Design, Evaluation and Synthesis of Novel Compounds 3,5-diphenil-1,2,4-oxadiazoles with Farnesoid X Receptor

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Abstract: Our research focuses on design and synthesis of 1,2,4-oxadiazoles compounds with anti-inflammatory properties. These compounds have great interest as bioactive compounds1, but only one is in the market: Translarna™, used on the treatment for Genetic Disorders. Through understanding the strategies of Molecular recognition and Dynamics simulation, our aim is to synthesize through rational drug design a product which can be a candidate as a potent farnesoid X receptor (FXR) agonist, involved in physiological regulator and inflammatory pathways3. In the present study we evaluate a small library of twelve 3,4-diphenyl-1,2,4-oxadiazoles in docking simulations with FXR using MOE, to create a computational model which can predict the biological activity and to propose a novel compound using these computational techniques.

I. Introduction

Oxadiazoles are heterocyclic compounds, they are weak bases, and have a variety of biological activities. Right now these compounds have a great scientific interest due to its potential form a pharmacological point of view and pharmaceutical applications. Benzothiazole and oxadiazole derivatives have been widely researched in bioorganic and medicinal chemistry with applications in drug discovery. Both the nucleuses are well acknowledged to have pharmaceutical, agrochemical, and biological applications. Substituted-oxadiazoles show a wide variety of biological activities; anti-inflammatory (Ali et al., 2014) , analgesic (Ali et al., 2010) and antibacterial (Shridhar et al., Desai et al., 2014, Sahin et al., 2002) antifungal (Oliveira et al., 2013) and anticancer activities (Abu-Zaied et al., 2012 and Valente et al., 2014). Benzothiazole derivatives have also been reported to show antinflammatory (Abbas et al., 2013 and Patil et al., 2015) analgesic (Sharma et al., 2013 and Sharma et al., 2013a) antifungal (Liu et al., 2013) anticancer (Gurdal et al., 2015) and antimicrobial (Sigmundova et al., 2007 and. Singh et al., 2013) activities. Non-steroidal anti-inflammatory drugs NSAIDs are a class of therapeutic agents that are most generally used because of their anti-inflammatory, analgesic and anti-microbial effects. Therefore, it was considered to prepare hybrid derivatives of benzothiazole with oxadiazole in order to get potential anti-inflammatory and analgesic compounds.

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II. Method

First we validated the docking procedure for the protein FXR with the ligand from PDB (PDB ID: 4QE6 the validation process was performed using the PDB structure to verify that the program was capable to reproduce experimental data. In this case for this system the program was able reproduce the data with a 1.02 A of RMSD.

A geometric optimization was performed at each of the twelve compounds studied by a stochastic analysis to obtain the most stable conformer in a relatively short time. Subsequently the optimization and preparation of the protein was carried out with the preparation protocol from MOE. These last protocol parameters were: T=37 K, pH=7.4, Dielectric=80. Resultant stable conformations had the reported ligand-protein interactions within the active site. For the dynamics simulation we started using the following protocol: Heating; 100 ps, Equilibrium; 500 ps, Production; 600 ps. At all moment velocity and position were calculated, the NPA algorithm was used and explicit solvent sphere were modeled around the

ISBN: 978-988-14048-2-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

ligand and the protein. For the dynamics the protein interaction ligand fingerprints were computed for the whole simulation.

According to the results the molecular docking process showed a favorable behavior regarding the ligands positions, Fig 1, however during the dynamics there is an inconsistency with some molecular interactions. This was observed with the protein ligand interactions fingerprints. Only two molecules showed this kind of behavior. But apparently the energetic profile was favorable as is showed in Fig 2. Here we can observe all the dynamic stages, but when we analyzed all the structures we found some regions that interfered with the complex stability. There is a ΔH analysis that shows how the blue atoms are in a forbidden region. This compromises the complex stability and during the dynamics these regions tend to overlap increasing the complex energy and modifying its stability.

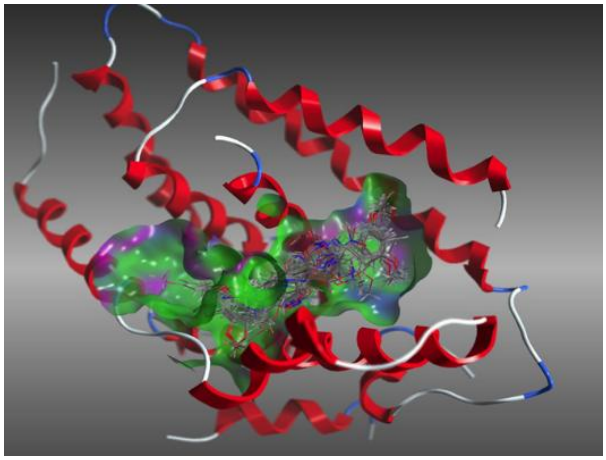

Fig 1.Final positions resulting from Molecular mechanic simulations.

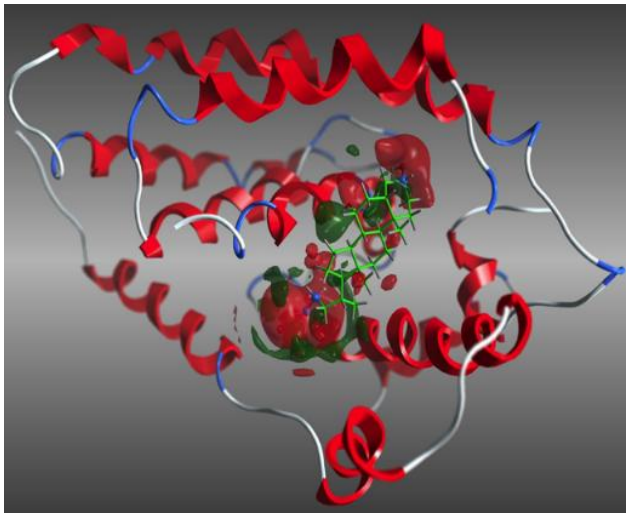

Fig 2.Energetic surface profile from a stable compound.

III. Conclusions

According to these results, further studies are required. However, we could elucidate a possible mechanism for our compounds to inhibit FXR. Preliminary data suggest that only two of the twelve compounds are not good candidates. The rest of our compounds are going to be studied with MM/QM to verify the thermodynamics and to get a better understanding of the systems.

Acknowledgements

Projects PAPIIT UNAM No IT200614; PAPIIT UNAM 26-RT202015; Cátedra, PACIVE FESC-UNAM

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