Acta Pharm. Sci. Vol 58 No: 4. 2020
DOI: 10.23893/1307-2080.APS.05823

Molecular Drug Design and Docking Study of Novel N- substituted Celecoxib Derivatives as Selective Cyclooxygenase-2 Inhibitors

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ABSTRACT

Celecoxib is one of the best potent nonsteroidal anti-inflammatory drug (NSAID) used as cyclooxygenase-2 (COX-2) selective inhibitor. For decades it effectively used in pain and inflammation treatment because the ability of reducing prostaglandin (PG) synthesis by obstruct the transformation of arachidonic acid to PGH2. But several serious side effects synchronized includes kidney failure, nausea, gastrointestinal tract bleeding, myocardial infarction, abdominal pain, and finally diarrhea. In this paper, a total of 155 Celecoxib derivatives were successfully docked inside crystal structure of cyclooxygenase-2 (COX-2) enzyme to estimate the potency of each derivative to bind inside active site. The highest twenty effective derivatives were recorded with docking score range of (-16.997 to -14.611) kcal/mol.

Keywords: Drug Design, Docking Study, Scaffold hopping.

INTRODUCTION

Inflammation is a spontaneous defense mechanism by immune system trying to heal the host body against any harmful or irritating stimulus that could threatens a part of our body[1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are a major class of used drugs in the treatment of mild pain feeling and rheumatoid arthritis disease due to their broad therapeutic efficiency. NSAIDs achieved their pro-inflammatory activities through the blocking of prostaglandins production from arachidonic acid by the inhibition of cyclooxygenase (COX) enzyme[2]. Moreover, at last two COX enzyme isoforms are already reported (COX-1 and COX-2). With the approve of COX-1 action in the protection

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(Received 27 December 2019, accepted 08 January 2020)

of maintaining homeostasis and gastric mucosa, COX-2 also used in preventing of proinflammatory stimulation at the inflammatory sites[3]. During the last two decades, many drugs manufacture pharmaceutical companies improves the selectivity of targeting COX-2 by developing several NSAIDs medications. The paramount objective of all these process is to decrease the inflammation and pain syndromes without missing the preservation of COX-1 enzyme in gastrointestinal tract, resulting to decrees a lot of side effects[4,5]. Among all these, Celebrex is the most effective COX-2 selective inhibitor which successfully remains for a years in the markets because the magnificent potency against several diseases including: ankylosing spondylitis, rheumatoid arthritis, and osteoarthritis[6]. The primarily euphoria of COX-2 inhibitors selectivity was short time studies because the indicating of serious cardiovascular complications risks during frequent therapy. Therefore, developing and design of novel active anti-inflammatory and painkiller molecular agents with much more attractive safety profile is incurably presents a presumed significant challenge in this field of research[7]which presents with axial and nonaxial features, affecting structures within the musculoskeletal system, as well as other bodily systems. Both pharmacological and nonpharmacological therapeutic options are available for SpA. For decades, nonsteroidal anti-inflammatory drugs (NSAIDs.

In theoretical chemistry field, the fundamental approach of developing, design and utilizing molecular derivatives from 2D descriptors, 3D descriptors, and 3D-QSAR concept is a substantial base rule in the lead molecules discovery and lead scaffold hopping field[8]. In practical, the goal of this approach is the attempt to model and discover novel molecules by replacement of selected chemical groups to generate new bioisosterism with better pharmacological therapeutic potency can be used as promising active drugs[9]. These approaches include many applications includes pharmacophore similarity search, molecular virtual screening, de novo model design, and topology similarity search. In a scaffold molecular hopping, the pharmacological information is parallelly gathered during the lead compound optimization prosses and used to develop better advanced drug model, with employing compounds database can be easily screened to virtually identify novel scaffold variants of data set lead compounds. The aim of this prosses is to reduce much more of chemical and biological side effects associated with to the chemical scaffold of available used drugs[10,11]. In addition, several combinatorial approaches are used to improve ADMET (absorption, distribution, metabolism, excretion, and toxicity) molecular profile and increase the ability of medication targeting by generating a package of analogous similar in scaffold to the available drug in market[12].

In this work, a new package of promising celecoxib derivatives designed and computationally evaluated with higher binding docking score to COX-2 enzyme. The result is a novel series of potent active molecules can be used in the medication of inflammation, pain and even for antiproliferation regarding to the significance role of COX-2 enzyme inhibition in the etiopathology to prevent all these syndromes.

METHODOLOGY

Computational Method

A total of 155 molecule of Celecoxib derivatives were collected from pervious literatures and the 3D conformation structure were optimize by running ChemDraw16.0 program from ChemOffice software (ChemOffice, 2016). Next, the 3D geometry optimization of each molecule was obtained by running MM+ force field method by supported under Hyperchem program ver. 8.0 and saved as .mol sprite files. Then, additional 3D geometry optimization by applying semi-empirical calculation method was obtained from RM1 (Recife Model 1) method. After that the lowest 3D energy conformation of each molecule was saved as .sdf file format by running Spartan 14.0 software (Spartan, 2014) supported by Monte Carlo calculation method and 100 cycles of optimization with 1000 interactions. Molecular drug design and docking score evaluation was perform by running Glide program from Maestro (Maestro 10.1) software under Schrodinger package (Schrodinger, 2015). All these prosses (preparation, minimization and docking) were perform on Windows 7 Service Pack 1 system on Dell Precision T-1570 workstation PC with Intel (R) Core (TM) i7 CPU 866, 3.60GHz, 32 GB RAM, 2 TB of HD). COX-2 enzyme crystal structure was downloaded from Protein Data Bank (PDB code: 3LN1) with resolution of 2.4. The preparation of enzyme crystal was applied by running (ProPrep) program under Maestro for optimization and minimization. This prosses used to fill back any missing amino acids and preparation with high ideal structure and saved in PDB file format.

Moreover, ligand preparation carried out by (LigPrep) software and docking score evaluation study to identify the best ionization level with hydrogen atom substations to record the lowest energy conformations state of each molecule by running OPLS 2005 force field calculation. The enzyme crystal grid box for docking was adjusted to 1.00 Å with atomic charge of 0.25 with ligand docking flexibly by Glide-extra (XP) simulation precision. During docking prosses, the enzyme was kept rigid while molecules were flexible and RMSD of enzyme crystal was saved. Molecular modeling design procedure was applied by generating several Celecoxib derivatives with deferent fragment chemical group replacement. All derivatives were generated by running R-Group Enumeration Gen-

eration method under Maestro program by the substitution at aromatic ring in Celecoxib and R-Group library was saved.

RESULTS AND DISCUSSION

For decades, cyclooxygenase (COX 1 & 2) enzymes were under intensive focuses as target for the discovery of novel drugs because its impressive role in the mediating of many diseases including inflammation and pain[13]. The previous crystallization procedures of both COX 1 & 2 enzymes encourage the scientists to design and evaluate docking affinity of all new molecules as inhibitor drugs[14]. In this work, drug modeling design and docking score affinity prosses were perform to discover novel molecules as promising inhibitor with higher binding score ability at COX-2 enzyme active site. The scaffold chemical structure of Celecoxib with N terminal substitution position used for building virtual screening data set is shown in Figure. 1.

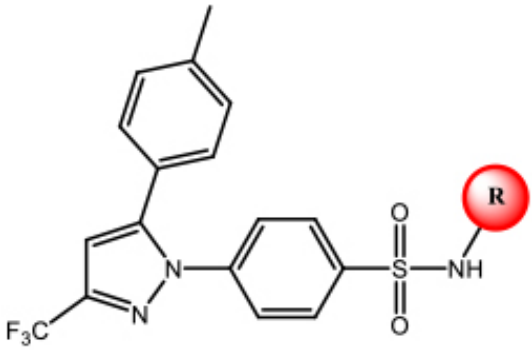
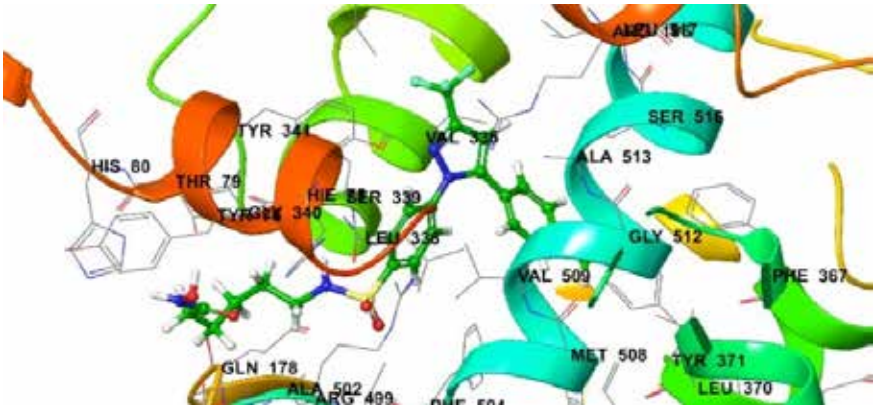


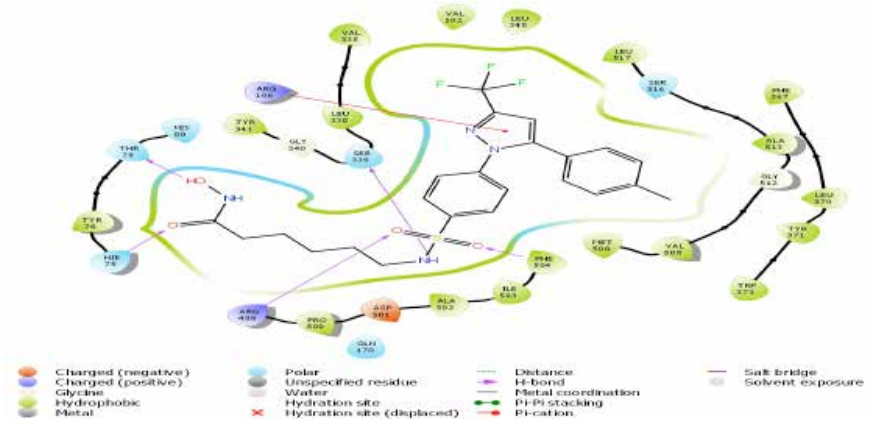
Figure. 1. The structure of celecoxib with N terminal substitution R in red cycle.

The result of molecular design with a list of 155 molecules used to build virtual screening data set to evaluate the docking binding score was within -14.027 to -8.241 kcal/mol and the binding docking ability of Celecoxib was at -11.453 kcal/mol. From resulted list the highest binding docking affinity molecule was N-hydroxy-6-((4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)sulfonamido)hexanamide is already reported[15]. The orientation and docking affinity of Celecoxib and the best compound from the data set list inside COX-2 enzyme active site surrounded by amino acids are shown in Figure 2.

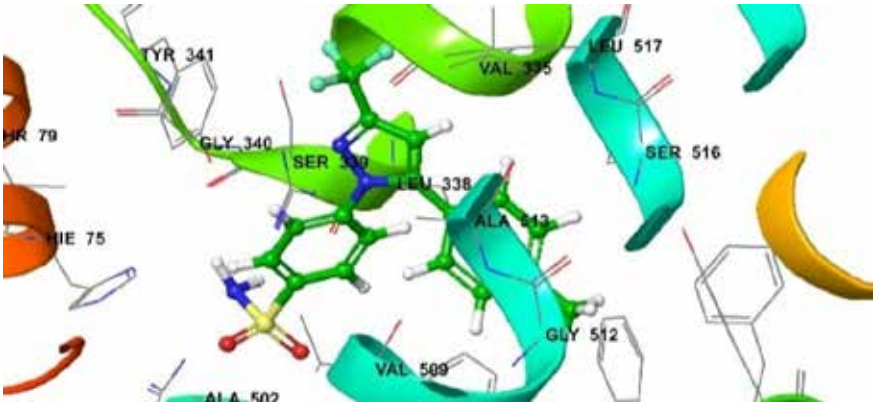
a.


TYR 341
VAL 335
HIS 80
THR 79
SER 516
ALA 513
GLY 512
LEU 338
VAL 509
PHE 367
GLN 178
MET 508
TYR 371
LEU 370
ALA 502

b.


Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure

c.


TYR 341
VAL 335
LEU 517
GLY 340
SER 516
LEU 338
ALA 513
HIE 75
GLY 512
VAL 509
ALA 502

d.

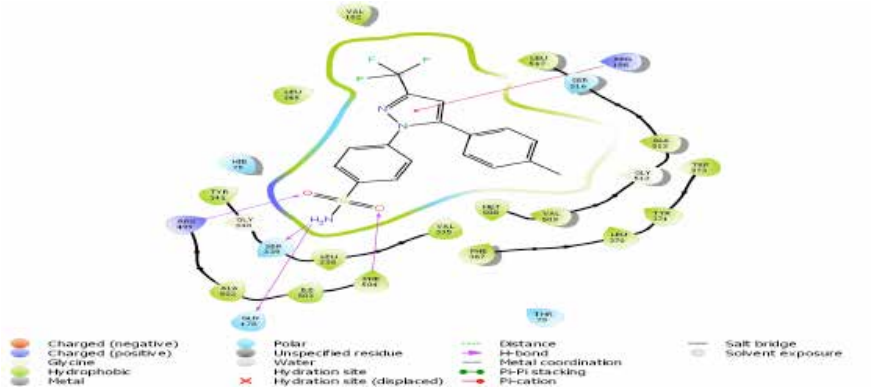
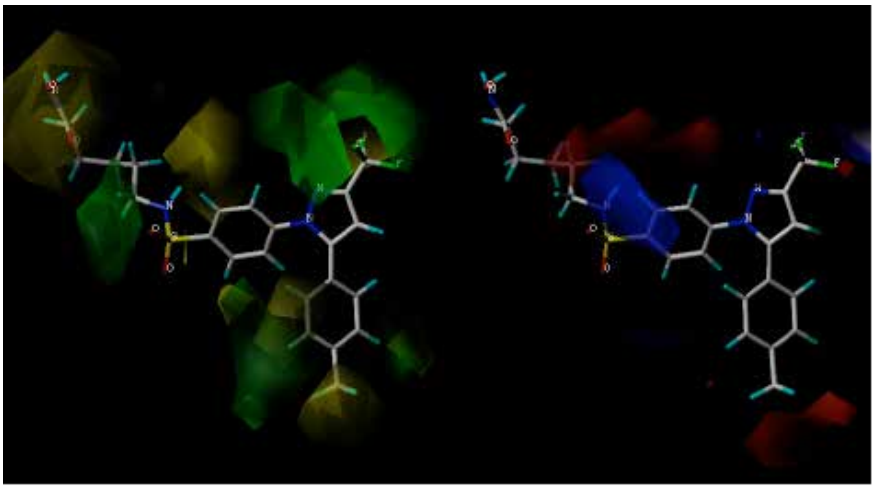


Figure 2. Celecoxib and the highest docking score compound surrounded by amino acids inside COX-2 enzyme pocket a. & c. compound as ball and stick, enzyme pocket as ribbon. b. & d. Ligand interaction pocket.

Inside the pocket of COX-2 enzyme active site, the highest binding compound bind by several various interactions appears as: one Pi-cation interaction appears between ARG106 and pyrazol ring, five H-bond interactions between HIS75, TYR79, SER339, ARG499, and PHE504 appears with amine, ketone, and hydroxyl groups in this compound. Furthermore, hydrophobic interaction support the binding of the compound with surrounded amino acids as following: HIS75, TYR76, THR79, HIS80, TYR341, GLY340, SER339, LEU338, ARG106, VAL335, VAL102, LEU345, LEU517, SER516, ALA513, PHE367, GLY512, LEU370, TYR371, TRP373, VAL509, MET508, PHE504, ILE503, ALA502, ASP501, GLN178, PRO500, and ARG499.

According to docking score result and by applying QSAR molecular evaluation, the best compound is pointed as lead molecular compound for the next drug design steps to apply specific chemical group replacement with another group at effective scaffold position. Figure 3 shows the best selected active lead compound surrounded by preferable desirable and undesirable contours reigns colored in green and yellow, respectively. These reigns are labeled based on: yellow contours represent steric bulk undesirable positions, green contours represent steric bulk desirable positions, blue represent desirable positive charge positions, red represent desirable negative charge positions.

a.



b.

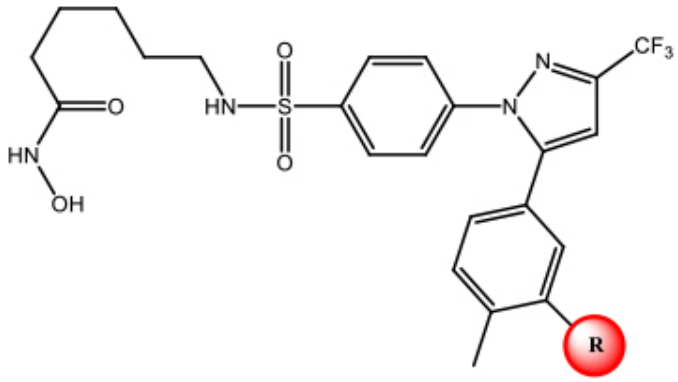
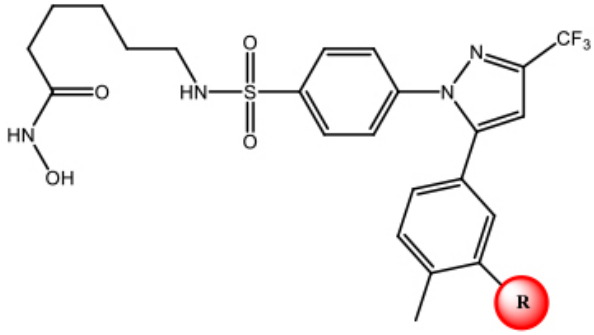


Figure 3. The best lead compound a. surrounded with desirable and undesirable region as contours b. Selected substation position in red shaded cycle.

From Figure 3, the selection of specific chemical group to be replace is based on the appearance of green contours regions that represent to the described positions to be replace this chemical group to increase pharmacological potency. Based on these findings, chemical group replacement at R position (in red) is applied to generate a total of 925 novel N-substituted Celecoxib derivatives. The docking study result a series of several new compounds with higher binding affinity and the highest docking twenty molecules score are listed descendingly in Table 1. From 925 molecules, a total of fifty-six molecules were higher binding score than Celecoxib. The substitution at N-amine with various R groups resulted a very higher active compound 1 with score of -16,997 kcal/mol.

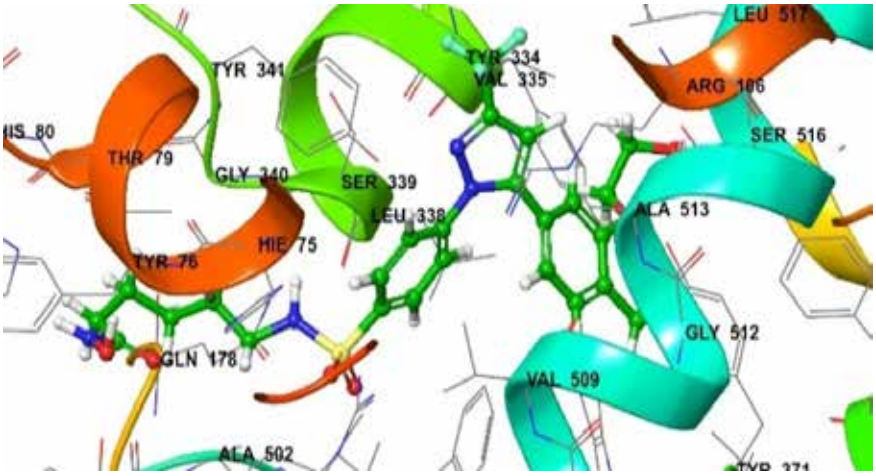
Table 1. Chemical structure and Docking score of N-substituted Celecoxib generated derivatives



Com.	R	Docking Score in kcal/mol
1	OCH_2CH_2OH	-16.997
2	$NHCH_2CH_2CH_2OH$	-16.454
3	$NHCH_2CH_2OH$	-16.252
4	$OCH_2CH_2NHCH_3$	-16.202
5	$NHCH_2CH_2CH_2OCH_3$	-15.737
6	$OCH_2CH_2OCH_3$	-15.608
7	CF_3	-15.379
8	$C(O)C(O)OCH_3$	-15.151
9	CH_3	-14.901
10	CN	-14.867
11	$C(O)CH_3$	-14.847
12	$CH_2C(O)OH$	-14.841
13	$O(CH_2)_2N(CH3)_2$	-14.833
14	$S(O)_2NHCH_3$	-14.820
15	OH	-14.786
16	$C(O)NH_2$	-14.740
17	$N(CH_3)_2$	-14.738
18	$NHC(O)CH_3$	-14.647
19	$C(O)CH_2CH_2CH_3$	-14.643
20	$C(O)CH_2Br$	-14.611

This high potency with prefect orientation of compound 1 inside COX-2 enzyme active site pocket surrounded with amino acids is shown in Figure 4.

a.



b.

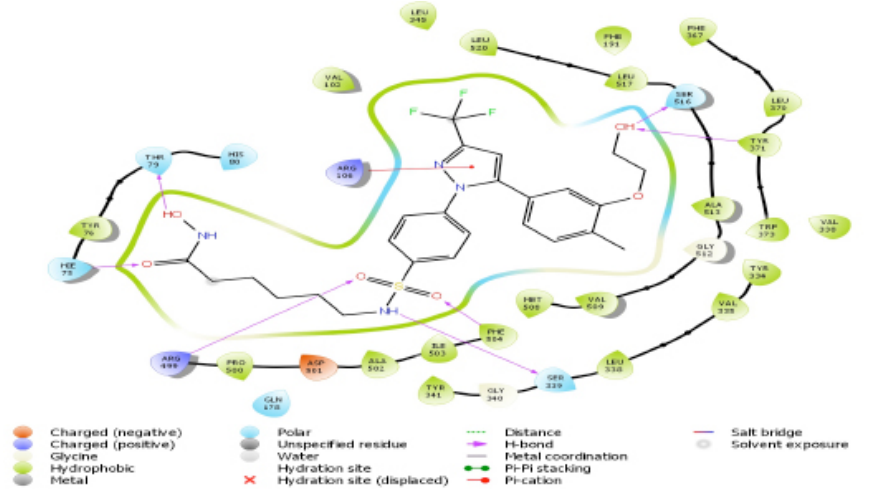


Figure 4. Compound 1 surrounded with amino acids inside COX-2 active site. a. Compound 01 as ball and stick, COX-2 enzyme as ribbon. b. Ligand interaction pocket.

Inside COX-2 active site, compound 1 highly bind similar to previous interactions one Pi-cation interaction appear between ARG106 and pyrazol ring with seven H-bond interactions appears between HIS75, THR79, ARG499, SER339, PHE504, TYR371, and SER516 with ketones, hydroxyl, and amines groups. As previous, several effective amino acids surrounding compound 1 is conformity with similar interactions by active derivatives. The appearance of these interactions proved the increasing of binding score affinity with increase of activity

and potency. Moreover, all novel derivatives are aligning inside enzyme active site in the same position and orientation by same side of substituted chemical groups referring to the favorability of substation at selected position (N-amine) of the most active compound in data set as shown in Figure 5. Finally, these novel fifty-six compounds are considered as novel scaffolds of active COX-2 inhibitors with promising less side effects pharmacotherapy.

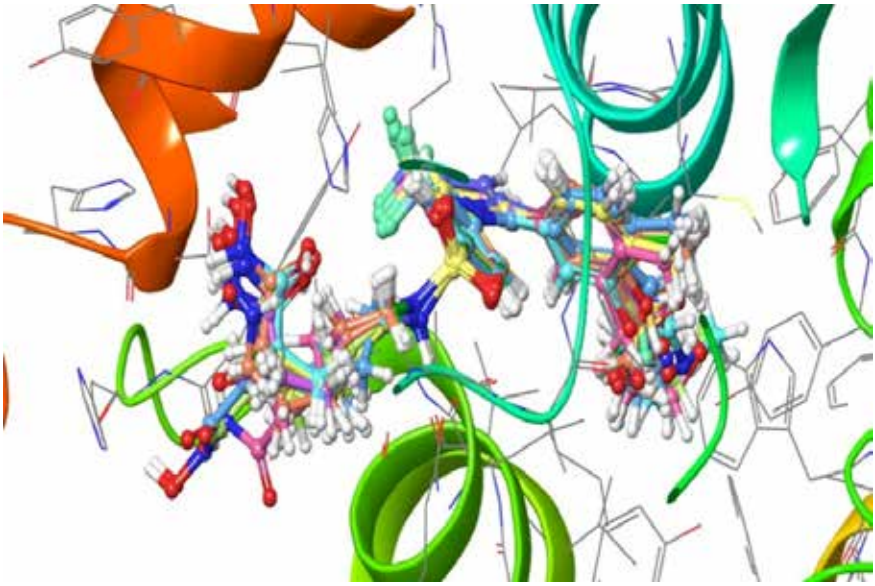


Figure 5. Novel derivatives aligning inside enzyme active site in the same position and orientation.

Finally, in this work scaffold hopping molecular approach is applied to generate novel N- substituted Celecoxib derivatives with higher potency and binding score inside COX-2 active site with score range of (-16.997 to -14.611) kcal/mol for the best twenty derivatives. Further, pharmacological studies are needed to evaluate the possible side effects and toxicity profiles of all generated novel N-substituted derivatives.

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