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Docking and QSAR studies of novel (E)-3-(4-methanesulfonylphenyl)-2-(aryl) acrylic acids as dual inhibitors of cyclooxygenases and lipoxygenases

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Abstract: It is recently proposed that compounds with equal capabilities of inhibiting COX-II and 5-LOX, both are key enzymes involved in the arachidonic acid (AA) cascade, are expected to be safer non-steroidal anti-inflammatory drugs (NSAIDs). To dig out helpful information in designing dual functional inhibitors against the two enzymes, , molecular modeling, automated docking, and QSAR analyses were performed in this study on COX-2/5-LOX dual inhibitors, namely, (E)-3-(4-methanesulfonylphenyl)-2-(aryl)acrylic acids analogues. The structures were built by HYPERCHEM program and Conformational studies were performed through semi-empirical method followed by PM3 method. QSAR descriptors were obtained from the EDRAGON. QSAR equations were got from multi linear regression method. Docking study was performed by using autoDock4 program on the all compounds that have already been reported by Kanus et al. Both the docking simulations and QSAR analyses suggest that new potent dual inhibitors. Therefore, the final QSAR models and the information of the inhibitor–enzyme interaction should be useful in developing new NSAIDs as anti-inflammation drugs with favorable safety profile.
Keyword: acrylic acids, Molecular modeling, Docking, QSAR, COXII, 5-LOX.

Introduction

Two major enzyme families that include the lipoxygenases (5-LOX) and the cyclooxygenases (COX 2) metabolize arachidonic acid (AA). Proinflammatory leukotrienes (LTs) produced via the LOX pathway, and prostaglandins (PGs) produced via the COX pathway, are associated with adverse physiologic processes such as inflammation, fever, arthritis, bronchospasm [1] and the etiology of cancer.[2] Two of the three major isoforms (5-, 12- and 15-LOX) observed in humans cause undesirable physiological effects. In this regard, 5-LOX is implicated in the production of LTs that are associated with inflammatory, bronchoconstrictor, hypersensitivity, anaphylactic and asthmatic actions.[1] and [3-4] Alternatively, PGs that induce undesirable inflammation, fever and pain are produced via the inducible COX-2 isozyme whereas PGs that regulate desirable gastrointestinal cytoprotective and renal functions are produced via the constitutive COX-1 isozyme.[1] and [5].It is generally agreed that a dual inhibitor of the LOX/COX enzymatic pathways6 constitutes a rational concept for the design of more efficacious anti-inflammatory agents with an improved safety profile relative to ulcerogenic non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors that increase the incidence of adverse cardiovascular thrombotic effects.[6-7] and [8].Based on mentioned subject the computational studies on these compounds plays main role to rational design of dual inhibitors.The structures of desired compounds were built by using HYPERCHEM program. Conformations of the designed compounds were optimized through semi-empirical method followed by PM3 calculation by using the HYPERCHEM software. Among all energy

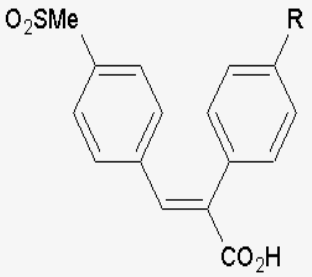
minima conformers, the global minimum was selected. The crystal structure of COXII and 5-LOX were obtained from the Protein Data Bank (PDB) server .Then Docking calculations were carried out using Auto Dock program (Ver4) program. The QSAR descriptors were obtained from the EDRAGON. Finally, via a stepwise regression analysis, some main independent factors affecting the activity of the compounds were selected out, and then the QSAR equation was established.

Materials and Methods

a) Data Set

Our QSAR models will be computed based on the COXII and 5-LOX inhibitors activity, PIC50, for a set of six derivatives that were synthesized in pervious experiment by kanus et al. The general formula of the derivatives, their chemical structure, experimental PIC50 and calculated PIC50 values are presented in Table 1,2.

Table 1. structures of (E)-2-(phenyl or biphenyl)-3-(4-methanesulfonylphenyl) acrylic acids agents and PIC_{50} of COXII.



Comp.	R	pIC_{50} Exp.[a]	pIC_{50} Calc.[b]
9a	H	5.52	5.55
9b	Br	5.44	5.47
9c	F	4.44	4.45
9d	OH	5.28	5.25
9e	OMe	5.72	5.73
9f	OAc	5.54	5.50

a) The Experimental PIC_{50}.
b) The PIC_{50} By using multi linear regression equation 1

Table 2. PIC_{50} of 5-LOX.

Comp.	pIC_{50} Exp.[a]	pIC_{50} Calc.[b]
9a	5.00	5.04
9b	4.98	5.04
9c	5.89	5.91
9d	6.25	6.29
9e	4.96	4.95
9f	5.00	5.04

a) The Experimental PIC_{50}.
b) The PIC_{50} By using multi linear regression equation 2.

b) Molecular Modeling

The chemical structures of inhibitors (table 1,2) were constructed using Hyperchem software (version 7, Hypercube Inc.) . Semi-empirical molecular orbital calculations (PM3) of the structure were performed using the Hyperchem program and the among all energy minima conformers (two favored tautomers), the global minimum of compounds were consider in docking calculations.

c) Docking

Docking calculations were performed using Auto dock software (version 4). The models of COXII and 5-LOX, (Fig1) that were generated by resorting to multi body molecular dynamics simulations were downloading from the PDB bank server (PDB entry 1T0J).

In order to assign the perfect grid of each ligand, grid box values that were obtained by trial and error and previous study (Fig 2) .Finally docking was performed using the implemented Lamarckin GL and the default parameters and ten independent docking runs were performed for each DHPs.

Fig1_ COXII receptor (PDB entry: 6COX)

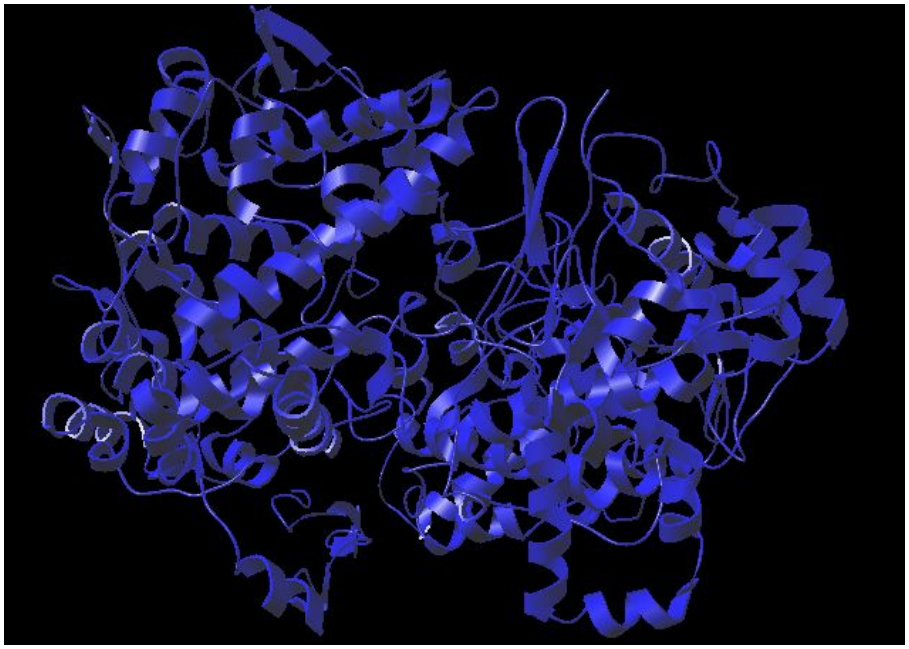
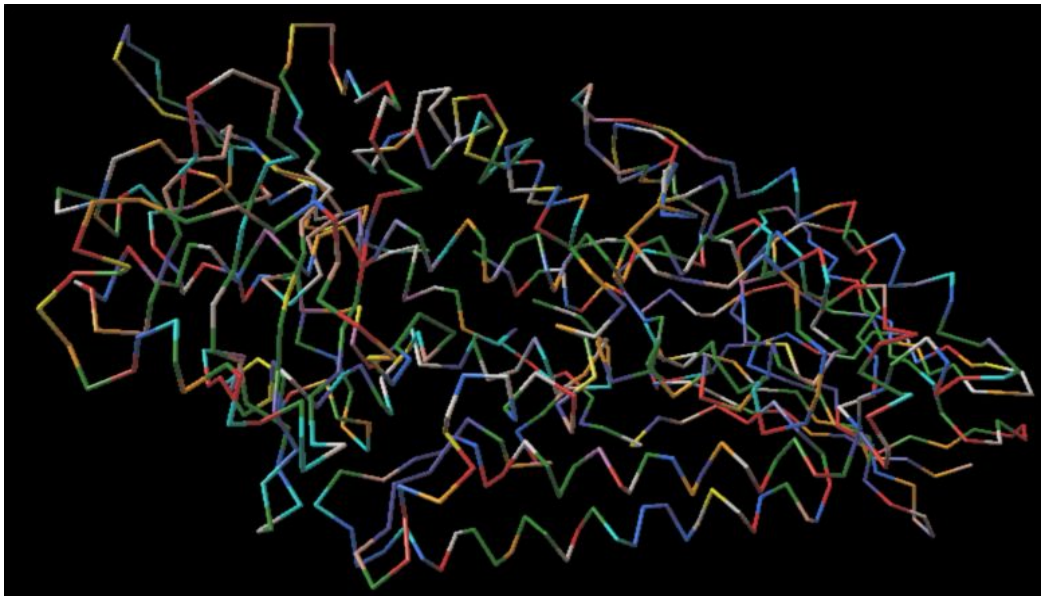


Fig2_ 5-LOX receptor.



d) Computation of Structural Descriptors and QSAR equations

Quantitative structure activity relationships (QSAR) are widely used in the drug design process whenever detailed structural information on the ligand-receptor interactions are not experimentally available [9-11]. QSAR models are mathematical equations relating chemical structure to their biological activity [12-15]. The first component in the definition of a QSAR model is the computation of the structural descriptors from the three-dimensional molecular structure; various geometrical, quantum, or molecular field descriptors were proposed in recent years to replace the Hansch substituent constants [9-11],The second component in a QSAR model is an explicit mathematical structure-activity equation establishing a statistical relationship between a dependent variable (biological activity) and a set of independent variables (descriptors)[9-11].The mathematical QSAR equations can be computed with the help of a large number of statistical models, such as multi linear regression, partial least squares (PLS) [16-19]. For this study, many descriptors were calculated by the EDRAGON programs for all the compounds[19]. To select the set of descriptors that are most relevant to the IC_{50} of these agents, the MLR models were built and the QSAR equations with stepwise selection and elimination of variables were established by MLR method.

Results

Docking

Flexible docking of all data sets used for the computational study was carried out on the active site of 5-LOX and COXII. The orientation of the most potent inhibitors, compounds 9e,9d , in the active site of COXII and 5-LOX respectively were examined by a docking experiment (Figure 3).[20] This molecular modeling shows the Oxygen of SO2 substituent forms a hydrogen bonding interaction with the OH of TYR385(distance=2.92) in 9e . The Hydrogen of OH forms hydrogen bond with the OH of GLU384 (distance=1.88) in 9d. The results of both receptors shown in table 3.These observations and experimental results provide a good explanation for the potent and selective inhibitory activity of these compounds.

Fig3_ Docked structures of 9e(a), 9e (b) in Model of COXII, and Docked structures of 9d(c) in Model of 5-LOX.

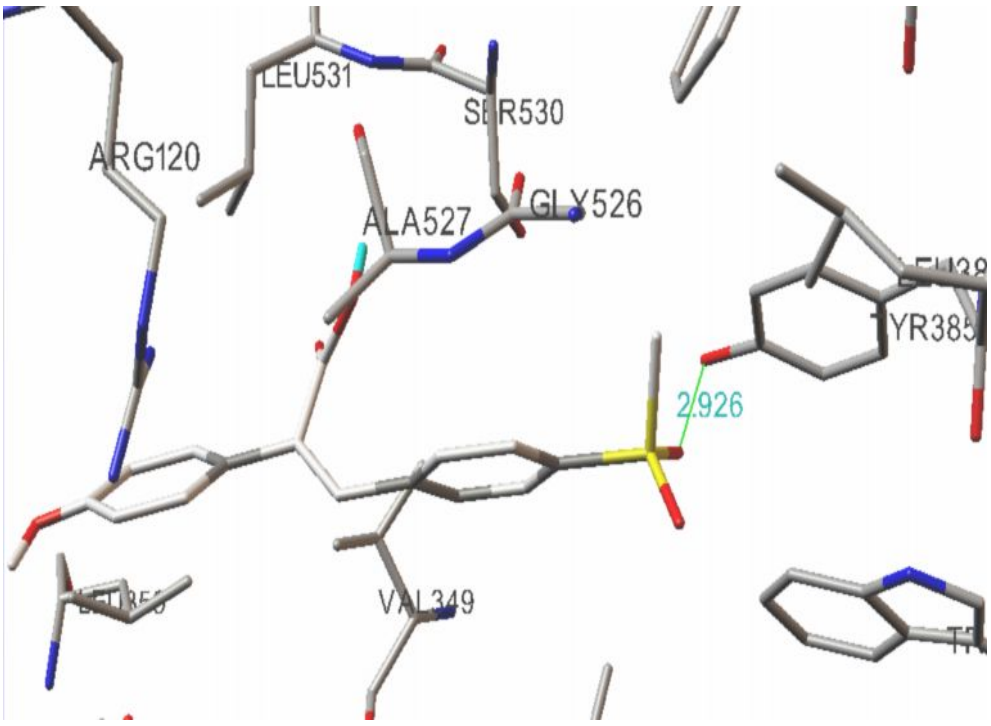


Fig 3(a)

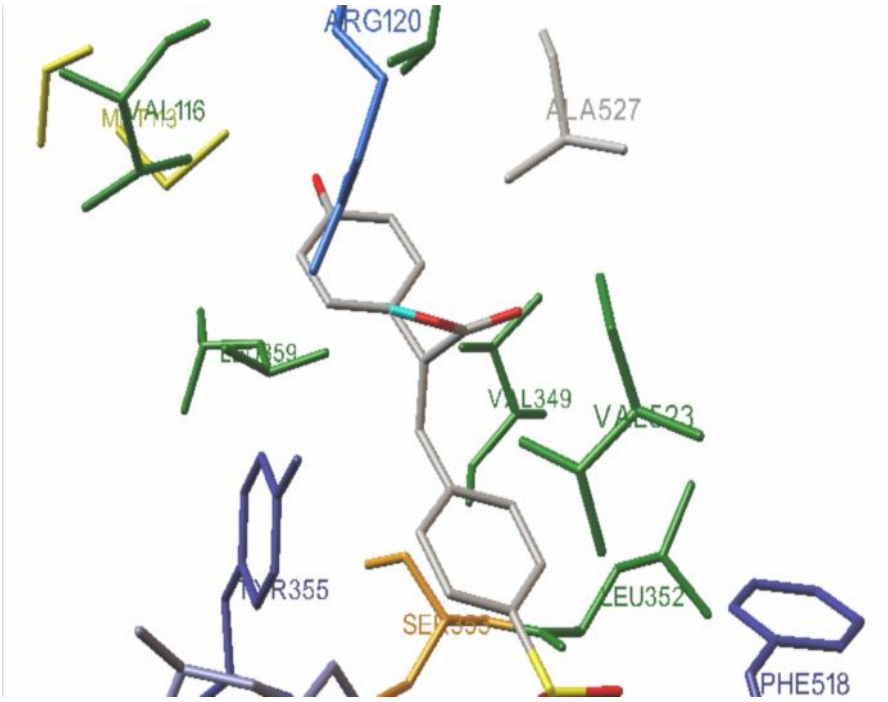

ARG120
ALA527
VAL349
TYR355
LEU352
PHE518

Fig 3(b)

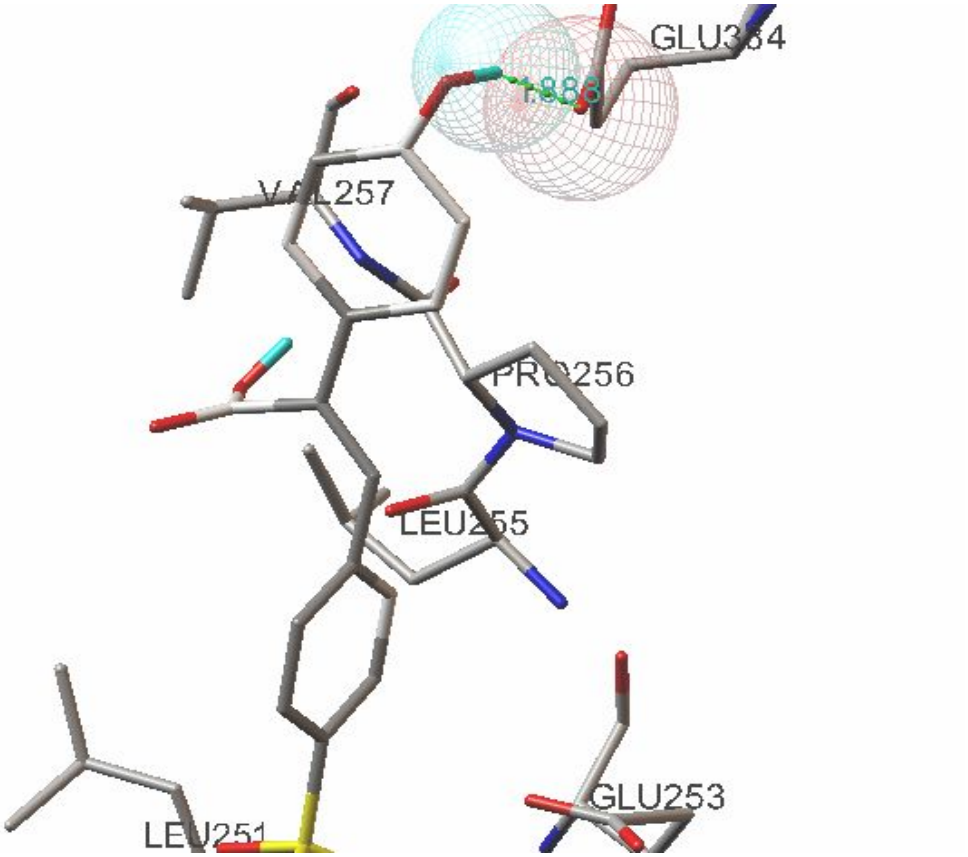

GLU354
1.886
LEU255
GLU253

Fig 3(c)

Table 3. Docking results by using AutoDock 4 software.

DHP's	Binding energy [a]	Binding energy [b]
9a	-7.55	-4.88
9b	-7.36	-4.56
9c	-7.03	-5.12
9d	-7.21	-5.33
9e	-7.88	-4.15
9f	-7.65	-4.13

a) The predicted binding energy for COXII inhibitors (kcal/mol)
b) The predicted binding energy for 5-LOX inhibitors (kcal/mol)

c) QSAR equation

By using a stepwise multiple linear regression method, two QSAR equations were obtained as Follows for each part. In the QSAR equations, n is the number of data points, R^2 is the correlation coefficient, S is the standard deviation, F is the Fisher's F-value, , q^2 is the LOO cross-validated coefficient, which was obtained by a multiple linear regression.

y_i is the actual activity ,y is the average actual activity,

y_i^ is the predicted activity of compound i computed

by the new regression equation.

$$q^2=1-\frac{\Sigma\left(y_i-\hat{y}_i\right)^2}{\Sigma\left(y_i-\bar{y}\right)^2}$$

Large F, small S, very small p-value, as well as R2 and q2 values close to one indicate a good QSAR model. In general, the regression model is significant at p-value <0.001 using the F statistics, so the below QSAR models are all significant.

Eq. (1) COXII pIC_{50}= -34.052*E3V-5.763*E1S +13.881

n=6 F=460 R^2=0.99 S=0.03 q^2= 0.88 p<0.0001

Eq. (2) 5-LOX pIC_{50}= 14.76*Hnar+32.04*H1e-87.64

n=6 F=750 R^2=0.99 S=0.04 q^2= 0.93 p<0.0001

In equation that belongs of COXII (Eq1), The E3v and E1s belong to the descriptors of WHIM descriptors. The WHIM descriptors appeared in our model indicating the relevant feature of electro-topological state factors that might be considered in compounds with COX receptor bindings. The appearance of E3v descriptor in this equation also considers, indirectly, the vdw volume weighted properties. E1s descriptor in this equation considers electro-topological state weighted. In equation that belongs of 5-LOX, H1e is the GETAWAY descriptors. The GETAWAY descriptors (Geometric Topology and Atom Weights Assembly) are related to the influence of the atoms in the determination of the molecular form, and to the distance between them. And Hnar is Narumi harmonic topological index, Topological descriptors, that most related about the structure of compounds [21]. Finally, plots of cross-validated calculated activity and the experimental values for equation c and d are represented in Figs. 4a and 4b, respectively.

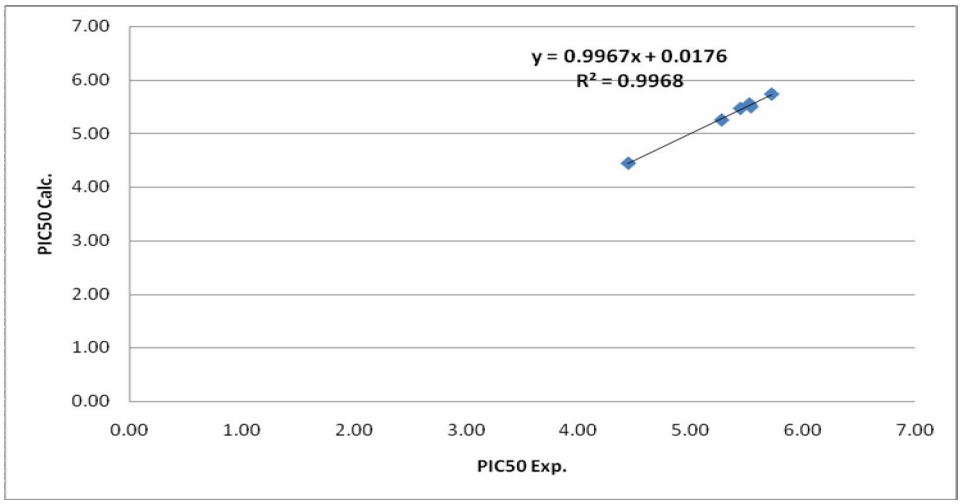


Figure 4a) Equation for COXII

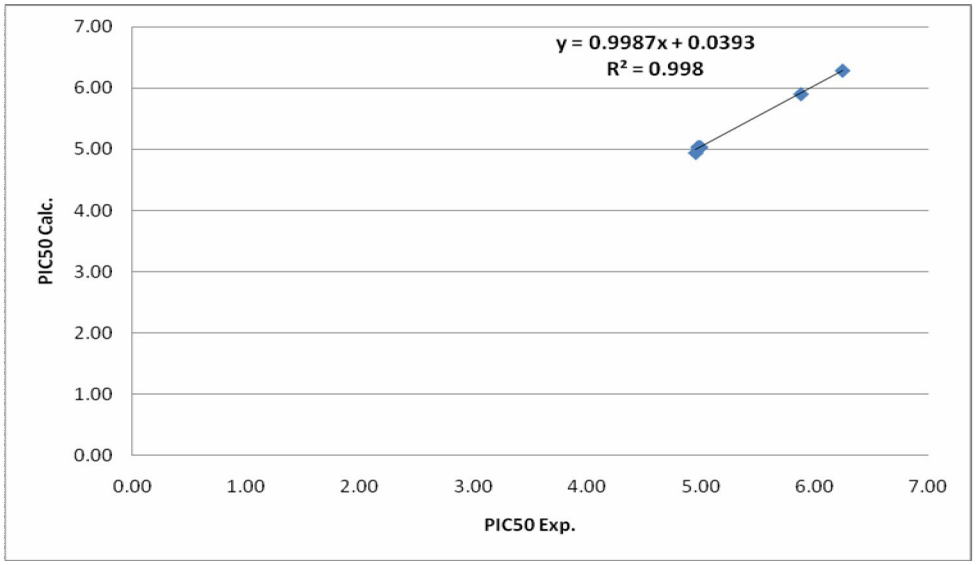


Figure 4b) Equation for 5-LOX

Conclusion

Based on the above results, In the main time the volume and size of molecule effect on results. By Docking study, we show the COXII inhibitors cited in known active site and for 5-LOX we need extra X-ray information about active site but the good interaction show this model can be reliable .The results obtained from QSAR equations emphasize that Mass , Volume and topological properties are so important in COXII and 5-LOX potency. We hope the results from the present Study are presently being used for the design of newer compounds with better activities.

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