RASĀYAN *J. Chem.*
Vol. 17 | No. 4 |1690-1698| October - December | 2024
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

# *In-silico* SCRENNING OF SOME HDROXYQUINOLINE ANALOGUES THROUGH ADMET AND MOLECULAR DOCKING STUDIES APPROACH USING CYCLOOXGENASE-2 (1CX2)

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**ABSTRACT**
COX (Cyclooxygenase) is the protein that imparts the degradation of PG (prostaglandins) from its substrate, AA (arachidonic acid). Quinoline is an admirable group of various bioactive substances ~~and~~ a hydroxy (-OH) group attached to one of the carbon atom known as Hydroxyquinoline. Due to the diversified biological activity of the quinoline ring interest has been increased in developing new bioactive moieties of the same nucleus.I n this present work, we intend to study the interaction of fifteen hydroxyquinoline derivatives against COX-2 (1CX2) enzyme for anti-inflammatory activity using molecular docking simulation carried out by virtual Swissdock freeware to predict the degree of each COX binding pocket. For the prediction of their binding modes, the scoring function, hydrogen bonding, their binding affinities, and orientation of these compounds at the active site of the enzyme were used. The computational studies are also used to predict absorption, distribution, metabolism, elimination, toxicity, and the pharmacokinetic profile of some hydroxyl quinoline analogs. The investigated analogue possesses GI absorption and some compound has good BBB permeability. The side effects during the investigations are Mutagenicity, Hepatotoxicity, etc.
**Keywords:** Hydroxyquinolines, Cyclooxygenase, ADMET, Molecular Docking, Pharmacokinetics, Drug Likeness, Toxicity.

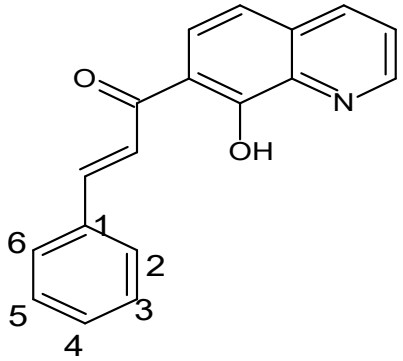


## INTRODUCTION

Inflammatory condition is the active process by which living tissues react with local vascular reactions and cellular responses to an injury inadequate to kill the tissue. Inflammation is basically a defensive response, the ultimate aim of which is to clear both the early cause of cell injury (*e.g.* microbes, toxins) and the significance of such injury (*e.g.* necrotic cells and tissues). Since cyclooxygenases (COX) play a significant role in inflammatory conditions, they have emerged as an appealing target for the development of new anti-inflammatory drugs. Cyclooxygenases (COX) is an enzyme responsible for the degradation of prostaglandins from their substrate, called arachidonic acid (AA) which is an enzyme's membrane-associated homodimers. In a two-step reaction First, AA is converted to the hydroperoxy endoperoxide PGG2 and then, in the successive step, is reduced to the hydroxyl endoperoxide PGH2.[1-4] Hydroxyquinoline, a derivative of quinoline, was first discovered in 1834[5] by Friedlieb Ferdinand Runge from coal tar. Quinolines are aromatic heterocyclic compounds that contain nitrogen. Among the most important N-heterocycle compounds are the quinolines. They are utilized extensively in the agrochemical and pharmaceutical industries.[6] Molecular docking aids in the identification of the ligand's correct Binding geometry (Pose) within the binding site (Binding mode) and Prediction of the binding affinity (Scoring Function) towards the receptor site.[7-19] They demonstrate biological activities such as anti-malarial, anti-fungal, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, and trichomonas.[20-27] In this study, we predicted the anti-inflammatory behavior of Hydroxyquinoline analogs by automated docking studies using Swiss-Docking freeware against CYCLOOXYGENASE-2 (PROSTAGLANDIN SYNTHASE-2) COMPLEXED WITH A SELECTIVE INHIBITOR, SC-558 1CX2.[28] At the enzyme's active site, these compounds' binding modes, binding affinities, and orientation can all be predicted using the scoring functions and hydrogen bonds formed with the surrounding amino


**http://doi.org/10.31788/RJC.2024.1748937**

acids. With COX-2 protein (1CX2) co-crystallized with S58 as the reference ligand, these molecules have a higher affinity for the active site of the receptor, as demonstrated by the obtained results, which confirm that compounds Nos. 1, 2, and 7 have the lowest dock score or minimum binding energy in Kcal/mole. It is evident that molecules with a lower dock score and binding energy have a greater affinity for the receptor. The Hydroxyquinoline class of COX-2 inhibitors that are the subject of the most recent study may present novel options for the treatment of inflammation. In addition, we predicted studies on toxicity and absorption, distribution, metabolism, and elimination (ADME).




(2E)-1-(8-hydroxyquinolin-7-yl)-3-phenylprop-2-en-1-one

## EXPERIMENTAL

### *In Silico* ADME Screening

The online pharmacokinetic properties evaluation of compounds is performed by the online software SwissADME.[29] Each compound's SMILES (Simplified Molecular Input Line Entry System) specification, which was created online in SMILES translator and provides a line notation for describing the structure of organic compounds, is summarized in Table-1.ChemDraw Ultra was used to draw the 2-D structures. Parameters like gastrointestinal absorption, blood-brain barrier (BBB), skin penetration, permeability glycoprotein substrate (P-gp), molecule interaction with cytochrome P450 (CYP), drug-likeness prediction like Lipinski, Ghose, and Veberrule, synthetic accessibility, and bioavailability score are all included in the Swiss ADME tool.

Table-1: Hydroxyquinolines Analogues

| Comp. Code | SMILES | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1 | Clc1cc(/C=C/C(=O)c2ccc3c(c2O)nccc3)c(c(c1)Cl)O | -OH | -Cl | H | -Cl | H |
| 2 | COc1ccc(c(c1)O)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -OH | -H | -OCH3 | -H | -H |
| 3 | Oc1ccc(c(c1)/C=C/C(=O)c1ccc2c(c1O)nccc2)O | -OH | -H | -H | -OH | -H |
| 4 | COc1ccc(c(c1)/C=C/C(=O)c1ccc2c(c1O)nccc2)O | -OH | -H | -H | -OCH3 | -H |
| 5 | CCOc1cccc(c1O)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -OH | $-OC_2H_5$ | -H | -H | -H |
| 6 | O=C(c1ccc2c(c1O)nccc2)/C=C/c1ccc(c(c1)O)O | -H | -OH | -OH | -H | -H |
| 7 | COc1ccc(cc1)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -H | -H | $-OCH_3$ | -H | -H |
| 8 | Brc1cc(/C=C/C(=O)c2ccc3c(c2O)nccc3)c(c(c1)Br)O | -OH | -Br | -H | -Br | -H |
| 9 | CCNc1ccc(c(c1)O)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -OH | -H | $-NHC_2H_5$ | -H | -H |
| 10 | O=C(c1ccc2c(c1O)nccc2)/C=C/c1ccccc1 | -H | -H | -H | -H | -H |
| 11 | O=C(c1ccc2c(c1O)nccc2)/C=C/c1cccc(c1O)O | -OH | -OH | -H | -H | -H |
| 12 | Oc1ccc(c(c1)O)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -OH | -H | -OH | -H | -H |
| 13 | Oc1ccc(cc1)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -H | -H | -OH | -H | -H |
| 14 | COc1cc(/C=C/C(=O)c2ccc3c(c2O)nccc3)cc(c1)Br | -H | -Br | -H | $-OCH_3$ | -H |
| 15 | Oc1cc(O)c(c(c1)O)/C=C/C(=O)c1ccc2c(c1O)nccc2 | -OH | -H | -OH | -H | -OH |

### Toxicity Prediction

The ProTox–II tool predicted the compounds' toxicity and adverse effects.[30,31] Hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, aryl hydrocarbon receptor toxicity, and

toxicity targets and their LD50 are all predicted by this online tool. The online PASS tool was used to predict the compounds' adverse effects and biological activity spectra. The online prediction of biological activity or toxic and side effects of compounds can be done with the Prediction of Activity Spectra of Substances (PASS) tool. The predicted activity can be easily understood using this approach, and the user can easily suggest structural changes.

**Molecular Docking**

Swiss-Docking online freeware[32] was used to conduct automated docking studies of Hydroxyquinoline one analogue's analgesic behavior. The scoring functions and hydrogen bonds formed with the surrounding amino acids are used to predict these compounds' binding modes, binding affinities, and orientation at the enzyme's active site. COX-2 protein (1CX2) co-crystallized with S58 as the reference ligand was tested for its analgesic activity.

## RESULTS AND DISCUSSION

Table-2 summarizes Swiss ADME's findings regarding each compound's pharmacokinetic properties and drug-likeness prediction. These findings indicate that each compound has high gastrointestinal absorption, good skin penetration, inhibits cytochrome CYP1A, and is involved in the metabolism of hydroxyquinoline. The ProTox-II computational tools revealed that all investigated hydroxyquinolines produce hepatotoxicity and mutagenicity, carcinogenicity, and Immunotoxicity summarized in Table-3 and radar pictures in Fig.-1 to 15. The molecular docking score accurately predicts the structure of a ligand within the constraints of a receptor binding site and correctly estimates the strength of binding. Table-4 indicates the docking score of all the compounds.

Table-2: Pharmacokinetic Profile

| Comp. Code | Predicted LD50 | Predicted accuracy | Hepato toxicity | Carcinoge nicity | Immuno toxicity | Mutagen ecity | Aryl Hydrocarbon Receptor Toxicity | Average Similarity (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 2500mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 53.02 |
| 2 | 3000mg/kg | 68.07 | Inactive | Inactive | Active | Active | active | 60.9 |
| 3 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 56.04 |
| 4 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Active | Active | 59.87 |
| 5 | 600mg/kg | 67.38 | Inactive | Inactive | Active | Active | Active | 57.74 |
| 6 | 1000mg/kg | 67.38 | Inactive | Active | Active | Active | Active | 55.61 |
| 7 | 3000mg/kg | 68.07 | Inactive | Inactive | Active | Active | Active | 60.86 |
| 8 | 1000mg/kg | 67.38 | Active | Inactive | Active | Inactive | Active | 50.25 |
| 9 | 603mg/kg | 67.38 | Inactive | Inactive | Active | Active | Active | 50.82 |
| 10 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 57.96 |
| 11 | 1000mg/kg | 67.38 | Inactive | Active | Active | Active | Active | 55.61 |
| 12 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 56.3 |
| 13 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 58.03 |
| 14 | 1000mg/kg | 67.38 | Active | Inactive | Active | Active | Active | 55.28 |
| 15 | 1000mg/kg | 67.38 | Inactive | Inactive | Active | Inactive | Active | 56.3 |

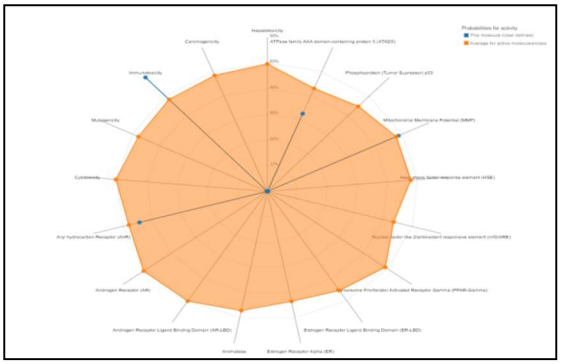


Fig.-1: Radar Chart of Molecule

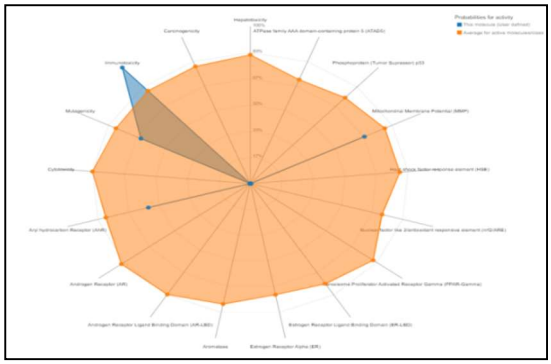


Fig.-2: Radar Chart of Molecule 2

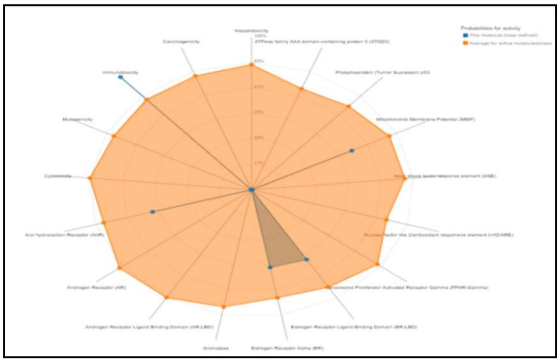


Fig.-3: Radar Chart of Molecule 3

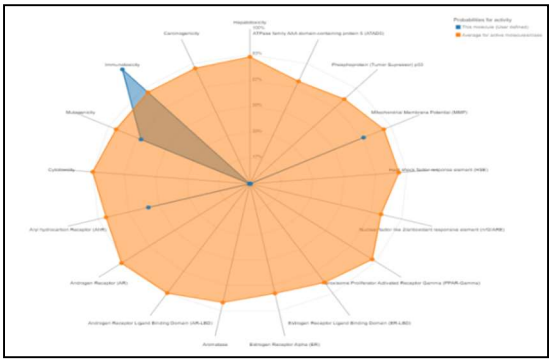


Fig.-4: Radar Chart of Molecule 4

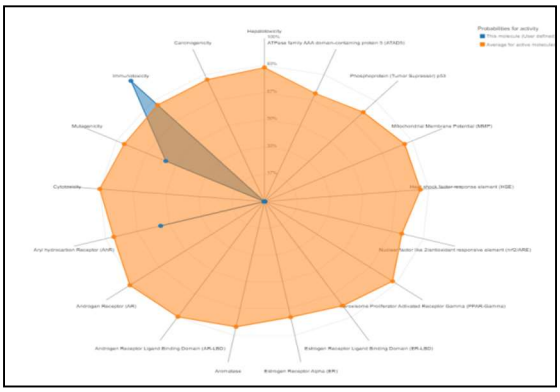


Fig.-5: Radar Chart of Molecule 5

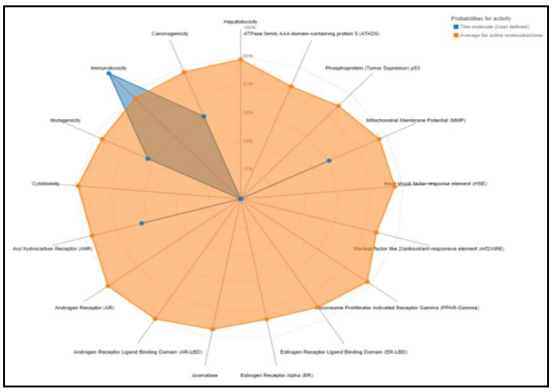


Fig.-6: Radar Chart of Molecule 6

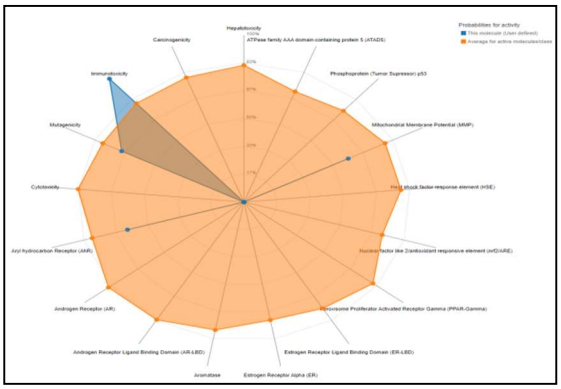


Fig.-7: Radar Chart of Molecule 7

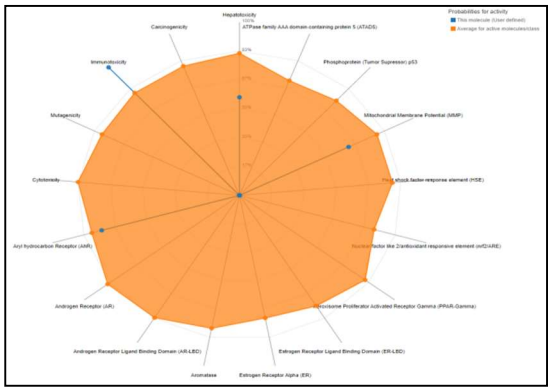


Fig.-8: Radar Chart of Molecule 8

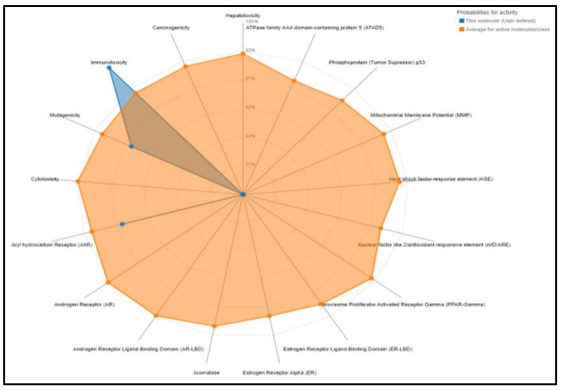


Fig.-9: Radar Chart of Molecule 9

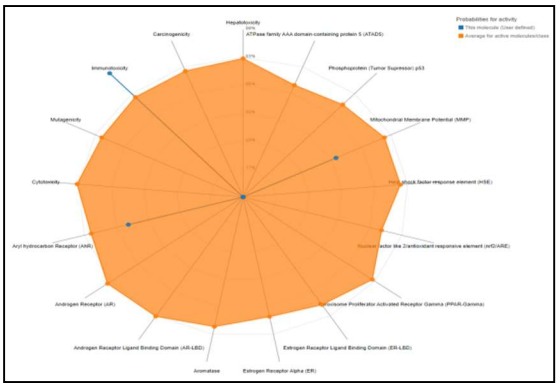


Fig.-10: Radar Chart of Molecule 10

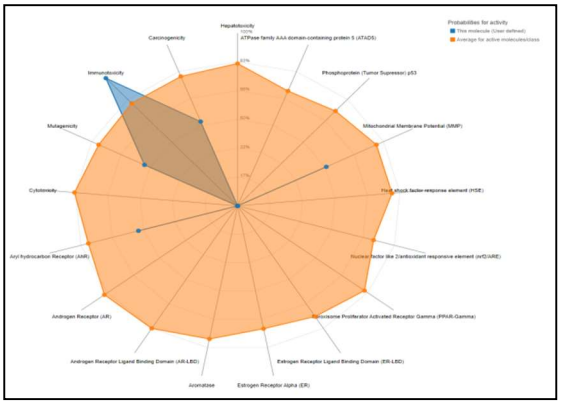



Fig.-11: Radar Chart of Molecule 11

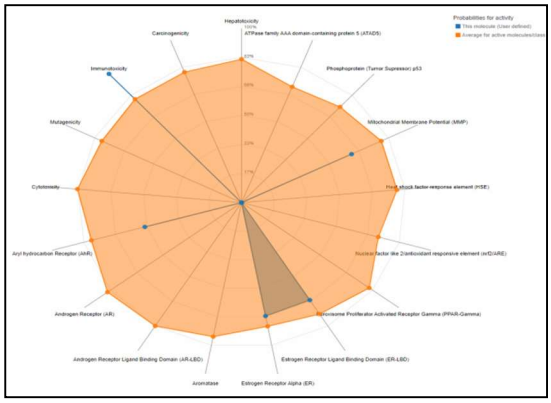



Fig.-12: Radar Chart of Molecule 12

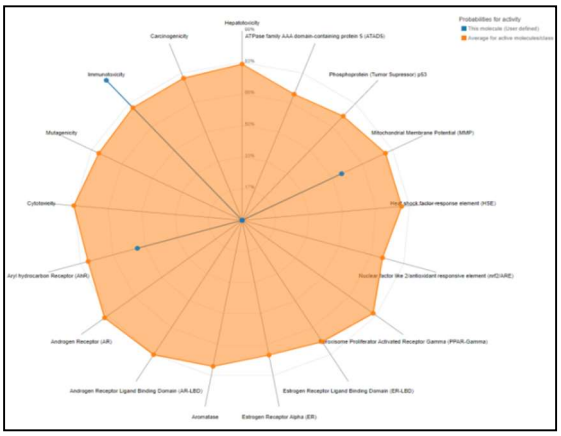



Fig.-13: Radar Chart of Molecule 13

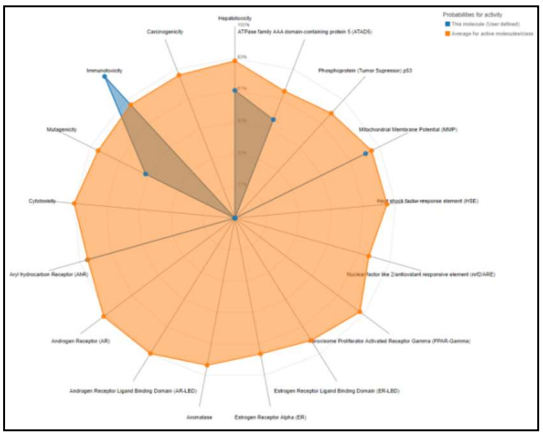



Fig.-14: Radar Chart of Molecule 14

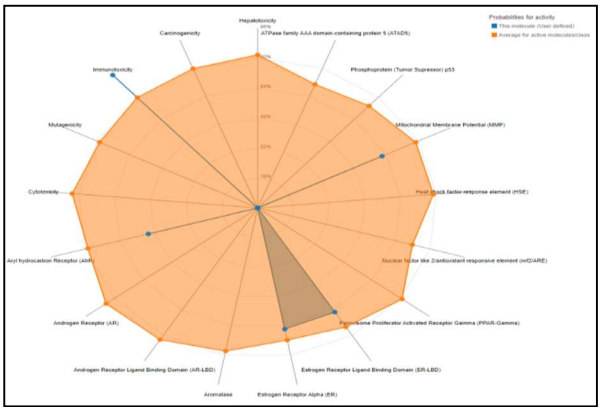



Fig.-15: Radar Chart of Molecule 15

Table-3: Toxicity Prediction

| Comp. Code | Mol. Wt. (g/mol) | TPSA (Å2) | GI | BBB | P- group | CYP 1A2 | Log Kp (Cm/s) | Bioavailability Score |
|---|---|---|---|---|---|---|---|---|
| 1 | 360.19 | 70.42 | High | Yes | Yes | No | -4.85 | 0.55 |
| 2 | 321.33 | 79.65 | High | No | No | No | -3.55 | 0.55 |
| 3 | 307.3 | 90.65 | High | No | No | No | -3.25 | 0.55 |
| 4 | 321.33 | 79.65 | High | No | No | No | -3.55 | 0.55 |
| 5 | 335.35 | 59.42 | High | No | No | Yes | -4.54 | 0.55 |
| 6 | 307.3 | 90.65 | High | No | No | No | -3.25 | 0.55 |
| 7 | 305.33 | 59.42 | High | Yes | No | Yes | -3.85 | 0.55 |
| 8 | 449.09 | 70.42 | High | No | No | No | -5.07 | 0.55 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9 | 334.37 | 82.45 | High | No | No | Yes | -4.05 | 0.55 |
| 10 | 275.3 | 50.19 | High | Yes | No | Yes | -3.84 | 0.55 |
| 11 | 307.3 | 90.65 | High | No | No | No | -3.25 | 0.55 |
| 12 | 307.3 | 90.65 | High | No | No | No | -3.25 | 0.55 |
| 13 | 291.3 | 70.42 | High | Yes | No | No | -3.54 | 0.55 |
| 14 | 384.22 | 59.42 | High | Yes | Yes | Yes | -4.61 | 0.55 |
| 15 | 323.3 | 110.88 | High | No | No | No | -2.95 | 0.55 |

Table-4: Estimated Binding Free Energy of Target Compounds

| Comp. Code | EstimatedΔG (Kcal/mol) |
|---|---|
| 1 | -7. 7145 |
| 2 | -7.4217 |
| 3 | -9.1521 |
| 4 | -10.5822 |
| 5 | -8.2592 |
| 6 | -8.7567 |
| 7 | -7.9776 |
| 8 | -9.4771 |
| 9 | -9.8786 |
| 10 | -8.7978 |
| 11 | -8.7978 |
| 12 | -10.0406 |
| 13 | -10.4933 |
| 14 | -8.7905 |
| 15 | -8.7637 |

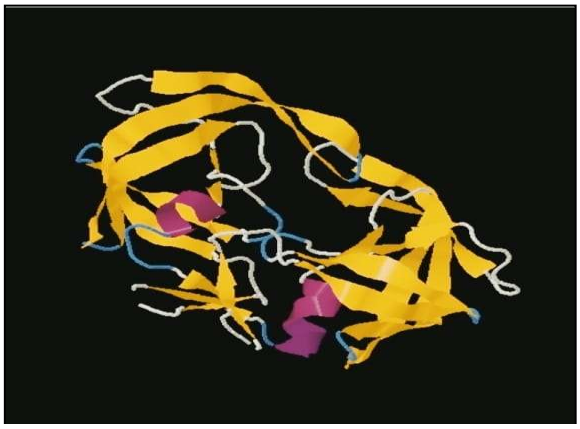


Fig.-16: Molecule no. 1 Shows the Hydrophobic Bonding towards the Active Site of the Receptor

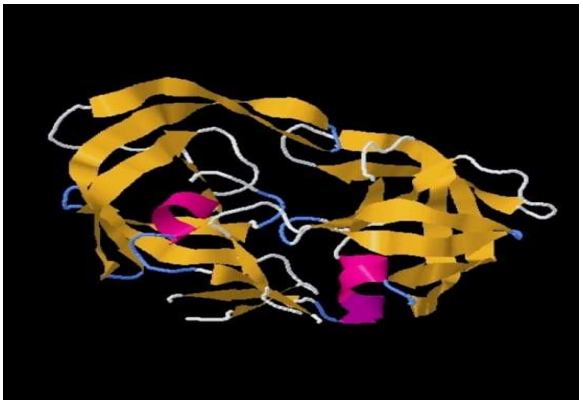


Fig.-17: The Molecule No.2Shows the Hydrophobic Bonding Towards Active Site of Receptor

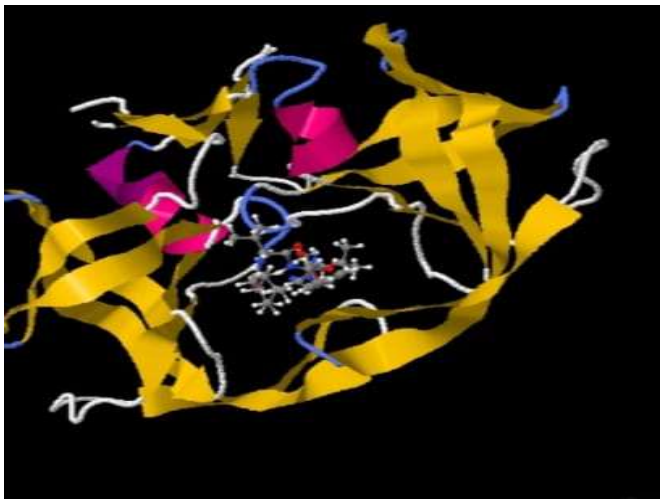


Fig.-18: Molecule no. 7 Shows the hydrophobic bonding towards the active site of the receptor

## CONCLUSION

This study confirmed that all compounds exhibit Gi-absorption and that some compounds have good BBB permeability, as well as predicted the biological activities and side effects of some hydroxyquinoline analogs. Compounds 8, 14, and 11 analogs, which are CYPIA2 inhibitors, demonstrated hepatotoxicity and carcinogenicity, respectively. Using the Lipinski rule and the bioavailability score, the drug-likeness prediction was also demonstrated. Using the free Swiss-Docking docking software, we also predicted the anti-inflammatory activity of Hydroxyquinoline analogs in this study.

At the enzyme's active site, these compounds' binding modes, binding affinities, and orientation can all be predicted using the scoring functions and hydrogen bonds formed with the surrounding amino acids. On COX-2 protein (1CX2) co-crystallized with S58 as a reference ligand, compounds 1, 2, and 7 were tested for their anti-inflammatory activity and demonstrated good binding affinities to receptors. The medicinal chemists who work in this field might find the information presented in this article to be a useful guide.

## ACKNOWLEDGMENTS

The authors are thankful to the Management and Principal of K. K. Wagh College of Pharmacy, Nasik for providing the necessary facilities.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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[RJC-8937/2024]