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Exploring Binding Modes of 5-Substituted 1h-Tetrazoles as Cyclooxygenase Inhibitors: A Molecular Docking Study

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ABSTRACT

Cyclooxygenases, which exists in two forms COX-1 and COX-2, are essential enzymes in the synthesis of Prostaglandin H, involves in the biosynthesis of Thromboxanes, and Prostacyclins. The inhibition of biological activity of these enzymes has very therapeutic importance in many pathological conditions. Many non-steroidal anti-inflammatory drugs (NSAIDs) have been used against these enzymes but mostly lead to side effects. Recently reported several synthetic compounds (5-substituted 1H-terazoles) which are experimentally shown to inhibit cyclooxygenases activity in the low micromolar range. We performed a computational study to help identify possible binding modes by docking these compounds onto the active site of cyclooxygenase-2 (COX-2) and to characterize the structures of binding complexes via MOE-Dock as docking software. Good correlations were found in docking scores and experimental values of these compounds against COX-2. The top-ranked conformation of each compound was interpreted for binding interactions with the residues of the binding cavity of the COX-2 enzyme. The predicted binding modes of these compounds prioritized structural features required for their biological activities. According to our study, the functional groups with nonpolar nature might be one of the reasons to enhance the biological activity of these inhibitors against cyclooxygenase, while the polar and bulky group might lead to less activity. The observed findings might be exploited to design more potential COX-2 inhibitors. The present computational analysis complements the corresponding experimental investigation and helps establish a good starting point for further refinement of COX-2 inhibitors.

KEYWORDS: Cycoloxygenase Inhibitor; Molecular docking; Tetrazole; MOE

1 INTRODUCTION

Cyclooxygenases (COXs) 1 and 2, also identified as Prostaglandin endoperoxidase H systhases (PGHSs) 1 and 2 (Rouzer and Marnett 2009; Schneider et al., 2007; Smith 2008; Smith et al., 2002; Van der Donk and Kulmacz 2002; Ranjinder et al., 2010) are indispensable enzymes in the synthesis of Prostaglandin H, which is involved in the biosynthesis of series-2 prostaglandins, prostacyclins and thromboxanes (Hamberg and Samuelsson 1973).

Three isoforms of this enzyme have been identified (COX-1, COX-2, COX-3). COX-1 is constitutively expressed in most tissues and is believed to generate prostaglandin (PG) for physiological functions such as the regulation of vascular homeostasis, protection of the gastric mucosa and renal maintaining integrity. COX-2, by contrast, was almost undetectable at physiological conditions in most tissues. However, its expression is up-regulated by pro-inflammatory stimuli, growth factors and mitogens, and is implicated in pathological conditions, including inflammation (Chandrasekharan et al., 2002). Recently, a third isoform COX-3 was cloned and shown to share the catalytic properties of the COX-1 and COX-2 (Vane et al., 1998).Both COXs (COX-1, COX-2) isoforms are homodimers made up of ~72 kDa subunits which are strongly bound to each other through an 2500 Å2 interface spanning (Laskowski et al., 1997). Every COXs monomer consists of a membrane binding domain (MBD), an epidermal growth factor-like domain of strange function, and a vast catalytic core (Picot et al., 1994). The bifunctional catalytic subunit keeps both Cyclooxygenase and peroxidase enzymatic activities (Garavito and Mulichak 2003). The 3-dimensional structure of the COX-2 enzyme protein was retrieved from Protein Data Bank (PDB) with ID 1CX2. The 1CX2 is a complex of four homologous chains with an inhibitor SC-558 (http://www.rcsb.org/pdb/home/home.do. Accessed 10 March 2013). Molecules that are inhibitors of this enzyme would be of therapeutic value (Qi et al., 2002). Both COXs isoforms are targets of non-selective (nsNSAIDs), for example ibuprofen and aspirin, whereas COX-2 can also be blocked selectively by diarylheterocyclic COX-2 specific inhibitors called coxibs (Prusakiewicz et al., 2009).

The discovery of COX-2 enzyme near the beginning in the 1990s and further its characterization led to the inception of the assumption that selective inhibitors of this isoform would posses similar clinical efficacy, although reduced ulcerogenicity than usual (NSAIDs), which were having both non-selective COX-1 and COX-2 inhibitors following Rofecoxib and Celecoxib where the first Cyclooygenase-2 selective inhibitors arrive at the market and then followed by Valdecoxib and Etoricoxib (Meade et al., 1993; Xie et al., 1991; Talley et al., 2000; Ormrod et al., 2002). The therapeutic applications of selective Cyclooygenase-2 inhibitors have been widely extended ahead of the field of inflammation and analgesia (Friesen et al. 1998; Riendeau et al., 2001).Conventional (NSAIDs) are employed at large scale in the treatment

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of osteoarthritis, rheumatoid Arthritis, and pain, etc. but, it as well has side-effects on the gastrointestinal tract (G.I.T), for example intestinal ulcers and gastric lesions, which happen frequently. The NSAIDs have the potential to inhibit the both COXs isoform, the key enzyme in prostaglandin biosynthesis (Qi et al., 2002). It is believed that the conventional NSAIDs inhibit both COX isoform activities and that Cyclooxygnse-1 inhibition causes the side-effects on the G.I.T, etc. Hence, COX-2 selective inhibitors were predictable to be the next generation NSAIDs with less side-effects on the G.I.T (Prusakiewicz et al., 2009).

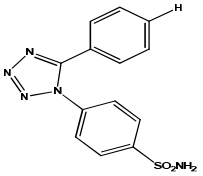
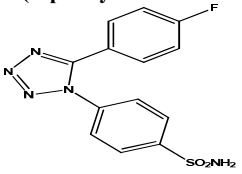
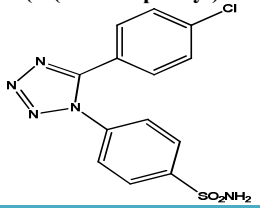
It has been reported that various 1,5-diaryl substituted tetra-zoles containing a 4-(methylsulfonyl) phenyl substituent attached to position 1 of the tetrazole ring have good inhibitory activities against COX-2 enzyme (Al-Hourani et al., 2011). All these tetrazoles possess a tricyclic scaffold containing a central heterocyclic ring system with two vicinal aryl substituents as typically found in many selective and potent COX-2 inhibitors. One series (1-8) contains a sulfonamide (SO2NH2) group; the other series of tetrazoles (9–16) contains a methylsulfonyl (SO2Me) group.There are different techniques used in in-silico drug design visualization, molecular dynamic, homology, energy minimization molecular docking and QSAR etc. (Wadood et al., 2013). Molecular docking is a computational method that can be used to explain the interactions of ligands with the receptor. There are a number of docking methods. Among them one is the MOE-Dock method (http://www.chemcomp.com). In MOE-Dock method, docking small molecules to macromolecular binding sites provide a database of conformations or conformations generated on the fly. Choose among several scoring functions, and optionally the force generated to satisfy a query positions pharmacophore search bias towards important interactions known. Refine the poses using a method based on force field to score MM / GBVI or a method based on the network quickly. FlexX is an interface for virtual screening provides high performance. The docking architecture is parallelized using technology MOE / smp (Labute P, 2008). We applied this method to explore the binding interactions of some 5-substituted 1H tetrazoles as COX-2 inhibitors.

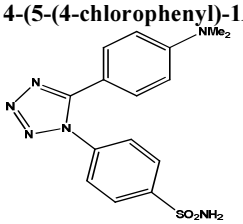
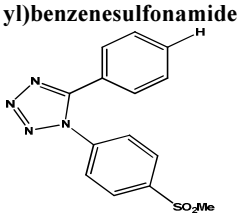
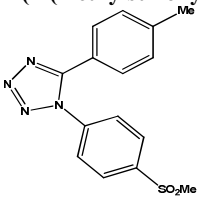
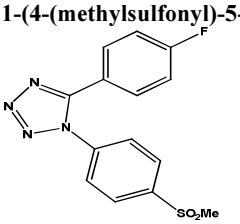
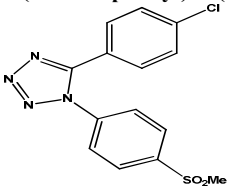
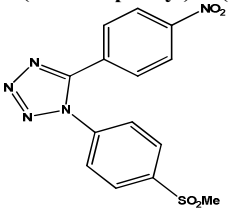
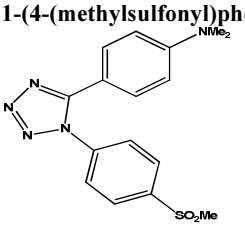
2.MATERIALS AND METHODS

In this study the molecular docking of some 5-substituted 1H tetrazoles into the binding pocket of COX2 (PDB: 1CX2) protein was performed using MOE-Dock as docking software implemented in MOE (Molecular Operating Environment) software package. LigPlot implemented in MOE was used to observe the interactions between COX-2 and ligands.

2.1. **Retrieval of modeling of ligands.** The structures and biological activities of known 5-substituted 1H tetrazoles as COX-2 inhibitors were collected from the published literature (Al-Hourani et al., 2012). The MOE-Builder tool was used to construct the structures of all the inhibitors. The 2D structures and their biological activities of these compounds are given in **Table 1**. The three dimensional (3D) structure of all the ligands was modeled using MOE. All the 3D structures were then energy minimized with default parameters via MOE energy minimization algorithm [gradient: 0.05, Force Field: MMFF94X].

Table 1. Structures, biological activities and docking scores of the compounds against COX-2 enzyme.

S.no	Structures	IC_{50} (µM)	Docking Scores	p Docking Scores
1	 **4-(5-phenyl-1*H*-tetrazole-1-yl)benzenesulfonamide**	**15**	**-13.4891**	**1.1299**
2	 **4-(5-(4-fluorophenyl)-1*H*-tetrazole-1-yl)benzenesulfonamide**	**56**	**-12.3298**	**1.0909**
3		**62**	**-12.0785**	**1.0820**

	4-(5-(4-chlorophenyl)-1*H*-tetrazole-1-yl)benzenesulfonamide			
4		**07**	**-13.8747**	**1.1422**
	4-(5-(4-(dimethylamino)phenyl)-1*H*-tetrazole-1-yl)benzenesulfonamide			
5		**30**	**-12.8920**	**1.1133**
	1-(4-(methylsulfonyl)-5-phenyl-1*H*-tetrazole			
6		**87**	**-12.0049**	**1.0793**
	1-(4-(methylsulfonyl)-5-p-tolyl-1*H*-tetrazole			
7		**15**	**-13.3966**	**1.1269**
	5-(4-fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole			
8		**32**	**-12.7158**	**1.1043**
	5-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole			
9		**69**	**-12.0518**	**1.0810**
	1-(4-(methylsulfonyl)phenyl)-5-(4-nitrophenyl)-1-*H*-tetrazole			
10		**6**	**-13.9205**	**1.1436**
	***N*,*N*-dimethyl-4-(1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole-5-yl)aniline**			

2.2.**Preparation of receptor protein.** The protein molecule of cyclooxygenase was retrieved from Protein Data Bank [PDB Code 1CX2]. The water molecules were removed and then 3D protonation of the protein molecule was carried out. The energy of the retrieved protein molecule was minimized using with most of the default parameters of MOE energy minimization algorithm [gradient: 0.05, Force Field: Amber99].

2.3.**Molecular docking.** The molecular docking of the ligands were carried out by the MOE-Dock program keeping with the default parameters. The ligands were kept flexible in order to find the correct conformations and obtained minimum energy structures. At the end of docking, the top-ranked conformation of each ligand was analyzed for their binding interaction.

3. RESULTS AND DISCUSSION

3.1. Validation of the docking procedure. In order to assess the accuracy of the MOE-Dock program the co-crystallized ligand was removed from the active site and redocked into the binding cavity of COX-2. The root mean square deviation (RMSD) between the co-crystallized ligand and top-ranked docked conformation was observed to be 0.5892 Å (**Figure 1**), suggesting a high docking reliability of MOE-Dock in reproducing the experimentally observed binding mode for COX-2 inhibitors and the protocol set for the MOE-Dock is reasonable for to reproduce the X-ray structure (Wadood et al., 2013). The MOE-Dock and the set protocol could be extended to explore the COX-2 binding modes for other inhibitors accordingly.

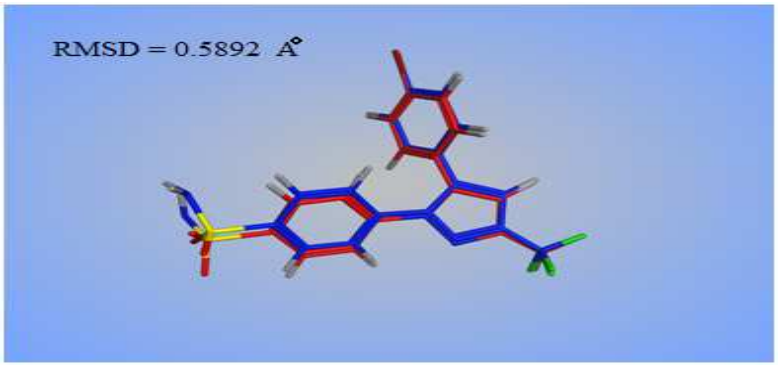


Figure 1. Conformational comparison of the co-crystalized ligand extracted from the complex structure (red) COX-2 enzyme and the docked conformation (blue).

3.2. Correlation between docking scores and IC50 values. From the docking results a good correlation between docking scores and biological activities of COX-2 was observed (**Table 1** and **Figure 2**). The observed correlation coefficient (r^2 = 0.931) between p-docking score and IC50 values of the ligands suggest that the docking protocol is reliable.

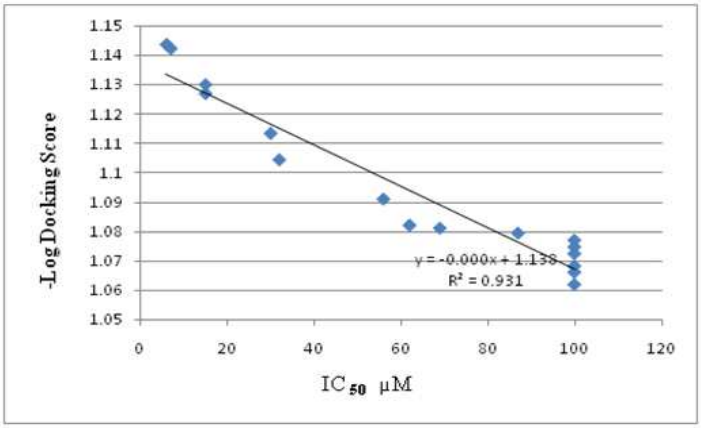


Figure 2. Correlation graph between docking scores and biological activities of the compounds.

3.3. Predicted binding modes in 5-substituted 1H-tetrazoles as COX-2 inhibitors. From the docking conformations of equipotent compounds 10 and 4 (Table 1) it was observed that both compounds established three hydrogen bonds with the active site residues of the COX-2 enzyme (**Figure 3A and 3B**). In case of compound 4 the oxygen atom of sulfur dioxide moiety of the compound formed hydrogen bonds with His90 and the amino group attached with sulphur dioxide moiety formed hydrogen bonds with Gln192 respectively, whereas the nitrogen atom of 1H-tetrazole

established hydrogen bonds to Tyr355 (Figure 3A). The remaining oxygen of sulphur dioxide moiety expressed Van der Waals interactions with Val349 residue and the same kind of interaction is shown in the benzene ring with Gly526. The Similar binding mode was observed for compound 10 as shown in Figure 3A, in which two oxygens of sulphur dioxide moiety formed two hydrogen bonds with residues His90 and Gln192 and one nitrogen of the 1H-tetrazole expressed hydrogen bonding with Tyr355 residue while both of the benzene rings of the compound showed Van dar Waals interactions with the Ser530 residue of the pocket. Although a similar binding mode for both compounds was observed, but a slight difference in activities might be due to the presence of methylsulfonyl moiety in compound 4 that become this compound more hydrophobic as compared to compound 8 that has sulfonamide moiety.

From the docking conformation of compound 1 it was examined that oxygen atom of a sulfonamide moiety of the compound established two hydrogen bonds with the active site residues Arg513 and Tyr355. The benzene ring of the compound expressed Van dar Waals interaction with the Met522 (**Figure 3C**), whereas, with compound 7, the oxygen of the sulphur dioxide moiety formed one hydrogen bond with Try355 residue of the pocket. The benzene rings of the compound 7 showed Van dar Waals interactions towards Met522 (**Figure 3D**). From the docking results it was observed that the presence of dimethylamine moiety in compound 4 and 10 might be one of the reasons for their more activities as compare to compound 1 and 7. Due to the presence of this moiety compounds 4 and 10 were able to form more hydrogen bonds with the active site residues as compare to compound 1 and 7 (**Figure 3A, B, C & D**).

About analogous binding modes were observed for compounds 5 and 8 (**Figure 3E and 3F**). In case of compound 5 the oxygen atom of sulfomethane moiety of the compound formed hydrogen to Ser530 and with Tyr358, Van dar Waals interactions were observed whereas in case of compound 8 the nitrogen atom of 1H-tetrazole moiety of the compound formed hydrogen bond to Tyr355 in binding pocket of COX-2 enzyme, and the chloro group of the compound also showed the Van dar Waals interactions with Val523, one of the nitrogen atom of 1H-tetrazole ring expressed Van dar Waals interactions towards Val349 residue, furthermore, the two benzene ring expressed Van dar Waals interactions towards Trp387. These two compounds have nearly same activities (IC50 30-32 µM) and both the compounds showed one interaction with the active site residues (**Figure 3 E & F**). The relatively low inhibitory activity of compound 8 might be due to the presence of the electronegative chlorine group in this compound. The lower activity of these two compounds as compared to the compound 10 might be due to the absence of dimethyl ammine group in these compounds.

The compounds 2, 3 and 9 are also almost equipotent in the series (Table 1). Almost similar binding modes were observed for these compounds in the active site of the COX-2 enzyme (**Figure 4A, 4B and 4C**). From the docking conformation of compound 2 it was observed that the oxygen atom of methylsulfonamide moiety and nitrogen atom 1H-tetrazole ring of the compound established hydrogen bonds to Tyr385 and Tyr355 respectively. The residue Ser530 showed Van dar Waals interactions with the one of the benzene ring of the compound (Figure 4A). In case of compound 3 only one hydrogen bond was observed between oxygen moiety of a methysulfonamide moiety of the compound and the active site residue Tyr355. The chloro benzene ring showed Van dar Waals interaction with Gly526 and the other benzene expressed the same type of interaction with Leu531 (Figure 4B).

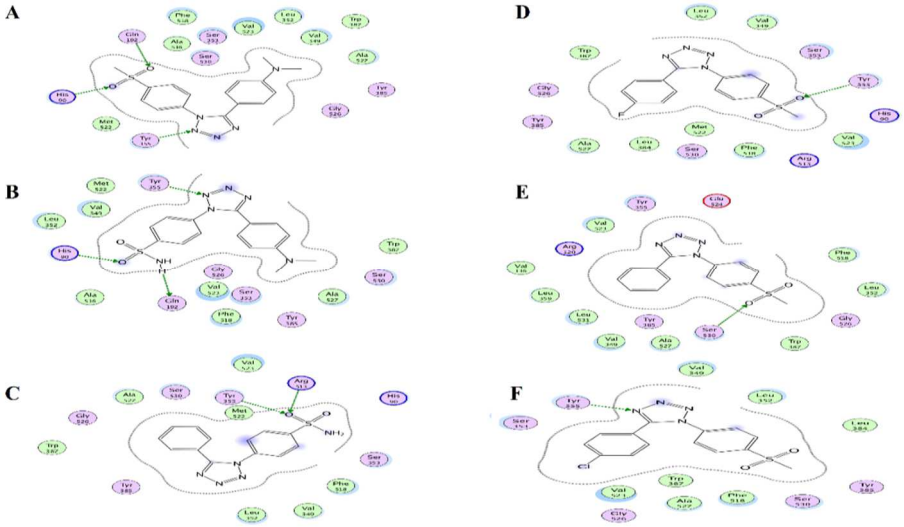


Figure 3. Docked conformation of compound 16 (A) and 8 (B) in the active site of COX-2 enzyme.

Docked conformation of compound 1 (C) and 12 (D) in the active site of COX-2 enzyme. Docked conformation of compound 9 (E) and 13 (F) in the active site of COX-2 enzyme. The docking conformation of compound 9 showed that two hydrogen bonds were formed between the oxygen atom hydrosulfonylmethane moiety and nitrogen atoms of 1H-tetrazole ring of the compound to the active site residues His90 and Tyr355 in the active site of the COX-2 enzyme

(**Figure 4C**). In these three compounds the groups with electron withdrawing inductive effect (F, Cl, N+O2) were observed to play an important role regarding interactions, docking score and inhibitory activity. Compound 2, containing fluorine group, was observed with good interaction, docking score and activity as compared to compound 3 containing chlorine, while these compounds have the same structural features with sulfonamide group. Compound 9, having Nitro group, was found almost similar to compound 2 regarding interaction and docking score, although, it is slightly less potent by activity. The relatively good docking score and interaction as compared to the activity of this compound might be due to the presence of methylsulfonyl group. Moreover, the structural features that make these compounds less active as compared to the most active compounds 4 and 10 are the presence of these polar electron withdrawing groups.
The remaining compounds 6, 7 and 5 also showed docking scores and predicted binding modes according to their inhibitory activities.

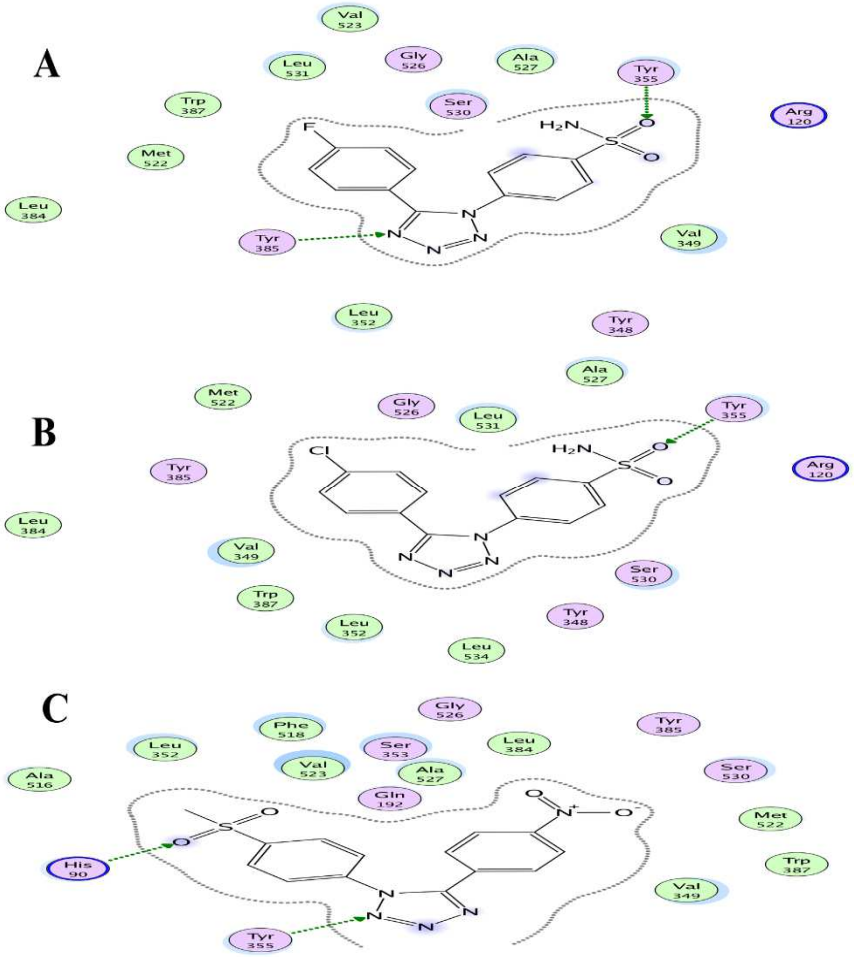


Figure 4. Docked conformation of compound 4 (A), 5 (B) and 15 (C) in the active site of COX-2 enzyme.

3.4. Designing of new compounds. New compounds were designed in MOE software by replacing functional groups R of 5-diaryl substituted tetra-zoles containing a 4-(methylsulfonyl) phenyl substituent or sulfonamide group substituent attached to the 1 position of the tetra-zole ring. The functional groups [-NH(C2H5), -NH-CH3, -NH2, -OH, -SH] were attached at R position as shown in **Table2**. As a result of that new inhibitors were obtained which were further docked with Cyclooxygenase (PDB code 1CX2) using MOE software.
The compound 1 and 2, which have similar functional group NH-CH3, has a good score of -24 and -22 respectively. Compound 1 formed four hydrogen bonds with active site residues (Tyr355, Arg513, Met522) and fit well in a pocket than the parent compound which have scores of -13 (compound 10 in **Table 1**), while compound D made three hydrogen bonds with active site residues (Tyr355, Tyr385, Ser530) and fit well in a pocket than the parent compound (compound 4 in **Table 1**). The parent compound of compound 1 and 2 also formed 3 hydrogen bonds with active site residues. The difference in hydrogen bonding network and docking score between compound 1 and 2 might be due to presence of SO2Me in compound 1, although both have the same functional group (**Figure 5A and 5B**).

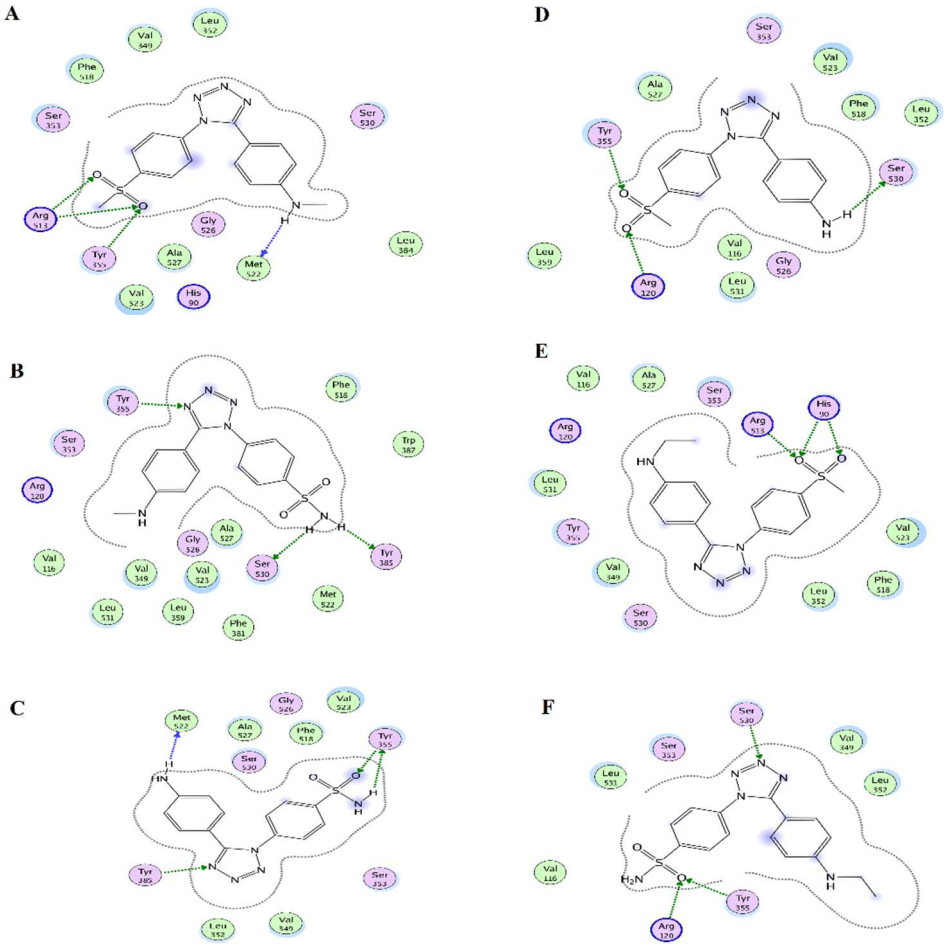


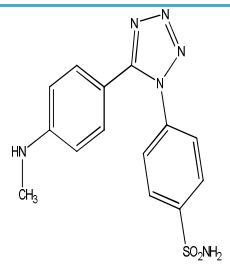
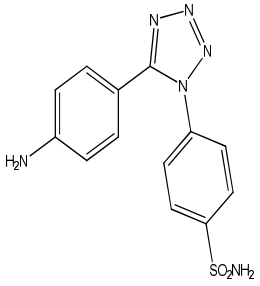
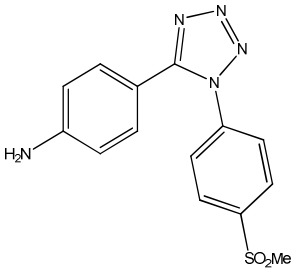
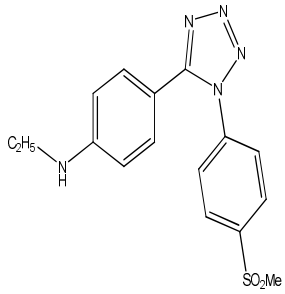
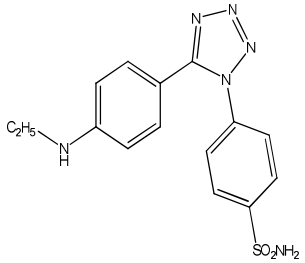
Figure 5. Docking conformation of compound**1** (A) &**2** (B), compound **3** (C) **4** (D) and compound **5** (E) &**6** (F).

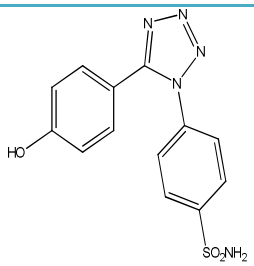
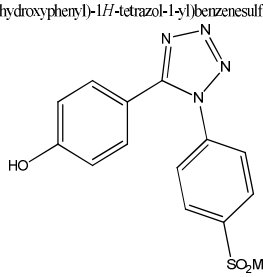
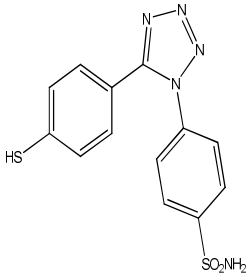
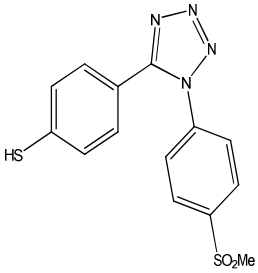
The compound 3 and 4, which have the same functional group NH2, have a good docking score, -22 and -20 respectively. Compound 3 made four interaction with the important binding site residues (Tyr355, Tyr385, Met522) and compound 4 made three interactions with the pocket residues (Tyr355, Ser530, Arg120). Both were well fitted in the pocket of the target protein (**Figure 5C and 5D**).

The compound 5 formed three hydrogen bonds with active site residues (His90, Arg513) as shown in (**Figure 5E**). The compound 5 has docking score -15 and fit well in the pocket of target enzyme than parent compound that has docked score -13. Similarly the compound 6 formed three hydrogen bonds with active site residues (Tyr355, Arg120, Ser530) (**Figure 5F**) and well fit in the pocket of target enzyme with a Docking Score of -14. The parent compound has a docking score of -13.

Table 2. Structures and docking scores of the predicted compounds against COX-2 enzyme

S.no	Structure	Docking Scores
1		**-24.9883**

2	 4-(5-(4-(methylamino)phenyl)-1*H*-tetrazol-1-yl)benzenesulfonamide	**-22.6629**
3	 4-(5-(4-aminophenyl)-1*H*-tetrazol-1-yl)benzenesulfonamide	**-22.8349**
4	 4-(1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazol-5-yl)aniline	**-20.7045**
5	 *N*-ethyl-4-(1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazol-5-yl)aniline	**-15.6503**
6	 4-(5-(4-(ethylamino)phenyl)-1*H*-tetrazol-1-yl)benzenesulfonamide	**-14.5969**

7	 4-(5-(4-hydroxyphenyl)-1*H*-tetrazol-1-yl)benzenesulfonamide	**-15.0404**
8	 4-(1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazol-5-yl)phenol	**-12.3156**
9	 4-(5-(4-mercaptophenyl)-1*H*-tetrazol-1-yl)benzenesulfonamide	**-11.4217**
10	 4-(1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazol-5-yl)benzenethiol	**-11.1189**

4. CONCLUSION

As a result of the docking study, we predicted the nature of some functional groups that may play an important role in the development of more potent inhibitors of cyclooxygenase. From our study, we suggest that the functional groups with nonpolar nature may enhance the activity of the cyclooxygenase inhibitors, while the polar and bulky group leads to less activity. For example, the methylsulphonyl group of the studied compounds, as a whole, showed a good docking score and interaction as compared to the sulfonamide group containing compounds. Similarly, the addition of some polar groups, (F, Cl, N+O2) and bulky groups (NO2, CF3, OMe) in the structures of these inhibitors was observed with low activity, docking score and poor interactions. Furthermore, new compounds were designed and docked into the receptor active site on the basis of our docking results. These new compounds showed good docking scores and interaction with the active site residues. The present computational analysis complements the corresponding experimental investigation and helps establish a good starting point for further refinement of COX-2 inhibitors.

REFERENCES

1. Al-Hourani BJ, Sharma SK, Mane JY, Tuszynski J, Baracos V, Kniess T, Suresh M, Pietzsch J,Wuest F (2011). Synthesis and evaluation of 1,5-diaryl-substituted tetrazoles as novel selective cyclooxygenase-2 (COX-2) inhibitors. Bioorg. Med. Chem. Lett. 21(6):1823-6.
2. Al-Hourani BJ, Sharma SK, Suresh M, Wuest F (2012). Novel 5-substituted 1*H*-tetrazoles ascyclooxygenase-2 (COX-2) inhibitors. Bioorg. Med. Chem. Lett. 22(6): 2235–2238.
3. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL (2002). COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc. Natl. Acad. Sci. USA. 99:13926-31.
4. Friesen RW, Brideau C, Chan CC, Charleson S, Deschenes D, Dube D, Ethier D, Fortin R, Gauthier JY, Girard Y, Gordon R, Greig GM, Riendeau D, Savoie C, Wang Z, Wong E, Visco D, Xu LJ, Young RN (1998). 2-Pyridinyl-3-(4-methylsulfonyl) phenylpyridines:selective and orally active cyclooxygenase-2 inhibitors.Bioorg. Med. Chem. Lett. 8(19):2777-82.
5. Garavito RM, Mulichak AM (2003). The structure of mammalian cyclooxygenases. Annu. Rev. Biophys. Biomol. Struct. 32:183–206.
6. Hamberg M, Samuelsson B (1973). Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. Proc. Natl. Acad. Sci. U.S.A. 70:899-903.
7. http://www.chemcomp.com Accessed 26 April 2013.
8. http://www.rcsb.org/pdb/home/home.do. Accessed 10 March 2013.
9. Labute P (2008). The generalized Born/volume integral implicit solvent model: estimation of the free energy of hydration using London dispersion instead of atomic surface area. J. Comput. Chem. 29(10):1693-8.
10. Laskowski RA, Hutchinson EG, Michie AD, Wallace AC, Jones ML, Thornton JM (1997). PDBsum: a Web-based database of summaries and analyses of all PDB structures. Trends. Biochem. Sci. 22(12):488–490.
11. Meade EA, Smith WL, DeWitt DL (1993). Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. J. Biol. Chem. 268(9):6610-14.
12. Ormrod D, Wellington K, Wagstaff AJ (2002). Valdecoxib. Drugs. 62(14):2059-71.
13. Picot D, Loll PJ, Garavito RM (1994). The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. Nature. 367(6460):243–249.
14. Prusakiewicz JJ, Duggan KC, Rouzer CA, Marnett LJ (2009). Differential sensitivity and mechanism of inhibition of COX-2 oxygenation of arachidonic acid and 2 arachidonoylglycerol by ibuprofen and mefenamic acid. Biochemistry. 48(31):7353-7355.
15. Qi Z, Hao CM, Langenbach RI, Breyer RM, Redha R, Morrow JD, Breyer MD (2002). Opposite effects of Cyclooxygenase 1 and 2 activities on the pressor response to bAngiotensin ii. J. Clin. Invest. 110(1):61-69.
16. Ranjinder SS, Jullia YL, Chong Y, Willium LS (2010). Comparison of Cyclooxygenase-1 Crystal Structure: Cross-Talk between Monomers Comprising Cyclooxygenase-1 Homodimers. Biochemistry. 49(33):7069-7079.
17. Riendeau D, Percival MD, Brideau C, Charleson S, Dubé D, Ethier D, Falgueyret JP, Friesen RW, Gordon R, Greig G, Guay J, Mancini J, Ouellet M, Wong E, Xu L, Boyce S, Visco D, Girard Y, Prasit P, Zamboni R, Rodger IW, Gresser M, Ford-Hutchinson AW, Young RN, Chan CC (2001). Etoricoxib (MK-0663): preclinical profile and comparison withother agents that selectively inhibit cyclooxygenase-2. J. Pharmacol. Exp. Ther. 296(2):558-566.
18. Rouzer CA, Marnett LJ (2009). Cyclooxygenases: structural and functional insights. J. Lipid. Res. 50:29-34.
19. Schneider C, Pratt DA, Porter NA, Brash AR (2007). Control of oxygenation in lipoxygenase and cyclooxygenase catalysis. Chem. Biol. 14(5):473-488.
20. Smith WL (2008). Nutritionally essential fatty acids and biologically indispensable cyclooxygenases. Trends. Biochem. Sci. 33:27-37..
21. Smith WL, DeWitt DL, Garavito RM (2000). Cyclooxygenases: structural, cellular, and molecular biology. Annu. Rev. Biochem. 69:145-182.
22. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, RogersRS, Shaffer AF, Zhang YY, Zweifel BS, Seibert K (2000). 4-[5-Methyl-3 phenylisoxazol4-yl]-benzenesulfonamide, Valdecoxib: A Potent and Selective Inhibitor of COX-2. J. Med. Chem. 43(5):775-777.
23. Van der Donk WA, Tsai AL, Kulmacz RJ (2002). The cyclooxygenase reaction mechanism. Biochemistry. 41(52):15451-15458.
24. Vane JR, Bakhle YS, Botting RM (1998). Cyclooxygenases 1 and 2. Annu. Rev. Pharmacol. Toxicol. 38:97-120.
25. Wadood A, Riaz M, Jamal SB, Shah M, Lodhi MA (2013). Molecular docking study of P4 Benzoxaborole-substituted ligands as inhibitors of HCV NS3/03 protease. Bioinformatics. 9(6): 309-314.
26. Wadood A, Ahmed N, Shah L, Ahmad A, Hassan H, Shams S (2013). In silico drug design: An approach which revolutionarised the drug discovery process. OA Drug Design and Delivery. 1(1):3.
27. Xie W, Chipman JG, Robertson DL, Erikson RL, Simmons DL (1991). Expression of a mitogen responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc. Natl. Acad. Sci. U.S.A. 88(7):2692-6.