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Molecular Modeling, Drug Design and Binding Evaluation of New Oxazole Derivatives as Cyclooxygenase Inhibitors

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Abstract

Furan, oxazole-derived Schiff base, and different aldehydes are to be combined to study their potential activities including anti-inflammatory action through COX enzyme inhibition. Molecular docking studies determine the most detailed probable view of drug-receptor interaction and have created a new rational approach to drug design. It suggests that these twelve compounds have strong interaction with COX-1 and COX-2 enzymes, which are responsible for the activity. In this article, 12 oxazole derivatives were docked inside cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzyme's crystal structures to calculate the binding potency of each derivative within the active site. Molecular modeling and *In silico* prediction of ADME properties approaches were conducted and the two most effective derivatives were chosen with docking binding range (-10.311 to -9.02) kcal/mol and (-9.642 to -9.18) respectively. The binding ability of indomethacin, aspirin, and mofezolac were selected as non-selective COX inhibitors. Whereas celecoxib, valdecoxib, rofecoxib, and parecoxib stand for selective COX inhibitors.

Keywords: Drug design, new oxazole derivatives, inhibitors,schiff base, aldehydes, in silico prediction, molecular docking;

1. Introduction

Recent novel therapeutic approaches propose that diverse biological Characteristics of multifunctional compounds present magnificent advantages in the treatment of complicated diseases. Since the inflammatory process is considered a multifactorial complicated phenomenon, additional beneficial effects of pleiotropic agents will be desired. Inflammation is a protective mechanism, in which the biological system naturally responds to numerous stimuli[1]. Particularly, it is a sequence of cellular and molecular reactions that arise to get rid of foreign agents and advocate tissue repair [2]. It involves the release of chemicals mostly prostaglandin from tissues and migrating cells[3]. Accordingly, inflammation is in a vicious circle of living cells injury and raised antioxidant activity could only bust into that circle[4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutic agents used as an anti-inflammatory, analgesic, and antipyretic activity, they constitute the first line of drugs indicated for the treatment of different inflammatory diseases for example rheumatism, arthritis, and ankylosing spondylitis[5]. The cyclooxygenase path generates thromboxane, pro-inflammatory prostaglandins (PGs), and different prostanoids. It exists in two isoforms: firstly(COX-1), the constitutive form which is a house-keeping enzyme that implicates in prostaglandins production, that are important for maintaining functions like gastric cytoprotection and homeostasis, and secondly(COX-2), the inducible form that takes part in inflammation[6] [7] [8]. Both COX isoforms are homologous: In which 61% of amino acids are identical while 84% are similar. The key residues involved in the binding of COX-2 inhibitors over COX-1 are ARG 120, TYR 355, and

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SER 530. A single methyl group difference creates extra space in the active site that is known as the COX-2 pocket, making it bigger than COX-1[9]. The importance of five-membered heterocyclic rings, specifically oxazole is known in drug discovery. These compounds are of significant activity including antitumor, antibacterial, antitubercular, antifungal, anti-inflammatory, antidiabetic, antiobesity, anti-progesterone activity, anticoagulant prostacyclin receptor antagonist, T-type calcium channel blocker, and antioxidant properties[4,10-12]. Furthermore, different oxazole derivatives already present with potent non-selective cyclooxygenase (COX) inhibitory activity such as oxaprozin (VI)[5], valdecoxib (VII) which is a non-selective COX-2 inhibitor, and parecoxib (VIII), the sulfonamide-based prodrug of valdecoxib, the only parenterally administered coxib available to date [13,14]. In the literature, a series of oxazole derivatives have been reported presenting COX inhibition [15], presented below in Figure 1.

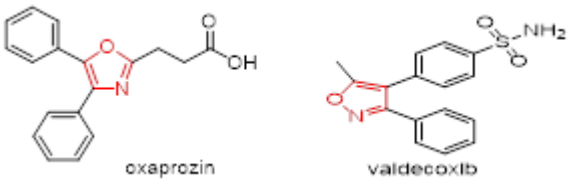


Fig. 1. COX inhibitors containing oxazole moiety.

The main target of NSAIDs is to minimize inflammation and provide pain relief without affecting COX-1 enzyme preservation in the gastrointestinal tract, leading to a decrease in most serious side effects. However, NSAIDs present disadvantages especially with the gastrointestinal tract including dyspepsia, gastric ulcers, and others. In order to alleviate these drawbacks, there is an urgent need for the design and synthesis of new chemical compounds with good anti-inflammatory responses and minimal side effects[16]. Consequently, to avoid loss in time and resources in the drug design process, a computational method has been used for its benefit in drug development with detailed information about ligands and/or targets to optimize new drugs[17] [18]. Additionally, this approach is also used to improve the ADME (absorption, distribution, metabolism, and elimination) profile and the ability of drug targeting by generating several analogous of the available drug[19]. Eventually, many theoretically active compounds have been designed to introduce new anti-inflammatory agents in the treatment of inflammation, pain, and antiproliferation contributing to the significant role of COX-2 in the etiopathology of all those diseases.

2. Computational method

A total of 12 oxazole derivatives molecular structures were designed according to a literature review made by our team. The 3D analogous conformations were procured by using the ChemDraw16.0 program under ChemOffice package software (ChemOffice, 2016). From this step, the lowest energy conformation of the molecule is saved in .sdf format and optimized by using the Spartan 14.0 package (Spartan, 2014) with the Monte Carlo method supported with 200 optimizations of 1500 interactions(15). Molecular modeling drug design and molecular docking evaluation study were performed by using Glide software (Maestro 11.4) under Schrodinger software (Schrodinger, 2018) running on Windows 7 operating system on the workstation (Intel(R) Core(TM) i7 CPU 895 @ 3.4GHz, 32 GB RAM, 1TB HD). The crystal structures of COX-1 and COX-2 enzymes and ligands were obtained from Protein Data Bank under PDB code:2OYU with 2.7.crystallographic resolution and 3LN1 with 2.4.crystallographic resolution respectively. The enzyme preparation steps are applied by the ProPrep program for optimization and minimization. Ligand structure preparation was applied by using Lig Prepprogram before docking to identify and add hydrogens to achieve the best orientation and ionization position with low energy conformations of all ligands by using OPLS 2005 force field. A series of inhibitors related to the class of NSAIDS and celecoxib derivatives together with their inhibitory concentration values (IC50) were selected for the study. Each compound was docked into the active site by constructing the molecule de novo method for initial placement. The grid box was adjusted at 1.20 Å with 0.27 partial atomic, a size that permits each member of the tested compound to freely rotate in the purpose of finding the best conformation with binding free energy, greatest docking orientation was saved to generate many derivatives with various replacement processes application. All oxazole derivatives were saved and used for drug design evaluation.

3. Results and Discussion

The most crucial target of drug discovery is to recognize new active compounds against a specific biological target with enhanced pharmacological properties[20].

In accordance with the role of the COX enzyme in the production of prostaglandins, which are main mediators of pain and are involved in pathological conditions mainly inflammation, hypertension, cancer, and functions of the female reproductive system[21], therefore efforts have been directed towards designing inhibitors for this enzyme with proper efficacy and minimal side effect[22]. X-ray crystallization of both cyclooxygenase enzymes encouraged researchers to assess the binding affinity between new ligands and enzymes as the main goal is to design new inhibitor drugs by structure-activity relationships application[17]. In this present research, binding affinity approaches and the theoretical modeling design were utilized for the invention of novel compounds as inhibitor ligands with increasing binding ability at the active site of COX enzymes. An oxazole Schiff base moiety connected to selected aldehydes as inhibitors with a high degree of binding at active sites compared to specific present powerful ligands. The addition of different aldehydes to 4-(furan-2-yl) oxazol-2-amine product as core moiety leads to the formation of various compounds with different docking scores on both COX-1 and 2 enzymes (table 1 and figure 2). During virtual screening (VS), certain compounds were selected by computer programs to detect their binding affinity with a target receptor[23]. The results of whole screening compounds were between (-10.311) to (-3.018) kcal/mol on COX-1 enzyme while the binding ability of indomethacin was at (-8.667) kcal/mol, aspirin was at (-6.68) kcal/mol and mofezolac was at(-8.62) kcal/mol determined in table 1. Furthermore, the docking score of all listed compounds on the COX-2 enzyme was between (-9.642) to (-4.343) kcal/mol, whereas celecoxib`s binding ability was at (-11.557) kcal/mol, valdecoxib was at (-10.84) kcal/mol, rofecoxib was a (-9.012) kcal/mol and parecoxib was at (-9.154) kcal/mol. Among all listed compounds, compounds 1 and 2, presented in figure 2, revealed the highest binding affinity with both COX-1 and COX-2 enzymes. The reasons for this highest activity is potency in binding affinity and a pretty good orientation of molecules inside the active sites of enzyme surrounded by amino acids that are essential for optimal interactions. However, compound 12 did not present a docking score in the COX-1 enzyme. The orientation of the best molecules from the list inside the active site of COX-1 and COX-2 enzyme surrounded by the most important amino acids are shown in Figures 3 and 4, 5 and 6 respectively.

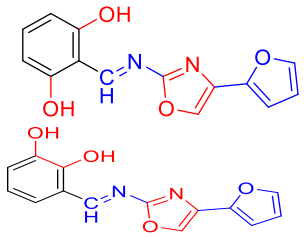


Fig. 2. Compounds 1 and 2, representing the highest docking scores.

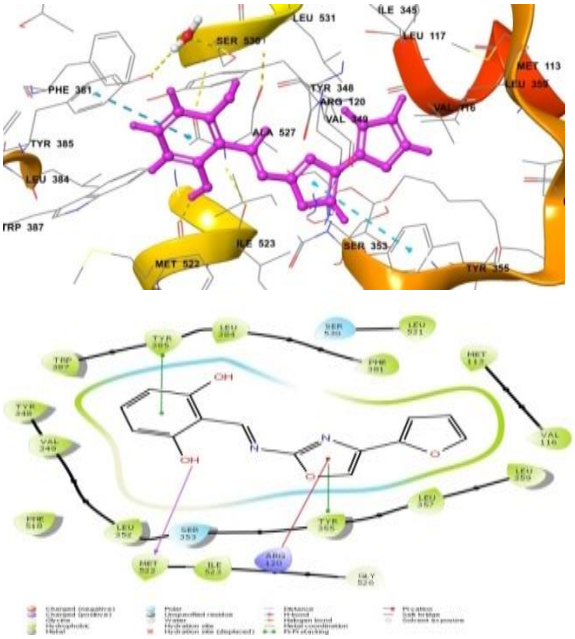
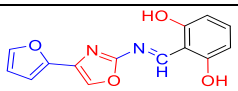
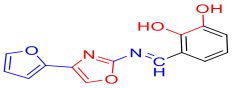
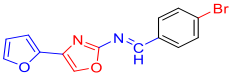
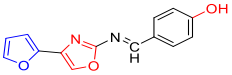
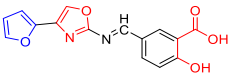
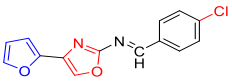
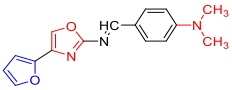
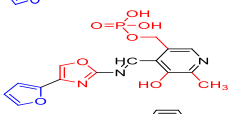
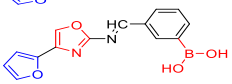
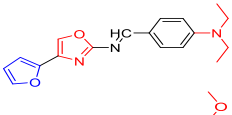
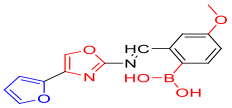
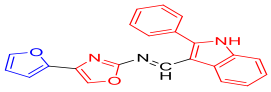


Fig. 3. The best compound (1) inside COX-1 enzyme surrounded by amino acids, (1)molecule as a ball and stick, enzyme as ribbon

Inside COX-1 enzyme active site, compound 1 binds through various interactions including one pi-cation interaction between ARG 120 and oxazole ring, two pi-pi stacking interactions one between TYR355 with oxazole ring and the other between TYR385 with a benzene ring. In addition one H-bond between MET522 and a hydroxyl group. Moreover, hydrophobic interactions occur with surrounding amino acids (TRP387, LEU384, PHE381, PHE518, ILE523, LEU531, MET113, VAL116, 9+LEU359, LEU357, TYR348, and VAL349), as presented above in figure 3.

Table 1. Docking scores for oxazole derivatives inhibition in COX enzymes.

No.	Compounds	Docking score for COX-1	Docking score for COX-2
1		-10.311	-9.642
2		-9.02	-9.18
3		-8.586	-5.024
4		-8.294	-6.244
5		-8.198	-6.778
6		-7.526	-8.183
7		-7.402	-4.343
8		-6.422	-8.249
9		-6.274	-5.804
10		-5.852	-7.199
11		-3.018	-7.893
12		Docking score for COX-1	-9.155

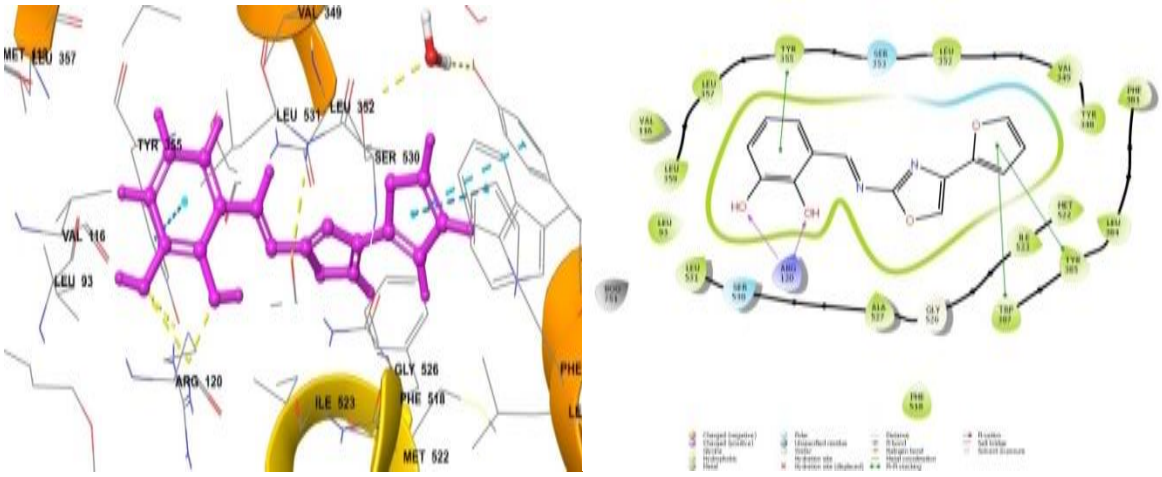


Fig. 4. The second best compound (2) inside COX-1 enzyme surrounded by amino acids, (2) molecule as a ball and stick, enzyme as ribbon

The interactions of compound 2 with active sites of COX-1 enzyme involve: two H-bond interactions between ARG120 and the two hydroxyl groups, three pi-pi stacking interactions, two from these between TRP385, TYR387 with furan ring and the third one is between TYR355 with a benzene ring. Additionally, hydrophobic interactions with embracing amino acids (MET522, ILE523, ALA527, LEU531, LEU93, PHE381, LEU384, PHE518, TYR348, VAL349, LEU352, LEU357, LEU359, and VAL116), as shown above in figure 4.

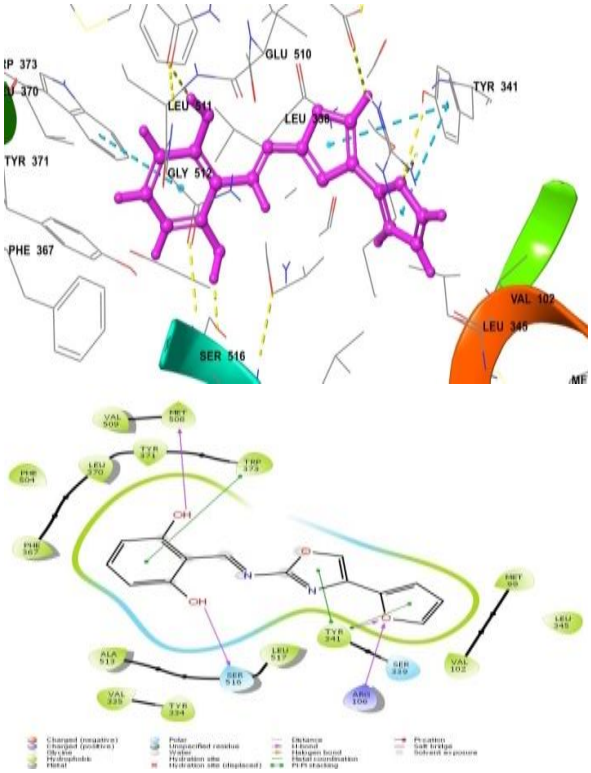


Fig. 5. The best compound (2) inside COX-2 enzyme surrounded by amino acids, (2)molecule as a ball and stick, enzyme as ribbon.

However, inside the COX-2 enzyme active site, compound 1 bind by three pi-pi stacking interactions two of which establish between TYR341 and furan and oxazole rings, the last occur between TRP373 and benzene ring. Moreover, three hydrogen bindings appear in the two hydroxyl groups and amino acids MET508 and SER516 respectively. Likewise, hydrophobic interactions with the surrounding amino acids (MET99, VAL102, TYR334, VAL335, LEU345, PHE367, LEU370, TYR371, PHE504, VAL509, ALA513, and LEU517), given in the above figure 5.

The interactions of compound 2 with active sites of COX-2 enzyme include three pi-pi stacking interactions, involving two between furan ring with TRP373 and TYR371 amino acids while the third one is between benzyl moiety with amino acid TYR341 that's already involved in two hydrogen bonding with both hydroxyl group presented within. As well, hydrophobic interactions with the surrounding amino acids (LEU78, MET99, VAL102, VAL335, LEU338, LEU345, PHE367, LEU370, PHE504, MET508, VAL509, ALA513, LEU517) shown below in figure 6.

All these interactions enhanced the binding affinity with the enzyme leading to better activity and potency of newly generated compounds.

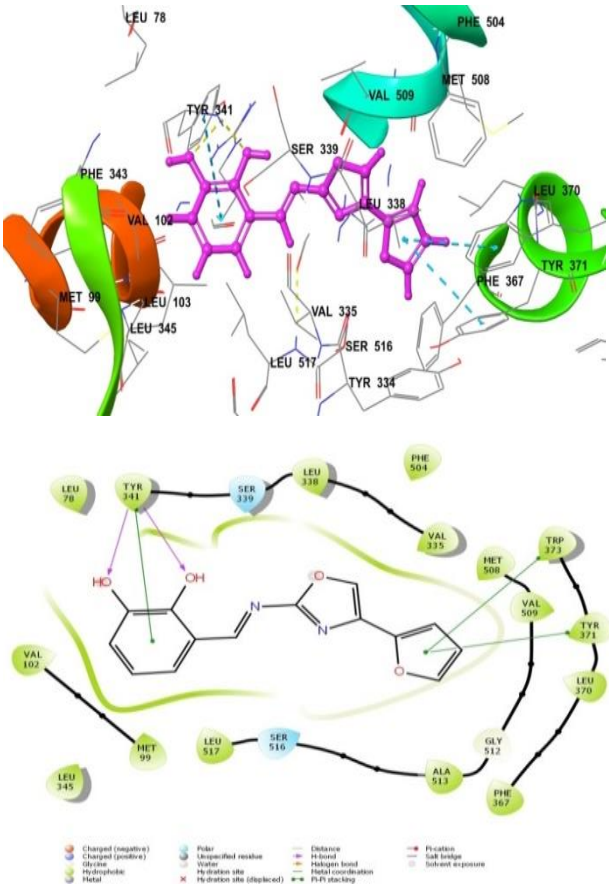


Fig. 6. The second best compound (2) inside COX-2 enzyme surrounded by amino acids, (2)molecule as a ball and stick, enzyme as ribbon.

Furthermore, since Drug development demands assessment of absorption, distribution, metabolism, and excretion (ADME) earlier in the discovery process, a quick accessible ADME study was

conducted using the new SwissADME web tool that provides freely available access to a pool of fast and solid predictive models for pharmacokinetics, physicochemical characteristics, medicinal chemistry properties and drug-likeness, including proficient methods such as ilog P, Bioavailability Radar and the BOILED-Egg[24]. Both, compound 1 and 2, has the same BOILED-Egg as seen below in figure 7.

The BOILED-EGG for the generated compounds represented in Figure 7. Illustrate those compounds 1 and 2 do not permeate BBB, on the other hand highly and passively absorbed from GIT. Both will not be exported out of the cells of CNS by p-glycoproteins.

Briefly, Lipinski rule related to the oral administration of the drugs that should have ≤ 5 hydrogen bonds donor, an octanol-water partition coefficient log P not greater than 5, ≤ 10 hydrogen bond acceptor and molecular weight (M.Wt.) ≤ 500 to be given orally[25]. Also, the topological polar surface area (TPSA) was calculated, because it is a very important property that has been associated with the bioavailability of the drugs. Thus, passively absorbed molecules with a TPSA >140 A^{o} are thought to have low oral bioavailability[26].

Our results showed that compounds 1 and 2 have TPSA below 140, which is (99.91) and the bioavailability for both ligands was 0.55 which means that they can reach the systemic circulation. They fulfilled the Lipinski rule, as shown in Tables 2 and 3 respectively. Also, it fulfilled the topological descriptors and fingerprints of molecular drug-likeness structure keys as Log P and Log S. "The gastrointestinal absorption score is an amount of the extent of absorption of a molecule from the intestine following oral administration". In our study, the GI absorption of all synthesized ligands was high expecting them to be well absorbed from the intestine.

Both have a quite similar physicochemical properties, pharmacokinetics, and bioavailability radar. Shown below in Tables 2 and 3 respectively.

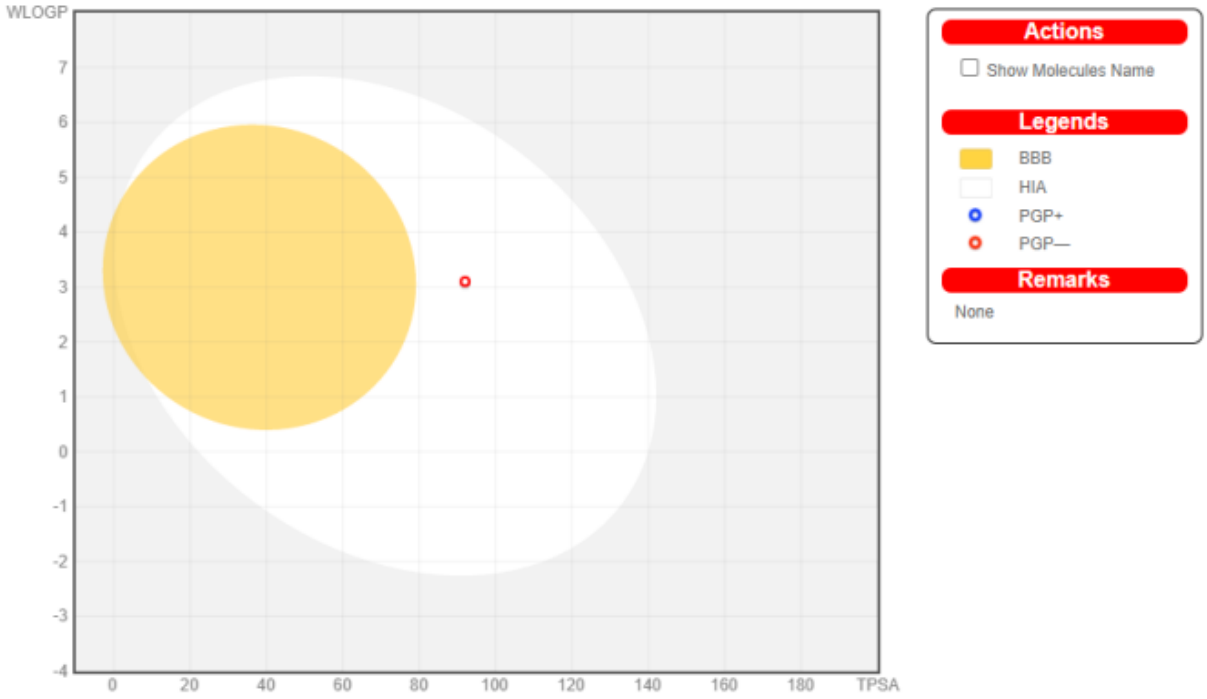
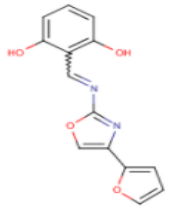
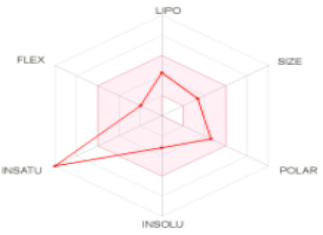


Fig. 7. BOILED-Egg for both compounds 1 and 2. Yellow ovule (yolk): are molecules predicted to passively permeate through blood-brain barriers. White ovule (white): are molecules predicted to passively absorb by the GIT. PGP+: Blue dots are for molecules predicted to be effluated from the CNS by the P-glycoprotein. PGP-: Red dots are for molecules predicted not to be effluated from the CNS by the P-glycoprotein

Table 2: Compound 1 virtual characteristics as predicted by the SwissADME web tool.

Molecule 1





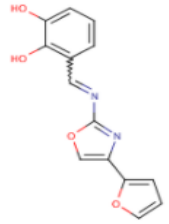
SMILES Oc1cccc(c1/C=N/c1occ(n1)c1ccco1)O

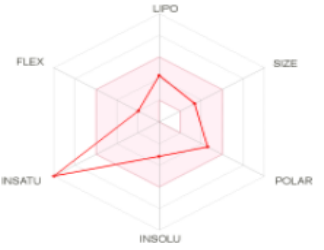
Physicochemical Properties	
Formula	C14H10N2O4
Molecular weight	270.24 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	71.95
TPSA	91.99 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.22
Log $P_{o/w}$ (XLOGP3)	2.02
Log $P_{o/w}$ (WLOGP)	3.10
Log $P_{o/w}$ (MLOGP)	0.44
Log $P_{o/w}$ (SILICOS-IT)	2.71
Consensus Log $P_{o/w}$	2.10

Water Solubility	
Log *S* (ESOL)	-3.18
Solubility	1.78e-01 mg/ml ; 6.58e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.58
Solubility	7.12e-02 mg/ml ; 2.64e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-4.43
Solubility	1.00e-02 mg/ml ; 3.72e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.51 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: imine_1
Leadlikeness	Yes
Synthetic accessibility	3.27

Table 3: Compound 2 virtual characteristics as predicted by the SwissADME web tool.

Molecule 2





SMILES Oc1cccc(c1O)/C=N/c1occ(n1)c1ccco1

Physicochemical Properties	
Formula	C14H10N2O4
Molecular weight	270.24 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	71.95
TPSA	91.99 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.55
Log $P_{o/w}$ (XLOGP3)	2.02
Log $P_{o/w}$ (WLOGP)	3.10
Log $P_{o/w}$ (MLOGP)	0.44
Log $P_{o/w}$ (SILICOS-IT)	2.71
Consensus Log $P_{o/w}$	2.16

Water Solubility	
Log *S* (ESOL)	-3.18
Solubility	1.78e-01 mg/ml ; 6.58e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.58
Solubility	7.12e-02 mg/ml ; 2.64e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-4.43
Solubility	1.00e-02 mg/ml ; 3.72e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.51 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	2 alerts: catechol, imine_1
Leadlikeness	Yes
Synthetic accessibility	3.27

4. Conclusion

One of the best methods in the molecular discovery that improve enzyme`s binding affinity and pharmacological potency is molecular modeling. The outcome of applying this method are novel series of oxazole derivatives designed and evaluated for their anti-inflammatory activity with a higher potency profile and binding within active sites of COX enzymes in addition to high docking scores (-10.311, -9.02) kcal/mol for compounds 1 and 2 respectively, of the twelve other derivatives, combined with Pi-Pi stacking, Pi-cation, and H- bond interactions. Both have quite similar physicochemical properties, drug-likeness, pharmacokinetics, and bioavailability radar. Moreover, compounds 1 and 2 fulfilled the Lipinski rule, the topological descriptors, and fingerprints of molecular drug-likeness structure keys. Finally, these compounds may be taken as lead compounds for the development of novel anti-inflammatory agents. A biological and pharmacological evaluation study is essential to understand the side effects and toxicity profile of all generated new derivatives.

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