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**Research Article**

# INSILICO TOOLS IN THE PREDICTION OF NOVEL COUMARIN DERIVATIVES AS POTENTIALLY ACTIVE COMPOUNDS

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**ABSTRACT**

Early calculation of ADMET properties direct to a major cost reduction in drug research. Coumarin and its derivatives are significant because of their wide spectrum of biological activities such as anticancer, antioxidant, antimicrobial and antifungal activities. The most commonly prescribed drugs today are painkillers that reduce pain, fever and inflammation Usage of NSAIDs are found to be at greater risk of developing serious gastro-intestinal (GIT) adverse effects. Hence, it is mandatory to improve the safety profile of NSAIDs or to discover better alternatives. In this study, weanalyzed3-acetyl coumarin derivatives for *in silico* ADMET properties to found oral drug like activities the and protein targets by using Swiss ADME, pkCSM, OSIRIS, Molinspiration, and Swiss Target Prediction Software's and showed acceptable results. Molecular docking investigations of designed coumarin derivatives With a known biological target named Cyclooxygenase2displayed remarkable inhibition ability with the binding energy of −9.9 kcal/mol (1(a-h),2(a-e)) than standard indomethacin for possible therapeutic applications.



## INTRODUCTION

A key goal of Drug Discovery and development is the recognition of new molecular entities is to know before hand, the pharmacokinetic parameters and ADMET properties of designed compounds.[1-5]In Silico methodologies have become a crucial part for predicting the molecular properties, Bioavailability and identification of targets of designed compounds. Computer-aided drug design (CADD) is a widely used term that represents computational tools, enables the development, modification and optimization of design process. [6]Molecular docking has been acknowledged with significant attention among all virtual screening methods. Coumarin moieties are oxygen-containing heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications.[7] They belong to class lactones and are a part of flavonoid family. Structurally constructed by a benzene ring fused to alpha-pyrone ring and the presence of an electronegative atom is effective for hydrogen bond formation and for solubility, to some extent aromatic ring is responsible for having hydrophobicity. Synthetic and natural coumarin derivatives are measured to have extensive range of biological activity, such as anti-diabetic[8], anti-inflammatory[9], anticancer[10], anti-coagulant[11],anti-oxidant[12], anti-HIV[13], anti-bacterial[14], antifungal[15], and antitubercular activities[16].

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There are numerous literatures on Coumarin derivatives in that 3-acetyl coumarin derivatives also have significant therapeutic applications.

Usually, the designed compounds always cannot show the suitability as potential drug. Hence, it is important to calculate ADME (absorption, distribution, metabolism, and excretion) including drug-likeness, identification of drug targets and toxicity to make a rational decision on further development.

The most important drugs today are painkillers that reduce, fever, pain and inflammation. Inflammation is a main symptom of many pathological conditions [17] to reduce pain and inflammation non-steroidal anti–inflammatory drugs are used as therapeutic agents. NSAIDs inhibit both COX-1 and COX-2, but with varying degrees of selectivity. Selective COX-2 inhibitors may eliminate side effects associated with NSAIDs because of COX-1 inhibition, such as gastric intolerance and renal effects.[18-21]

In this study, according to reported literature [22-24] some new 3-acetyl coumarin derivatives were designed and evaluated for Potentially active compounds by predicting the Pharmacokinetic parameters and Drug likeness using Swiss ADME Software, Bioactivity using Molinspiration Software, Toxicity using pkCSM and OSIRIS Software's, Human Protein Targets using Swiss Target Prediction. As per the data collected from this software's of all newly designed 3-acetyl

coumarin derivatives has examined thoroughly and most Potent compounds are selected It incorporates the use of *insilico* molecular modelling tool Auto dockVina The receptor grid that was generated will helps in locating the protein active site and preparing the grid for the ligands to be docked in the shape and properties of the receptor and are represented on a grid by different sets of fields that provide gradually more precise scoring of the ligand poses. The binding energies of mentioned analogs, further clarify the design of potential drug candidates against COX - 2 protein.

***Experimental***

The compounds were designed according to the reported literature and to those designed compounds (Figure 1) the pharmacokinetic properties, toxicity, Drug likeness, and bioactivity has been calculated by using software's such as Swiss ADME (http://www.swissadme.ch/index.php),Mol inspiration (https://www.molinspiration.com/cgi-bin/properties),OSIRIS:(//www.organicchemistry.org/prog/peo/),pkCSM http:// biosig.unim elb .edu.u/pkcsm/prediction), Swiss Target Prediction **(**www.swisstargetprediction.ch**).**
The hardware used in this study was a PC with x64-based with 4 gigabytes and Windows 10 pro-F3F9TVII operating system. The software used were chemsketch(https://www.acdlabs.com/ resources/freeware/chem sketch/download.php.

Figure 1 shows the core structures a, b, and c are gathered from the reported literature in which core structure (a) derivatives were reported by Sunil Dutt Durgapal *et al*.,(b) derivativeswere reportedby Valeria La pietra i.e., taking a solution of 3-bromo acetyl coumarin[25}(c) derivatives are reported by Shokhan Jamal Hamid *et al*., The molecular docking was performed using AUTO DOCK Vina software installed on a single machine running on an Intel Core i5-3317U CPU @ 1.70 GHz Processor with 6 GB RAM and Windows7 with 64-bit Operating System.

With a known biological target named Cyclooxygenase 2 (PDB ID: 4COX) for coumarin derivatives. A grid was created around the co-crystallized ligand. The coordinates (x = 22.51, y = 22.24 z = 16.19) were generated with the help of MGL Tools & Pharmit: interactive exploration of chemical space (http://pharmit.csb.pitt.edu/).[31] Prepared pdbqt files for both target & ligands. The created in house batch file of ligands & target and docking was performed in the absence of water molecules for all 17 molecules (16 + 1 standard drug Indomethacin). The molecules were analysed after docking and visualized in the discovery studio for the interactions with the active site amino acids

## RESULTS AND DISCUSSION

According to the literature, a simple procedure was utilized in this work to design and evaluate new 3-acetyl coumarin derivatives with possible therapeutic applications. 3-acetyl Coumarin compound derivatives were screened by using various softwares like swiss ADME, PKCSM, Osiris, Mol inspiration and Molsoft

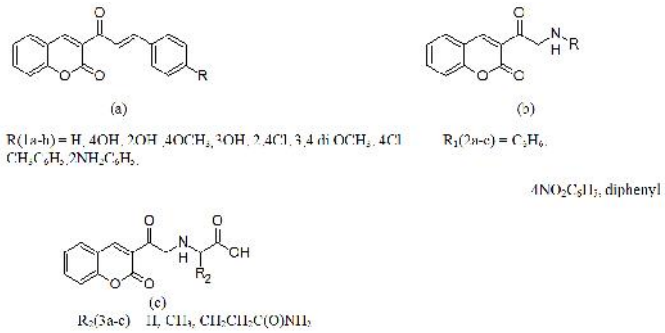



**Figure 1** shows the designed 3-acetyl coumarin derivatives in which (a), (b), (c) and (d) are the core structures.

**Table 1** Shows the ADME, drug likeness properties of newly designed 3-acetyl coumarin derivatives was predicted by Swiss ADME

| M | MW | MR | TPSA | GI | BBB | Log P | Pgp | nLv | DL | DS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1a | 276.29 | 82.29 | 47.28 | High | Yes | 3.11 | No | 0 | **-3.07** | 0.38 |
| 1b | 292.29 | 84.31 | 67.51 | High | Yes | 2.7 7 | No | 0 | 0.31 | 0.58 |
| 1c | 292.29 | 84.31 | 67.51 | High | Yes | 2.77 | No | 0 | 0.05 | 0.55 |
| 1d | 306.31 | 88.78 | 56.51 | High | Yes | 3.04 | No | 0 | 0.36 | 0.34 |
| 1e | 292.29 | 84.31 | 67.51 | High | Yes | 2.77 | No | 0 | 0.23 | 0.57 |
| 1f | 345.18 | 92.31 | 47.28 | High | Yes | 4.32 | No | 0 | 1.11 | 0.54 |
| 1g | 336.34 | 95.27 | 65.74 | High | Yes | 3.72 | No | 0 | 2.26 | 0.67 |
| 1h | 310.73 | 87.3 | 47.28 | High | Yes | 2.97 | No | 0 | 0.85 | 0.58 |
| 2a | 279.29 | 81.51 | 59.31 | High | Yes | 2.07 | No | 0 | -2.11 | 0.42 |
| 2b | 293.32 | 84.77 | 59.31 | High | Yes | 1.78 | No | 0 | 0.7 | 0.5 |
| 2c | 294.3 | 85.91 | 85.33 | High | No | 1.40 | No | 0 | -1.17 | 0.47 |
| 2d | 324.29 | 90.33 | 105.13 | High | No | 2.98 | No | 0 | -10.01 | 0.13 |
| 2e | 355.39 | 106.64 | 50.52 | High | Yes | -1.90 | No | 0 | -0.61 | 0.47 |
| 3a | 261.23 | 66.87 | 96.61 | High | No | -1.54 | No | 0 | -2.04 | 0.43 |
| 3b | 275.26 | 71.67 | 96.61 | High | No | -2.64 | No | 0 | 3.42 | 0.76 |
| 3c | 314.38 | 89.65 | 92.42 | High | No | 0.35 | yes | 0 | -1.16 | 0.47 |

Where, M-molecule, MW- Molecular Weight, MR- Molecular Refractivity, TPSA-Topological polar surface area, GI- Gastro Intestinal absorption, BBB-Blood Brain Barrier, Log P- partition coefficient, Pgp- P-glyco protein, nLv- Lipinski rule of Five, DL- Drug likeness, DS- Drug Score.

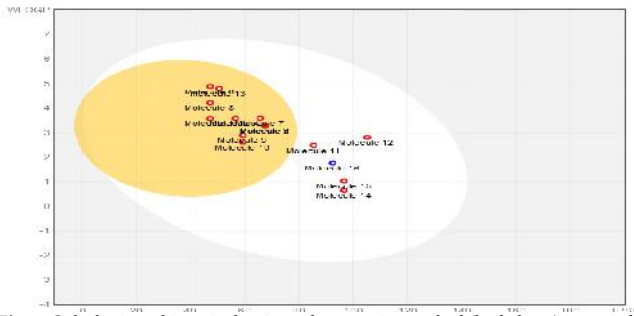


**Figure 2** the brain and intestinal estimated permeation method (boiled egg) is carried to get an accurate predictive model that works by computing the lipophilicity and polarity of small molecules

The Compounds Placed in Yellow region, has highest probability of being absorbed by brain and the compounds in the white region has the highest probability of being absorbed by the gastrointestinal track.

All the Coumarin Derivatives, are following Lipinski rule of five Molecules 1a,-2b and are showing Blood Brain Barrier(BBB) penetration molecules 2e, 2c, 2d,3a,3b and 3c are showing high Gastrointestinal absorption. All molecules show good Bioavailability (0.55), drug likeness properties, Bioactivity and less toxicity. Target prediction of molecules of all derivatives was also done only top 15 targets has been taken for this study.

**Table 2** shows the bioavailability and bioactivity of newly designed 3-acetyl coumarin derivatives predicted by molinspiration

| M | BA | Lln | Log S | GPCRL | ICM | KI | NRL | PI | EI |
|---|---|---|---|---|---|---|---|---|---|
| 1a | 0.55 | 1 | -3.96 | -0.43 | -0.55 | -0.59 | -0.24 | -0.36 | -0.07 |
| 1b | 0.55 | 1 | -3.66 | -0.34 | -0.48 | -0.49 | -0.04 | -0.3 | -0.01 |
| 1c | 0.55 | 1 | -3.66 | -0.39 | 0.54 | -0.53 | -0.11 | -0.32 | -0.04 |
| 1d | 0.55 | 1 | -3.97 | -0.41 | -0.59 | -0.55 | -0.19 | -0.34 | -0.12 |
| 1e | 0.55 | 1 | -3.66 | -0.35 | -0.49 | -0.51 | -0.03 | -0.31 | -0.01 |
| 1f | 0.55 | 1 | -5.43 | -0.37 | -0.52 | -0.65 | -0.19 | -0.35 | -0.17 |
| 1g | 0.55 | 1 | -3.99 | -0.38 | -0.56 | -0.5 | -0.2 | -0.32 | -0.12 |
| 1h | 0.55 | 1 | -4.69 | -0.39 | -0.53 | -0.56 | -0.22 | -0.36 | -0.11 |
| 2a | 0.55 | 1 | -3.41 | -0.52 | -0.61 | -0.47 | -0.41 | -0.31 | -0.14 |
| 2b | 0.55 | 0 | -3.22 | -0.3 | -0.52 | -0.51 | -0.36 | -0.13 | -0.02 |
| 2c | 0.55 | 0 | -3.48 | -0.47 | -0.58 | -0.32 | -0.45 | -0.22 | 0.04 |
| 2d | 0.55 | 0 | -3.87 | -0.56 | -0.58 | -0.53 | -0.41 | -0.34 | -0.23 |
| 2e | 0.55 | 2 | -5.4 | -0.22 | -0.37 | -0.38 | -0.1 | -0.16 | -0.06 |
| 3a | 0.55 | 0 | -1.68 | -0.36 | -0.53 | -0.78 | -0.3 | -0.1 | 0.1 |
| 3b | 0.55 | 0 | -2.05 | -0.3 | -0.5 | -0.77 | -0.44 | 0 | 0.05 |
| 3c | 0.55 | 1 | -2.14 | 0.35 | 0.09 | -0.26 | 0.10 | 0.43 | 0.30 |

Where, M-molecule, BA-Bioavailability, Lln- Lead likeness, SA- Synthetic Accessibility, Log S- Solubility, GPCRL- G-Protein Coupled Receptors Ligand, ICI- Ion Channel Modulator, KI- Kinase Inhibitors, NRI- Nuclear Receptor Inhibitors, PI- Protease Inhibitors, EI- Enzyme Inhibitors.

**Table 3** shows the target prediction of the designed 3-acetyl coumarin derivatives predicted bySwiss target prediction

| M | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1a | 13.3 | 33.3 | - | 6.70% | 6.7 | |
| 1b | 53.30% | - | - | 33.30% | 13.30% | |
| 1c | 13.30% | - | 26.70% | 13.30% | 20% | |
| 1d | 53.30% | 13.30% | - | 13.30% | 13.30% | |
| 1e | 40% | 6.70% | - | 13.30% | 26.70% | 6.70% |
| 1f | 13.30% | - | 6.70% | 13.30% | 13.30% | 6.70% |
| 1g | 40% | - | 20% | 13.30% | 13.30% | - |
| 1h | 6.70% | 6.70% | 6.70% | 40% | 13.30% | - |
| 2a | 33.30% | 6.70% | 13.30% | 6.70% | 6.70% | 6.70% |
| 2b | 20% | 46.70% | 6.70% | 6.70% | 6.70% | - |
| 2c | 33.30% | - | 6.70% | 6.70% | 6.70% | 6.70% |
| 2d | 13.30% | - | 46.70% | 6.70% | 6.70% | - |
| 2e | 20% | 20% | 13.30% | 13.30% | 6.70% | 6.70% |
| 3a | - | 26.70% | 6.70% | 6.70% | 6.70% | - |
| 3b | 20% | 26.70% | - | 6.70% | - | - |
| 3c | - | 26.70% | 13.30% | 6.70% | 6.70% | - |

Where, 1- Kinase, 2- Protease, 3- Family A.G Protein Coupled Receptor, 4- Enzyme, 5-Oxidoreductase, 6- cytochrome P450.

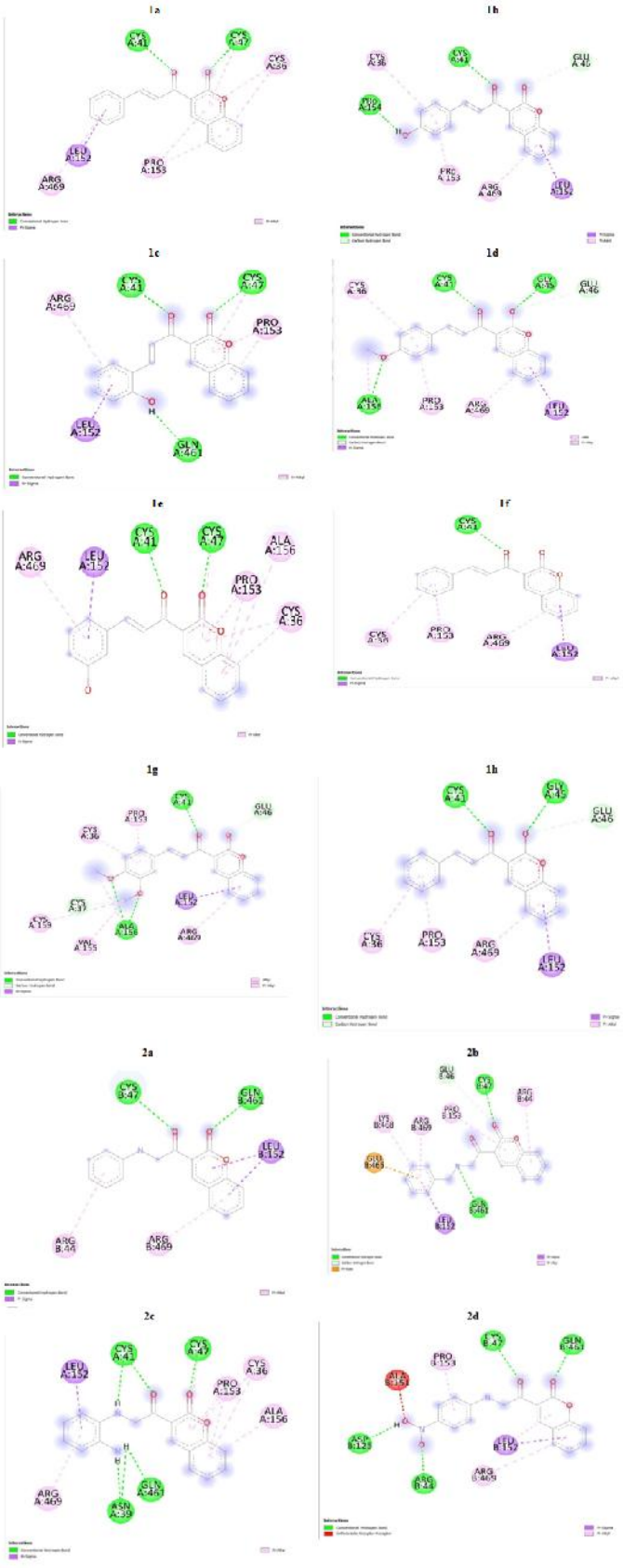
**Table 4** The binding energy and hydrogen bonds of all the inhibitors (designed 3-acetyl coumarin derivatives) against protein cyclooxygenase 2 complexed with indomethacin inhibitor using molecular docking.

| LIGAND | AMINO ACID RESIDUE | | |
|---|---|---|---|
| | Hydrogen bond interactions | Hydrophobic interaction | VINA SCORE |
| 1a | CYSA:41,CYSA:47 | ARGA:469,PROA:153,CYSA:36 | -9.5 |
| 1b | PRoA:154,CYSA:41, GLUA:46 | CYSA:36,PROA:153, ARGA;469 | -9.2 |
| 1c | CYSA:41,CYSA:47, GLNA:461 | PROA:153,ARGA:469 | -9.9 |
| 1d | CYSA:41,GLYA:45, ALAA:156,GLUA:46 | CYSA:36,PROA:153, ARGA;469 | -9.2 |
| 1e | CYSA:41,CYSA:47 | CYSA:36,PROA:153, ARGA;469,ALAA:156 | -9.6 |
| 1f | CYSA:41, | CYSA:36,PROA:153, ARGA;469 | -9.3 |
| 1g | CYSA:37,CYSA:41, ALAA:156,GLUA:46 | CYSA:36,CYSA:159, PROA:153,ARGA;469,VALA:155 | -9.9 |
| 1h | CYSA:41,GLYA:45, GLUA:46 | CYSA:36,PROA:153, ARGA:469 | -9.1 |
| 2a | CYSB:47,GLNB:461 | ARGB:44,ARGB:469 | -8.9 |
| 2b | CYSB:47,GLNB:461, GLUB:46 | LYSB:468,ARGB:469 | -8.9 |
| 2c | CYSA:41,CYSA:47, GLNA:461,ASNA:39 | LYSB:468,ARGB:469, PROB:153,ARGB:44 | -9.5 |
| 2d | CYSB:47,GLNB:461, ASPB:125,ARGB:44 | CYSA:36,PROA:153, ARGA:469,ALAA:156 | -9.8 |
| 2e | GLNA:372,SERA:126, LYSA:532,ILEA:124 | PROB:153,ARGB:469 | -9.2 |
| 3a | GLUA:524,ARGA:513,IM NA:701,TYRA:115,PROA :86,HISA:90 | PROB:542 | -8.2 |
| 3b | CYSA:37,ALAA:156,AS NA:39 | PROA:153,ARGA:469 | -8.4 |
| 3c | ASNB:39,ASNB:34 | PROB:153,LYSB:468, ARGB:469 | -8.6 |
| Standard (Indomet hacin) | PROA:154,ASNA:39, ASNA:34 | TYRA:130,PROA:153,CYSA:47,C YSA:36 | -8.8 |

Mostly all molecules show the highest target towards Kinase, Protease, Family AG protein Coupled receptor, Enzyme, Oxidoreductase and Cytochrome P450. In Boiled Egg (Figure 2) the Compounds Placed in Yellow region, is the space where highest probability of being absorbed by brain and remaining compounds are in the white region, where highest probability of being absorbed by the Molecular docking study was carried out for the designed derivatives. The potential active site amino acids of 4COX complex were predicted using CASTp. The target protein and inhibitors were geometrically optimized. All the 16 derivatives were docked against active site of target protein using AUTODOCK VINA. Out of the 16 inhibitors 1(a-h),2(a-e) has showed best binding energy of more than standard indomethacin score(-8.8kcal/mol) with 2 hydrogen bond against the target protein. Among the above 1c,1g (-9.9) and 2d(-9.8) are having good affinity towards the target when compared with standard ligand. (Table: 4).

Figure 3 the target prediction of the designed 3-acetyl coumarin derivatives predicted bySwiss target predict.all molecules show the highest target towards Kinase, Protease, Family AG protein Coupled receptor, Enzyme, Oxidoreductase and Cytochrome P450(Table:3)

In this study, the molecules which have less toxicity has chosen for further development. All 16 coumarin derivatives follow Lipinski rule of Five, good Drug likeness and drug score. Out of the 16 inhibitors analysed 1(a-h),2(a-e) has showed best binding energy of more than -8.8kcal/mol (indomethacin) with 2 hydrogen bond against the target protein. Therefore, all derivatives are taken into consideration for further development



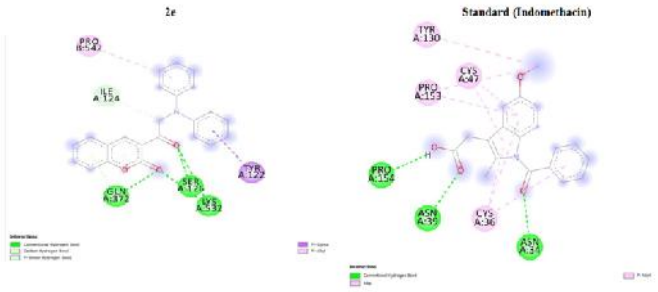



**Figure 3** Dock poses of compound 1(a-h), & 2(a-e) into Cyclooxygenase2 protein (4COX) showing hydrogen bond interactions (▬)and Hydrophobic interactions(▬)

## CONCLUSION

In this study, coumarin derivatives were designed and analysed for ADME (absorption, distribution, metabolism, and excretion) properties, toxicity, Drug likeness, and bioactivity using software's such as Swiss ADME, Molinspiration, OSIRIS, PkCSM and Swiss Target Prediction. This Analysis revealed that coumarin derivatives have good oral drug like properties and could be developed as oral drug candidates. Designed coumarin derivatives were subjected to docking against Cyclooxygenase-2 (4COX) using AUTODOCK VINA software. All the 16 coumarin derivatives showed greatest binding interactions (ranging -8.2 to -9.9 kcal/mol) than standard indomethacin (-8.8 kcal/mol).Thus, compounds may act as an effective anti-inflammatory drug. This attempt is to select the drug molecule which shows desired therapeutic effect.

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