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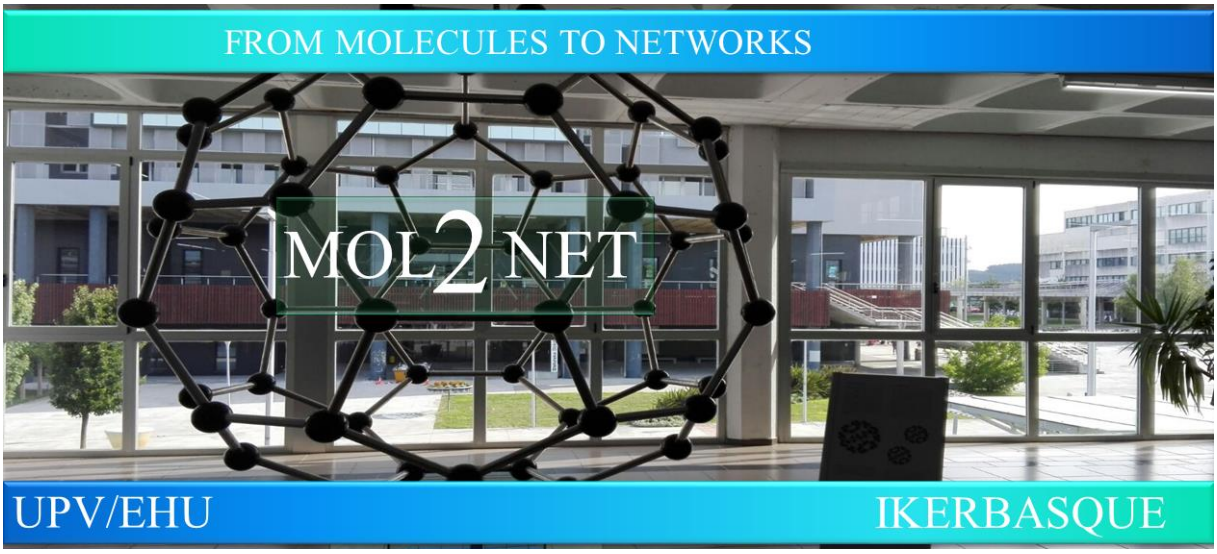

MOLECULAR DOCKING INVESTIGATIONS OF NEW GLYCOSIDES WITH POTENTIAL ANTICANCER ACTIVITIES

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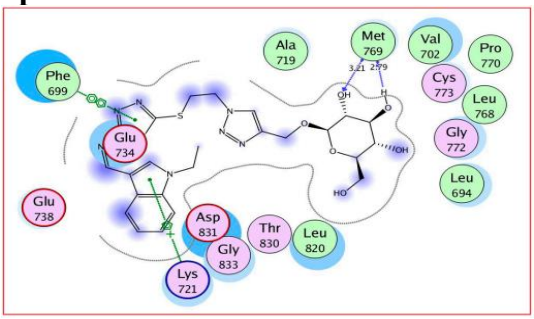
Graphical Abstract



Abstract

Molecular docking analysis of two articles with themes that cover the synthesis of new glycosides that have anticancer activity, where the purpose of these syntheses is the development of new drugs with reduced side effects and more selective. The molecular docking analysis was carried out with the aim of verifying which software was used in the entire molecular docking process.

Keywords: Glycosides; Anticancer; Docking; Software; syntheses.

INTRODUCTION

Cancer is recognized as one of the most common fatal diseases of mankind, described as the uncontrolled growth and spread of abnormal cells, it has recently become one of the leading causes of death.[1] Some agents used in the treatment of cancer (chemotherapy) cause numerous side effects due to their cytotoxic and mutagenic effects on healthy cells.[2] This aroused interest on the part of the scientific community for the development of alternative drugs that do not have side effects, that are effective and selective. In recent years molecular hybridization has gained prominence, this technique consists of combining two or more bioactive pharmacophores to obtain a single molecule.

Recently, using this approach, researchers have reported the synthesis of glycosides coupled to biologically active heterocyclics, showing an improvement in the pharmacological properties and bioavailability of the compounds, contributing to the water solubility and stability of organic molecules.[3,4] In this study, molecular docking simulations carried out in two articles will be analyzed: "*Design, synthesis, anticancer activity and molecular anchorage of new glycosides based on 1,2,3-triazole containing 1,3,4-thiadiazlil, indolyl and scaffolds of arylacetamide*" and "*New pyridines-N-β-D-glycosides: synthesis, biological evaluation, and molecular docking investigations*", by the respective authors, Hussein H. Elganzory and Nuran Kahriman, for analysis of the software used in molecular editors and descriptors , database and ligand-receptor docking.[5]

MATERIALS AND METHODS

Molecular Editors

The graphical representation of a chemical compound demonstrates how its atoms are arranged and connected to each other, it is a great resource for compounds to be visualized and understood by humans, currently there are several software programs for creating representations of chemical structures, called molecular editors. Examples of molecular editors for obtaining structures in 2D are: ChemDraw, MarvinSketch and JMSE. To obtain optimized 3D structures through molecular mechanics and semi-empirical methods, the HyperChem program can be used. There are programs like OSRA that are designed to convert graphical representations of chemical structures into computer-interpretable formats such as SMILES or SDfile.

Molecular Descriptors

For a chemical structure to be understood and processed by a computer, it needs to be described in a unique numerical sequence, it is the end result of a mathematical and logical procedure that transforms chemical information (graphic representation of a chemical compound) into a set or sequence of numbers. These descriptors can be classified according to their dimensionality and nature. Several programs can be used to calculate molecular descriptors: DRAGON, CDK and CODESSA.

Data base

Currently, there are several databases that bring relevant information available on the web. As an example, information related to the structure of molecules, name, physical properties, we have the ChemSpider and Chemicaliza databases. The ChEMBL and PubChem database provides biological information for chemical structures, as well as in vitro and in vivo assay results. The PDB (Protein Data Bank) and the BMRDB are repositories of proteins, nucleic acids and other complex biomacromolecules.

Molecular Docking

For anchoring the molecules, the Molegro Virtual Docker 6.0 or Schrödinger Release 2021-2 software can be used, in which the molecules are imported together with the base protein in a database. In addition to docking, redocking is performed with the ligand complexed with the protein under the same computational conditions as the original docking, making it possible to estimate the RMSD (Root Mean Square Deviation), which is the value of the deviation between the same atoms of the ligand complexed with the protein and the same imported ligand, with it is possible to validate the protocol used for the coupling, the lower the RMSD the better the precision of the molecular fitting performed, commonly adopted values smaller than 3Å.

RESULTS

According to the author, Hussein H. Elganzory, with the article entitled: “Design, synthesis, anticancer activity and molecular anchorage of new glycosides based on 1,2,3-triazole containing 1,3,4-thiadiazlyl, indolyl and arylacetamide scaffolds”, have developed new 1,3,4-thiadiazole thioglycosides linked to a substituted arylidine system. They were synthesized via heterocyclization via dipolar 1,3-cycloaddition click. The click strategy was used for the synthesis of new indolyl systems based on 1,3,4-thiadiazole and 1,2,3-triazole hybrid glycosides as new hybrid molecules by reaction of azide derivatives

with the corresponding terminal glycosyl acetylated acetylenes. The cytotoxic activities of the compounds were studied against HCT-116 (human colorectal carcinoma) and MCF-7 (human breast adenocarcinoma) cell lines using the MTT assay. The results showed that the main thiadiazolthione compounds, the triazole glycosides linked to p-methoxyarylidine derivatives and the free hydroxyl glycoside had potent activity comparable to the reference drug, doxorubicin, against MCF-7 human cancer cells. The interactions of the newly synthesized targets 7, 8 and 15, illustrating the higher inhibitory activities of EGFRWT, EGFRT790M and HER-2, were examined and fitted to the active sites of the target enzymes to study their binding modes and orientations using PDB IDs: 1M17, 3UG2 and 3RCD, respectively using MOE-Dock software version 2014.0901. The 2D structures of the newly synthesized triazole-based glycosides 7, 8 and 15 were drawn using ChemDraw. The protonated 3D structure was employed using standard bond lengths and angles. Then geometry optimization and energy minimization were applied to get the Conf Search module into the MOE, and the MOE file was saved for the subsequent fitting process. The cocrystallized structures of EGFRWT, EGFRT790M and HER-2 with their linkers, erlotinib, gefitinib and TAK-285, were downloaded (PDB codes: 1M17, 3UG2 and 3RCD, respectively) from the Protein Data Bank (www.rcsb.org). All minimizations were performed using MOE until reaching an RMSD gradient of 0.05 kcal·mol−1Å−1 with an MMFF94x force field, and partial loads were automatically calculated. Enzyme framework preparation was performed for molecular docking using the Protonate 3D protocol with the default options in the MOE. The London dG scoring function and the Triangle Matcher placement method were used in the matching protocol. First, validation of the docking processes was established by docking the native ligands, followed by docking derivatives 7, 8 and 15 on the ATP binding sites of EGFRWT, EGFRT790M and HER-2 after elimination of the co-crystallized ligands.

The author, Nuran Kahriman, of the article: “Novel pyridines-N-β-D-glycosides: synthesis, biological evaluation, and molecular docking investigations”, performed syntheses of new N-β-glycosides and tetra-O-acetyl coupled derivatives to pyrimidine. All glycoconjugates were investigated in comparison with known chemotherapeutic agents in terms of their anticancer functions and DNA/protein binding affinities. Spectral data showed that all glycoside derivatives were obtained by diastereoselectivity as β-anomers. Both tested groups exhibited strong antiproliferative activity (2.29–66.84 µg/mL), but some of them had sufficiently optimal % cytotoxicity values (10.01%–16.78%).

Overall bioactivity results suggest that these compounds may be candidates for new chemotherapeutic agents and deserve further pharmacological evaluation. Molecular docking studies were performed to determine the interactions of compounds 4, 7, 13 and 16 and different crystal structures (PDB IDs: 4QL3, 6MPP, 4E26, 6QGG, 5MU8, 4QUG, 2DBF, 6SL6, 1CGL, 5Z62, 6EB6, 5ITD, 4EKK, 6GU7, 7BG9, 3GUS). Schrödinger 2021-2 molecular modeling software was used to determine these interactions. Parameters such as MM-GBSA ΔGBind, fit score and complex energy values were calculated with Schrödinger 2021-2. According to these values, the strength of the

interactions between the ligand and the target was calculated and the values were compared with each other and the proteins that could have the best interaction were determined.

The free binding energy, docking score and complex energy values of the compounds that interact *in silico* with the proteins obtained from the Protein Data Bank (www.rcsb.org) are shown in Table 10. The values in Table 10 indicate that NRAS, BRAF, PI3K alpha, cytochrome c oxidase and Akt1 was more effective than the other targets listed in the table. Although the data for the cited proteins are very good, according to Table 10, we can say that the values of the PI3K alpha binding parameters (PDB ID: 5TID) were the best. When the results of the interaction of PI3K alpha with molecular docking were examined in detail, the d values

CONCLUSION

The author, Hussein H. Elganzory, started using the ChemDraw software to obtain the 2D structures of the glycosides, with subsequent geometry optimization and energy minimization in the MOE Software. Molecular modeling, docking interactions (ligand-Receptor), were performed in the MOE-Dock software version 2014.0901, the cocrystallized structures with their respective ligands were downloaded from the Protein Data Bank (PDB).

The author, Nuran Kahriman, did not inform in his article which software he used to represent the 2D structures of molecules and subsequent optimization, but to determine the interactions between ligand and protein, the author used the molecular modeling software Schrödinger 2021-2. having the proteins obtained from the protein database, PDB.

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