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IN SILICO ANALYSIS OF SYNTHESISED BENZIMIDAZOLES AS COX INHIBITORS BY MOLECULAR DOCKING AND PHARMACOPHORE MODELING APPROACHES

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Abstract

Benzimidazole derivatives occupied an important part in medicinal chemistry because of their multifarious therapeutic actions. Inflammation is a protective response involving immune cells, blood vessels and molecular mediators. The key enzyme required for the conversion of arachidonic acid to prostaglandins is cyclooxygenase (COX). The two isomers of this enzyme are COX-1 and COX-2 and inhibiting this enzyme is very crucial in alleviating inflammation. The present study has performed an in silico analysis to determine the inhibitory effect of some synthesized benzimidazoles on COX enzymes, which were previously reported for their anti-inflammatory activity. The physicochemical and ADMET properties were determined by qikprop application of Schrodinger. The molecular docking studies of the synthesised benzimidazole derivatives with active protein sites was performed by docking program, Glide and pharmacophore model was developed by phase module of Schrodinger. All the synthesized compounds possessed their physicochemical properties within the limit and obeyed Lipinski Rule of five. The ADMET properties, predicted that the compounds have better values within the recommended values. The benzimidazole derivatives were docked towards COX-1 (2OYE) and COX-2 (4COX) to determine their anti-inflammatory activity and the pharmacophoric features responsible for their COX inhibition was determined. Among the 11 benzimidazole derivatives, BI3 and BI5 showed good docking score towards COX-1 and COX-2 respectively.

Key words: Benzimidazoles, Cyclooxygenases, Physicochemical properties, ADMET properties, Molecular docking, Pharmacophore modeling.

Introduction

Benzimidazole is a heterocyclic aromatic organic compound, which consists of the fusion of benzene and imidazole. They have occupied an important part in medicinal chemistry because of their wide range of therapeutic actions (Shaharyar *et al.*, 2017) such as, anti-cancer (Refaat *et al.*, 2010, anti-ulcer (Patil *et al.*, 2008), anti-tubercular (Mohanty *et al*., 2018), anti-viral (Tonelli *et al*., 2010), anti-convulsant (Siddiqui *et al*., 2016) and anti-inflammatory (Gaba *et al*., 2014).

Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants and is a protective response involving immune cells, blood vessels and molecular mediators. The key enzyme required for the conversion of arachidonic acid to prostaglandins is cyclooxygenase (COX), which exists as COX-1 and COX-2 (Garavito *et al.*, 1999). COX-1 is responsible for the supply of prostaglandins, whereas COX-2 is an enzyme which is expressed after the inflammatory stimulus (Limongelli *et al.*, 2010; Kalgutkar *et al.*, 2000. COX-2 plays a role in cell proliferation and cell death in human malignancies and also in angiogenesis (Sobolewski *et al.*, 2010; Williams *et al.*, 1999; Leahy *et al.*, 2000).

Molecular docking is a method that determines the interaction between protein and ligand, which explains the orientation, binding interactions and binding energy of the molecule (Barua *et al.*,2019; Patel *et al.*, 2014; Berry *et al.*, 2015; James*et al.*, 2018). Pharmacophore approaches are necessary to predict the common steric and electronic features, that participate in the molecular interactions with a specific biological target and to trigger its biological response (Wolber *et al.*, 2008; Pauli *et al.*, 2013).

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This study was designed to screen the physicochemical and ADMET properties of the synthesized compounds and to find their molecular interactions and binding energy between benzimidazoles and COX enzymes. In addition, characteristic features were also analyzed by pharmacophore modeling studies. The benzimidazole derivatives have reported theiranti-inflammatory activities; hence proving their mechanism of action is imperative. So, these compounds were docked towards COX-1 (2OYE) and COX-2 (4COX) to determine theirs *in silico* inhibitory action. Therefore, *in silico* studies assists in determining the role of the benzimidazoles in inhibiting COX enzymes, which is responsible for their anti-inflammatory actions.

Material and Methods

The scheme was based on the report by Achar, K.C. *et al*., 2010. The SMILES was generated using Chem Biodraw and given in table 1.

In silico studies

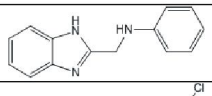
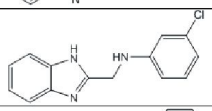
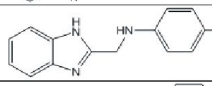
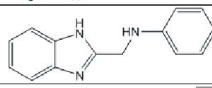
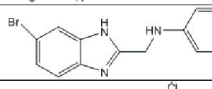
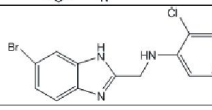
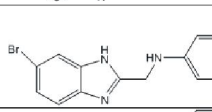
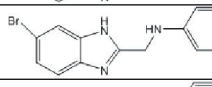
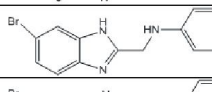
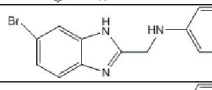
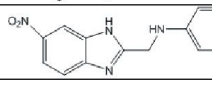
• Modeling platform:

All computational analysis was carried out on Maestro 11.9 version (Schrödinger, 2019-1; Maestro) (LigPrep, Glide XP docking, grid generation, free energy calculations, Prime and ADMET). This software package programmed on DELL Inc.27" workstation machine running on Intel Core i7-7700 CPU@ 3.60 GHz x8, processor with 8GB RAM and 1000 GB hard disk with Linux –x86_64 as the operating system. The program was used for the study of druglikeness, interactions, physicochemical properties and ADMET properties of the synthesized compounds.

• Physicochemical properties and Rule of Five properties:

To develop good oral drugs, the compounds should possess standard physicochemical properties and should obey Lipinski's Rule of Five. This was determined by Qikprop (Schrödinger, 2019-1: QikProp) module of Schrodinger.

Table 1: Chemical Structures and Smiles of Synthesized Benzimidazole Derivatives.

S. NO.	Chemical structure	SMILES
BI1		C12=CC=CC=C1NC(CNC3=CC=CC=C3)=N2
BI2		ClC1=CC(NCC2=NC3=CC=CC=C3N2)=CC=C1
BI3		BrC(C=C1)=CC=C1NCC2=NC3=CC=CC=C3N2
BI4		COC(C=C1)=CC=C1NCC2=NC3=CC=CC=C3N2
BI5		BrC1=CC=C(N=C(CNC2=CC=CC=C2)N3)C3=C1
BI6		BrC1=CC=C(N=C(CNC2=CC=CC=C2Cl)N3)C3=C1
BI7		BrC1=CC=C(N=C(CNC2=CC=CC(Cl)=C2)N3)C3=C1
BI8		BrC1=CC=C(N=C(CNC2=CC=C(Br)C=C2)N3)C3=C1
BI9		BrC1=CC=C(N=C(CNC2=CC=C(OC)C=C2)N3)C3=C1
BI10		BrC1=CC=C(N=C(CNC2=CC=C(C)C=C2)N3)C3=C1
BI11		BrC(C=C1)=CC=C1NCC2=NC3=CC=C([N+]([O-])=O)C=C3N2

• ADMET studies:

QikProp program was used for the calculation of

Table 2: Physicochemical Properties of Benzimidazoles.

Ligands ID	Molecular weight	Log P	Donor HB	Acceptor HB	PSA	volume	rotor
BI1	223.27	2.69	2.000	2.500	40.902	799.767	3
BI2	257.72	3.25	2.000	2.500	40.905	843.954	3
BI3	302.17	3.52	2.000	2.500	40.898	853.105	3
BI4	253.30	2.56	2.000	3.250	48.575	864.047	4
BI5	302.17	3.52	2.000	2.500	40.902	853.103	3
BI6	336.61	4.08	2.000	2.500	39.307	893.925	3
BI7	336.61	4.08	2.000	2.500	40.901	897.158	3
BI8	381.07	4.35	2.000	2.500	40.898	906.166	3
BI9	332.20	3.39	2.000	3.250	49.196	928.155	4
BI10	316.20	4.01	2.000	2.500	40.899	913.265	3
BI11	347.17	3.54	2.000	3.500	85.800	925.782	4
Indomethacin	343.809	3.58	1.000	2.750	60.832	1074.630	5

Table 3: Predicted ADMET Properties of Benzimidazoles.

Ligand ID	QPP Caco	QP log BB	% Human oral absorption	SASA	Rule of five	Rule of three
BI1	2670.035	-0.174	100.000	491.301	0	0
BI2	2669.172	-0.012	100.000	515.396	0	0
BI3	2670.428	-0.001	100.000	520.723	0	0
BI4	3085.975	-0.167	100.000	514.158	0	0
BI5	2669.295	-0.001	100.000	520.665	0	0
BI6	3157.449	0.225	100.000	541.457	0	0
BI7	2669.250	0.161	100.000	544.707	0	0
BI8	2669.747	0.173	100.000	549.750	0	0
BI9	2667.324	-0.076	100.000	557.799	0	0
BI10	2671.038	-0.018	100.000	553.000	0	0
BI11	320.139	-1.039	89.183	558.990	0	0
Indomethacin	323.854	-0.468	89.805	610.930	1	1

ADMET (absorption, distribution, excretion and toxicity) properties of compounds. QikProp (Schrödinger, 2019-1: QikProp) generates physically relevant descriptors, the toxicity a ligand is considered necessary for the ligand to act as an effectual drug discovery of new drug development.

• Molecular docking:

The ligands used in the study were prepared using Ligprep (Schrödinger, 2019-1: Ligprep) module. The protein preparation was carried out in protein preparation wizard. The X-ray crystal structures of COX-2 (PDB ID:4COX) (Amin *et al.*, 2010) and COX-1 (PDB ID:2OYE) (Uddin *et al.*, 2014) was obtained from the PDB data bank. Receptor grid generation wizard was used for the generation for grid. The ligand was docked with the protein by Glide XP (Schrödinger, 2019-1: Glide) and the interactions were observed. The scoring function gives scores based on the best ligand- protein interaction. The docking poses were evaluated in the extra- precision mode. The algorithm identifies the hydrogen bonding, hydrophobic, metal-ligation interactions and steric clashes.

Table 4: Molecular Docking Scores and Binding Energy of Benzimidazoles with COX- 1 (2OYE) & COX-2 (4COX).

Ligand ID		XP Score	MMGBSA dG Bind
BI1	COX-1 (2OYE)	-8.595	-51.96
	COX-2 (4COX)	-7.438	-47.26
BI2	COX-1 (2OYE)	-9.40	-59.35
	COX-2 (4COX)	-8.431	-39.95
BI3	COX-1 (2OYE)	-9.57	-56.79
	COX-2 (4COX)	-8.198	-40.62
BI4	COX-1 (2OYE)	-8.875	-55.3
	COX-2 (4COX)	-7.486	-45.34
BI5	COX-1 (2OYE)	-8.334	-58.55
	COX-2 (4COX)	-9.122	-60.27
BI6	COX-1 (2OYE)	-9.15	-76.52
	COX-2 (4COX)	-8.41	-75.56
BI7	COX-1 (2OYE)	-8.706	-63.07
	COX-2 (4COX)	-9.107	-63.18
BI8	COX-1 (2OYE)	-8.721	-62.57
	COX-2 (4COX)	-8.484	-63.62
BI9	COX-1 (2OYE)	-7.665	-67.67
	COX-2 (4COX)	-8.668	-59.99
BI10	COX-1 (2OYE)	-8.281	-56.23
	COX-2 (4COX)	-8.363	-65.34
BI11	COX-1 (2OYE)	-7.872	-73.03
	COX-2 (4COX)	-7.977	-57.54
Indomethacin	COX-1 (2OYE)	12.11	-103.78
	COX-2 (4COX)	-11.964	-89.56

• Prime MM-GBSA Binding Free Energy:

The receptor binding free energy and a set of ligands were predicted using the calculation of prime module (Schrödinger, 2019-1:Prime). The software estimates the total free energy of binding, dGbind (kcal/mol) as:ΔG bind = Gcomplex - (Gprotein+Gligand), where G = MME + GSGB + GNPMME (molecular mechanics energies) + GSGB (SGB solvation model for polar solvation) + GNP (nonpolar solvation).

• Pharmacophore Modeling:

The phase application of Schrodinger software (Schrödinger, 2019-1: Phase), was used to generate the pharmacophore models. The method employed was structure-based pharmacophore, which is based on the algorithm that interprets receptor-ligand interactions as charge transfer, hydrogen bonds and hydrophobic regions of their macromolecular environment from PDB files. The inaccessible areas along any potent ligand was represented by the receptor based excluded volume spheres.

Results

Physicochemical properties and rule of five properties

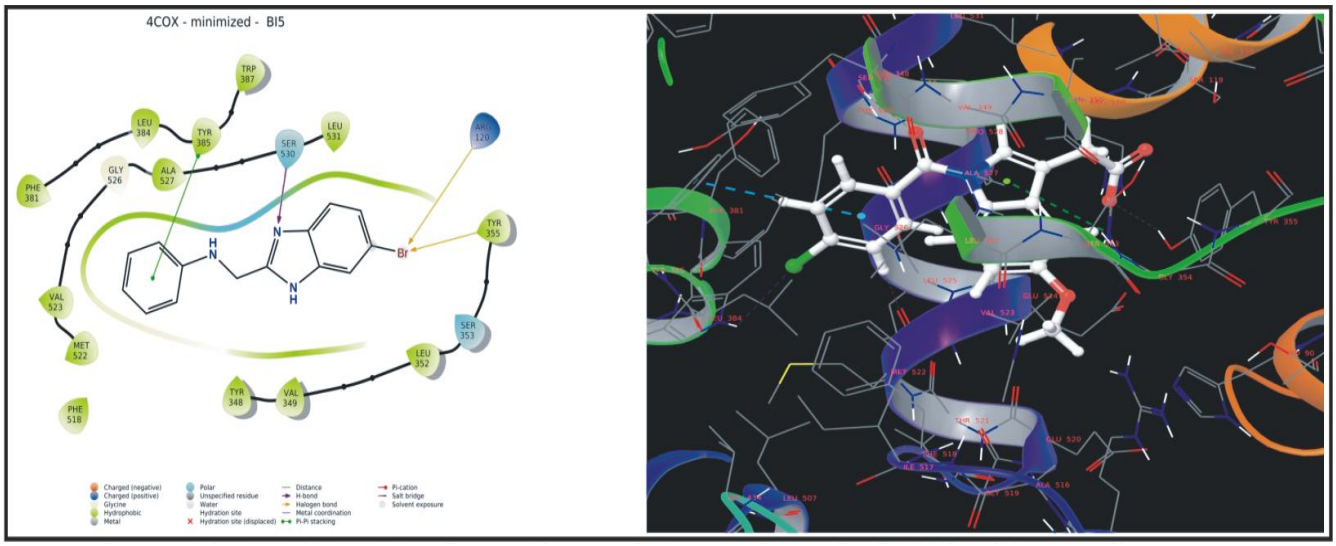


Fig. 1b: 2D & 3D Conformations of Benzimidazole (B15) with 4COX.

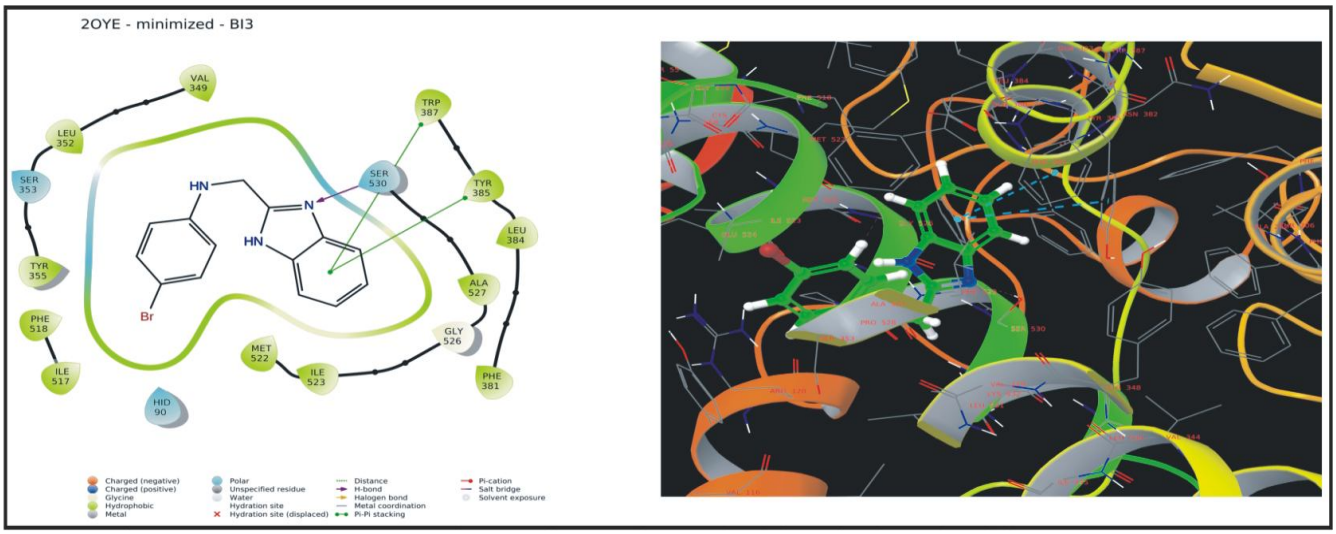


Fig. 1a: 2D & 3D Conformations of Benzimidazole (B13) with 2OYE.

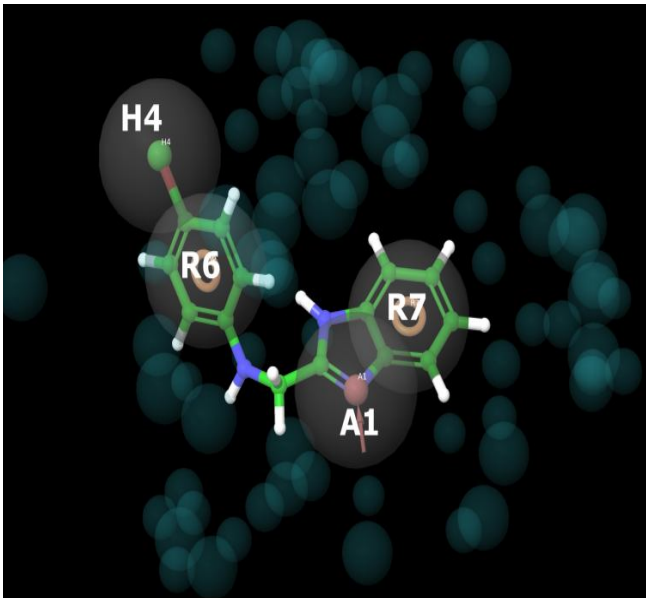


Fig. 2a: Pharmacophore Model of B13 with 4OYE.

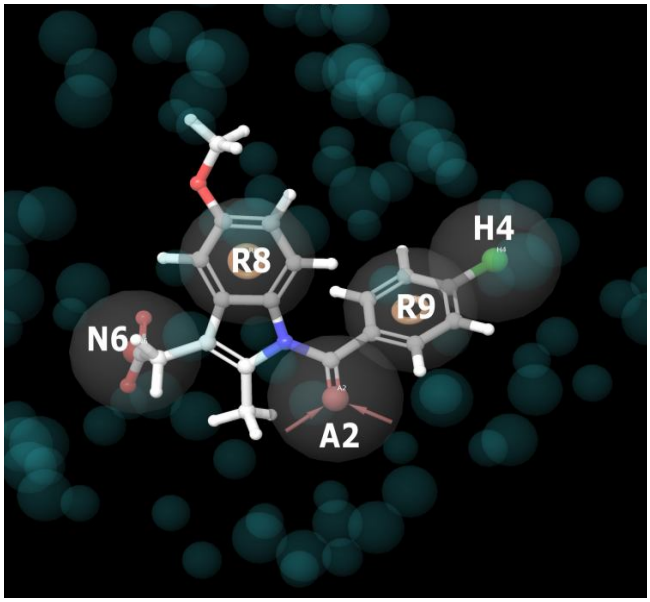


Fig. 2b: Pharmacophore Model of B15 with 4COX.

Table 5: Molecular Docking Interactions of Benzimidazoles with COX- 1 (2OYE).

Ligand ID	Polar interaction with amino acids	HB	Pi-pi stackings
BI1	Ser530, Ser353	Ser530	Tyr385, Trp387
BI2	Ser530, Ser353	Ser530	Tyr385
BI3	Ser530, Ser353, Hid90	Ser530	Tyr385, Trp387
BI4	Ser530, Ser353, Hid90	Ser530	Tyr385
BI5	Ser530, Ser353, Hid90	-	Tyr355, Tyr385, Trp387
BI6	Ser530, Ser353	Met522	Tyr385
BI7	Ser530, Ser353, Hid90	-	Tyr385, Tyr355
BI8	Ser530, Ser353	Met522	Tyr385
BI9	Ser530, Ser516, Gln192, Hid90, Ser353	Ile523	Tyr385, Tyr355
BI10	Ser530, Ser353	-	Tyr385
BI11	Ser530, Ser353, Ser516, Gln192, Hid90	-	Tyr385, Tyr355
Indomethacin	Ser530, Ser353, Ser516, Gln192, Hid90	Tyr355, Arg120	-

All the compounds have their molecular weight below 500 ranging from 223-381. The calculated log P value of the compounds ranges from 2.56-4.35. The compounds under investigation possess hydrogen bond donors (<5) and hydrogen bond acceptors (<10) within the limit. Based on the experimental values (Table 2), it was found that all the compounds of have values within the normal range and there is no violation of Lipinski's rule of five. Hence the compounds are expected to possess good oral bioavailability (Table 2).

ADMET studies

The results show that compounds have better Caco-2 permeability score, high human oral absorption score and QP Log BB value within the recommended limit (Table 3).

Molecular docking

The compounds were docked with two COX enzymes and their molecular interactions were analysed. The docking scores and binding energy were computed and tabulated in the table 4. The chemical interactions between the compounds and active amino acid residues are listed in the table 5 & 6 and 2D and 3D conformations of the molecular bindings are showed in the fig. 1a & 1b.

Pharmacophore modeling

The compound BI3 and BI5 with good docking scores were considered for pharmacophore modeling studies and the significant chemical features which are responsible for the biological activity were determined (Fig. 2a & 2b).

Discussion

The synthesized benzimidazole derivatives which were reported for anti-inflammatory activity were analysed for the binding interactions with COX-1 and COX-2 enzymes. The active amino acids in the enzyme COX-1 (2OYE) was found to be Phe381, Leu384, Tyr385, Trp387, Phe518, Gly526, Met522, Tyr348, Val349, Leu352, Ser353, Tyr355, Leu531, Ser530, Ala527, Ile523, Ile517, Ser516, Gln192, Hid90 and Gly354. BI3 and BI1 showed hydrogen bonding with Ser530 through nitrogen of benzimidazole ring and Pi-Pi stacking with Tyr385 and Trp387 throgh benzimidazole ring. BI2 showed hydrogen bonding with Ser530 and Pi-Pi stacking with Tyr385 through benzimidazole ring. BI6 showed hydrogen bonding with Met522 through nitrogen and Pi-Pi stacking with Tyr385 through benzene ring. Among the 11 benzimidazole derivatives BI3 showed good docking score -9.572 kcal/mol, when compared with the standard Indomethacin (-10.705kcal/mol).

Table 6: Molecular Docking Interactions of Benzimidazoles with COX-2 (4COX).

Ligand ID	Polar interaction with amino acids	HB	Pi-pi stackings
BI1	Ser530, Ser353	Ser530	Tyr385
BI2	Ser530, Ser353, Hid90	-	Tyr385
BI3	Ser530, Ser353	-	Tyr385
BI4	Ser530, Ser353	Tyr355, Arg120	Tyr385
BI5	Ser530, Ser353	Ser530	Tyr385
BI6	Ser530, Ser353	-	Tyr385
BI7	Ser530, Ser353	-	Tyr385,Trp387
BI8	Ser530, Ser353	-	Tyr385,Trp387
BI9	Ser530, Ser353, Hid90, Gln192	Ser530	Tyr385
BI10	Ser530, Ser353, Hid90	-	Tyr385,Tyr355
BI11	Ser530, Ser353	-	Tyr385,Trp387
Indomethacin	Ser530, Ser353, Hid90	Ser530, Tyr355	Tyr385

The active amino acids in the enzyme COX-2 (4COX) was found to be Phe381, Leu384, Tyr385, Trp387, Phe518, Gly526, Val523, Met522, Tyr348, Val349, Leu352, Ser353, Tyr355, Arg120, Val116, Leu531, Ser530, Ala527, Met113. BI5 showed Pi-Pi stacking with Tyr385 through

benzene ring and hydrogen bonding with Ser530 nitrogen of benzimidazole ring. BI7 showed Pi-pi stacking with Tyr385 and Trp387 through benzene ring and also showed Pi-cation interaction with Arg120 through benzimidazole ring. BI9 showed Pi-Pi stacking with Tyr385and hydrogen bonding with Ser530 through benzimidazole ring. Among the 11 benzimidazole derivatives BI5 showed highest docking score -9.122kcal/mol, when compared with the standard Indomethacin (-10.099 kcal/mol) (Table 5, Fig. 3,4). The binding affinity score observed for the compound BI3 with the target 2OYE is -56.79 kcal/mol and compound BI5 with 4COX is -60.27 kcal/mol, respectively. The pharmacophore hypothesis BI3 consists of one hydrogen bond acceptor (A1), two aromatic rings (R6, R7) and one hydrophobic interaction (H4), which are contributing for the bindings of BI3 with 2OYE.The hypothesis for BI5 is of one hydrogen bond acceptor (A2), two aromatic rings (R8, R9) and one hydrophobic interaction (H4), which are contributing for the bindings of BI5 with 4COX.

Conclusion

The benzimidazole derivatives were docked towards COX-1 (2OYE) and COX-2 (4COX) in order to determine their anti-inflammatory activity. It was found that all the compounds have values within the normal range and there is no violation of Lipinski's rule of five. Hence the compounds are expected to possess good oral bioavailability. Among the 11 benzimidazole derivatives, the ligand BI5 showed good docking score with COX-2 (-9.122 kcal/mol); and BI3 showed good docking score with COX-1 (-9.572 kcal/mol). In addition, their pharmacophoric features responsible for their biological activity was also revealed. Thus, these in silico approaches has assisted in determining the binding interactions and affinity between the synthesized benzimidazoles and the COX enzyme, which might be accountable for their anti-inflammatory potential.

Acknowledgement

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Conflict Of Interest

The authors declare no conflict of interests.

References

Amin, K.M., M.M. Kamel, M.M. Anwar, M. Khedr and Y.M. Syam (2010). Synthesis, biological evaluation and molecular docking of novel series of spiro [(2H, 3H) quinazoline-2, 12 -cyclohexan]-4 (1H)-one derivatives as anti-inflammatory and analgesic agents. *E. J. Med. Chem.*, **45(6):** 2117-2131.

Achar, K.C., K.M. Hosamani and H.R. Seetharamareddy (2010). *In-vivo* analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. *E. J. Med. Chem.*, **45(5):** 2048-2054.

Gaba, M., S. Singh and C. Mohan (2014). Benzimidazole: an emerging scaffold for analgesic and anti-inflammatory agents. *E. J. Med. Chem.*, **76:** 494-505.

Garavito, R.M. and D.L. DeWitt (1999). The cyclooxygenase isoforms: structural insights into the conversion of arachidonic acid to prostaglandins. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, **1441(2-3):** 278-287.

James, J.P, K.I. Bhat, U.A. More and S.D. Joshi (2018). Design, synthesis, molecular modeling and ADMET studies of some pyrazoline derivatives as shikimate kinase inhibitors. *Med. Chem. Res.*, **Feb 1; 27(2):** 546-59.

Kalgutkar, A.S., B.C. Crews, S.W. Rowlinson, A.B. Marnett, K.R. Kozak, R.P. Remmel and L.J. Marnett (2000). Biochemically based design of cyclooxygenase-2 (COX-2) inhibitors: facile conversion of nonsteroidal antiinflammatory drugs to potent and highly selective COX-2 inhibitors. *Proceedings of the National Academy of Sciences*, **97(2):** 925-930.

Leahy, K.M., A.T. Koki and J.L. Masferrer (2000.) Role of cyclooxygenases in angiogenesis. *Current medicinal chemistry*, **7(11):** 1163-1170.

Limongelli, V., M. Bonomi, L. Marinelli, F.L. Gervasio, A. Cavalli, E. Novellino and M. Parrinello (2010). Molecular basis of cyclooxygenase enzymes (COXs) selective inhibition. *Proceedings of the National Academy of Sciences*, **107(12):** 5411-5416.

Márquez-Navarro, A., B. Nogueda-Torres, A. Hernández-Campos, O. Soria-Arteche, R. Castillo, S. Rodríguez-Morales, L. Yépez-Mulia and F. Hernández-Luis (2009). Anthelmintic activity of benzimidazole derivatives against Toxocara canis second-stage larvae and Hymenolepis nana adults. *Acta Tropica*, **109(3):** 232-235.

Mohanty, S.K., A. Khuntia, N. Yellasubbaiah, C. Ayyanna, B.N. Sudha and M.S. Harika (2018). Design, synthesis of novel azo derivatives of benzimidazole as potent antibacterial and anti tubercular agents. *Beni-Suef University journal of basic and applied sciences*, **7(4):** 646-651.

Patil, A., S. Ganguly and S. Surana (2008). A systematic review of benzimidazole derivatives as an antiulcer agent. *Rasayan J. Chem.*, **1(3):** 447-460.

Pauli, I., R.N. Dos Santos, D.C. Rostirolla, L.K. Martinelli, R.G. Ducati, L.F. Timmers, L.A. Basso, D.S. Santos, R.V. Guido, A.D. Ricopulo and O. Norberto de Souza (2013). Discovery of new inhibitors of Mycobacterium tuberculosis InhA enzyme using virtual screening and a 3D-pharmacophore-

based approach. *J.Chem. Inform. Mod.*, **53(9):** 2390-2401.

Refaat, H.M. (2010). Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. *E. J. Med. Chem.*, **45(7):** 2949-2956.

Schrödinger release (2019-1). Maestro, Schrödinger, New York, NY, 2019.

Schrödinger release (2019-1). QikProp, Schrödinger, LLC, New York, NY, 2019.

Schrödinger release (2019-1). Ligprep, Schrödinger, LLC, New York, NY, 2019.

Schrödinger release (2019-1). Prime, Schrödinger, LLC, New York, NY, 2019.

Schrödinger release (2019-1). Phase, Schrödinger, LLC, New York, NY, 2019.

Sobolewski, C., C. Cerella, M. Dicato, L. Ghibelli and M. Diederich (2010). The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. *International journal of cell biology*, **2010**.

Shaharyar, M. and A. Mazumder (2017). Benzimidazoles: A biologically active compounds. *Arabian Journal of Chemistry*, **10:** S157-S173.

Siddiqui, N., M.S. Alam, R. Ali, M.S. Yar and O. Alam (2016). Synthesis of new benzimidazole and phenylhydrazinecarbothiomide hybrids and their anticonvulsant activity. *Med. Chem. Res.*, **25(7):** 1390-1402.

Tonelli, M., M. Simone, B. Tasso, F. Novelli, V. Boido, F. Sparatore, G. Paglietti, S. Pricl, G. Giliberti, S. Blois and C. Ibba (2010). Antiviral activity of benzimidazole derivatives. II. Antiviral activity of 2-phenylbenzimidazole derivatives. *Bioorganic & medicinal chemistry*, **18(8):** 2937-2953.

Uddin, M.M.N., T.B. Emran, M.M.R. Mahib and R. Dash (2014). Molecular docking and analgesic studies of Erythrina variegataós derived phytochemicals with COX enzymes. *Bioinformation.*, **10(10):** 630.

Williams, C.S., M. Mann and R.N. DuBois (1999). The role of cyclooxygenases in inflammation, cancer and development. *Oncogene*, **18(55):** 7908-7916.

Wolber, G., T. Seidel, F. Bendix and T. Langer (2008). Molecule-pharmacophore superpositioning and pattern matching in computational drug design. *Drug discovery today*, **13(1-2):** 23-29.