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Theoretical affinities study of some hypothetical proposed triazoles derivatives with main enzymes responsible on inflammations and fungal infections.

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ABSTRACT

The triazole compounds constitute a very important pharmacological class which is subjected to constant development because of their different convincing therapeutic results. It is well established that triazole compounds give very good therapeutic results in treatment of fungal infections and inflammation. In our present study, we established a series of triazole compounds that we subjected to an *in-silico* study in order to identify new triazole compounds that may have fungicidal and anti-inflammatory effects. Molecular modeling through Molecular Docking was our workhorse to identify the best hypothetical molecules that could be candidates for drug development. We used the Molecular Operating Environment software (MOE) for the Docking study and the physicochemical properties calculation. We also used ChemDraw software to design the hypothetical compounds in 3D. The obtained results showed that the [5-((5-(1,3-oxazepan-3-yl)oxy)furan-2-yl)thio)-1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)pentan-1-one] molecule was the best candidate which could have a dual role in the treatment of fungal infections and inflammation taking in account the Lipinski's rule. The obtained results are encouraging and merit further *in-silico* studies such as QSAR and QSPR before moving to synthesis and *in vitro* tests stage.

Key words: Triazoles deviratives, Drug design, fungal infection, inflammation, Docking, MOE.

INTRODUCTION

Many diseases, whether viral, bacterial or parasitic, have always accompanied the human species; among these diseases are fungal infections and inflammation (Casadevall, 2018; Aghasafari et al., 2019). Inflammation is defined as the response shown by the body when it is invaded by an antigen or any type of damage (physical, chemical or traumatic) that causes the inflammation. It is also defined as the immune response to infection or injury (Ashley et al., 2012). Usually, the inflammation signal is activated when under attack by intruders or tissue damage (Nunes, 2020). Inflammation is characterized by redness, swelling, warmth, pain, and loss of tissue function. The basic purpose of the inflammatory response is to locate and eliminate harmful agents; then get rid of damaged tissue components to achieve healing of affected tissues, organs or system (Chen et al., 2018). Different agents can promote inflammatory events involving lipid and peptide chemical mediators (Ward and Ayoub, 2010). Lipid mediators, such as prostaglandins and leukotrienes, have been valued for many years for their activities which promote and improve inflammatory responses (King, 2014).

Among lipid mediators, there are two cyclooxygenase isoenzymes which are COX-1 and COX-2. The COX-1 is constitutively expressed in the body and it is involved in the maintenance of the gastrointestinal lining, kidney function and platelet aggregation (Choi et al., 2008). The 5-Lipoxygenase (5-LOX) is also involved in catalyzing two steps in the biosynthesis of leukotrienes (Lts), a group of lipid mediators of inflammation derived from arachidonic acid (AA) (Rådmark and Samuelsson, 2009). COX-2 shows constitutive expression in the brain, kidneys, and female reproductive system, but is a highly inducible enzyme in

response to cytokines and other inflammatory stimuli. The COX-2-derived prostanoids are formed in large quantities in response to inflammation, pain and fever (Waller and Sampson, 2020).

The activities of cyclooxygenase (COX-1 and COX-2) or lipoxygenase (5-LOX), leukocytes rapidly synthesize these lipid mediators from arachidonic acid derived from the membrane in seconds to minutes. The main endogenous lipid mediators released by cells that infiltrate the site of the immune challenge are prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) (King, 2014). To treat inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used around the world and constitute a large group of cyclooxygenase (COX) inhibitors also called aspirinlike drugs, due to their therapeutic similar activity (Brooks,1998). Nonsteroidal anti-inflammatory drugs work by inhibiting the formation of prostaglandins by prostaglandin H synthase (COX, also called cyclooxygenase), which converts arachidonic acid (AA) released by membrane phospholipids into prostaglandins. Two isoforms of prostaglandin H synthase, COX-1 and COX-2, have been identified, and a variant (COX-3) has also been reported recently (Vane and Botting, 1998). Steroids are also used for the treatment of inflammation and have a strong immunosuppressive and anti-inflammatory effect because they indirectly inactivate a wide range of transcription factors (Mak et al., 2014). But high dose, long-term or oral use of corticosteroids can have serious and harmful consequences for humans (Yasir et al., 2020). The development of new compounds with anti-inflammatory activity and improved safety are of great importance. The incorporation of NSAIDs and a 1,2,3-triazole moiety into a single molecular entity is a current approach for the manufacture of new and interesting bioactive molecules (Dasari et al., 2019). Among the many applications in biology and medicine, 1,2,3-triazoles have significant potential for synthetic accessibility through click chemistry, chemotherapy and as anti-inflammatory agents(Kumar et al., 2016).

During last decades, fungal diseases have caused more than 1.6 million deaths per year and more than one billion people suffer from serious fungal diseases which are caused by micromycetes, yeasts, and filamentous fungi (Almeida et al.,2019). Human fungal diseases differ fundamentally from other infections in a number of ways. As eukaryotic pathogens, the fungal tropism is highly variable, as the pathogens infect a wide range of cell types. A single fungal pathogen can infect multiple tissues in the same patient, they differ from most bacterial diseases because they tend to be chronic and kill the host slowly (Casadevall, 2018; Rodrigues and Nosanchuk, 2020). Cryptogamic diseases are caused by phytopathogenic fungi which constitute a group of ubiquitous heterotrophic microscopic organisms with extremely diverse structures and biological characteristics(Heitman et al., 2020). The main mechanism of adhesion of fungi is based on the specific recognition between fungal adhesins and receptors in the host. The adhesins identified in pathogenic fungi are mainly proteins and mannoproteins (Baldo et al., 2007). Fungal species have a dual protection against the outside environment: an inner plasma membrane and an outer cell wall which are closely related. The treatment of fungal infections is based on the inhibition of protein targets(Garnaud and Cornet, 2020; Mambro et al., 2019).

Cytochrome P450 is one of the main protein targets for treatment of fungal infections(Shin et al., 2018). The cytochromes of fungi contribute to cellular respiration, to the generation of ATP and also to the biosynthesis of several cellular components (Yoshida,1988). Lanosterol 14α-demethylase (CYP51) is a cytochrome P450 which co-catalyzes the 14α demethylation of lanosterol, an essential step in sterol biosynthesis (Ramakrishnan,)[28]. Azole antifungals are a popular therapeutic class where triazoles have become the standard for azoles to manage some forms of systemic mycoses that inhibit cytochrome P450 dependent enzymes involved in ergosterol biosynthesis (Peyton et al., 2015). Due to the high degree of similarity between 1,2,3triazole, imidazole and 1,2,4-triazole, 1,2,3-triazoles are said to exhibit antifungal activity similar to that of commercially available azole drugs (Valdés and Cuevas-Yañez,). Among the antifungal agents currently in use, the triazoles (for example, fluconazole, itraconazole, posaconazole) are known for their better therapeutic properties (Nami et al., 2019).

Thanks to technological advances over the past two centuries, man-made chemical drugs, biological and gene therapies are now available for the treatment of fungal infections and inflammation(Vallabhaneni and Chiller, 2016; Lomax and Calder, 2008). In addition, new technologies have widened the possibilities of discovering new treatment. The use of computer methods in the preclinical design of therapeutic molecules as part of "Drug Design" strategy, is an inventive process for new drugs based on the knowledge of a biological target (Nadendla, 2004; Calabrese, 2019; Leach, 2007; Aminpour, 2019; Haghighatlari and Hachmann, 2019). Among molecular modeling methods; molecular Docking is a computational computer modeling method based on molecular dynamics and mechanics and which consists of the study of the interaction between active site and substrate by predicting the type of interactions between an active site and a bioactive molecule (Chaudhary and Mishra, 2016; Ferreira et al., 2015; Saileela et al., Salim, 2018; Santos et al., 2019; Tripathi and Misra, 2017). Considering the biological and pharmaceutical importance of molecular docking, considerable efforts have been made to improve the methods used to predict docking (Salim, 2018; Santos et al., 2019; Tripathi and Misra, 2017; Jakhar, 2020). Heterocyclic chemistry constitutes a vast and important field in therapeutic organic synthesis (Belen'kii and

Evdokimenkova, 2019; Thakral and Singh, 2019). Among the heterocyclic compounds, the triazole derivatives occupy an important pharmaceutical class; they are applied as antiviral and anti-proliferative products. 1,2,3-triazoles derivatives are also applied as an antimicrobial and fungicide (Dheer, 2017; Wojaczynska and Wojaczynski, 2018; Kharb et al., 2011).

In this study, we evaluated by molecular docking the interaction between hypothetical proposed triazoles molecules and the active sites of three enzymes responsible for inflammation and fungal infections.

MATERIALS AND METHODS

Used software

Molecular Operating Environment software (MOE) (Chemical, Computing Group Inc., Molecular Operating Environment (MOE), 2014) is a combined application environment and methodological development platform that integrates visualization, simulation and application development in unique software. MOE contains a large base of scientific applications for general modeling, drug design, homology modeling, and library design. It is a fully integrated suite of computational chemistry, molecular modeling and computer science software for life science applications. The applications in the suite are written in an integrated programming language, Scientific Vector Language (SVL). ChemDraw software was also used to design new proposed triazoles.

Three dimensional (3D) enzymes structure preparation

We chose three enzymes for the study. The enzymes chosen are; Cytochrome P450 14 alpha-sterol demethylase (CYP51, PDB ID 1E9X), Cyclooxygenase1 (COX-1, PDB ID 1EQG), and Cyclooxygenase2 (COX-2, PDB ID 1CX2). The 3D structures of those enzymes were obtained from PROTEIN DATA BANK (www.rcsb.org).

The purpose of this operation which is done with MOE software is to determine the active site of each enzyme. The active site of a receptor is the privileged region of the receptor that interacts with the ligand. To simplify the enzyme, one should download the enzymes from the rcsb database (Bookhaven Protein Data Bank). Water molecules and some residues (those which do not participate in the catalytic reaction of the enzyme) and co-crystallization molecules must be removed to arrive at a simplified model. Using the “Site Finder” module from MOE software which includes a tool for the detection of the enzymatic cavity, we identified and presented the residues which form the active site of each chosen enzyme based on the largest amino acid content and which is the most favorable site for the 'interaction. Studied enzymes and their isolated active site are shown in Table 1 (Figures 1,2,3,4,5). Both enzyme and ligands energy minimizing was done under temperature and pH default parameters. The geometry was performed using the field strengths MMFF94x, and Hamiltonian AM1.

Hypothetical proposed triazole (ligands) preparation

Ligands are molecules that are able to lodge in the active site of the enzyme. In our case, the molecules chosen for the study are completely hypothetical imagined by combination of several results study from the literature on triazoles which have an approved therapeutic effect. The proposed designed ligands are shown in Table 2. The 3D ligand structures were generated by ChemDraw software in pdb.* format. The preparation of the ligand consists of minimizing the molecule energy by semi-empirical quantum mechanical methods which are techniques for calculating quantum chemical electronic structure based typically on a formalism for ab-initio quantum mechanics (for example, molecular orbital) or density functional theory (van der Kamp, 2013). In or study, we used the Austin Model 1 (AM1) method developed at the University of Texas at Austin, and introduced by Dewar et al. (1985). AM1 is an improved version of MNDO (Lewars, 2016).

Docking and scoring function

The Docking procedure consists of positioning the selected ligand in the active site of the enzyme and calculating the energy of the complex formed using the Dock module (molecular docking) inserted in MOE software (Chemical, Computing Group Inc., Molecular Operating Environment (MOE), 2014; Khanna et al., 2019). The interaction between the ligand and the enzyme is determined by molecular mechanics. The obtained score represents the energy of the complex formed between the enzyme and the ligand, which is calculated by the scoring function (Chaudhary and Mishra, 2016; Salim, 2018; Prieto-Martínez, 2019). The molecular docking process can be separated into two main stages which are search and scoring. For the search, it is necessary that the conformational search algorithm can explore conformational space as exhaustively and efficiently as possible.

The scoring function provides a mode to rank the placement of ligands in proportion to others. Ideally, the score should correspond directly to the ligand's binding affinity for the protein, so that the best scoring ligands are the best binders. Scoring functions can be empirical, knowledge-based, or molecular mechanics. Scoring is actually made up of three different expressions applicable to docking and drug design (Chaudhary and Mishra, 2016).

Table 1: 3D structures of studied enzymes and their corresponding isolated active site.

The 3D structure of COX-1 was downloaded from the protein database under the code 1EQG and at a three-dimensional resolution equal to 2.61 Å obtained by X-ray diffraction.	
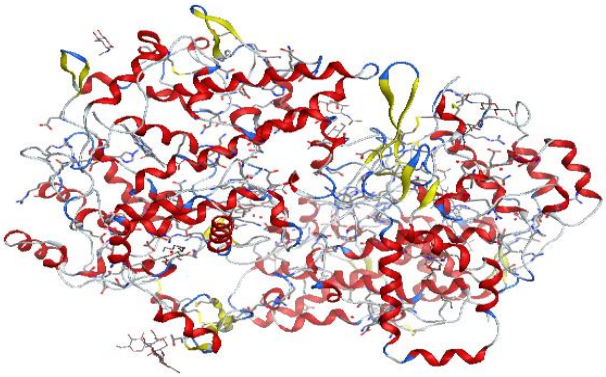	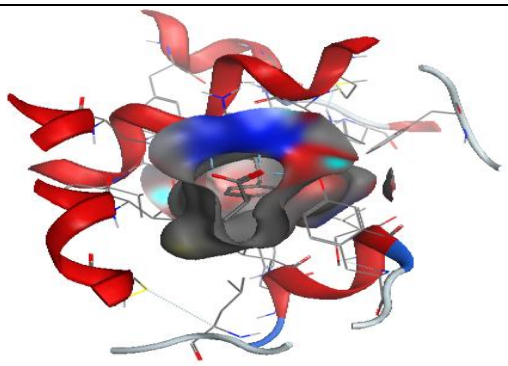
Figure 1: 3D structure of the COX-1(1EQG) enzyme	**Figure2**: Isolated active site of the COX-1(1EQG) enzyme.

The 3D structure of COX-2 was downloaded from the protein database under the code 1CX2 at a three-dimensional resolution equal to 3.00 Å obtained by X-ray diffraction.

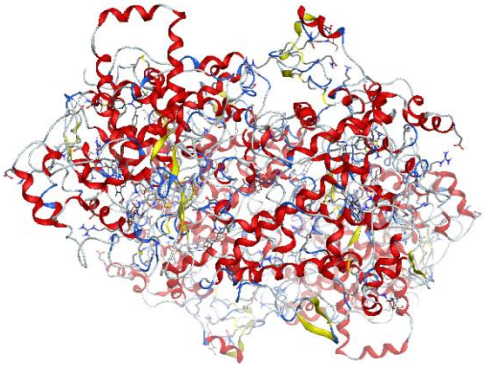	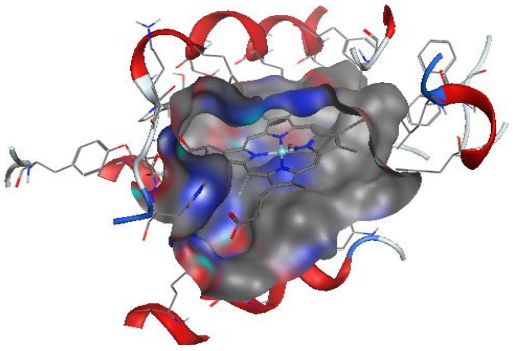
Figure 3: 3D structure of the COX-2 enzyme (1CX2)	**Figure 4:** Isolated active site of the COX-2 (1CX2)

The 3D structure of CYP51 was downloaded from the protein database under the code 1E9X under three-dimensional resolution equal to 2.10 Å obtained by X-ray diffraction.

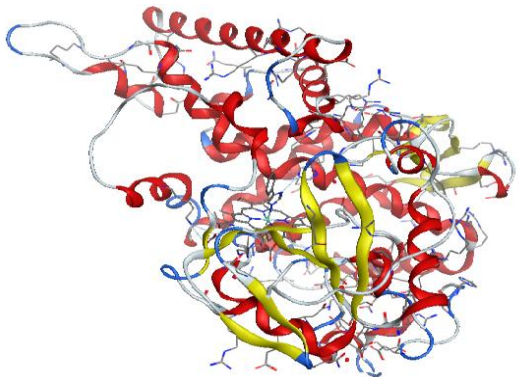	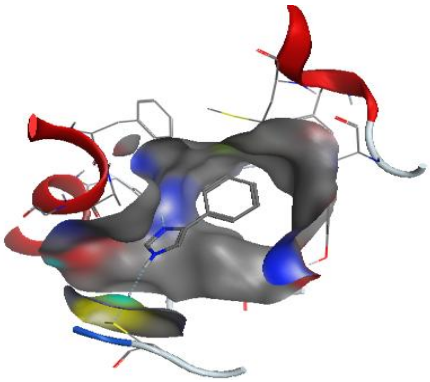
Figure 5: 3D structure of the CYP51 enzyme (1E9X)	**Figure 6:** Isolated active site of the CYP51 enzyme (1E9X)

- Generated configurations classified by docking search.
- Classification of the different ligands compared to the proteins (virtual screening).
- One or more ligands classified with respect to the

Table 2: 2D structures and IUPAC names of proposed hypothetical ligands.

	Nomenclatures (IUPAC)	Hypothetical molecules (ligands) structure
A	1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)-4-(5-nitropyrazin-1(2H)-yl)butan-l-one	
B	(2-(4,4-difluorocyclohexa-1,5-dien-1-yl)-1 H-benzo[d]imidazol-1-yl)(1-(4-(hexyloxy)phenyl)-1H-1,2,3 triazol-4-yl)methanone	
C	S-methyl 3-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)-2-(3-nitrobenzamido)-3-oxopropanethioate	

Table 2: Contd.

D	ethyl 2-2-(1-4-hexyloxy)phenyl)-1 H-1,2,3-triazole-4-carbonyl)thio)acetamido) thiazole-4-carboxylate
E	(4-1-(2,4-dichloro-5-fluorophenoxy)ethyl)phenyl) (1-(4-(hexyloxy)phenyl)-1 H-1,2,3-triazol-4-yl)methanone
F	(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)(8-(trifluoromethyl)quinolin-6-yl)methanone
G	3-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazole-4-carbonyl)-1,2,4-oxadiazol-5(4H)-one
H	1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)-3-(2-mercapto-3,3a-dihydro-4H benzo[4,5]imidazo[1,2-b][1,2,4]triazol-4-yl)propane-1,3-dione
I	5-((5-(1,3-oxazepan-3-yl)oxy)furan-2-yl)thio)-1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)pentan-1-one

Table 2: Contd.

J	1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)-6-(4-methylpiperazin-1-yl)-6-(3-nitrophenyl)hexan-l-one

Table 3: Obtained RMSD and Score after re-docking of reference ligands.

Enzyme	Reference ligand	RMSD (Å)	Score (kcal/mol)
COX-1 (PDB ID 1EGQ)	Ibuprofen (IBP)	1.17	-7.7006
COX-2 (PDB ID1CX2)	Protoporphyrin IX containing FE (HEM)	1.32	-8.7574
CYP51 (PDB ID 1E9X)	4-Phenyl-1H-Imidazole (PIM)	1.67	-4.4939

different proteins by their binding affinity (selectivity and specificity)(Ferreira et al., 2015; Saileela et al., Jr et al., 2010).

The force field-based scoring functions estimate the bond energy by summing the contributions of the bound (bond stretch, angle bend, and dihedral variation) and unbound (electrostatic and Van der Waals interactions) terms in a general main function (Stahl and Rarey, 2001). This type of scoring function applies an ab-initio method to calculate the energy associated with each term of the function using the equations of classical mechanics (Warren et al., 2006) known as force field. The Force Field is a mathematical function that returns the energy of a system according to the conformation of the system. Forces can be written in terms of potential energy functions of various structural characteristics such as bond lengths, bond angle, unbound interactions, etc (Guha,). The force field is the combination of these potential energy terms (Lewars, 2016). The functional form of any force field involves bound terms which refer to atoms which are bound by covalent bonds, and unbound (non-covalent) terms which describe long-range electrostatic forces and that of Van der Waals (Pissurlenkar et al., 2009).

$$E_{Total} = E_{covalent} + E_{non-covalent} \quad (1)$$

The following equations indicate the connectivity terms that compose the covalent and non-covalent terms of force.

$$E_{covalent} = E_{bond} + E_{angle} + E_{dihedral} \quad (2)$$

$$E_{non-covalent} = E_{Electrostatic} + E_{Van\ der\ Waals} \quad (3)$$

In our study, we used the scoring function based on the Assisted Model building with energy refinement force field (**AMBER**) (Wang et al., 2003).

Method validation and obtained results

Classically, we evaluate the quality of the docking procedure by measuring the Root Mean Square Deviation (RMSD) on heavy atoms between the pose obtained in docking and the pose observed experimentally if it exists. This is what we commonly call the validation of the docking method (Salim, 2008). In general practice, in docking method, validation is often required, it consists of re-docking the reference ligand of each enzyme to obtain at least a similar superposition of the co-crystallized ligand to that of co-crystallized inhibitor, where the mean square deviation (RMSD) must be less than 2 Å (Prieto-Martínez,). Obtained RMSD and scores after red-docking of reference ligands are shown in Table 3. Docking score results of

Table 4: Obtained scores from energy interaction of formed complexes (enzyme-ligand).

	Score Kcal/mol		
Ligands	**COX-1(1EGQ)**	**COX-2(1CX2)**	**CYP51 (1E9X)**
A	-7 .8270	-8.9740	-7.9008
B	-6.0237	-8.3506	-7.9900
C	-7.7995	-9.1695	-8.3728
D	-7.1128	-8.6499	-7.5846
E	-6.9025	-8.6034	-8.1459
F	-7.5217	-7.7514	-7.3190
G	-7.2339	-8.1264	-6.7237
H	-7.7872	-8.5372	-8.1170
I	-7.6113	-9.3667	-8.8098
J	-7.4994	-7.2989	-7.9270

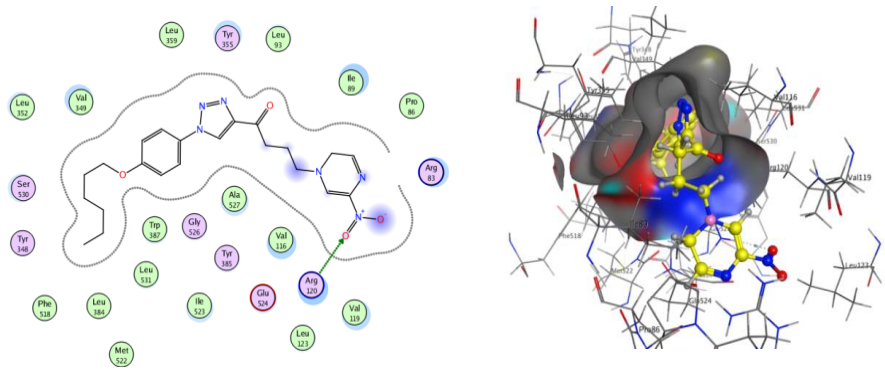

Figure 7: 2D and 3D diagram interaction between ligand **A** and COX-1 enzyme.

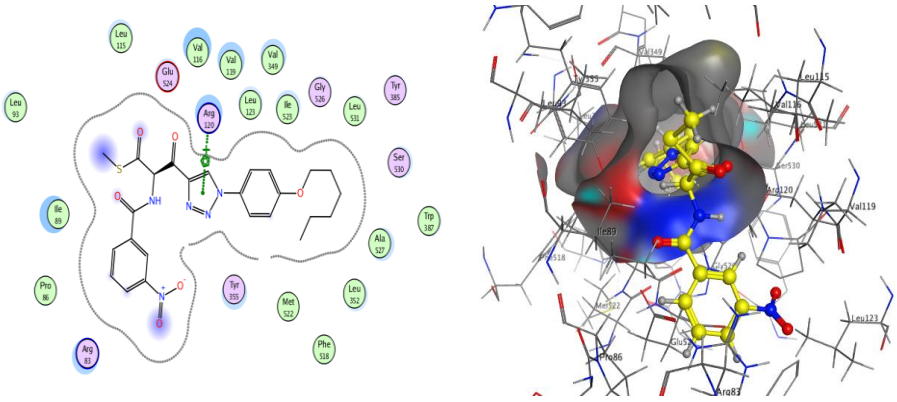

Figure 8: 2D and 3D diagram interaction between ligand **C** and COX-1 enzyme.

hypothetical proposed ligands and studied enzymes are shown in Table 4.

RESULTS INTERPRETATION AND DISCUSSION

For COX-1

As reported in Table 4, we notice that ligands A, C, H give the best scores (-7.8270; -7.7995; -7.7872) compared to the reference ligand (Table 3). This implies that compounds A, C, H can interact with COX-1 better than other proposed triazoles compounds, and therefore they constitute better candidates for inhibition of the enzyme. The figures 7, 8, and 9 show the interactions of ligand A, C, and H which give the lowest complex energies. We see in Figure 7 a possible hydrogen interaction of arginine (ARG 120) of distance 3.12 Å and energy of -1.1 kcal / mol. In figure 8, two pi-cation interaction with arginine (ARG 120) are perceptible with a distance of 3.37 Å, 3.13 Å and energy of -3.3 kcal / mol and -

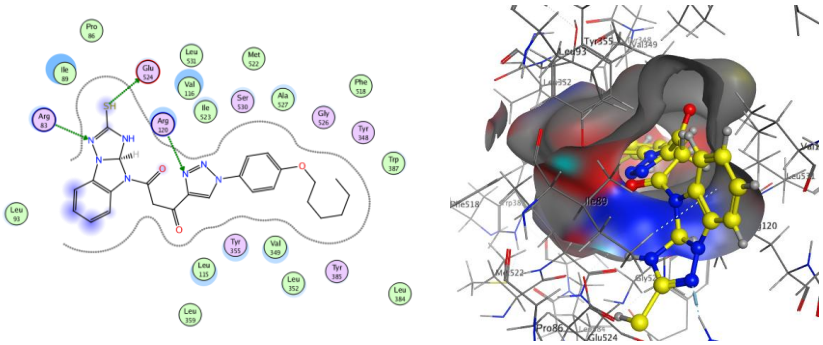

Figure 9: 2D and 3D diagram interaction between ligand **H** and COX-1 enzyme.

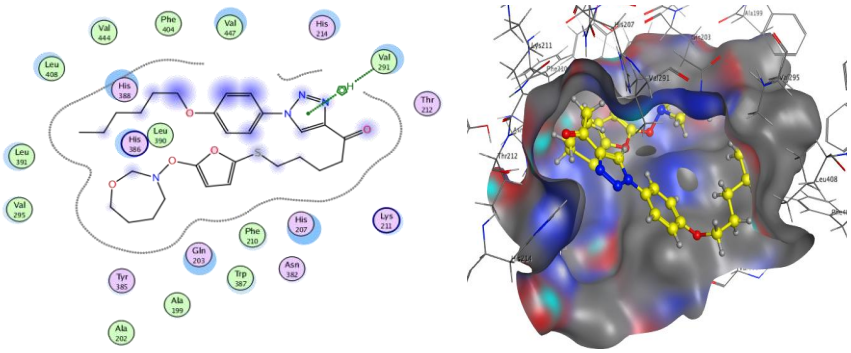

Figure 10: 2D and 3D diagram interaction between ligand **I** and COX-2 enzyme.

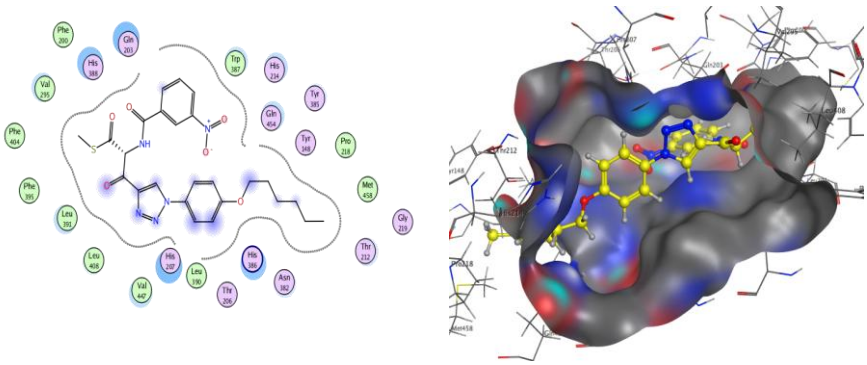

Figure 11: 2D and 3D diagram interaction between ligand **C** and COX-2 enzyme.

1.3 kcal / mol respectively. Figure 9 shows three possible hydrogen interactions; two interactions with arginine (ARG 120) at a distance of 2.70 Å, 2.83 Å and an energy of 0.2 kcal / mol and -6.2 kal / mol respectively, and an interaction with Glutamic acid (GLU 524) at a distance of 3.19 Å, and an energy of -3.0 kcal / mol.

For COX-2

According to Table 4, we notice that ligands I, C, and A give the best docking scores (-9.3667kcal / mol, -9.1695kcal / mol, -8.9740kcal / mol). The obtained scores are higher than the score obtained in comparison with the reference ligand (Table 3), which implies that these ligands are the best candidate triazole compounds for inhibiting of COX-2. Figures 10, 11 and 12 show the interactions of ligand I, C, and A which gives the lowest energy. We notice in Figure 10 one pi-H interaction with distance of 4.04 Å and energy of -0.9. In Figure 11 no interactions are perceptible. Figure 11 shows three H-pi interactions where two are linked to Tryptophan (TRP 387) with a distance of 4.19 Å, 3.80 Å and energy of -0.6 kcal / mol and -3.5 kcal / mol respectively, and one pi-H interaction to Histidine (HIS 386) with

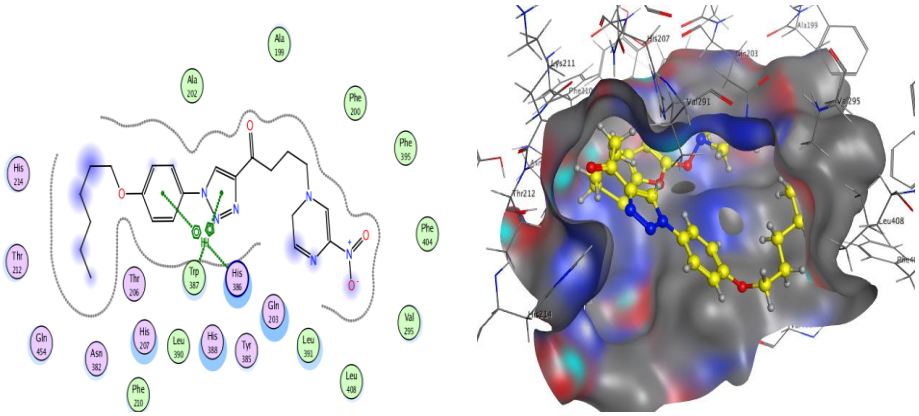

Figure 12: 2D and 3D diagram interaction between ligand **A** and COX-2 enzyme.

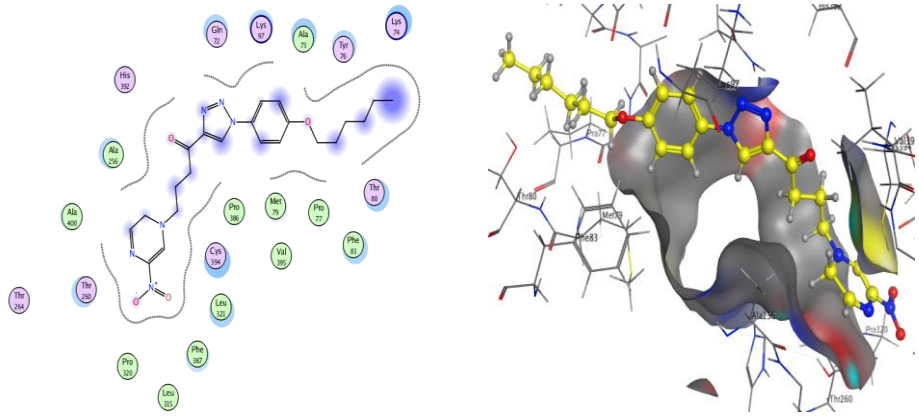

Figure 13: 2D and 3D diagram interaction between ligand **A** and CYP51 (1E9X) enzyme.

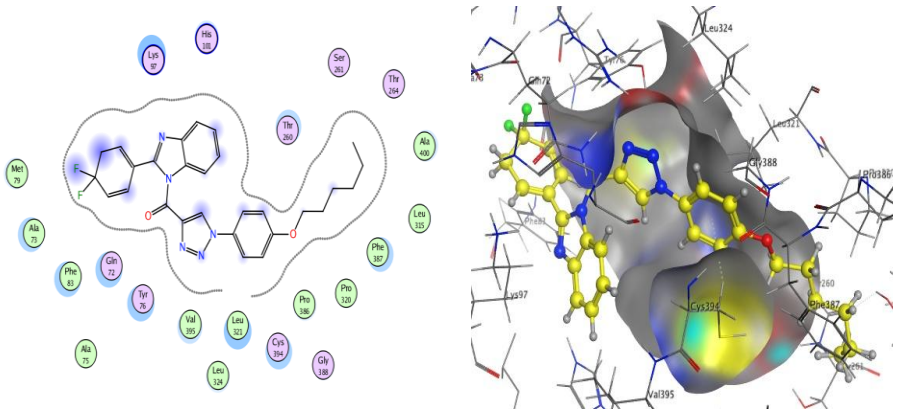

Figure 14: 2D and 3D diagram interaction between ligand **B** and CYP51 (1E9X) enzyme.

distance of 4.12 Å and an energy of -0.6 kcal / mol.

For CYP51 (1E9X)

From Table 4 it can be seen that all the ligands proposed from A to J give the best scores relative to the reference ligand (Table 03). The scores obtained are higher than the score obtained with the reference ligand, which implies that these ligands are the best triazoles candidate compounds for inhibiting CYP51.

From Figures 13,14,15,16, 17 we notice no perceptible

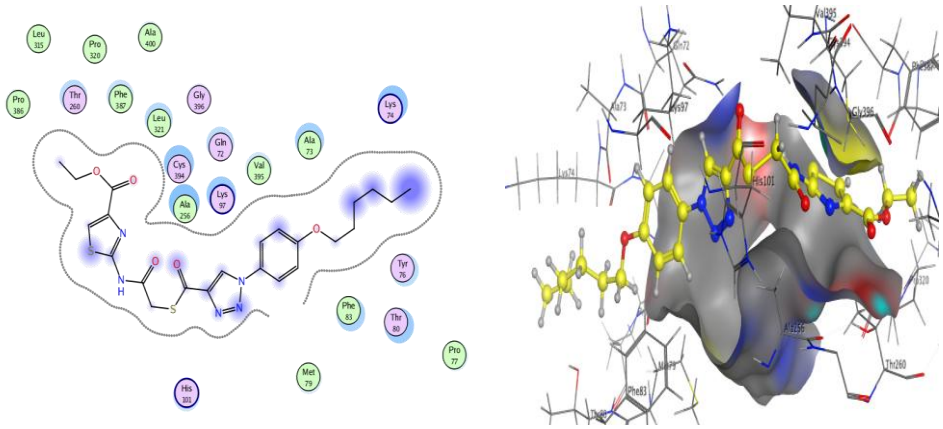

Figure 15: 2D and 3D diagram interaction between ligand **D** and CYP51 (1E9X) enzyme.

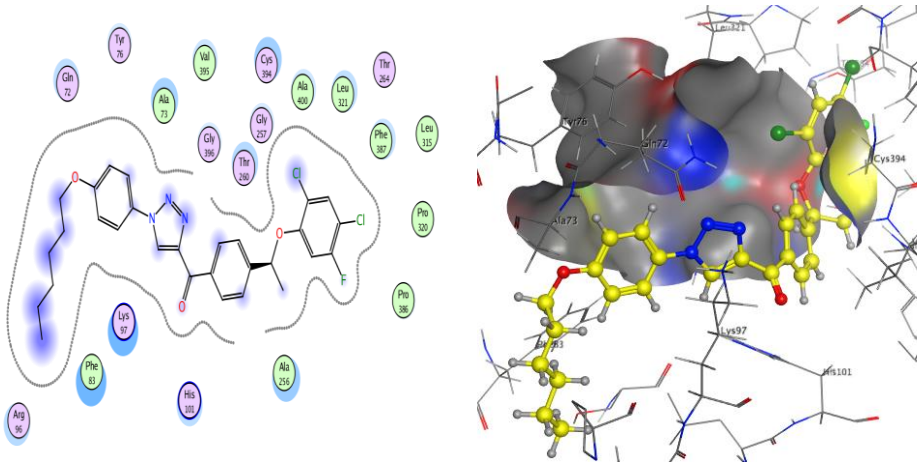

Figure 16: 2D and 3D diagram interaction between ligand E and CYP51 (1E9X) enzyme.

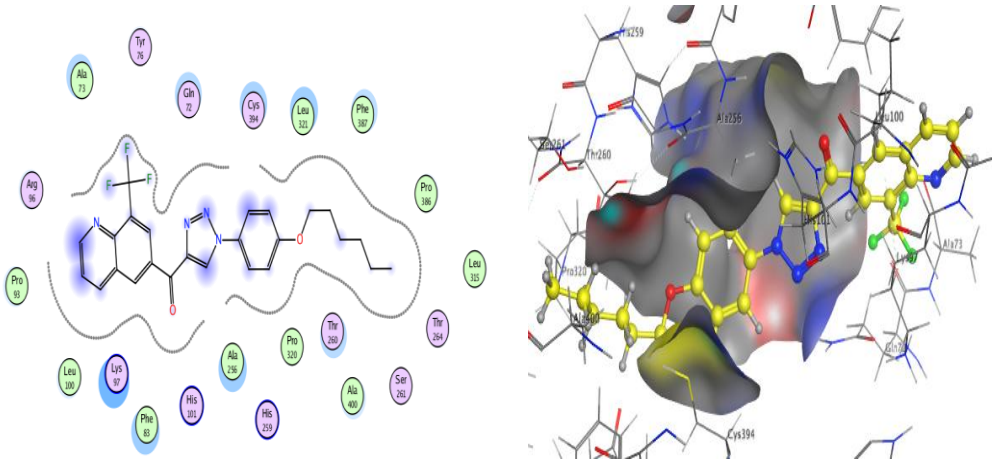

Figure 17: 2D and 3D diagram interaction between ligand F and CYP51 (1E9X) enzyme.

interactions with ligands A, B, D, E, and F. In Figure 18 we notice three pi-H interactions; the first one to Leucine (LEU 321) with a distance of 3.86 Å and an energy of -0.7 kcal / mol, the second one is linked to Cysteine (CYS 394) with distance of 3.91Å and an energy of -0.7 kcal / mol. The third interaction is linked to Glycine (GLY 396) with a

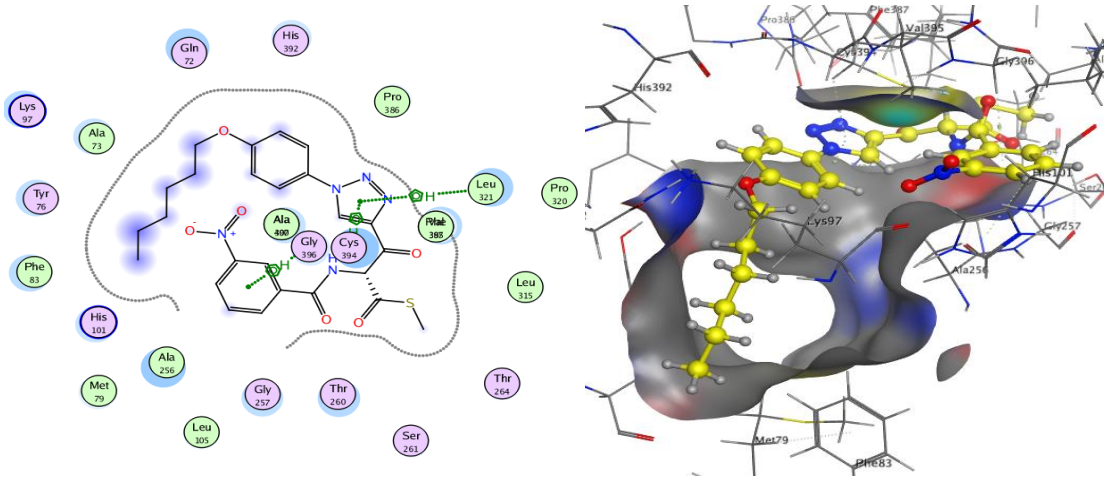

Figure 18: 2D and 3D diagram interaction between ligand **C** and CYP51 (1E9X) enzyme.

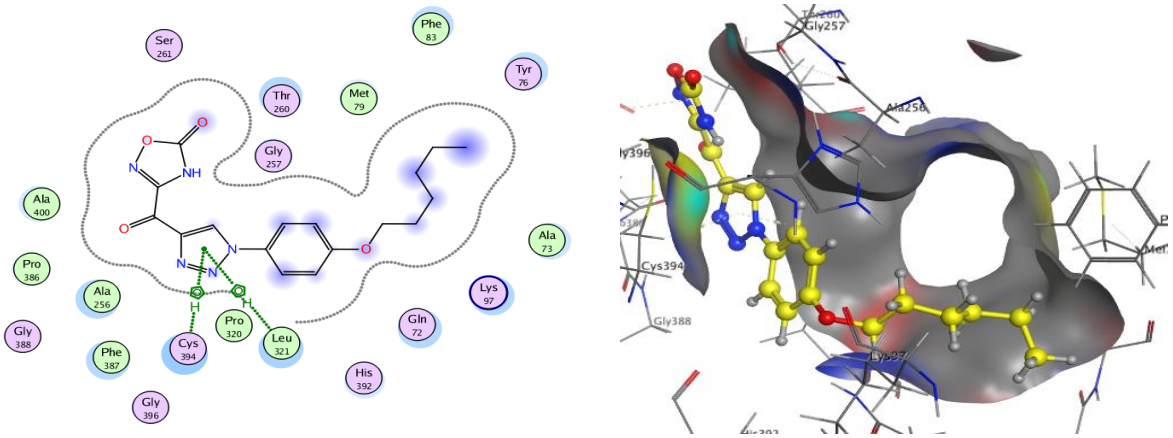

Figure 19: 2D and 3D diagram interaction between ligand **G** and CYP51 (1E9X) enzyme.

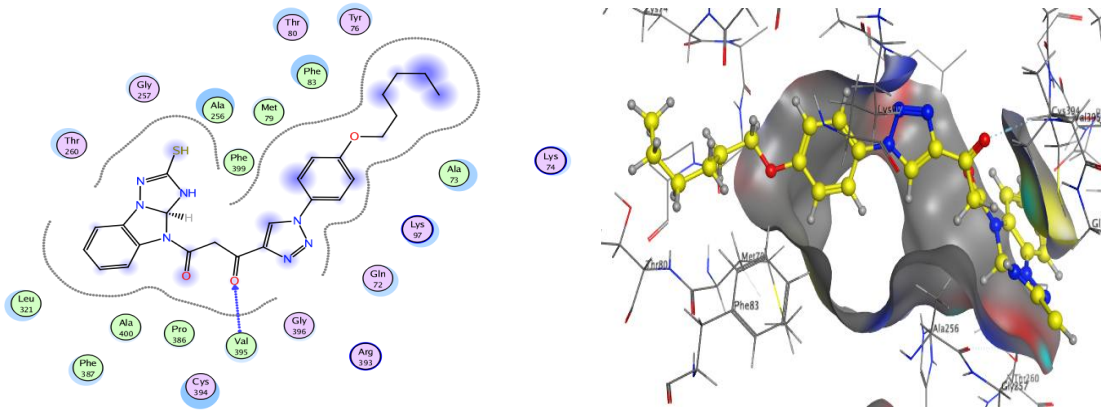

Figure 20: 2D and 3D diagram interaction between ligand **H** and CYP51 (1E9X) enzyme.

distance of 3.82 Å and energy of -1.2 kcal / mol. Figure 19 shows two pi-H interactions with Leucine (LEU 321) with a distance of 3.94 Å and energy of -0.7 kcal / mol, and the second interaction is with Glycine (GLY 394) with a distance of 3.78 Å and energy of -0.9 kcal / mol. Figure 20 shows H-acceptor interaction with Valine (VAL 395) with

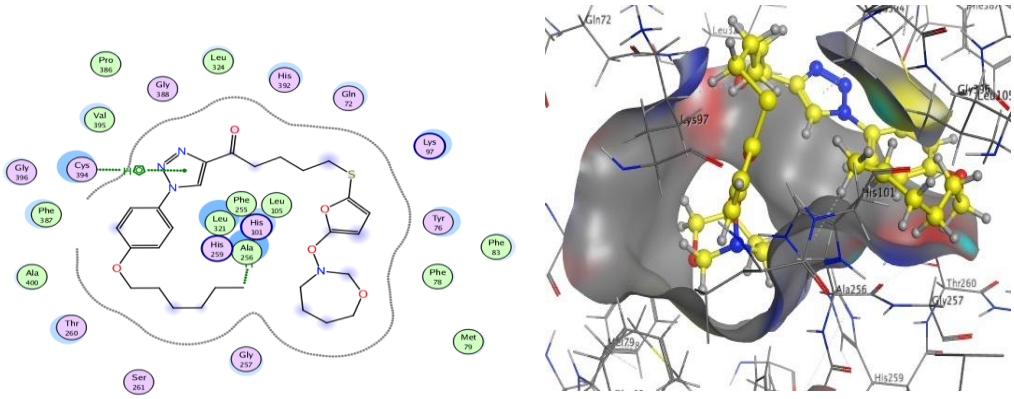

Figure 21: 2D and 3D diagram interaction between ligand **I** and CYP51 (1E9X) enzyme.

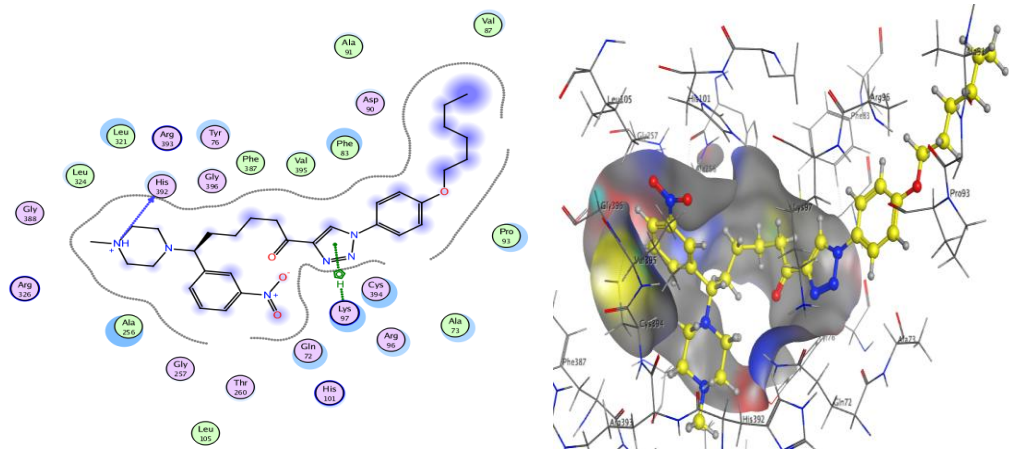

Figure 22: 2D and 3D diagram interaction between ligand **J** and CYP51 (1E9X) enzyme.

distance of 3.35Å and energy of -1.7 kcal / mol. In Figure 21 we notice two H-pi interactions with Cysteine (CYS 394) with a distance of 3.64Å and an energy of -0.7 kcal / mol and the other H-pi interaction is with Alanine (ALA 286) with a distance of 4.33Å and energy of -0.7 kcal / mol.

According to Figure 22 we notice H-donor interaction with Histidine (HIS 392) with a distance of 2.98Å and energy of -2.9 kcal / mol and we notice the pi-H interaction with Lysine (LYS 97) with a distance of 1.6Å and energy of -1.0 kcal / mol.

LIGANDS PROPERTIES STUDY

We studied the properties of ligands according to Lipinski's rule as shown in Table 5 to determine whether the compounds giving a good score are likely to have the physicochemical properties necessary to be bioavailable orally to humans. Lipinski's rule helps in industrial pharmacy to correctly choose the drug and to know if it is suitable for oral formulations. According to Lipinski's "rule of five", there are five important physicochemical parameters which are molar mass, lipophilicity, polar surface area, hydrogen bond, and charge (Lipinski et al., 2001; Lipinski, 2004; Winiwarter et al., 2007). The properties studied were obtained by the MOE software (Chemical, Computing Group Inc., Molecular Operating Environment (MOE), 2014).

Molar mass

Molar mass has been suggested as the most readily available indicator of limited chemical uptake and should be less than or equal to 500 g/mol [62,63,65]

Distribution coefficient Log (P)

Lipophilicity (synonymous with hydrophobicity) is defined by the partition of a compound between an aqueous phase and a non-aqueous phase. Nowadays, the partition

Table 5: The physico-chemical properties of ligands according to the lipinski's rule.

Ligands	Molar Mass (g/mol)	Log (P)	Log(S)	TPSA (Å²)	H-donor	H-acceptor	Toxicity
A	440.50	3.65	-5.05	118.43	0	5	Yes
B	503.55	6.24	-7.37	74.83	0	5	No
C	525.59	4.01	-7.75	149.00	1	6	Yes
D	517.63	4.37	-7.02	125.30	1	7	No
E	556.46	8.14	-9.32	66.24	0	5	No
F	468.48	6.34	-7.05	69.90	0	5	No
G	357.37	2.46	-4.95	107.70	1	6	No
H	505.60	3.74	-6.26	143.75	1	6	No
I	542.70	6.33	-7.19	91.85	0	6	No
J	562.71	5.96	-6.63	109.31	0	6	Yes

coefficient (P) is defined as the ratio of the concentrations of substances in the organic and aqueous phases of a two-compartment system under conditions of equilibrium. The partition coefficient (Log P) should generally be less than or equal to 5 (Lipinski et al., 2001; Lipinski, 2004; Van de Waterbeemd, 2007).

Solubility Log (S)

Solubility is one of the most important properties in drug discovery. Low solubility in water can lead to poor absorption; erratic assessment of bioactivity poses additional problems at later stages of development. The solubility is expressed in log S and the acceptable values must be greater than -4 (Lipinski et al., 2001; Lipinski, 2004; Bergström and Larsson, 2018).

The Topological Polar Surface (TPSA)

Polar area is defined as the amount of molecular area derived from polar atoms (nitrogen and oxygen atoms with their attached hydrogen atoms; some definitions also include sulfur atoms and their attached hydrogen atoms. It has been shown that a single conformation is sufficient to calculate the TPSA and that the TPSA of the compound should not exceed 140 Å² (Lipinski et al., 2001; Lipinski, 2004; Clark, 2011).

Number of donors and acceptors hydrogen bonds

It does not accept more than 5 donor hydrogen bond (total number of oxygen-hydrogen and nitrogen-hydrogen bonds), and not more than 10 acceptor hydrogen bonds (H-donor ≤ 5 and H-acceptor ≤ 10) (Lipinski et al., 2001; Lipinski, 2004; Kubinyi, 2007; Caron et al., 2019).

According to results shown in Table 5, we can see that ligands B, D, E, F, G, H, I respect the physicochemical properties according to Lipinski's rules and can be administered orally if further studies are done. However, compounds A, C, J are not considered as potential candidates because of their toxicity.

CONCLUSION

The results given by the present *in-silico* study, the interaction between hypotitical triazoles compounds and enzymes COX-1, COX-2 and CYP51 enzymes as well as the physicochemical properties of the hypothetical ligands have been demonstrated. We found that the molecule (**I)** [5-((5-(1,3-oxazepan-3-yl)oxy)furan-2-yl)thio)-1-(1-(4-(hexyloxy)phenyl)-1H-1,2,3-triazol-4-yl)pentan-1-one] can be exploited pharmacologically to develop fungicidal and anti-inflammatory drug at the same time. The molecule respects the Lipinski rules in general, so we can consider it as the best candidate for development into an oral fungicidal and anti-inflammatory drug.

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