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Insilico Inhibitory Analysis of Supramolecular Compounds against COX-1 and COX-2

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Abstract

In the this study owing to these side effects anti-inflamantery drugs we have selected some of synthetic supramolecular compounds containing sulphones and hydrazones, SM (1-5) for the inhibition of COX-1 and COX-2. All selected SM (1-5) compound were optimized by using Avogadro, gaussian09 software, using B3LYP theory and 6-31g basis sets through density functional theory. The title target enzymes were obtained from protein data bank, the

optimized supra-molecular compounds (SM1-SM5) were theoretically docked in an active pocket of target enzymes COX-1 and COX-2 by using MGL tools, Auto Dock vina. For each compound ten conformers were generated in which top ranked conformations with lowest binding energy of each compound was selected for further analysis. The inhibitors-protein interaction was visualized after docking in Pymol, BIOVIA discovery studio and ligplot which help in visualization of ligand-receptor hydrogen bonding, π...π interaction, aromatic interactions and hydrophobic interactions. The test compounds show better inhibitory activity against COX-1 and COX-2. The results of molecular docking analysis reveal promising binding interactions, from -10.13 to 17.48 kcal/mol best than the standard Ibrofen -8.81 kcal/mol. These findings suggest that the these compounds have significant inhibitory potential against COX-1 and COX-2 and could serve as promising lead compounds for future in vitro and in vivo studies aimed at developing new anti-inflamantery condidates.

INTRODUCTION

Cyclooxygenase (COX) is a rate limiting enzyme involve in conversion of arachidonic acid into prostaglandin (1) in human body [1]. COX exist in two forms COX-1 and COX-2 involved in prostaglandins biosynthesis [2]. COX-1 is a housekeeping enzyme that is found in all tissues in human body [3]. COX-1 has recently gained significant attention for its role in both cancer and inflammation. The participation of COXs, especially COX-1, in various physiological and pathological activities with a slightly earlier inflammatory component serves as the primary justification for it (i.e., cancer and neurological and neurodegenerative diseases) [4]. Thrombosis, atherosclerosis, and cancer are a few pathological situations where COX-1 is involved [5]. In the development and progression of various physiological conditions and diseases understanding the role of the COX-1 isozyme, as discussed its use on the clinical and preclinical evidence that only supports the role of COX-1 in the pathophysiology of acute and chronic disorders [6]. COX-2 is found in the kidney, brain and ovaries. COX-2 is associated with tumor initiation and progression in many cancer types [7]. COX-1 and COX-2 enzymes produced

prostaglandins product [8]. During the reaction in human body which cause inflammation, pain and fever and also effect the normal function of kidney [9]. As from the above discussion that these enzymes (COX-1 and COX-2) have been potentially utilized as a therapeutic target for anti-inflammatory medications such as ibuprofen (2), naproxen (3), diclofenac (4) and piroxicam (5) [10-13]. Up to date COX-2 selective inhibitors (COXIBS), and phenol, bisphenol, hydrazones and sulphone derivatives are also used as a potent inhibitors against COX-1 and COX-2 [14]. On the other hand some Non-steroidal anti-inflammatory drugs (NSAIDS) [15]. Which are the most familiar as a first line anti-inflammatory therapy [16]. As reported that in the previous literature NSAIDS works by inhibiting COX to prevent the production of anti-inflammatory prostaglandins, which are extremely beneficial in the treatment of a variety of inflammatory diseases [17].

Another class of potential organic compound such as Curcumin (6) and their related compounds is a naturally occurring phenolic molecule that have a wide range of therapeutic applications, including anticancer, antigiogenesis, antibacterial, and antifungal applications [18-22]. Curcuminoids and their synthetic derivatives have a strong anti-inflammatory effect [23]. most of gastrointestinal side effects and cardiovascular side effects are due to COX inhibitors. Similarly, hydrazones (7) and their derivatives were also used as anti-inflammatory agents. Hydrazido-hydrazones (8) are excellent selective COX inhibitory activity and used for cancer treatment [24, 25]. Sulfonyl hydrazones (9) Aryl hydrazone (10) and eterocoxib (11) having sulphones moiety have potential anticancer apoptosis-inducing, antioxidant activities and COX enzymes inhibition activities [26-29].

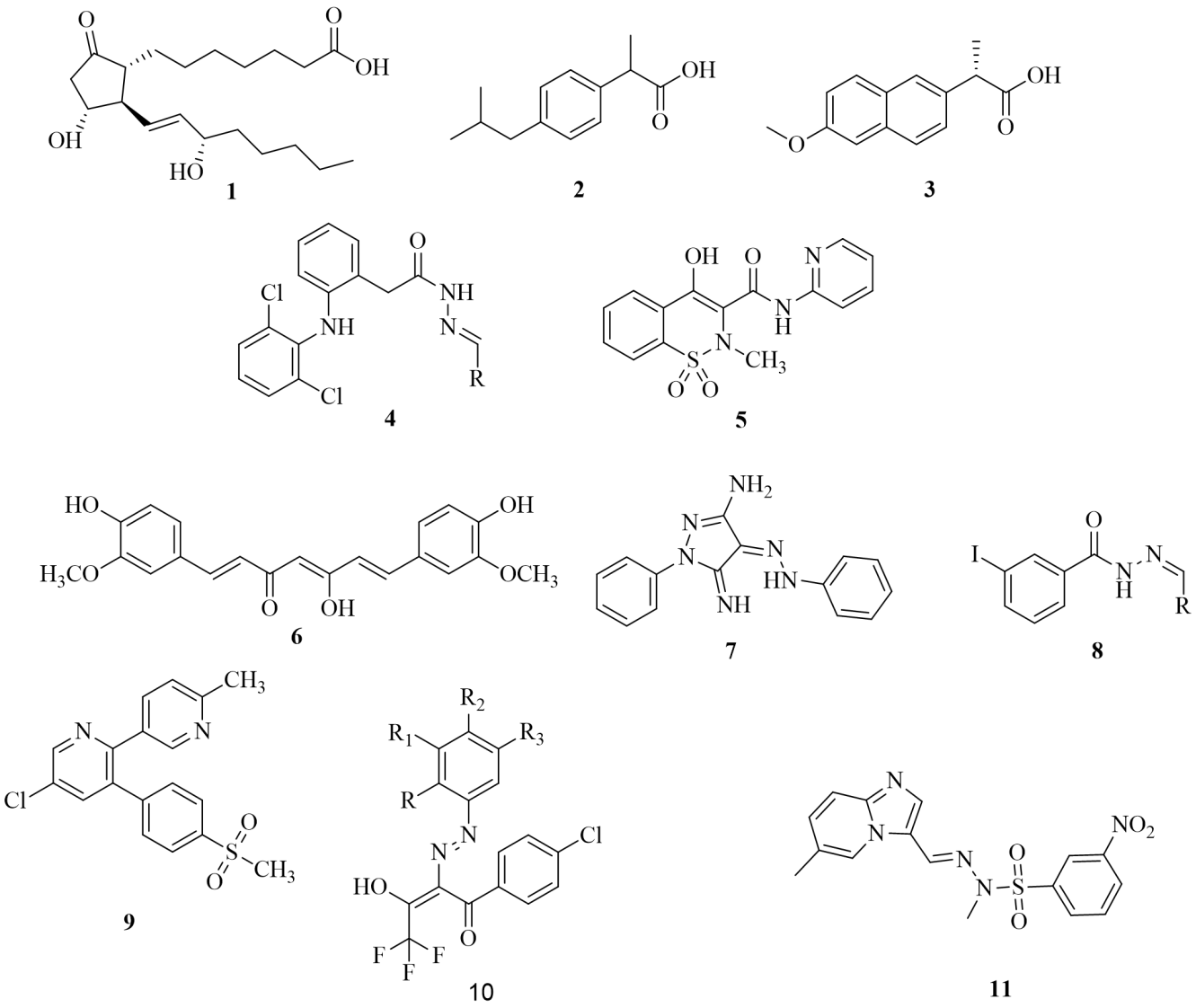

FIGURE 1. STRUCTURAL FORMULAE OF SOME SULPHONES, PHENOLS AND HYDRAXONES AS A COX INIHIBITORS

Keeping in mind the above-mentioned applications of hydrazone and sulphones derivatives we are planning to evaluate the inihibition potential of Supra molecular compounds containing all of these functionalities i.e. bisphenol, hydrazones and sulphones against COX-1 and COX-2.

The objectives of this study to evaluate the molecular docking of sulphonyl-hydrazide to confirm the best binding energy with the analyte of interest, To develop a promising novel class of anti-inflamantery condidates

and based on these studies, we identified potent drugs that can target COXs enzymes

METHODOLOGY

For molecular docking and virtual screening of ligands, the following software tools and databases were used in title study chem-office, MGL tools1.5.4, AutoDock vina, BIOVIA Discovery Studio, PyMol, Open babel and LigPlot.

OPTIMIZATION OF SUPRA-MOLECULAR COMPOUNDS

All selected **SM (1-5)** compound were optimized by using Avagadro, gaussian09 software, using B3LYP theory and 6-31g basis sets through density functional theory.[30]

COX-1 AND COX-2 TARGET

The title target enzymes were obtained from protein data bank given in **Figure 2**

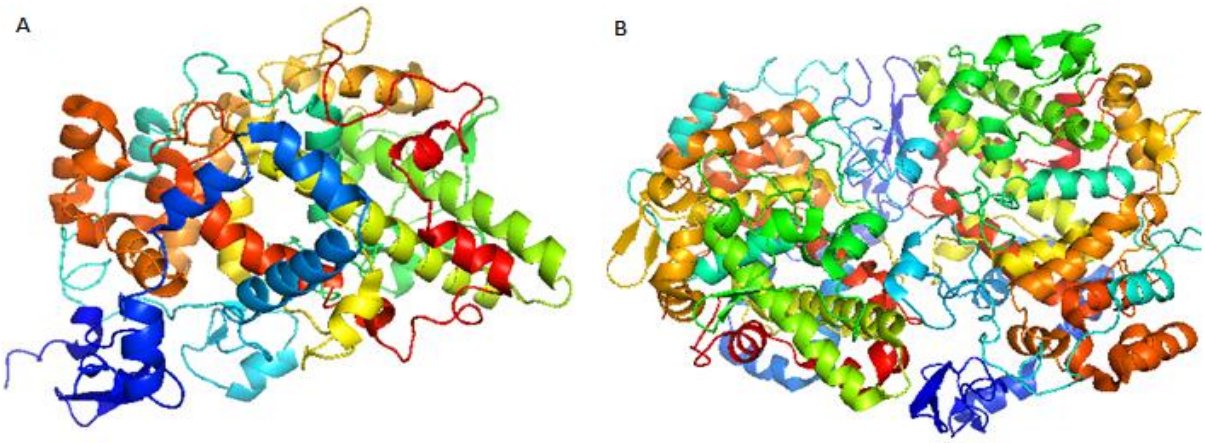

FIGURE 2. 3D STRUCTURE OF COX-1 (A) AND COX-2 (B)

PREPARATION OF TARGET PROTEINS

The structure of COX-1 and COX-2 were obtained from PDB have many problems that may need to be resolved. The said enzymes were prepared by removal of water molecules, heteroatoms and cofactors. The protein targets are modified by adding polar hydrogen and charges in AutoDock vina

MOLECULAR DOCKING OF COMPOUNDS (SM1-SM5) WITH COX-1 AND COX-2

The molecular docking are the important tools experiencing the interactions between target proteins and inhibitors, the optimized supra-molecular compounds **(SM1-SM5)** given in **Figure 3** were theoretically docked in active pocket of enzymes target COX-1 and COX-2 by using MGL tools, AutoDock vina [31]. For each compound ten conformers were generated in which top ranked conformations of each compound was selected for further analysis the inhibitors-protein interaction was visualized after docking in Pymol, BIOVIA discovery studio and ligplot which help in visualization of ligand-receptor hydrogen bonding, π...π interaction, aromatic interactions and hydrophobic interactions.

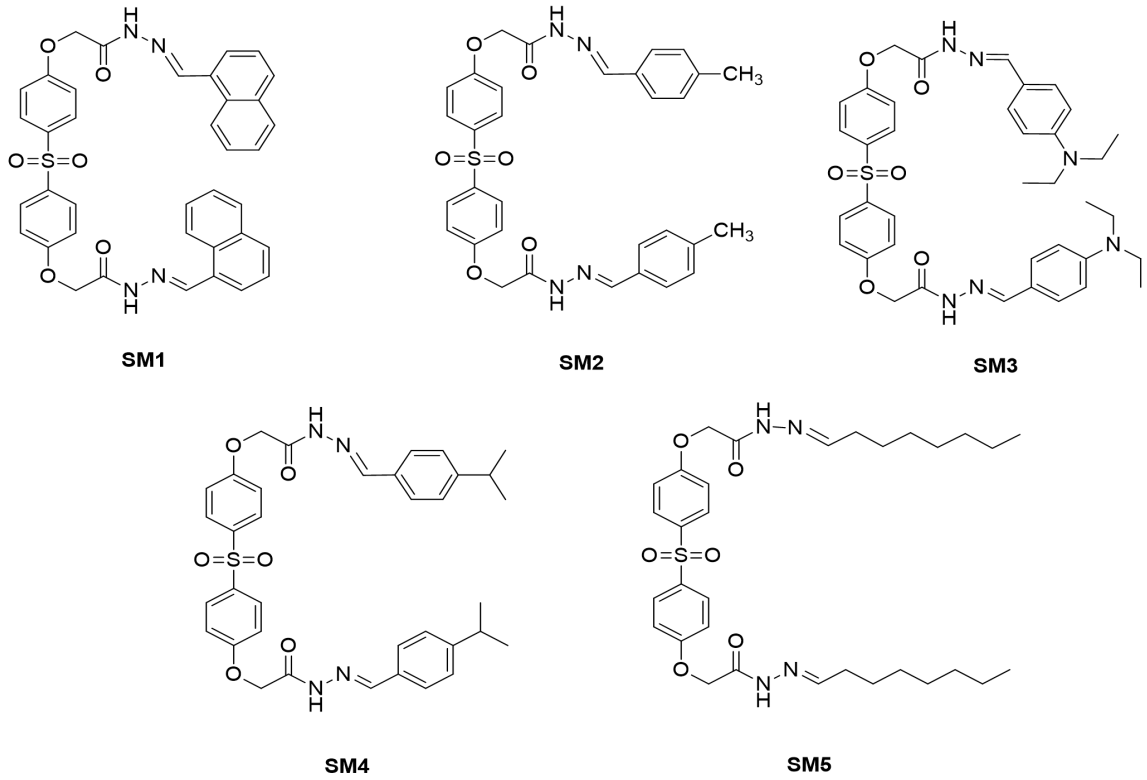

FIGURE 3. STRUCTURAL FORMULAE OF GROUP-1 COMPOUNDS SM1-SM5

RESULT AND DISCUSSION

MOLECULAR DOCKING (SM1-SM5)

The literature studies shows that structural variation link between the active site of COX-1 and COX-2 plays a key role in designing of targeted inhibitors. Molecular docking investigation of Group-1 **(SM1-SM5)** against COX-1 and COX-2 was carried out to predict binding and orientation nature of selected compounds in active packet of COX-1 and COX-2. Auto dock study were used for docking, which successfully docked the title compounds **(SM1-SM5)** in the active pocket of COX-1 and COX-2. Binding energy, and residue involved in hydrogen bonding are summarized in **Table 1**. The selected compound **SM1-SM5** exhibit docking score of -17.48 kcal/mol, -16.01 kcal/mol, -15.60 kcal/mol, -14.73 kcal/mol, -10.13 kcal/mol against COX-1 and -10.60 kcal/mol, -9.85 kcal/mol, 9.80 kcal/mol, -7.98 kcal/mol, -7.01 kcal/mol against COX-2. The description of **SM1** were selected according to lowest binding energy pose.

SM1 compound fitted best into COX-1 active binding sites. **SM1** form Hydrogen bonding (S=O...HN, S=O...HN) interaction with CYS-47 and CYS-41 residues of COX-1 with bonds distances 2.1Å and 2.3Å but also one weak π...π interaction (S=O...O=N, 2.5Å)GLY-45 and form hydrogen bonds (S=O...HN, 1.9Å) ARG-222, (O...HN, 2.3Å) ARG-240 (C=O...HN, 2.7Å) ARG-240, (C=O...HN,1.7Å) GLU-272 residues of COX-2 and form 2 weak π...π interaction (N...O=C,3.6Å) GLU-236,(N...O=C,3.2Å) GLN-270 . to demonstrate **SM2** was also selected according to lowest binding energy pose, compound **SM2** fitted best into COX-1 active binding sites. SM2 form Hydrogen bonds with GLN-461 (S=O...HN, 2.6Å) residues of COX-1 and form weak π...π interactions (S=O...O=S,2.8Å)GLN-461,(N...O=N,3.0Å)ASP-135 given in and ARG-222 (S=O...HN, 2.5Å), GLU-236(S=O...HN,2.2Å), GLU-236 (NH...O=C, 2.0Å), ASR-239 (NH...O=C, 2.2Å), and form weak π...π interactions residues of COX-2 (S=O...O=C, 3.1Å)GLU-290,(N...O=C,3.0Å) ASR-237. Interaction study of COX-1

with **SM3** possess three hydrogen bonds with CYS-41 (S=O…HN, 2.1Å), ARG-469 (C=O…HN, 2.3Å), TYR-130 (O…HO, 2.6Å) residues and form weak π…π interactions (N…O=N,.3.5Å) ARG-469 given in. the interaction of COX-2 with **SM3** possess no hydrogen bond but form a weak π…π interactions with (N…O=S.3.0Å) ASN-375. The interaction pattern of **SM4** was selected according to lowest binding energy pose SM4 fitted best into COX-1 active binding sites which allows compound **SM4** to form Hydrogen bonding with (C=O…HO, 2.0Å) TYR-130, (NH…O=N, 2.3Å) GLY-45, (O…HN, 1.9Å) CYS-47 residues of COX-1 and form weak π…π interactions (S=O…O=N, 3.4Å) CYS-41, (S=O…O=N, 3.4Å) TYR-39, (S=O…O=S, 2.4Å) GLU-465 (S=O…O=S, 2.4Å) GLN-461 and (C=O…HN, 3.3Å) ARG-240, (NH…O=C, 2.5Å) GLU-272 residues of COX-2 and form weak π…π interactions (S=O…O=C,3.3Å) ASP-213. the interactive study of COX-1 with SM5 exhibit only one hydrogen bond (O…HN, 2.8Å) with ARG-469 and having no π…π interactions and possess two hydrogen bond when interact with COX-2 (C=O…HN, 1.9Å) THR-212, (C=O…HO, 2.2Å) THR-212 residues and having no π…π interactions. The 3D interaction of COX-1 with SM1-SM5 are given in **Figure 4** and The 3D interaction of COX-2 with SM1-SM5 are given in **Figure 5** The commercially available drug standard Ibrofen which having binding energy -8.81 kcal/mol against COX-1 and -7.13 kcal/mol against COX-2 (Mousa, Al-Obaidi, & Alkhafaji, 2021). Among the tested compounds, SM1 (-17.48 kcal/mol) exhibit best inhibitory activity against COX-1 and SM1 compound (-10.60kcal/mol) against COX-2 as compared to other tested compounds and as well as standard Ibrofen.

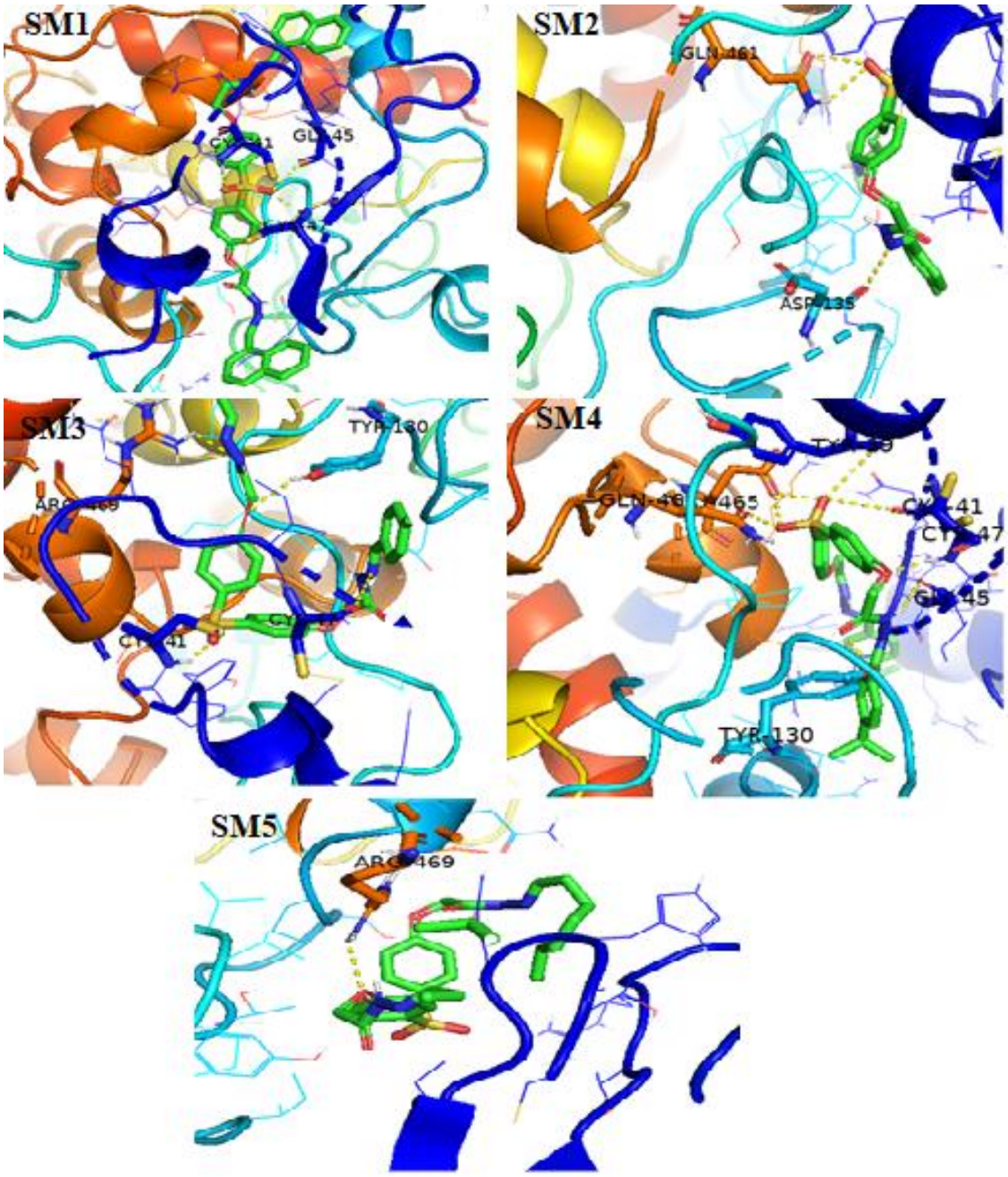

FIGURE 4. BINDING POSES OF SM1-SM5 WITH COX-1

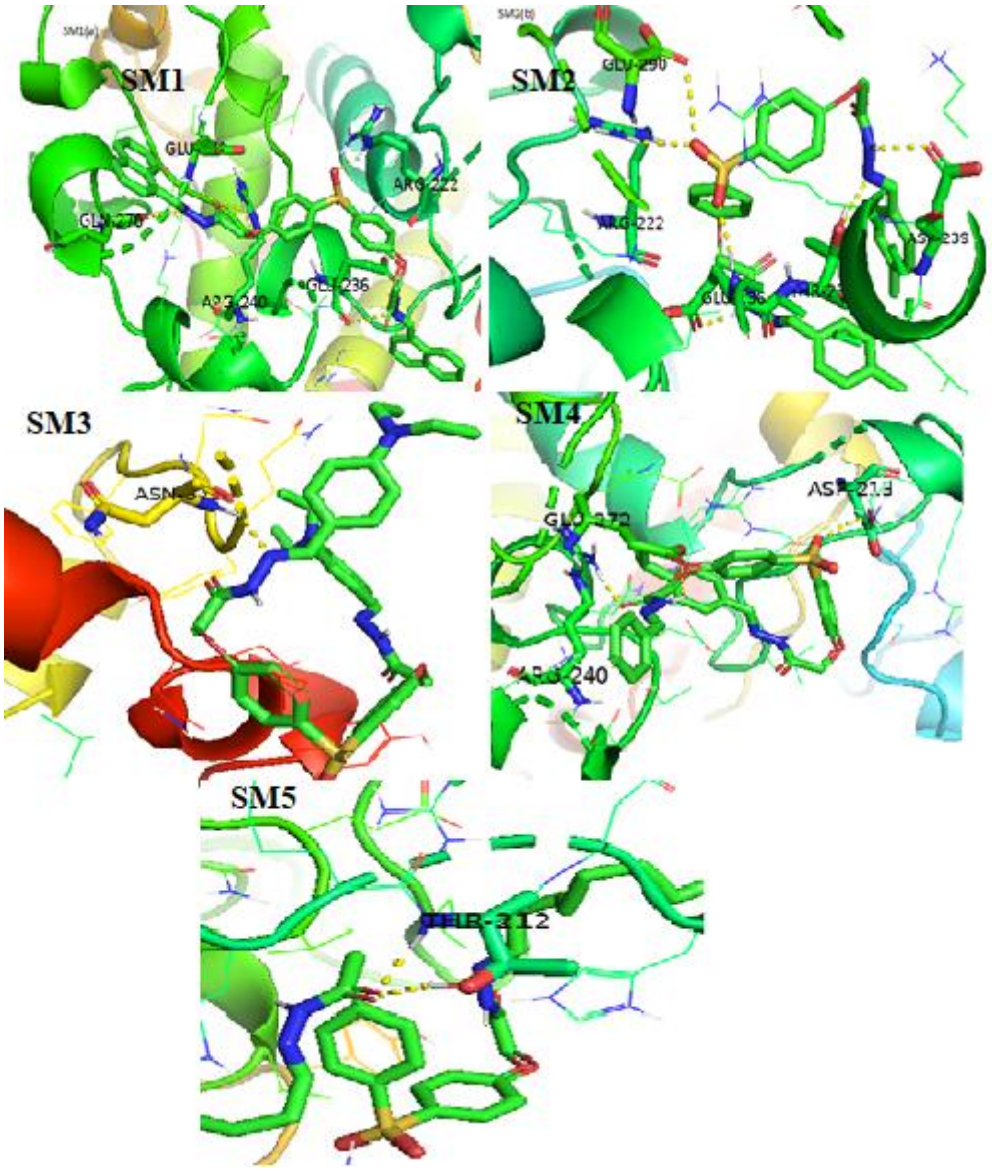

FIGURE 5: BINDING POSES OF SM1-SM5 WITH COX-2

TABLE 1 SUMMARY OF BINDING ENERGY AND INTERACTION OF COX-1 AND COX-2 WITH COMPOUNDS (SM1-SM5)

Ligands	Binding score of COX-1(kcal/mol)	Residue of COX-1 involved in hydrogen bonding	Binding score of COX-2(kcal/mol)	Residue of COX-2 involved in hydrogen bonding
SM1	-17.48	CYS-47, CYS-41	-10.60	ARG-222, ARG-240, GLU-272
SM2	-16.01	GLN-461	-9.85	ARG-222, GLU-236, ASR-239
SM3	-15.66	CYS-41, ARG469, TYR-130	-9.80	No hydrogen bond
SM4	-14.73	TYR-130, GLY-45, CYS-47	-7.98	ARG-248, GLU-273
SM5	-10.13	GLN-44, ARG-61, ARG-83 ARG-79, ARG-79	-7.01	THR-212
Ibrofen	-8.81	CYS_41	-7.13	Gly-533

CONCLUSION

Sulphones and hydrazone-containing synthetic open chain supramolecular compounds that we have chosen include SM (1-5). Molecular docking shows that supramolecular compounds exhibit binding energy - 17.48 kcal/mol to -10.13 kcal/mol against COX-1 and -10.60 kcal/mol to -7.01 kcal/mol against COX-2 Compare with standard drug Ibrofen which having binding energy -8.81 kcal/mol against COX-1 and -7.13 kcal/mol against COX-2. The above-mentioned compounds show better inhibitory activity against COX-1 and COX-2. These inhibitors will be useful in future against COX-1 and COX-2

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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