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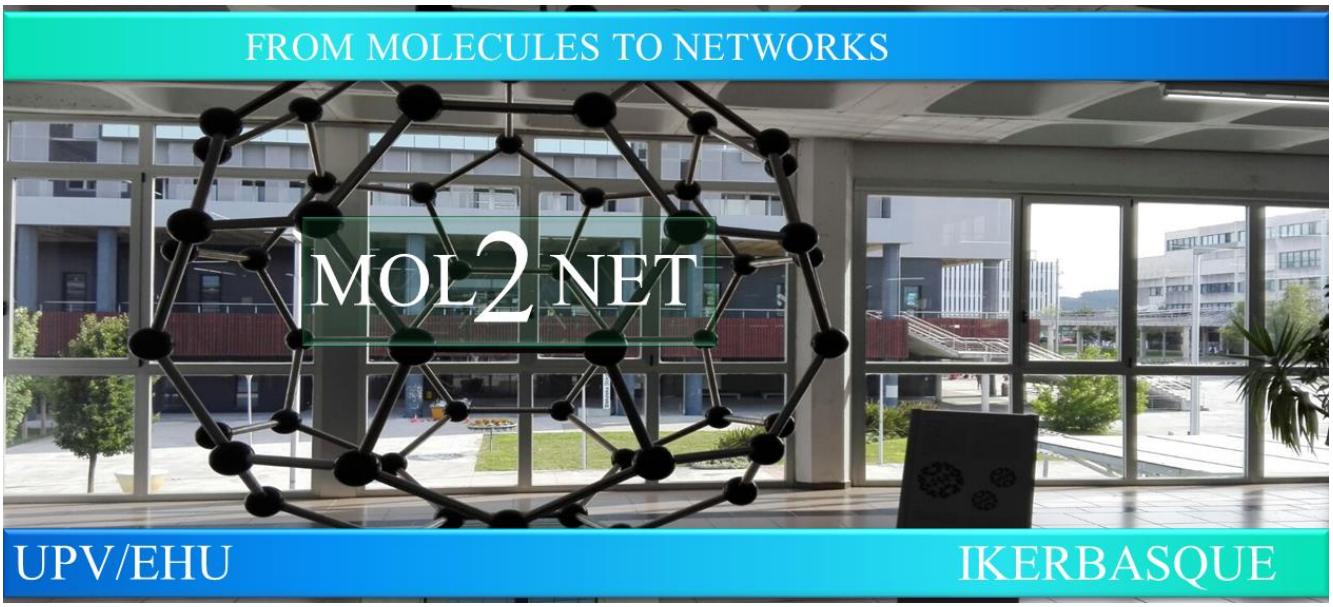
MOL2NET'23, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 8th ed.



Mini review: Molecular docking: an expanded summary on anticancer activity of oxadiazole derivatives

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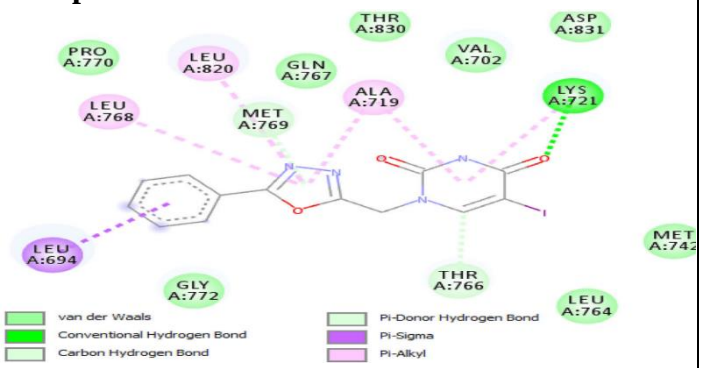
Graphical Abstract



Abstract

cancer is one of the diseases that most causes death in the world, so it is necessary to develop new promising molecules to be a possible medicine against this terrible disease. In this work, two scientific articles containing molecular docking studies of oxadiazole derivatives were selected to verify the possible anticancer activities. Where it was verified that two molecules of each work presented promising results.

Keywords: oxadiazole; Molecular docking; anticancer; heterocyclics; *in silico*.

Introduction

Cancer is one of the main causes of death in the world, this disease is characterized by the uncontrolled proliferation of mutant cells, by their ability to spread throughout the body through the invasion of blood or lymphatic vessels, and by inducing the process of angiogenesis and metastasis. [1-2] According to the world health organization, in the year 2020 there were about 19.3 million cases, in 2040, this number could reach 30.2 million new cases.[3]

The search for new drugs for the treatment of this disease has been motivating generations of researchers, in organic chemistry heterocyclics appear as an alternative compound to be explored due to their oxygen and nitrogen atoms in their nucleus. In this summary we will report two works on oxadiazole, the same has been studied because its derivatives have different biological activities, some of these biological activities can be predicted using the molecular docking technique, this technology allows simulating the interaction of the molecule against different proteins and predicting the possibility of molecules presenting biological activities, the use of molecular docking is very important to have a brief interpretation of the behavior of the molecule in the studied organism. This present study aims to bring two different articles that present the molecular docking technique in oxadiazole derivatives aiming at antitumor activity.

Materials and Methods

To carry out this study, two articles were selected the first with the following title: Design, synthesis, chemical characterization, biological evaluation, and docking study of new 1,3,4-oxadiazole homonucleoside analogs (Az-Eddine El Mansouri et all 2020). In this *in silico* computational docking studies were performed using AutoDock 4.2. The X-ray crystal structures of HER2 and EGFR were downloaded from the RCSB Protein Data Bank (PDB) ID: 1PP0[49] and 1M17 as the proteins were prepared separately by removing water and co-crystallised ligands bound to the proteins to make the receptor free of any binding prior to fitting. Then polar hydrogens and Gastieger charges were added using MGL tools and proteins saved in PDBQT format. Linker structures were created separately using ChemDraw Ultra 12.0, energy minimized in Chem3D, linker torsional links were set to flexible 3 and saved in PDBQT format. the second selected article has the following title: Synthesis, molecular docking study and anticancer activity of novel 1,3,4-oxadiazole derivatives as potential tubulin inhibitors (Tarek A. Yousef et all 2023), the UCSF Chimera tool was used, the molecular docking study of newly synthesized potent molecules was carried out. To couple with potent molecules, the tubulin-colchicine protein complex (PDB ID: 402B) was chosen as the ideal target protein. The X-ray crystal structure of the target proteins was retrieved from the Protein Data Bank (PDB). Both articles perform a molecular docking study to learn about the possible antitumor activities of the synthesized compounds.

Results and Discussion

In the first selected article, a series of compounds were synthesized, these compounds were evaluated for their cytotoxic activity against mana cancer cell lines, compounds 6b and 4g showed better results, these same compounds were selected for the study of molecular docking at the site EGFR active (PDB: 1M17) and HER2 (PDB: 3PP0).

Protein	Ligand	Estimated binding energy (kcal/mol)	Estimated inhibition constant Ki (μM)
EGFR	**4g**	−8.05	1.25
	6b	−7.5	3.18
HER2	**4g**	−8.66	0.45
	6b	−8.81	0.35

Tabela 1. result of molecular docking (Az-Eddine El Mansouri et all 2020)

Ligands 4g and 6b are deeply bound to the active site with estimated binding free energy of 8.05 and 7.5 kcal/mol, respectively in relation to EGFR, in addition it was observed that compounds 4g and 6b inhibit the EGFR protein with estimated inhibition constants (Ki): 1.25 and 3.18 mM, respectively. Compound 6b showed a hydrogen bond between MET769 and N9 (1.995 Å). However, HER2 interacts

with ligands 4g and 6b with estimated binding free energy of 8.66 and 8.81 kcal/mol, respectively. Compounds 4g and 6b inhibit the HER2 protein with estimated inhibition constants of 0.45 and 0.35 mM, respectively. Compound 4g showed two hydrogen bonds THR862—O ¼ C4 (2424 Å) and ASP863—Noxadiazole (2634 Å). While ligand 6b interacted with HER2 showing three H-binding interactions MET801—N ¼ C9(2,104 Å), THR862—O ¼ C2(1,962 Å) and ASP863— Ooxadiazole (2,181 Å).

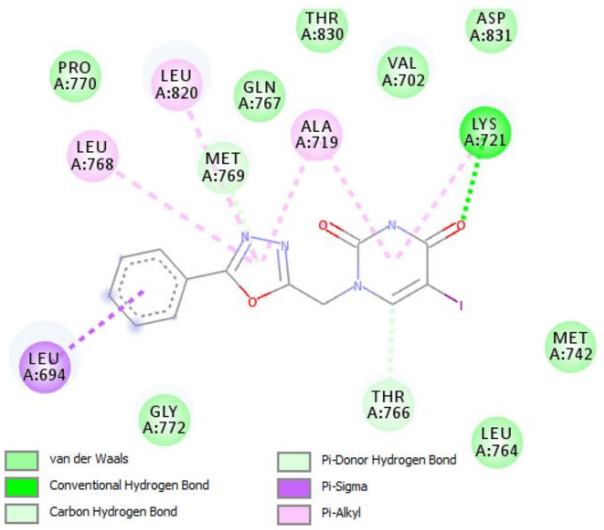


Figure 1. 2D interactions of compound 4g in the binding sites of EGFR protein (PDB ID: 1M17) (Az-Eddine El Mansouri et all 2020)

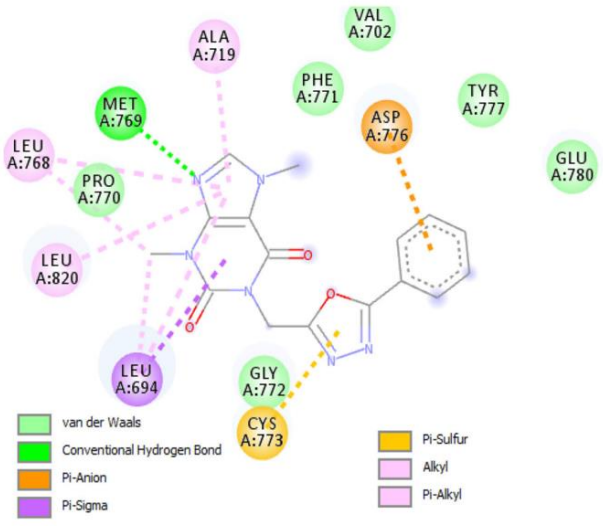


Figure 2. 2D interactions of compound 6b in the binding sites of EGFR protein (PDB ID: 1M17) (Az-Eddine El Mansouri et all 2020)

The second article selected to interact with the target molecules, the complex of tubulin with colchicine (PDB ID: 4O2B) was selected, two derivatives of oxadiazole 8e and 8f showed good results with docking scores higher than the reference drug colchicine (-13 .69 kcal/mol) at -13.69 and -13.61, respectively. Furthermore, compound 8e connected to protein residues Cys-797 and Tyr-801 via hydrogen bonds and Ile-821 and Val-843 via a π-alkyl interaction. The protein residues Cys-797 and Tyr-801, compound 8f formed two hydrogen bonds with them and formed a π-π and π-alkyl bond with Trp-817 and Val-845, respectively.

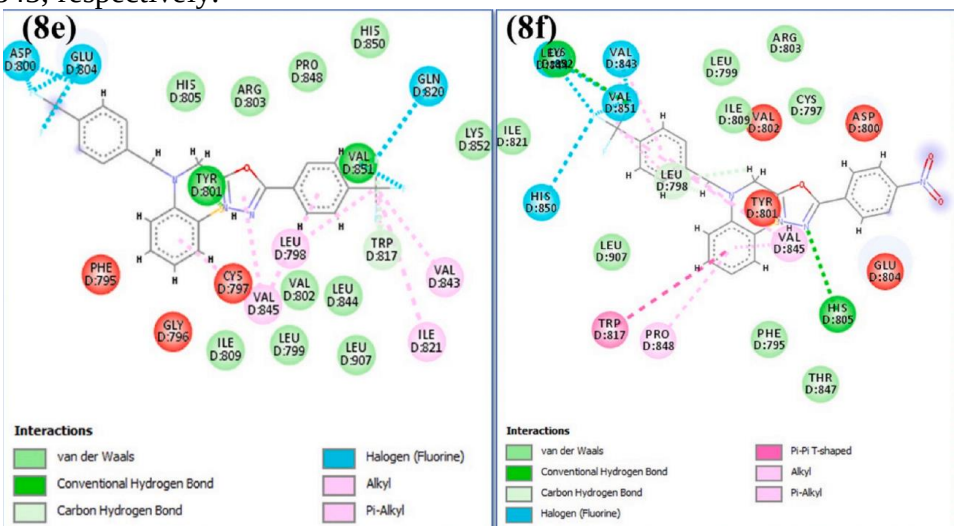


Figure 3. 2D Interactions of potent compounds 8e and 8f with the target tubulin-colchicine complex (PDB ID: 4O2B). (Tarek A. Yousef et all 2023)

Conclusions

The molecular docking study of the first reported paper showed that the anticancer activities of compounds 6b and 4g mediated by inhibition of EGFR/HER2 dual proteins proved to be a good candidate. In addition, the first article reported in the second article presented two compounds 8e and 8f that have shown to be very promising and can be used as potential molecules for further research in the creation of anticancer drugs.

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