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Anti-inflammatory Potentials of Various Oxine Compound Series as Cyclooxygenase-2 (COX-2) and Lipoxygenase (LOX) Inhibitors: Induced-Fit Molecular Docking and Pharmacokinetic Prediction Studies

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Abstract

The present investigation is an exploration of multiple oxine series in inhibiting crucial anti-inflammatory targets such as cyclooxygenase-2 (COX-2) (PDB ID: 3LN1) and lipoxygenase (LOX) (PDB ID: 1N8Q) by employing the Glide module of Maestro 9.1 software for induced fit docking (IFD). The study also focuses in exploration towards the essential pharmacokinetic parameters (QPlogPo/w, QPlogS, predicted aqueous solubility, QPPCaco, QPPMDCK, and percentage of human oral absorption). The study highlighted the prime importance of oxine-based hererocycles in the upcoming anti-inflammatory drug discovery research programs and their further development as emerging candidates in the near future.

Keywords: *Oxine, docking, anti-inflammatory, COX-2, LOX*

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INTRODUCTION

Heterocyclic compounds have emerged as potent medicinal agents in the 21st century. In the market, nearly 75% of the modern drugs are of heterocyclic origin [1]. The combination of heteroatoms in the low molecular weight compounds offers strong binding with the biological targets which may be a receptor, enzyme or a channel by forming hydrogen bonding, Van der Waals forces, or may even covalent bonding in extreme cases [2]. The availability of starting material, ease of synthesis, easy separation techniques for purification, and multifarious pharmacological activities made them very popular among the scientific community [3]. In the last decade, the chemical databases have been flooded with numerous nonsteroidal anti-inflammatory candidates (NSAIC) of various heterocycles such as pyrimidine, pyridine, oxazole, coumarin, thiazole, thiadiazole, pyrrole, carbazole, etc [4].

The substituted oxine compounds are not much studied in details against their anti-inflammatory potential with a well-defined mechanism. Oxine or Pyran are six-membered nonaromatic heterocyclic compound, known for exhibiting multifarious pharmacological activities such as antirheumatic [5], antimicrobial [6], anticancer[7], anti-anxiety [8], anti-allergic [9], anti-inflammatory [10], anti-ulcer [11], antidepressant [12], antileishmanial [13], antihypertensive [14], immunopotentiator [15], anti-estrogenic [16], antiviral [17], antitubercular [18], anti-hepatitis [19], anti-HIV [20], anti-oxidant [21], anti-emetic [22], antidiabetes [23], etc.

The current investigation is a molecular docking study which involves exploration of anti-inflammatory potentials of three pyran molecule series; first, 2,5-disubstituted pyrans series which comprises of 2-(but-3-en-1-yl)-5-nonyltetrahydro-2*H*-pyran **(1)**, 5-(7-butoxydodecyl)-2-(2-ethylbut-3-en-1-yl)-3,6-dihydro-2*H*-pyran **(2)**; second 2-substituted pyrans series, (*R*)-2-(but-3-enyl)-tetrahydro-2*H*-pyran **(3)**, (*R*)-2-((*S*)-2-ethylbut-3-enyl)-3,6-dihydro-2*H*-pyran **(4)**, and third pyran-

1,4(5*H*,9*H*)-dione series, (5a*R*)-8-ethyl-6-vinyl-3,3a,5a,6-tetrahydroazuleno[1,8-cd]pyran-1,4(5*H*,9*H*)-dione **(5)** as nonsteroidal anti-inflammatory candidates (NSAIC) by inhibiting the most imperative biological target cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), utilizing Glide module of Maestro 9.1 software. Additionally, abbreviated ADME studies were performed to determine the significant parameters such as probable toxic effects, pharmacokinetic profiling, and suitability in oral administration of the candidates.

MATERIALS AND METHODS

Sketching and Preparation of Ligands

The 2-substituted pyran compounds were initially made in 2D format using ChemDraw® Ultra and saved as Mol file. The drawn molecules were prepared for docking by suitable modification of ligand torsion and assigning to protonation states using LigPrep module of Schrodinger Maestro 9.1 software. In Glide module, 25 stereochemical structures were generated per ligand with possible states at target pH 7.0±2.0 using Epik ionizer. The tautomerized, desalted, and optimized by producing low energy 3D structure for the ligand under the OPLS 2006 force field [24].

Validation and Preparation of Protein

The 3D crystal structure of COX-2 (celecoxib bound at the active site) was downloaded from PDB (PDB ID: 3LN1) for the docking studies. The LOX protein structure was procured from the protein data bank (PDB) in a complexed form with the protocatechuic acid (PDB ID: 1N8Q). The preparation of selected proteins includes deletion of crystallographic water molecules beyond 5 A° distance, metal ions, and cofactors. The hydrogen atoms were added and formal charges along with bond orders were assigned to the structures [25].

Induced Fit Docking (IFD)

The molecular docking was performed using Schrodinger-Maestro 9.1 utilizing IFD protocol which offers flexibility to both the receptor and ligands. The docking studies were performed to get crucial information regarding the orientation of the inhibitors in the binding pocket of the target protein. The initial Glide docking for each ligand was carried out with some modulations. Van der Waals scaling was done to 0.70 for receptor and 0.50 for the ligand, respectively. The side chain prediction and minimization were carried out. The RMSD value of cutoff 0.18 A° was selected. The number of poses generated was set to be 20. The residues were refined within 5.0 A° of ligand poses. The ligand was thoroughly docked into the induced-fit receptor structure and the generated results were expressed as Glide score [26].

Profiling of ADME

The sketched ligands were *in silico* predicted for their pharmacokinetic profile utilizing the QikProp module of Maestro 9.1. The parameters of QPlogPo/w, the predicted octanol/water partition coefficient (log P); QPlogS, predicted aqueous solubility (in mol/l); QPPCaco, predicted Caco-2 cell permeability (in nm/s); QPPMDCK, predicted apparent MDCK cell permeability for the blood–brain barrier; and percentage of human oral absorption were calculated using the module [27].

RESULTS AND DISCUSSION

Molecular Docking Studies

2,5-disubstituted pyrans

The best ligand binding pose with the highest Glide/IFD score or energy was chosen. The protein–ligand binding interactions of COX-2 with the compounds were analyzed after performing IFD. The amino acid residue Gln 172 seems to play a major role in the protein–ligand interaction. Both the structures **1** and **2** successfully made hydrogen bonding interaction with the inflammatory target COX-2 (Figure 1). Structure **2** fits relatively more stable at the active site of COX-2 owing to the formation of one more stable hydrogen bonds with Thr 181 and also having a higher Glide score (-8.28 kcal/mol) than the structure **1** (-8.01 kcal/mol). There were total 1603 Van der Waals interaction to structure **1** and 1736 Van der Waals contacts to the structure **2** which additionally provides structural stability to the protein–ligand complex. The Glide score, Van der Waals contacts, and residues involved in the interaction of each compound at the active site of COX-2 are shown in Table 1. The docking studies of the compounds **1** and **2** with the COX-2 demonstrated the environment in the

active site of the receptor close vicinity to the ligands. The active site amino acid residues of the acceptor are conserved in the entire ligand and these favor the binding of structures through hydrogen bonds with the pyran ring. Since the pyran ring of both structures initiate the interaction through hydrogen bonds, it must be considered that the pyran ring plays material role in the enzyme inhibition.

The molecular docking studies displayed perfect binding of the compounds at the active site of 5-LOX. Surprisingly, both the inhibitors displayed several similarities. The structures **1** displayed Glide score of -5.47 kcal/mol whereas the structure **2** displayed Glide score of -5.53 kcal/mol (Table 2). It was found that both the compounds bind perfectly by forming hydrogen bonding with the polar amino acid residues; Gln514 and Asn554 (Figure 2). The structure **1** formed hydrogen bonding with the oxygen atom present in the pyran ring whereas the structure **2** made hydrogen bonding with the oxygen atom present in the chain and the water molecule present in the protein. This kind of interactions might be given flexibility as well as the force to the ligands to penetrate at the active site cavity. The Van der Waals contacts of structure **1** and **2** were found to be 1958 and 2720, respectively, which represented high structural stability to the protein–ligand complex. From results, it was evidenced that there was no such hydrophobic interaction at the active site. Instead, all the interactions happened through polar amino acid residues only. The active site of 5-LOX consists of a deep bent-shaped cleft containing amino acid residues and a non-heme iron cofactor which is capable of strong interactions with the ligand at active site cavity.

2-substituted pyrans

After performing IFD, the binding interactions of COX-2 with the ligands were analyzed. A lot of similarities were observed in the docking study of both the compounds. Both the molecules formed a single stable hydrogen bonding with the polar amino acid residue Gln172 present in the active site cavity via oxygen moiety (Figure 3). This kind of interactions might be given flexibility as well as the force to the ligands to penetrate at the active site cavity. They also had nearly identical dock Glide score of -5.69 kcal/mol **(3)** and -6.09 kcal/mol **(4)**, respectively, along with Van der Waals interactions of 603 and 742 (Table 1). The Van der Waals interaction was found to be less as compared to macromolecular structures by additionally providing structural stability to the protein–ligand complex. However, in the case of COX-2, the comparatively bigger active site is present which offers better stability to the structures and provide enough stability to the enzyme–inhibitor complex.

A good molecular docking at the active site of 5-LOX was demonstrated where the ligands interacted with the enzymatic target with nearly identical dock Glide score of -6.92 kcal/mol **(3)** and -7.17 kcal/mol **(4)**, respectively along with Van der Waals interactions of 953 and 1048 (Table 2). It was evidence that both the pyran compounds formed a single stable hydrogen bonding via oxygen moiety with the polar amino acid residue Gln514 present in the active site cavity of 5-LOX (Figure 4). A deep insight into the 5-LOX active site cavity, a deep bent-shaped cleft consisting of amino acid residues and a non-heme iron cofactor is present, which offers strong interactions with the ligand. The observed interaction is found to present adequate flexibility for ligands penetration at the active site cavity. Although from the interaction studies, no such hydrophobic interaction of the active site has been seen clearly. The high Van der Waals interaction proffers high stability to the structure to form protein–ligand complex. The pyran compounds stopped the entrance of the inflammatory substrate at the catalytic site of 5-LOX by binding firmly with the open cavity.

Pyran-1,4(5H,9H)-dione

The IFD technique revealed the possible ligand–protein interactions of (5a*R*)-8-ethyl-6-vinyl-3,3a,5a,6-tetrahydroazuleno[1,8-cd]pyran-1,4(5*H*,9*H*)-dione **(5)** with both the biological targets (COX-2 and 5-LOX) (Figure 5). The molecule exhibited interaction with COX-2 via formation of stable hydrogen bonding through Tyr324 with the =O (carbonyl) moiety present in the five-membered portion, demonstrating Glide score of -8.86 kcal/mol (Table 1). In contrast, the molecule displayed interaction with the 5-LOX via formation of stable hydrogen bonding through

Gln514 with =O (carbonyl) moiety present in the pyran part, demonstrating Glide score of -8.22 kcal/mol (Table 2). The Van der Waals interactions of the compounds were monitored to be 704 and 1942, respectively, which furthermore alleviate the complex formation. No hydrophobic or other types of interactions have been detected. On the contrary, all the interactions happened through polar amino acid residues only. A good binding with COX-2 have been observed which may be due to larger active site cavity present in the mediator which offer a sufficient steadiness of the enzyme–inhibitor complex. An impressive 5-LOX inhibitory potential has been observed by the candidate, which may be because the active site consists of a bent-shaped crevice surrounding active amino acid residues which is capable of mediating sturdy interactions with the ligand.

Pharmacokinetic Predictions

The ADME prediction for the designed structures **1** and **2** revealed that the affinitive compounds satisfied the Lipinski's rule of five. The QikProp program based prediction displayed that the compounds are nontoxic and have all parameters in the acceptable ranges; QPlogPo/w (−2.0 to 6.5), QPlogS (−6.5 to 0.5), QPPCaco (<25 is poor and >500 is good), QPPMDCK (<25 is poor and >500 is good), and % oral absorption (< 25% is poor and >80% is high). Thus, the two 2,5-disubstituted compounds have the perspective of desired pharmacokinetic and safety profile, which makes them perfect for successive studies, improvisation, and applications.

The QikProp assisted prediction of ADME of the 2-substituted pyran compounds (**3** and **4**) has showed to follow the Lipinski's rule of five and is completely nontoxic. The derivatives have low lipophilicity (<3) which may compromise the biological effect by hindering the crossing through biological membranes. The striking oral absorption of 100% was observed for both the molecules. All the parameters were found to be in the acceptable ranges. Overall, both the compounds have desired pharmacokinetic profile which emphasizes better druggability. Table 3 describes the pharmacokinetic parameters for the compounds.

Table 1: *Glide Score, Hydrogen Bonding, Van Der Waals Contacts, and Interacting Residues Involved at the Active Site of COX-2.*

Inhibitors	Glide score (kcal/mol)	No. of H bonds	No. of VdW contact	Interacting residues
1	- 8.01	1	1603	Gln 172
2	- 8.28	2	1736	Gln 172 and Thr 181
3	-5.69	1	603	Gln 172
4	-6.07	1	742	Gln 172
5	-8.86	1	704	Tyr 324

Table 2: *Glide Score, Hydrogen Bonding, Van Der Waals Contacts, and Interacting Residues Involved at the Active Site of LOX.*

Inhibitors	Glide score (kcal/mol)	No. of H bonds	No. of VdW contact	Interacting residues
1	- 5.47	1	1603	Gln 514
2	- 5.53	1	1736	Asn 554
3	- 6.92	1	953	Gln 514
4	- 7.17	1	1048	Gln 514
5	- 8.22	1	1942	Gln 514

Table 3: *ADME Prediction of Oxine Compounds by Using QikProp Module.*

Inhibitors	QPlogPo/w	QPlogS	QPPCaco	QPPMDCK	% Oral absorption
1	2.227	-2.794	9991.357	5872.826	100
2	2.863	-3.737	9947.159	5881.634	100
3	5.515	-8.431	9917.138	5893.479	100
4	7.754	-12.471	9906.038	5899.293	100

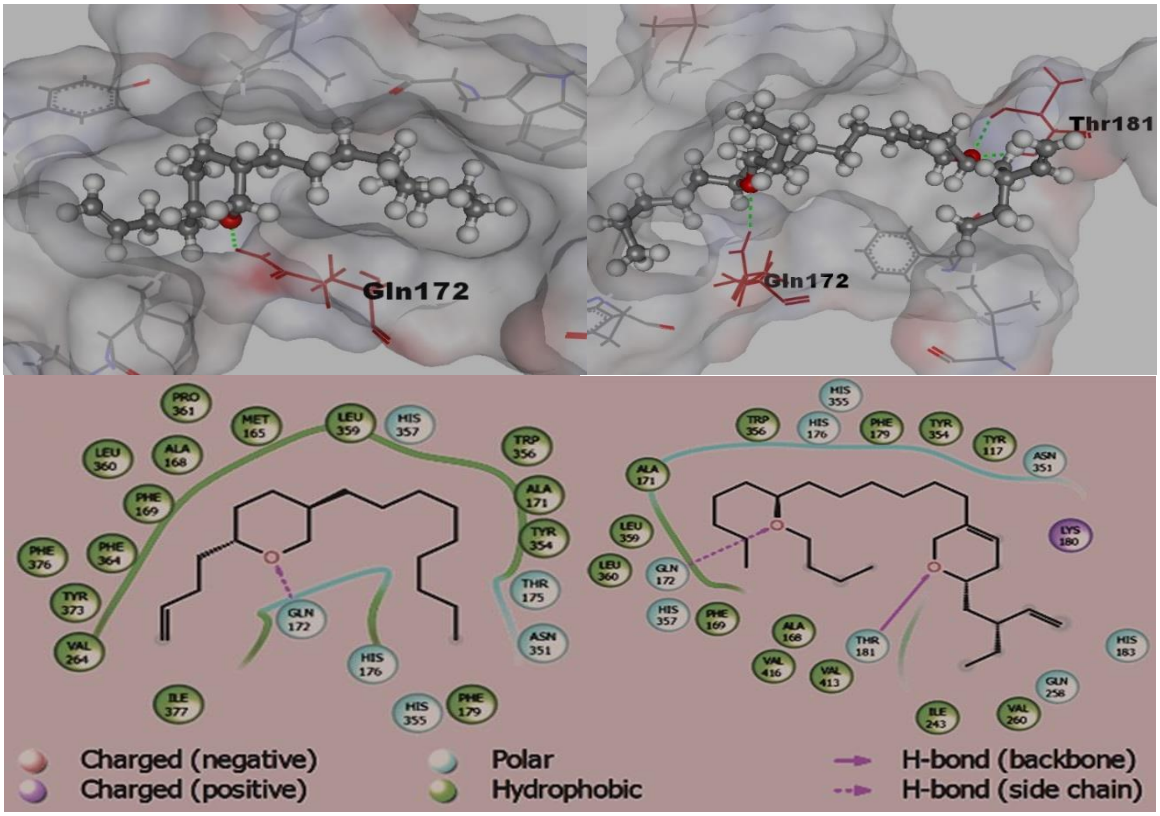

Fig. 1: *Binding Surface Model of the Pyran Compounds **1** and **2** (Above). Molecular Interaction of Molecules **1** and **2** at the Active Site of COX-2 (Below).*

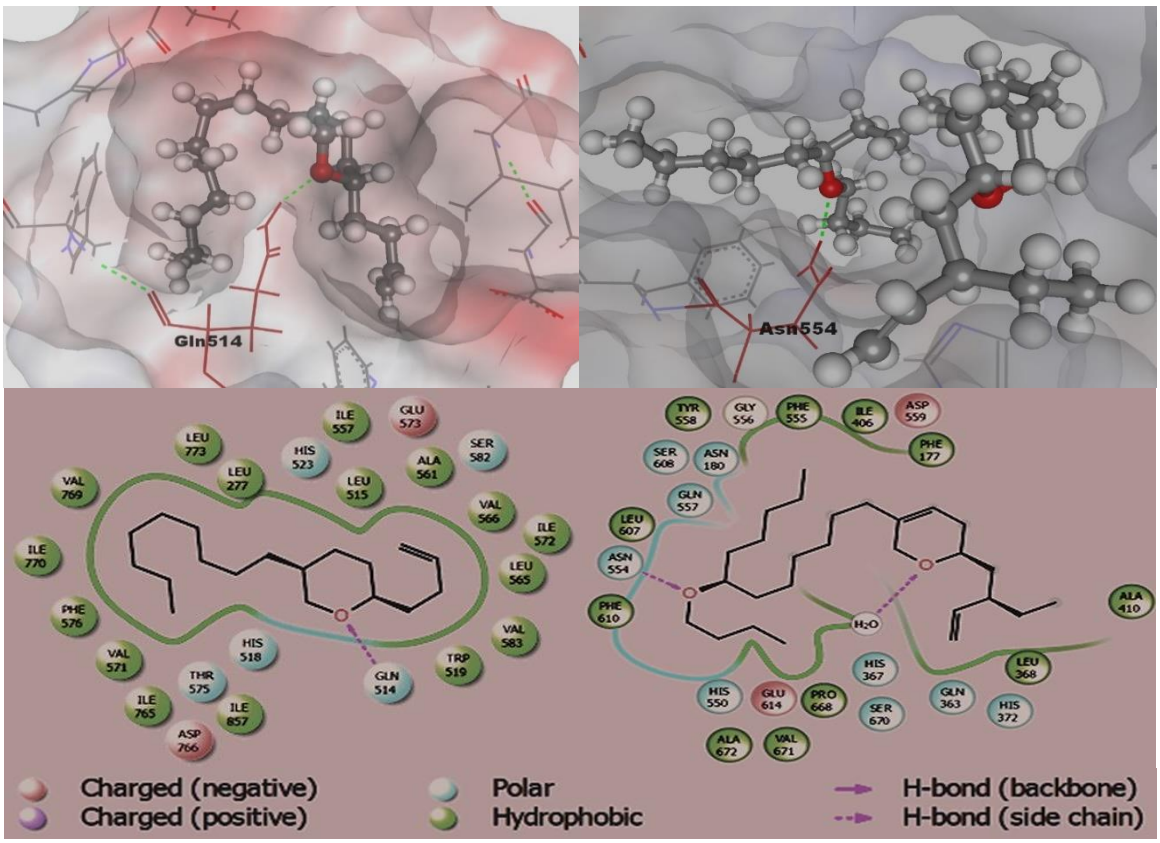

Fig. 2: *Binding Surface Image of the Inhibitors **1** and **2** (Above). Interaction of Pyran Compounds at the Active Site of 5-LOX (Below).*

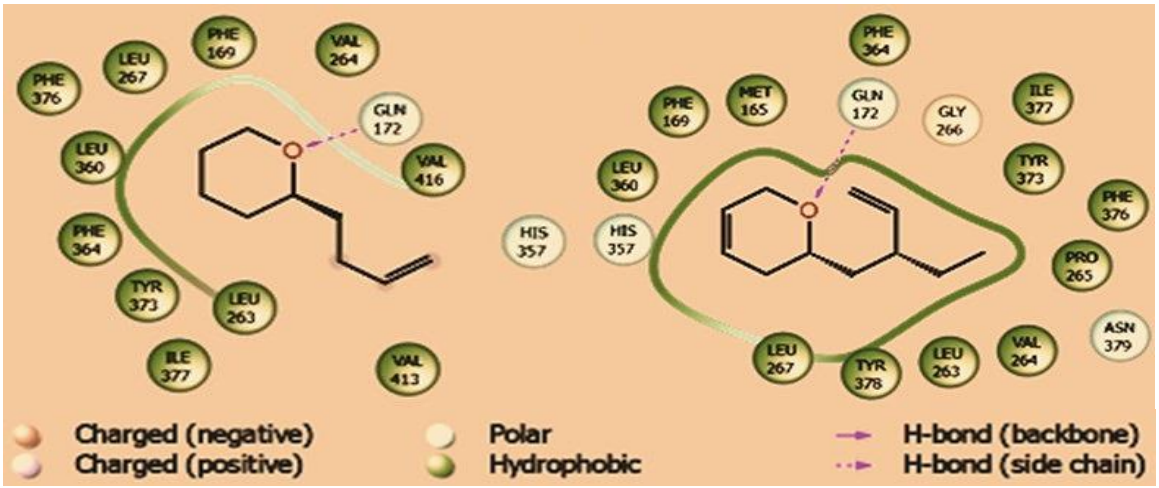

Fig. 3: *Interaction of the 2-Substituted Pyran Compounds **3** and **4** at the Active Site of COX-2.*

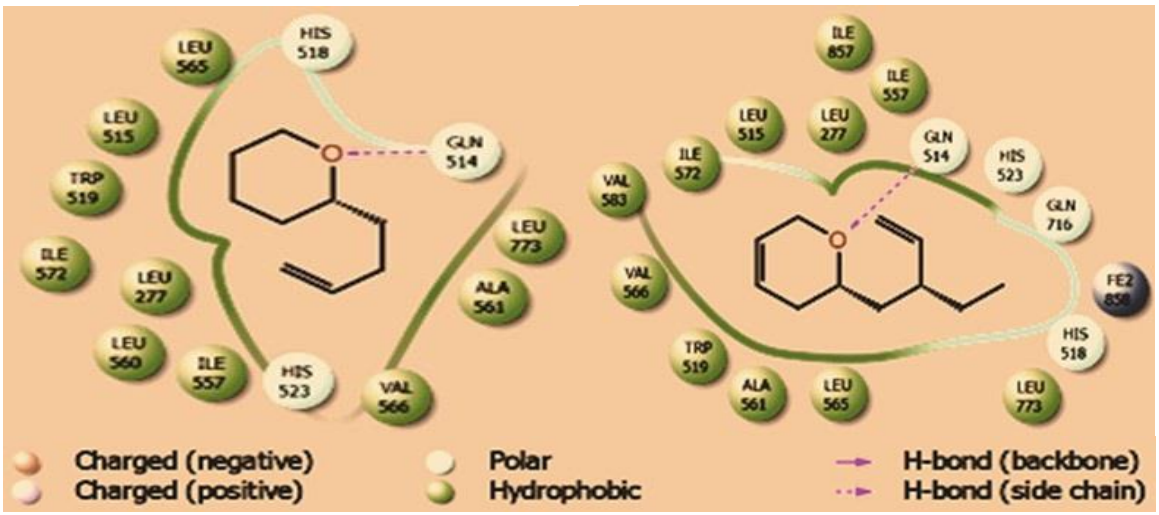

Fig. 4: *Interaction of the 2-Substituted Pyran Compounds **3** and **4** with Amino Acid Residues at Active Site of 5-LOX.*

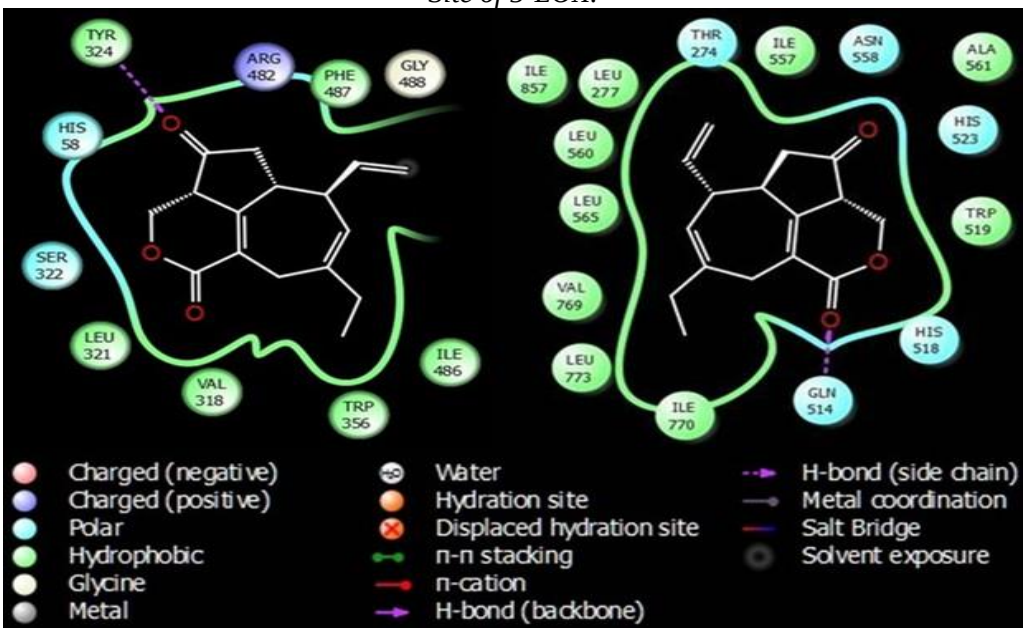

Fig. 5: *COX-2 (Left) and 5-LOX (Right) Inhibitory Potential of (5aR)-8-ethyl-6-vinyl-3,3a,5a,6-tetrahydroazuleno[1,8-cd]pyran-1,4(5H,9H)-dione.*

CONCLUSION

In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of compounds. The docking studies of the inhibitors have shown that hydrogen bonds formed through the oxygen atoms present in pyran ring play a key role in inhibitor binding at the enzyme active site of COX-2 and LOX. The studies have also shown that the inhibitors bind firmly to the open cavity and may thus prevent the access of the substrate to the catalytic site of the inflammatory mediators. The QikProp program predicts that the compounds are nontoxic and can be used as a drug. The results of the present investigation can be useful for the successive design and development of novel compounds having better inhibitory activity against inflammation.

REFERENCES

1. Chhajed SS, Upasani C, Wadher SJ, *et al*. *Medicinal Chemistry*, 1st Edn. Nashik: Career Publications Private Limited; 2017.
2. Mahapatra DK, Bharti SK. *Drug Design*, 1st Edn. New Delhi, India: Tara Publications Private Limited; 2016.
3. 3.Mahapatra DK, Bharti SK. *Handbook of Research on Medicinal Chemistry*, 1st Edn. New Jersey: Apple Academic Press; 2017.
4. Mahapatra DK, Bharti SK, Asati V. Chalcone derivatives: Anti-inflammatory potential and molecular targets perspectives. *Curr Top Med Chem.* 2017; 17(28): 3146–69p.
5. Smith CW, Bailey JM, Billingham ME, *et al*. The anti-rheumatic potential of a series of 2, 4-di-substituted-4H-naphtho[1, 2-b] pyran-3-carbonitriles. *Bioorg Med Chem Lett.* 1995; 5(23): 2783–8p.
6. Nandakumar A, Thirumurugan P, Perumal PT, *et al*. One-pot multicomponent synthesis and anti-microbial evaluation of 2′-(indol-3-yl)-2-oxospiro (indoline-3, 4′-pyran) derivatives. *Bioorg Med Chem Lett.* 2010; 20(14): 4252–8p.
7. Kasaplar P, Yılmazer Ö, Çağır A. 6-Bicycloaryl substituted (S)-and (R)-5, 6-dihydro-2H-pyran-2-ones: Asymmetric synthesis, and anti-proliferative properties. *Bioorg Med Chem Lett.* 2009; 17(1): 311–18p.
8. Archer RA, Eli Lilly and Co Ltd (GB). *Hexahydro-dibenzo {8 b, d {9 pyran-9-ones as an anti-anxiety drug*. United States Patent US3928598; 1975.
9. Coudert P, Couquelet JM, Bastide J, *et al*. Synthesis and anti-allergic properties of N-arylnitrones with furo-pyran structure. *Ann Pharm Franc.* 1998; 46(2): 91p.
10. Mohareb RM, Zaki MY, Abbas NS. Synthesis, anti-inflammatory and anti-ulcer evaluations of thiazole, thiophene, pyridine and pyran derivatives derived from androstenedione. *Steroids.* 2015; 98: 80–91p.
11. El-Sayed NN, Abdelaziz MA, Wardakhan WW, *et al*. The Knoevenagel reaction of cyanoacetylhydrazine with pregnenolone: Synthesis of thiophene, thieno [2, 3-d] pyrimidine, 1, 2, 4-triazole, pyran and pyridine derivatives with anti-inflammatory and anti-ulcer activities. *Steroids.* 2016; 107: 98–111p.
12. Archer RA; Eli Lilly and Co Ltd (GB). *Hexahydro-dibenzo [b, d,] pyran-9-ones as psychotropic, particularly anti-depressant drugs*. United States Patent US3953603; 1976.
13. Mohareb RM, Schatz J. Anti-tumor and anti-leishmanial evaluations of 1, 3, 4-oxadiazine, pyran derivatives derived from cross-coupling reactions of β-bromo-6H-1, 3, 4-oxadiazine derivatives. *Bioorg Med Chem.* 2011; 19(8): 2707–13p.
14. Evans JM, Buckingham RE, Willcocks K; Beecham Group PLC. Anti-hypertensive benzo [b] pyran-3-ols. United States Patent US 4,555,509; 1985.
15. Morahan PS, McCord RS. Resistance to herpes simplex type 2 virus induced by an immunopotentiator (pyran) in immunosuppressed mice. *J Immunol.* 1975; 115(1): 311–13p.
16. Kharkwal G, Fatima I, Kitchlu S, *et al*. Anti-implantation effect of 2-[piperidinoethoxyphenyl]-3-[4-hydroxyphenyl]-2H-benzo (b) pyran, a potent antiestrogenic agent in rats. *Fert Ster.* 2011; 95(4): 1322–7p.
17. Gopalsamy A, Aplasca A, Ciszewski G, *et al*. Design and synthesis of 3, 4-dihydro-1H-[1]-benzothieno [2, 3-c] pyran and 3, 4-dihydro-1H-pyrano [3, 4-b] benzofuran derivatives as non-nucleoside inhibitors of

HCV NS5B RNA dependent RNA polymerase. *Bioorg Med Chem Lett.* 2006; 16(2): 457–60p.
18. Ferreira SB, de Carvalho da Silva F, Bezerra FA, *et al*. Synthesis of α-and β-Pyran Naphthoquinones as a New Class of Antitubercular Agents. *Archiv Pharm.* 2010; 343(2): 81–90p.
19. Su CR, Yeh SF, Liu CM, *et al*. Anti-HBV and cytotoxic activities of pyranocoumarin derivatives. *Bioorg Med Chem.* 2009; 17(16): 6137–43p.
20. Hamilton HW, Tait BD, Gajda C, *et al*. 6-Phenyl-6-alkylamido-5, 6-dihydro-2H-pyran-2-ones: novel HIV protease inhibitors. *Bioorg Med Chem Lett.* 1996; 6(6): 719–24p.
21. Rho HS, Baek HS, You JW, *et al*. New 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one derivative has both tyrosinase inhibitory and antioxidant properties. *Bull Korean Chem Soc.* 2007; 28(3): 471–3p.
22. Archer RA, Lemberger L; Eli Lilly and Co Ltd (GB). Hexahydro-dibenzo [b, d] pyran-9-ones as antiemetic drugs. United States Patent US4087545; 1978.
23. Wei YB, Yang XD. Synthesis, characterization and anti-diabetic therapeutic potential of a new benzyl acid-derivatized kojic acid vanadyl complex. *Biometals*. 2012; 25(6): 1261–8p.
24. Mahapatra DK, Das D, Shivhare RS. Substituted thiazole linked murrayanine-Schiff's base derivatives as potential anti-breast cancer candidates: Future EGFR Kinase inhibitors. *Int J Pharm Sci Drug Res*. 2017; 9(3): 139–44p.
25. Chhajed SS, Chaskar S, Kshirsagar SK, *et al*. Rational design and synthesis of some PPAR-γ agonists: substituted benzylideneamino-benzylidene-thiazolidine-2,4-diones. *Comp Biol Chem*. 2017; 67: 260–5p.
26. Mahapatra DK, Das D, Shivhare RS, *et al*. Murrayanine-hydantoin and -thiohydantoin analogs as promising anti-convulsant agents: Synthesis, Characterization and Molecular Docking Studies. *MOJ Bioorg Org Chem*. 2018; 2(2): 47–51p.
27. Joseph TM, Mahapatra DK. A Nascent Step towards the Discovery of New Generation Non-Steroidal Anti-inflammatory Agents (NSAIDs): Induced-Fit Molecular Docking and Pharmacokinetic Prediction Studies of Some Chromene Derivatives as Potential Cyclooxygenase-2 (COX-2) and Lipoxygenase (LOX) Inhibitors. *Res Rev J Boinformat*. 2018; 5(2): 1–7p.

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