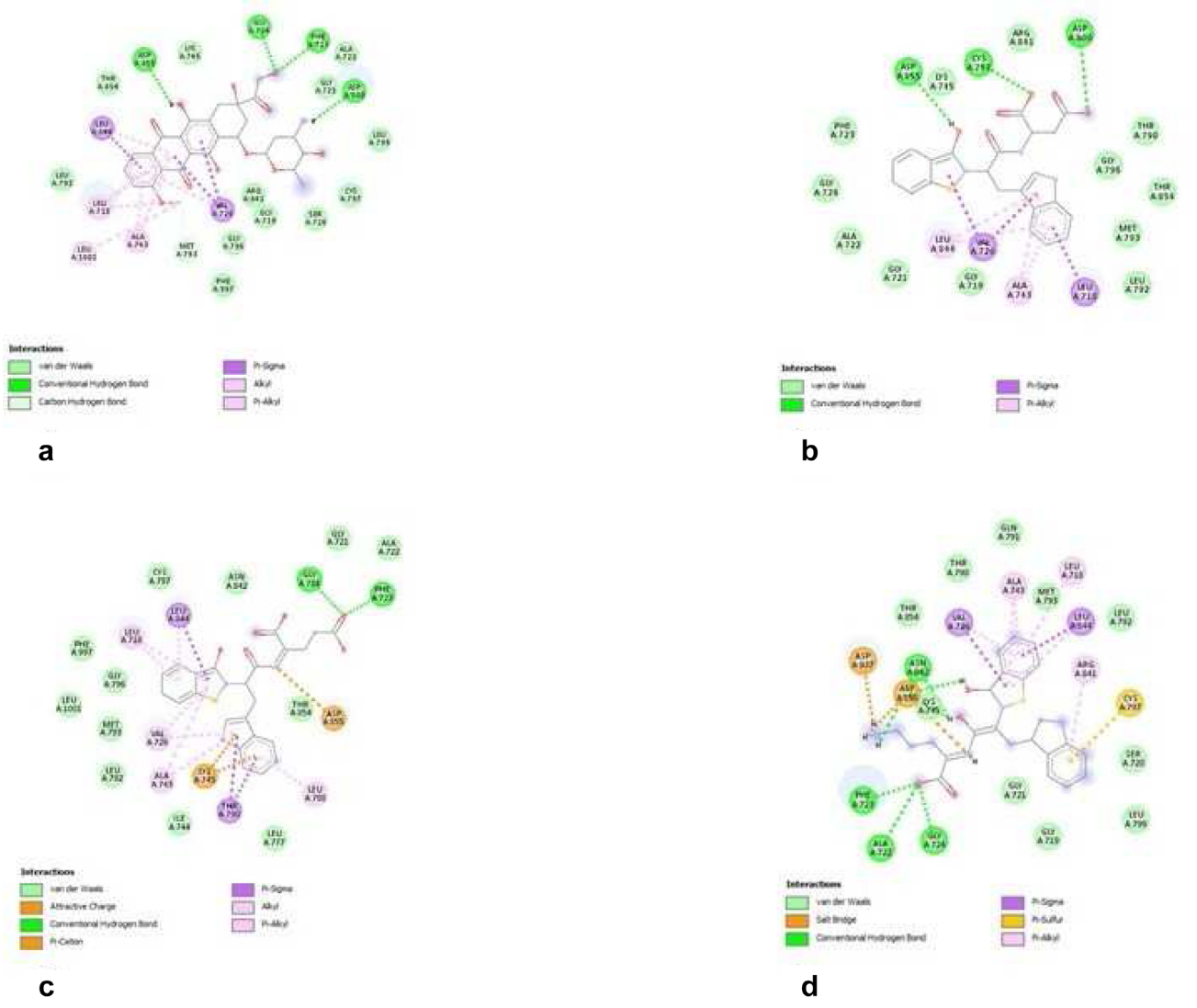

Fig. 5. 2D interactions of the target protein and the ligands visualized in BIOVIA discovery studio. a. 2D interaction of 3W2S with Doxorubicin (standard ligand), b. 2D interaction of 3W2S with Eb-Trp-Asp, 13, c. 2D interaction of 3W2S with Eb-Trp-Glu, 14, d. 2D interaction of 3W2S with Eb-Trp-Lys, 15.

5. Conclusion

Epidermal growth factor receptor (EGFR) is one of the anti-cancer medication targets for specific malignancies including non-small cell cellular breakdown in the lungs (NSCLC), colorectal disease (CRC), and head and neck squamous cell carcinoma. Since the revelation of human epidermal development factor receptor/HER3 interceding protection from EGFR-inhibitors, serious examinations on HER3, focusing on medicines have uncovered their benefits and impediments. Selenium is utilized in the therapy of malignancy like chemotherapy, radiotherapy, and so forth, to lessen the symptoms of these disease therapies. Selenium is utilized as the little particles in cancer therapy, as the outcomes must be concentrated widely dependent on the decreasing malignancy.

This examination was completed to look at and break down the counter malignancy movement of three peptides with selenium and ebselen as their spine to hinder the transcendent proteins engaged with the disease movement. When compared to doxorubicin, all the ligands had nearly good binding affinity. With all of the protein target's active site residues, the Eb-Trp-Glu, 14 molecule had the lowest binding energy and the best binding affinity. Hence it can be concluded from the examination that the Eb-Trp-Glu, 14 ligand can be utilized as a decent option in contrast to the standard medications.

Author contribution

SSB, SP, and GJ-concept, design, literature search, data analysis, statistical analysis, manuscript preparation; CS, SPK and SKP- manuscript editing and manuscript review.

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Conflict of interest

The authors report there are no competing interests to declare.

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