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# IN SILICO DESIGN OF 1,2-BENZOPYRONE DERIVATIVES

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## ABSTRACT

Drug discovery refers to the process by which new molecules are identified, designed, and developed for clinical use. The process of drug discovery is very much complex and requires an interdisciplinary effort to design effective and commercially feasible drug. Drug design involves the process of discovering new molecules based on the understanding of biological targets and their interactions with potential drugs. The problems with conventional methods are long design cycle and high cost. Modern approach of drug design with the help of informatic technologies and computational methods has speeded up the drug discovery process in an efficient manner. *In silico* drug design refers to the use of computer simulations and modelling to discover and optimize new drug candidates. The present study focuses on the development of 1,2- benzopyrone commonly called as coumarin derivatives with the aid of various computational software. Five novel derivatives of coumarin namely CO1, CO2, CO3, CO4, CO5 are drawn using ACD Lab Chemsketch. Properties such as Log P, Molecular weight, and pharmacological actions were determined using various software. Docking were done for five novel ligand molecules for Anti-inflammatory and Anti-oxidant activity using selected targets. The derivatives with maximum binding affinity can be developed after further studies as promising therapeutically active moieties.

**KEYWORDS:** *In silico* drug design, Coumarin, Anti-inflammatory activity, Antioxidant activity, Drug discovery.

## INTRODUCTION

Medicinal chemistry is a multidisciplinary field at the intersection of chemistry, pharmacology, and biology. Its primary focus is on the design, development, and synthesis of pharmaceutical drugs.[2] The process of drug discovery is very complex and requires an interdisciplinary effort to design effective and commercially feasible drugs. Drug design involves the process of discovering new medications based on the understanding of biological targets and their interactions with potential drugs. It includes Target identification, Target validation, Lead identification, Lead optimization. After passing the pre-clinical and clinical studies, this compound becomes a drug available to patients.

Conventional drug design methods include random screening of chemicals found in nature or synthesized in laboratory. The problems with this method are long design cycle and high cost. Modern approach includes drug design with the help of informatic technologies and computational methods that has speeded up the drug discovery process in an efficient manner and it is referred to as Computer Aided Drug Design (CADD). It is cost and time saving approach as well as provides a clearcut information about drug receptor interaction.

*In silico* drug design refers to the use of computer simulations and modelling to discover and optimize new drug candidates. It includes Structure based drug design and Ligand based drug design. Structure based drug design relies upon the knowledge of 3D structure of biological target which is a protein or enzyme whereas, Ligand based drug design relies upon the knowledge of ligand which bind to the receptor.

Beyond the mentioned advantages the method is bit complex due to the involvement of multiple software, moreover there are chances of false positive results.

Coumarin which is also known as 1,2-benzopyrone is a large class of oxygen heterocycles, generally found as plant secondary metabolite in plant kingdom. It can be obtained from Tonka beans, Liquorice, Cassia cinnamon. It has various therapeutic activities such as Anti-inflammatory, Anti-oxidant, Anti-cancer, Anti-coagulant, Anti-microbial, Anti-convulsant, Anti-hypertensive etc. Computer aided drug design of novel coumarin derivatives can be

conducted using various softwares like ACD Lab ChemSketch, Molinspiration, PASS software, ADMET software and AutoDock Vina AM Dock software.

Coumarin molecule can be structurally modified using ACD Lab ChemSketch software. Its properties are predicted using Molinspiration software. PASS Software is used to predict the Pharmacological activities of the molecule. ADMET software is used to predict the Pharmacokinetic profile and toxicity profile of molecule. Drug-receptor interactions are conducted using AutoDock Vina AM Dock software.

## MATERIAL AND METHODS

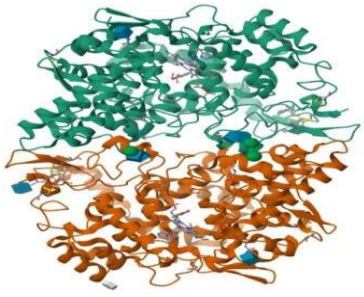
### Ligand preparation

The chemical structure of designed Coumarin compound were drawn using ACD Lab Chemsketch and SMILES and IUPAC were established using ACD Lab Chemsketch. The druglikeness and Rule of five compliance is determined by assessing various properties using molinspiration.

### Retrieval of 3d structure of target protein

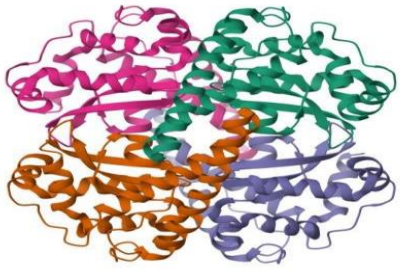
The crystal structure of salicylate bound human cyclooxygenase (COX-2) (PDB ID: 5F1A) was retrieved from the protein data bank for anti-inflammatory activity. It belongs to the class of oxidoreductase/inhibitor with a resolution of 2.38Å.

Also, the crystal structure of Human Manganese Superoxide Dismutase (PDB ID: 2P4K) with resolution of 1.48 Å was retrieved for antioxidant activity. It belongs to oxidoreductase class.



**Cyclooxygenase 2 (COX-2)**

**PDB ID: 5F1A**



**Superoxide Dismutase 2 (SOD-2)**

**PDB ID: 5F1A**

**Admet analysis**

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and SAR (Structure-Activity Relationship) software is an important tool in drug discovery and development. This software helps to predict how a compound is likely to behave in terms of absorption into the body, distribution within tissues, metabolism by enzymes, excretion from the body, and potential toxicity. They are essential for prioritizing lead compounds in drug discovery and development, saving time and resources by focusing experimental efforts on the most promising candidates.

**Prediction of activity spectra**

PASS online software is designed to predict the biological activity spectrum of chemical compounds based on their structure. In PASS software, Pa and Pi values refer to probabilities associated with the predicted biological activities of chemical compounds.

Pa -Probability of Activity

Pi -Probability of Inactivity

- ✓ If Pa > 0.7, the substance is very likely to exhibit the activity in experiments, and the chance of being the analogue of a known pharmaceutical agent is also high.
- ✓ If 0.5 < Pa < 0.7, the substance is very likely to exhibit activity in experiments, but probability is less, and the substance is unlike known pharmaceutical agents.
- ✓ If Pa < 0.7, the substance unlikely to exhibit the activity. However, if the presence of activity is confirmed in experiments the substance might be a new chemical entity.[6]

**Molecular docking studies**

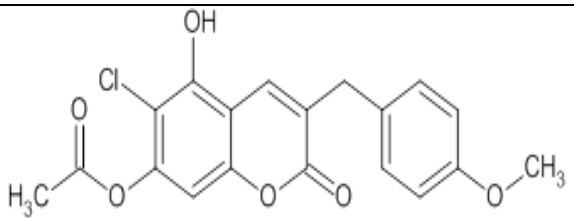
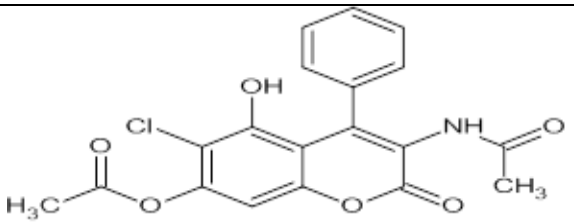
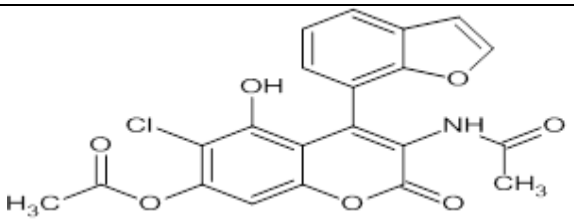
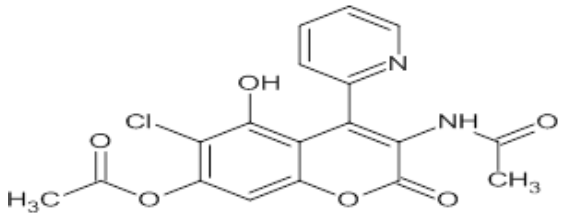
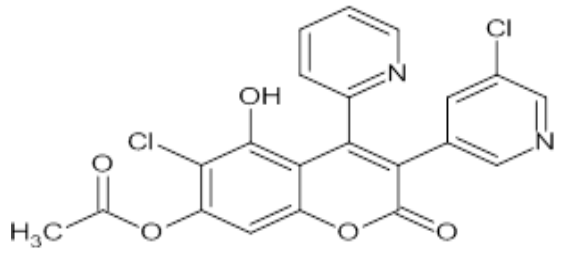
Molecular docking simulations utilized the 3D structure of the target molecule to identify compatible compound that fit the binding site's properties. AutoDock Vina is a molecular docking software used for predicting the binding modes of small molecules to protein targets.

**RESULTS AND DISCUSSION**

*In-silico* design of novel coumarin derivatives was done using various softwares like Chemsketch, Molinspiration, PASS software, admetSAR and AutoDock Vina AMDock. The results are as follows.

**ACD Lab Chemsketch**

**Table 1: Data from ACD Lab Chemsketch.**

| Compound Code | Structure | Smiles/IUPAC Name |
|---|---|---|
| CO1 |  | O=C1Oc2cc(OC(=O)C)c(Cl)c(O)c2C=C1Cc1ccc(cc1)OC 6-chloro-5-hydroxy-3-[(4- methoxyphenyl)methyl]-2-oxo-2H-1-benzopyran7-yl acetate |
| CO2 |  | O=C1Oc2cc(OC(=O)C)c(Cl)c(O)c2C(=C1NC(=O)C)c1ccccc1 3-acetamido-6-chloro-5- hydroxy-2-oxo-4-phenyl2H-1-benzopyran-7-yl acetat |
| CO3 |  | O=C1Oc2cc(OC(=O)C)c(Cl)c(O)c2C(=C1NC(=O)C)c1ccccc2ccoc12 3-acetamido-4-(1-benzofuran7-yl)-6-chloro-5-hydroxy-2- oxo-2H-1-benzopyran-7-yl acetate |
| CO4 |  | O=C1Oc2cc(OC(=O)C)c(Cl)c(O)c2C(=C1NC(=O)C)c1ccccn13-acetamido-6-chloro-5-hydroxy-2-oxo-4-(pyridin-2-yl)-2H-1-benzopyran-7-yl acetate |
| CO5 |  | O=C1Oc2cc(OC(=O)C)c(Cl)c(O)c2C(=C1c1cncc(Cl)c1)c1ccccn1 6-chloro-3-(5-chloropyridin-3- yl)-5-hydroxy-2-oxo-4- (pyridin-2-yl)-2H-1- benzopyran-7-yl acetate |

These are the coumarin derivatives which are modified using ACD Lab Chemsketch software. The substitutions in the coumarin molecule are done in such a way that it should give anti-inflammatory and anti-oxidant activities and should have properties which make a molecule druggable.

**Molinspiration**

**Table 2: Details of Lipinski rule of five.**

| Compound Code | Molecular Weight (<500 D) | Log P (<5) | No. of Hydrogen Bond Acceptors (<10) | No. of Hydrogen Bond Donors (<5) | Violations |
|---|---|---|---|---|---|
| CO1 | 374.78 | 3.80 | 6 | 1 | 0 |
| CO2 | 387.77 | 2.73 | 7 | 2 | 0 |
| CO3 | 427.80 | 3 | 8 | 2 | 0 |
| CO4 | 388.76 | 1.58 | 8 | 2 | 0 |
| CO5 | 443.24 | 3.91 | 7 | 1 | 0 |

These are the properties of the molecule that has been predicted using molinspiration software. All the novel derivatives found to follow the 'Lipinski rule of five' without any violation.

**Table 3: Drug likeness analysis of novel compounds.**

| Compound Code | GPCR Ligand | Ion Channel Modulator | Kinase Inhibitor | Nuclear Receptor Ligand | Protease Inhibitor | Enzyme Inhibitor |
|---|---|---|---|---|---|---|
| CO1 | -0.27 | -0.47 | -0.35 | -0.01 | -0.18 | -0.00 |
| CO2 | -0.40 | -0.55 | -0.36 | -0.26 | -0.41 | -0.09 |
| CO3 | -0.29 | -0.51 | -0.22 | -0.17 | -0.46 | -0.06 |
| CO4 | -0.28 | -0.39 | -0.16 | -0.25 | -0.34 | -0.04 |
| CO5 | -0.21 | -0.18 | 0.01 | -0.06 | -0.12 | 0.25 |

Drug likeness analysis of novel compounds was conducted using molinspiration software. This is used for prediction of target-specific bioactivity and its pharmacological effects. Experimental validation is essential to confirm predicted bioactivity.

**admetSAR**

**Table 3: admet properties of novel compounds.**

| Compound code | ADME Prediction | | | | Toxicity prediction | |
|---|---|---|---|---|---|---|
| | Human Intestinal Absorption | Subcellular Localization | CYP450-IA2 | Biodegradation | AMES Toxicity | Carcinogen |
| CO1 | 0.8230 | 0.4795 | Inhibitor | NRB | Non-Toxic | Non-Carcinogen |
| CO2 | 0.9278 | 0.4775 | Non-inhibitor | NRB | Non-Toxic | Non-Carcinogen |
| CO3 | 0.9637 | 0.5237 | Non-inhibitor | NRB | Non-Toxic | Non-Carcinogen |
| CO4 | 0.9407 | 0.4225 | Non-inhibitor | NRB | Non-Toxic | Non-Carcinogen |

| | | | | | | |
|---|---|---|---|---|---|---|
| CO5 | 0.9845 | 0.5427 | Non-inhibitor | NRB | Non-Toxic | Non-Carcinogen |

Through admetSAR software the pharmacokinetic and toxicity of a compound can be predicted. The predicted ADME and toxicity of the compound are listed above. It streamlines drug discovery and development by identifying potential issues early, enabling informed decision-making and improving drug quality.

**PASS Software**

**Table 5: Biological activity computed from PASS software.**

| Compound code | Biological activity | Pa | Pi |
|---|---|---|---|
| CO1 | Anti-inflammatory<br>Antioxidant | 0.507<br>0.503 | 0.055<br>0.010 |
| CO2 | Anti-inflammatory<br>Antioxidant | 0.321<br>0.211 | 0.143<br>0.068 |
| CO3 | Anti-inflammatory<br>Antioxidant | 0.339<br>0.208 | 0.130<br>0.051 |
| CO4 | Anti-inflammatory<br>Antioxidant | 0.283<br>0.156 | 0.177<br>0.121 |
| CO5 | Anti-inflammatory<br>Antioxidant | 0.556<br>0.172 | 0.042<br>0.103 |

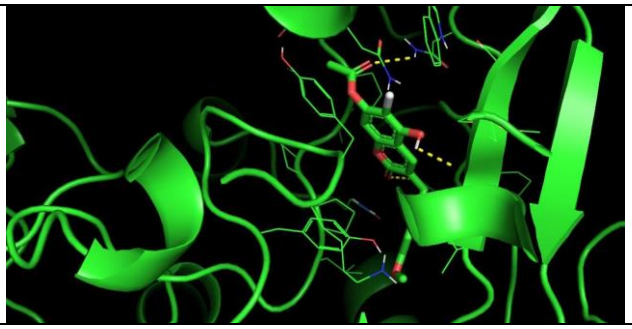
Through PASS online software the biological activities of modified coumarin derivatives were predicted.

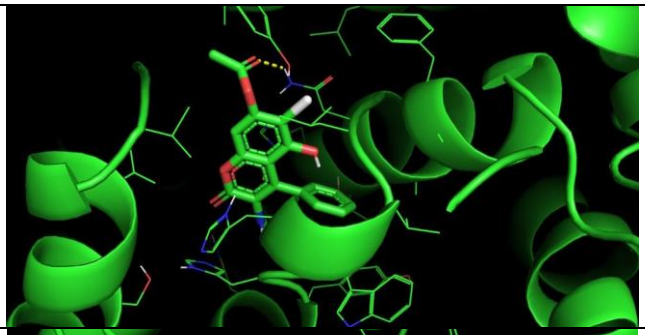
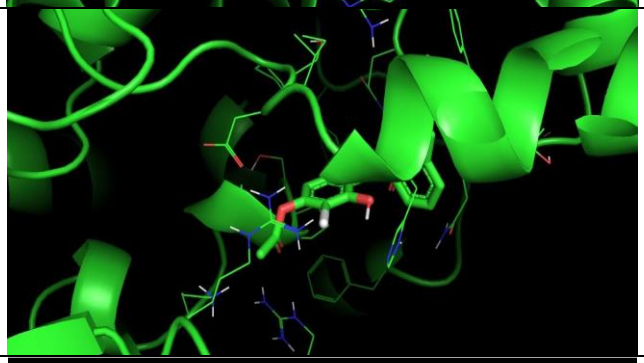
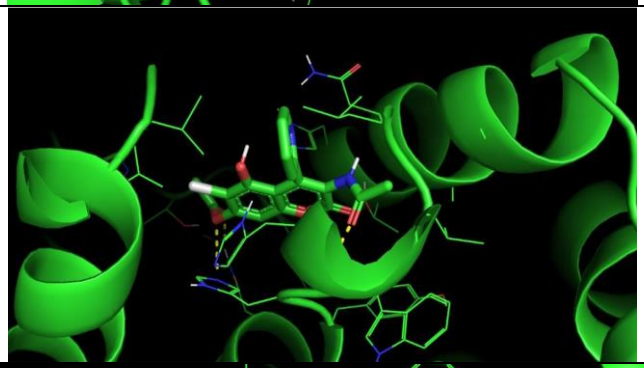
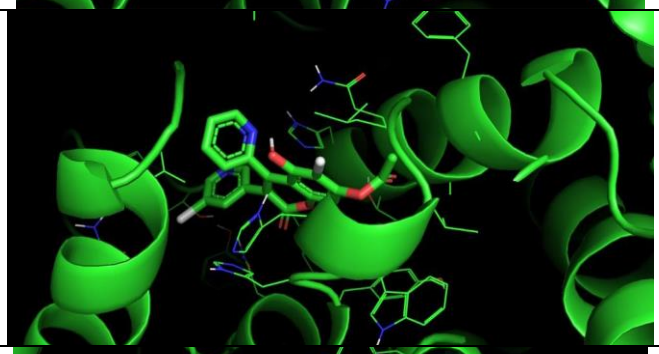
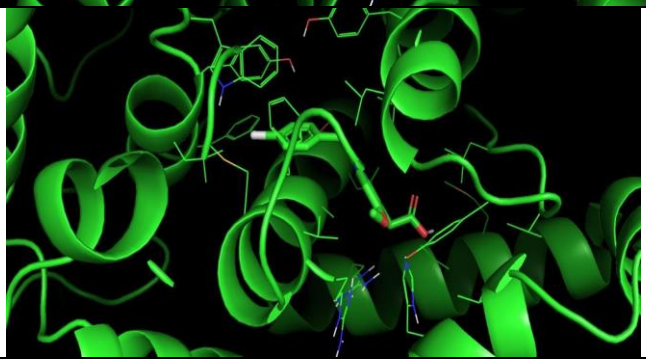
**AutoDock Vina AMDock**

Docking studies of novel coumarin derivatives with the selected biological targets are done using AutoDock Vina AMDock software. Docking is done to predict the orientation and binding affinity of a ligand to the receptor.

**Docking studies for Anti-inflammatory activity:**

**Table 6: Ligand-receptor interaction and binding affinity from AutoDock Vina.**

| Compound code | Ligand-receptor interaction | Binding Affinity (Kcal/mol) |
|---|---|---|
| CO1 |  | -9.5 |

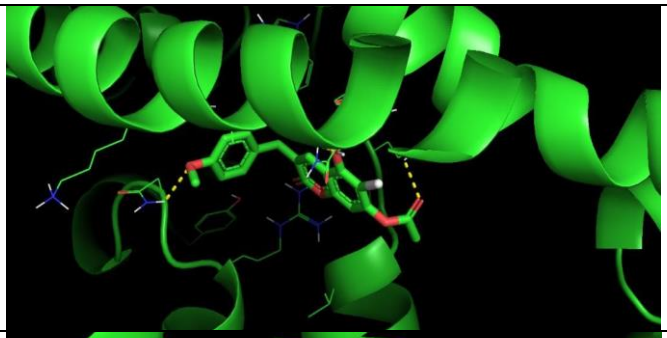
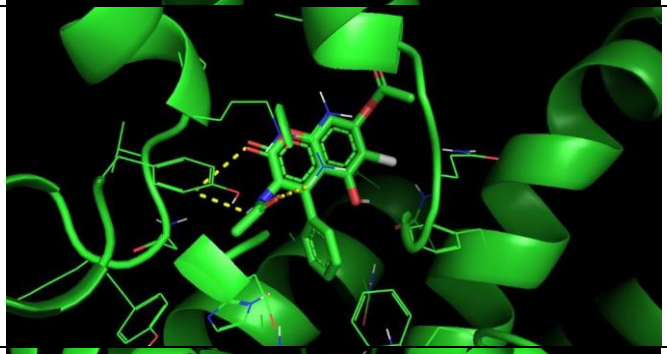
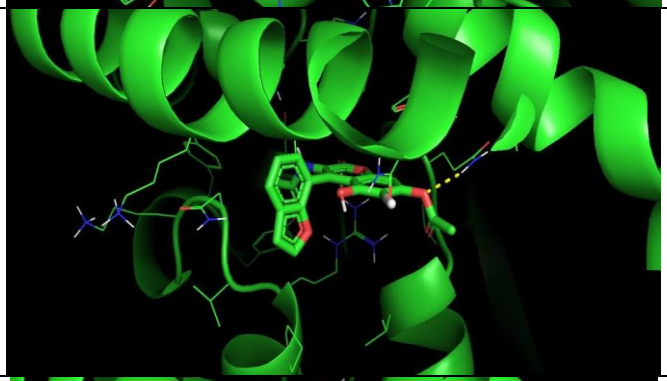
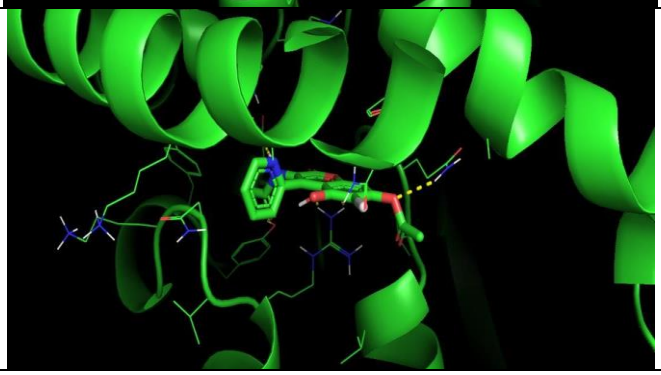
| | | |
|---|---|---|
| CO2 |  | -8.8 |
| CO3 |  | -8.8 |
| CO4 |  | -8.8 |
| CO5 |  | -8.6 |
| Standard (Indomethacin) |  | -9.9 |

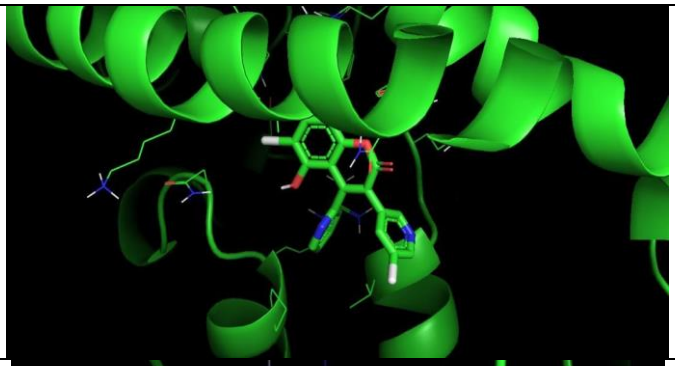
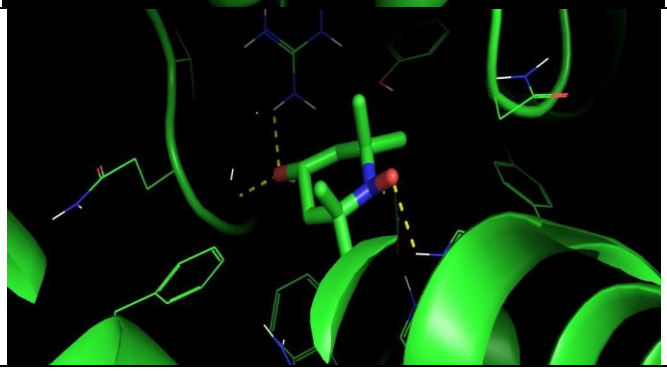
The docking of novel coumarin derivatives with COX-2 is done using AutoDock Vina. The ligand-receptor interaction and binding affinity of the compounds are given in the above

table. According to this study CO1 (6-chloro-5-hydroxy-3-[(4- methoxyphenyl)methyl]- 2-oxo-2H-1-benzopyran7-yl acetate) shows more binding affinity towards the receptor for Anti-inflammatory activity. The results were compared with a standard drug Indomethacin.

**Docking studies for Anti-oxidant activity**

**Table 7: Ligand-receptor interaction and binding affinity from AutoDock Vina.**

| Compound code | Ligand-receptor interaction | Binding affinity (Kcal/mol) |
|---|---|---|
| CO1 |  | -7.4 |
| CO2 |  | -7.9 |
| CO3 |  | -8.6 |
| CO4 |  | -8.0 |

| | | |
|---|---|---|
| CO5 |  | -8.0 |
| Standard (Tempol) |  | -6.0 |

The docking of novel coumarin derivatives with SOD-2 is done using AutoDock Vina. The ligand-receptor interaction and binding affinity of the compound are given in the above table. According to this study CO3 (3-acetamido-4-(1-benzofuran7-yl)-6-chloro-5-hydroxy-2- oxo-2H-1-benzopyran-7-yl acetate) shows more binding affinity towards the receptor for Anti-oxidant activity. The results were compared with a standard drug Tempol.

## CONCLUSION

Drug design involves the process of discovering of new medications based on the knowledge of target or ligand and their interaction. *In silico* drug design refers to the use of computer simulations and modelling to discover an optimize new drug candidates.

Five derivatives of 1,2-benzopyrone, namely CO1, CO2, CO3, CO4, CO5 were drawn using ACD Lab Chemsketch. Molecular properties and drug likeness analysis of these derivatives were done using Molinspiration software. admetSAR is used to obtain the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile of modified derivatives. Different biological activities of these derivatives were predicted using PASS software and Anti-inflammatory and Anti-oxidant activities were chosen for further studies.

The present study focused on the Anti-inflammatory activity and Antioxidant activity of the novel coumarin derivatives. Five derivatives (CO1, CO2, CO3, CO4, CO5) were docked with COX-2 for Anti-inflammatory activity and with SOD-2 for Antioxidant activity. Among these CO1 (6-chloro-5-hydroxy-3-[(4-methoxyphenyl) methyl]-2-oxo-2*H*-1-benzopyran-7-yl

acetate) shows more affinity with COX-2 than remaining compounds for Anti-inflammatory activity while CO3 (3-acetamido-4-(1-benzofuran-7-yl)-6-chloro-5-hydroxy-2-oxo-2*H*-1-benzopyran-7-yl acetate) shows more affinity with SOD-2 for Antioxidant activity which consider for further studies.

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