IN-SILICO DESIGN, MOLECULAR DOCKING AND ADME STUDY OF NOVEL BENZOTHIAZOLE COX-2 INHIIBITORS AS PROMISING ANTI-CANCER AGENTS

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Abstract Cycloxygenase-2 enzyme is expressed in different types of cancer it contributes to carcinogenesis and further which causes the formation of tumor. A new series of Benzothiazole N-(5-benzyl-1,3,4-thiadiazol-2-yl)benzo[*d*]thiazol-2-amine are designed using Molecular docking technique that inhibits Cycloxygenase-2 enzyme. The PDB: 5IKR is imported from the RCSB PDB data base. Benzothiazole derivatives are docked into the COX-2 binding receptor using Molegro Virtual Docker software. The interaction of hydrogen bond, Moldock score and Rerank-score analysis was done based on the docking results. The docked molecule provides the estimation of inhibitory activities. From the docked Benzothiazole derivatives Bdz 4, 14, 15 and 17 exhibited potent activity into the COX-2 receptor site.

Key Words- Benzothiazole, Molecular docking, ADME Study, COX-2 inhibitors, Anticancer activity.

I. INTRODUCTION

Drug design has always been an interesting aspect of scientific research. Discovery of newer and more potent analogs of molecules with prior established activities are a key part of research in the pharmaceutical field [1]. Bringing about slight change in the parent compound and also in most cases eliminates adverse effects or toxicity associated with the parent drug [2].

Molecular docking is a key tool in structural molecular biology and computer assisted drug design [3 4]. It predicts the preferred orientation of one molecule to the second when bound into a active site to form a stable complex [5]. Molecular docking study is aimed to achieve an optimized conformation for both receptor and ligand such that the free energy of the overall system is minimized [6,7]. Inflammation is a body defense mechanism; it is also an early phase of some serious diseases such as cancer, cardiovascular diseases and Alzheimer's dementia. A grave health problem across the globe 'Cancer' is a chronic pathological condition, where there is a rapid uncontrolled proliferation of abnormal premature cells [8 9]. Experimental studies have shown the role of NSAIDs in the prevention of human cancers. NSAIDs block prostaglandin synthesis through inhibition of cyclooxygenase (COX) enzymatic activity [10 11]. COX-2, an isoenzyme converts arachidonic acid to prostaglandins, is effected by various means such as growth factors and tumor promoters, and is frequently over expressed in various tumors[12] ,fig 1.

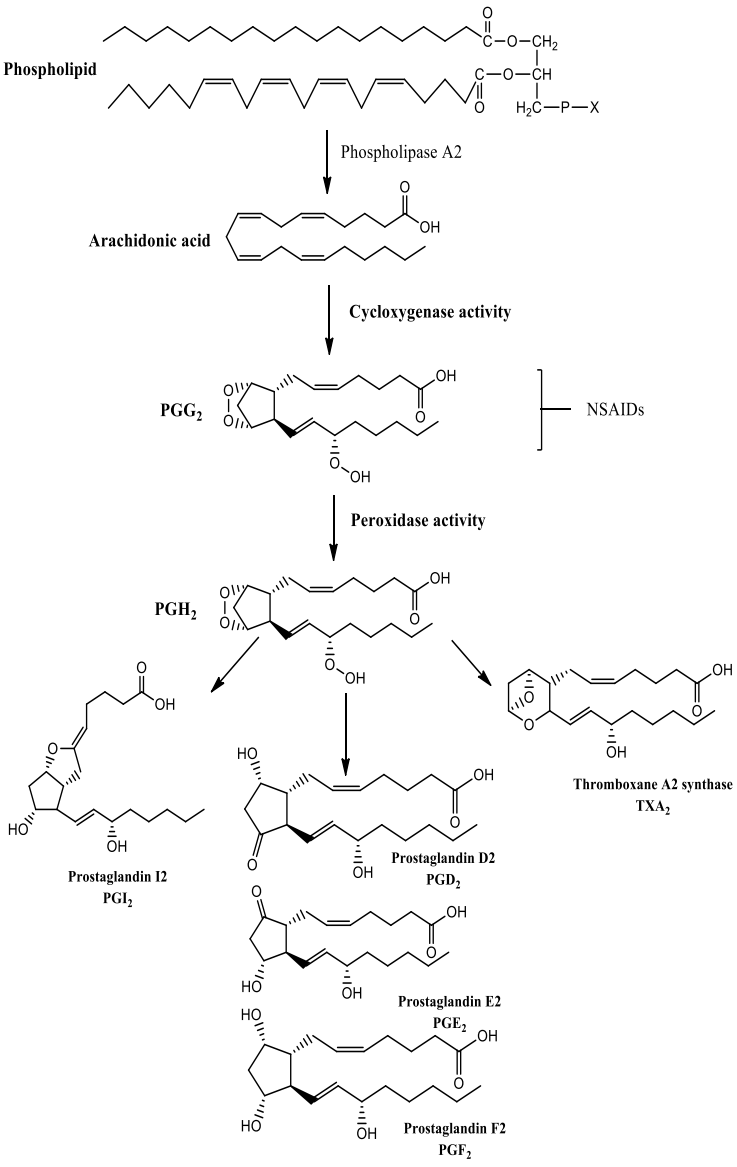


Figure 1: Schematic representation of synthesis of prostaglandins.

The expression of COX-2 in cancer can cause: (i) produce higher level of prostaglandins (ii) inhibits cancer cell death, (iii) Promotes formation of new blood vessels, (iv) regulate inflammation and immune function, (v) tumor extension to other tissues [13,14].

The aim of this study is to develop selective COX-2 inhibitors as promising anticancer agents. Thus, studies on the anti-cancer effects depicts that COX-2 selective NSAIDs drugs have provided space for new research areas [15-17]. Due to the noxious side-effects of various anti-cancer agents in the market, it is crucial to develop potent anti-cancer agents with less adverse effects [18] .Molecular docking method estimates the stable response between two molecules when bound to each other [19] . Orientation and binding affinity of two molecules can be estimated by using scoring functions. A cell responds to substances outside and inside the surface of molecule through signaling into proteins, nucleic acids, carbohydrates and lipids which play vital role in signal transduction [20,21] . The interaction of two molecules predicts the type of signal that is produced (eg.agonism and antagonism).Therefore, strength and signal produced are very important and hence docking plays an important role in drug design process [22,23]. We can find several types of computational methods that are available. The potent ligands are ranked based on their interactions with the target. The fitness of different pose of molecule of the scoring function is obtained into biological target [24,25]. In continuation with our research on novel derivatives of five and six membered heterocyclic compounds having potent biological and pharmacological activity,[28,27,28] here we have designed novel benzothiazole derivatives possessing anticancer activity.

Benzothiazole is a heterocyclic compound that consists of broad spectrum of biological activities [29, 30]. It acts against several cancers, and its potential effects are exclaimed through several researches [31]. The core moiety of Benzothiazole consist of antiproliferative activity and due to their Pharmaceutical utilities, the synthesis of these compounds is of considerable interest [23, 32,] . In the view of above considerations, Molecular docking studies are considered for the search of new potent bio-active drug molecules. Thus, a series of Benzothiazole molecules were designed and synthesized using CADD software.

II.MATERIALS AND METHODS

The docking study was performed using CADD software i.e., Molegro Virtual Docker (MVD 2013, 6.0) and Molegro Molecular Viewer .Protein Data Bank (PDB) was obtained from RCSBPDB (www.rcsb.org.pdb) .The PDB 5IKR was deposited by Ornaldo.B.J and Markowski.M.G in 2016.The series of 23 Benzothiazole compounds were designed in 2D form by Chemdraw Ultra 12.0 and further energy minimized to 3D using Chem3D Pro 12.0 software. (Molegro Virtual Docker)MVD 6.0 docking software was used to perform molecular docking studies on Benzothiazole derivatives. Swiss ADME software was utilized for the study of physiochemical and pharmacokinetic properties of the drug and target prediction of the drug.

III.RESULTS AND DISCUSSION

The 3-D crystal structure of a receptor was taken from Protein data bank PDB: 5IKR that belongs to class Oxidoreductase with a resolution of 2.34 Å. The PDB was imported into Molegro Virtual Docker (MVD) by removing all the water molecules, fig.8. The standard Molegro Algorithm was utilized for rendering the missing charges, protonation states and assigning the polar hydrogen to the receptor. The Ligands were drawn on Chemdraw Ultra 12.0 and then converted to 3D on Chemdraw 3D Pro 12.0 & the file was saved in Mol format .Further , the 3D ligands are subjected to energy minimization. The energy minimization helps the docking programme for identifying the bioactive conformer. The 2D structures of 23 ligands are given in fig.8.To make an accurate prediction of docking it is important to note that the selected structures are assigned properly such as its bond connectivity and partial charges are appropriate. The hydrogen atoms and the bond order of the PDB must be rectified before importing for docking.

Since, the required PDB structures of enzyme COX-2 present in a dimer form; is converted to monomer by extracting the bioactive receptor site. To ensure that ligand docked in MVD represent valid score and accurate binding, a Validation is performed on docked receptor ligand complex structures. The MVD scoring algorithm is to be validated with its crystal structure. Therefore, PDB: 5IKR is tested with its crystal structure Mefenamic acid, Fig:8 .

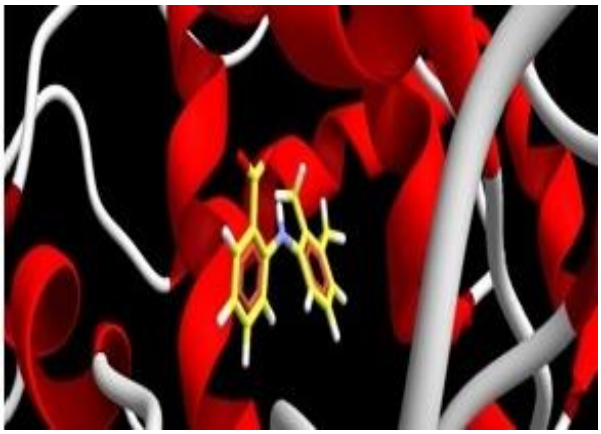
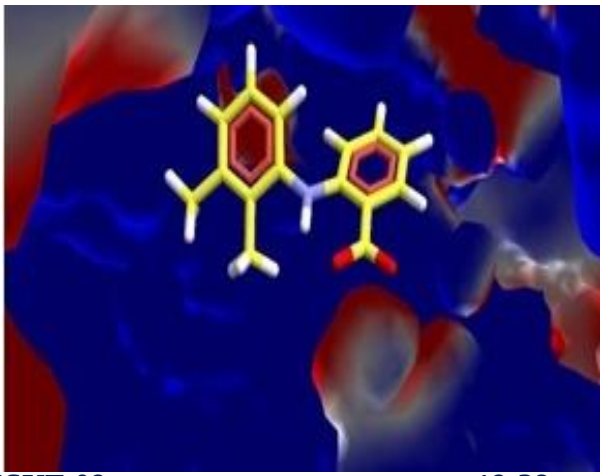


Figure 2 (a) 3D image of RCS Protein data bank (PDB: 5IKR) showing the strands of α and β helices.(b)Surface map of COX-2 enzyme with Mefenamic acid present into the binding pocket.



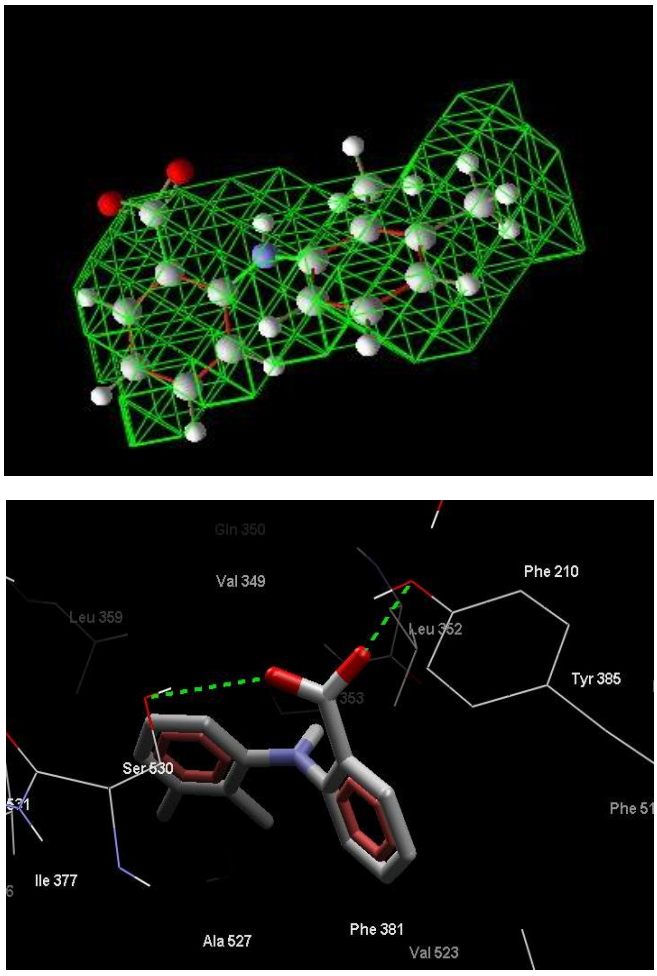


Figure 3: (a) The crystal structure Mefenamic acid into the predicted cavity ;(b) The interaction of Crystal structure Mefenamic acid into the binding site.

The Molecular docking was performed for all the 21 molecules into the predicted cavities of the receptor. Initially, five cavities were identified in the protein and further the suitable cavity (vol = 67.32 kcal/mol) with the bound crystal structure was selected. The cavities are identified by MVD using its cavity detection algorithm. The Search algorithm uses cavity detection algorithm to focus on specific area for docking. The MolDock score (GRID) function was used with a grid resolution 0.30 Å and a binding site radius 15 Å along with the centre (X=31.86, Y=11.49, Z=60.21) with respect to cavities. The "MolDock Optimizer" search algorithm with 10 runs using a maximum of 2000 iterations with a total population size 50 was applied. The energy threshold used for the minimized final orientation is 100. Best poses are identified based on the basis of total mean of Rerank scores in each run. The Re-Rank score of the crystal structure Mefenamic acid is -80.14 kcal/mol. Ten independent docking runs gives ten different poses which are Re-Ranked to give the accurate docking results. The MolDock score of the crystal structure Mefenamic acid is -96.27 kcal/mol and its molecular weight is 241.28g/mol.

Out of 21 Ligands for which Molecular docking was performed .fig.10, four Ligands showed higher activity into the binding site .Molecules are docked into the binding site to find its lowest potential energy. Docking results obtained for each ligand were analyzed based on docking energy, binding modes and interaction of each ligand. The Moldock score of the derivatives are between -83.27 to -124.25.The best poses of Benzothiazole molecules with its docked results are summarized in Table 1.

The orientation and binding interactions of the selective COX-2 binding site was evaluated by Molecular docking. Results obtained from docking showed that the Pose BDZ 5, 13, 16 and 17 exhibited potent activity into the binding site of the enzyme COX-2 with the MolDock score -83.27, -124.85, -105.63 and -93.63 .Compound 4 forms hydrogen bond interactions with amino acid residues Tyr385 and Ser530. Whereas, Nitro group forms interaction with Tyr385 and amine group shows interaction with Ser530 amino acid.

The amino acids in the active site are represented by thin sticks and the ligands are represented by colour based on its element. Compound BDZ 17 has the Moldock score of -93.26 kcal/mol which is closer to Moldock score of Mefenamic acid .

Compound Bdz 14, has a Moldock score of -124.85 and Re-rank score -67.78 kcal/mol where in ,the sulphonyl groups in Benzothiazole moiety shows hydrogen bond interaction with Ser530 and nitro group forms a hydrogen bond with Tyr385 amino acid. Similarly, Bdz 15 with the highest MolDock score compared to crystal structure forms hydrogen bonds with Tyr385 and Ser530 amino acid residues linked to two nitro groups. Bdz 17 shows hydrogen bond interaction linked through amino and nitro group with the same amino acid residues Tyr385 and Ser530,fig.12.

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ADME Properties

A drug must be bioactive in order to reach the target in the body to give the expected biological effects. Drug assessment involves pharmacokinetics i.e., Absorption, distribution, Metabolism and Excretion. Swiss ADME provides access to the predictive models for physiochemical properties, pharmacokinetics, solubility, drug likeliness and the in-house proficient methods such as BOILED-Egg, iLogP and bioavailability Radar. SwissADME web tool is an efficient interface through the login-free website http://www.swissadme.ch developed and maintained by Molecular modeling group of the SIB (Swiss Institute of Bioinformatics).It provides various models for ADME and Pharmacokinetic studies.

A two-dimensional structures are drawn in the window and converted to canonical SMILES (Simplified molecule input line entry system) notation, fig.15. The structure can be imported to change into SMILE notation. SMILES can also be copied from the data bases like pubchem. Then a run is made for the provided molecules. The complete result of physicochemical properties are observed in the below window .The coloured zone beside the structure is the suitable physiochemical space for oral bioavailability that involves Lipophilicity(LIPO),Flexibility(FLEX)), Insaturation (INSAT), Insolubility(INSOLU), polarity(POLAR) and size(SIZE).The ideal parameter values for the physiochemical properties are LIPO: -0.7 < XLOGP3 < -5.0 , SIZE :150g/mol < MW < 500g/mol , POLAR :20Å < TPSA <130Å ,INSOLU:0 < Log S (ESOL) < 6, INSAT:0.25< Fraction Csp3 < 1, FLEX : 0 < Num. rotatable bonds < 9 (Fig.16).

Lipophilicity: The Lipophilicity of a drug can be measured experimentally by testing drugs relative distribution in an n-Octanol layer and water mixture .Swiss ADME gives predictive models for Lipophilicity; ILOGP, an in-house physics based method implemented. XLOP3, atomistic method with knowledge based library. WLOGR, implementation of atomistic methods based on fragmental system. MLOGP, topological method implementation of linear relationship with molecular descriptors. SILICOS-IT, an hybrid method that calculates fragments and topological descriptors. Consensus log $p_{o/w}$ is the average prediction of all the above models.

Water solubility: Two topological methods are involved in water solubility. One is LogS (ESOL) is the estimated solubility and the other is Log (Ali).

Pharmacokinetics: The compiled prediction of different models gives ADME properties. The gastrointestinal absorption is based on the White of the BOILED-Egg and the Blood brain barrier (BBB) permeation results are according to the yolk of the BOILED-Egg. Further , the five major isoform of Cytochrome P450 isozyme inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) predictions are displayed. Log Kp, for skin permeation implemented by QSPR module. More negative value indicates higher skin permeation.

Drug-Likeness: It is a quantitative concept used in drug designs that assess "drug likeness" with respect to bioavailability. The Lipinski rule of five, Ghose, Veber, Egan, Muegge methods and Bioavailability scores are mentioned.

Medicinal Chemistry: PAINS (Pan Assay interference compounds) are the chemical compound that gives false positive results in high throughput screenings. It tends to react non specifically with numerous biological targets. Brenk, lead likeness and synthetic accessibility predictions are implemented.

Figure 4: Swiss ADME submission page

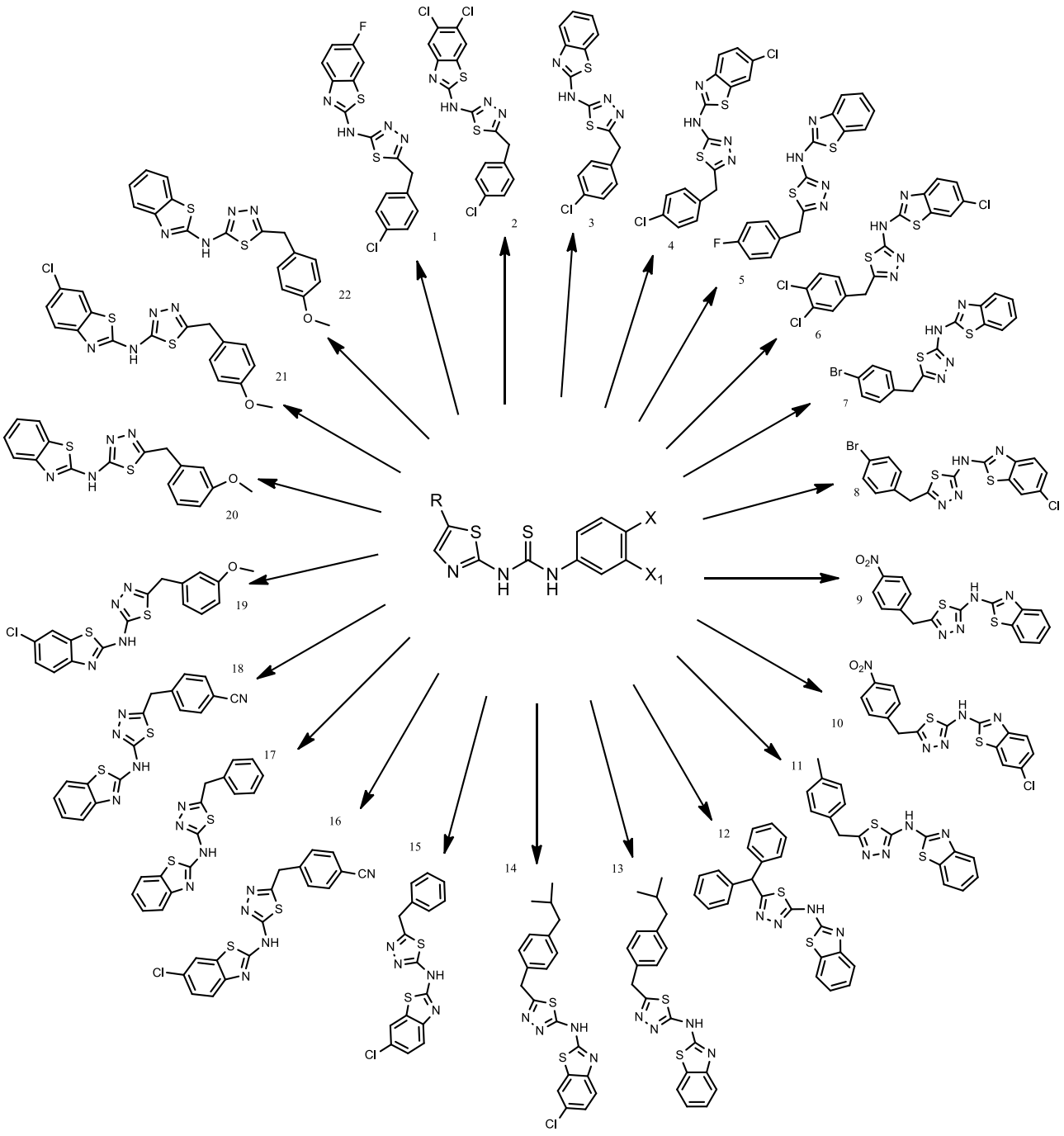
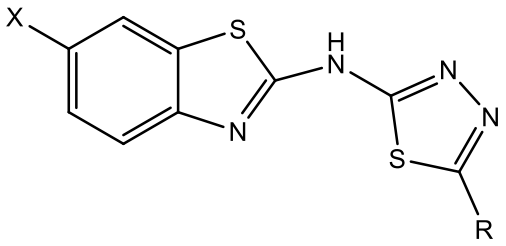
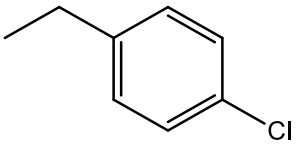
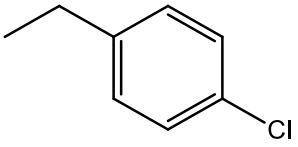
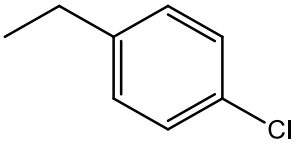
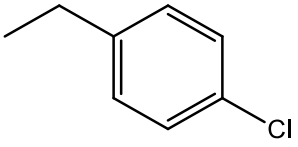
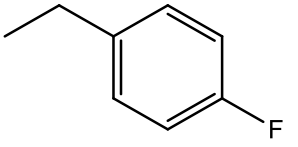
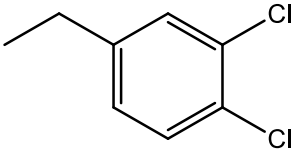
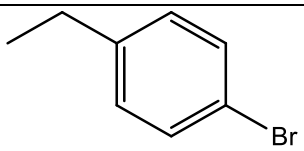
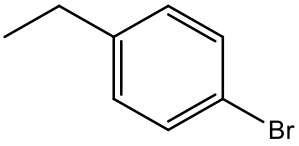
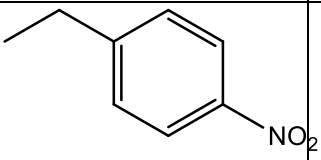
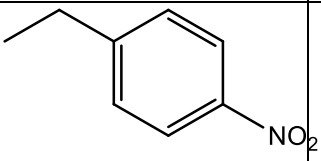
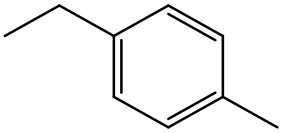
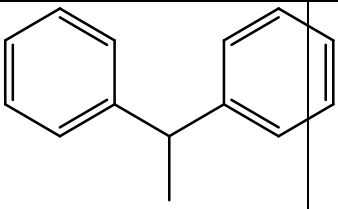
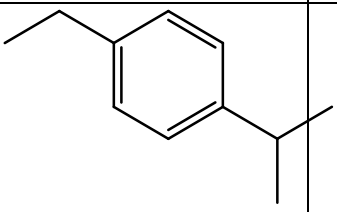
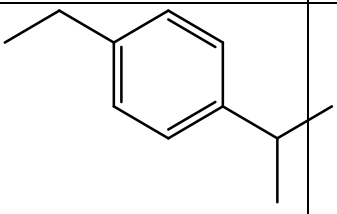
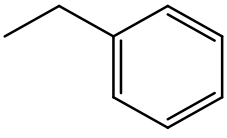
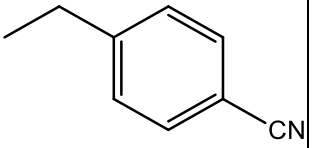


Figure 5: Series of Benzothiazole derivatives

List of the docked substituted Benzothiazole molecules



Compound	R	X	Molecular weight
BDZ 1		F	140.61
BDZ 2		Cl	140.61
BDZ 3		H	140.61
BDZ 4		Cl	140.61
BDZ 5		H	124.16
BDZ 6		Cl	175.06
BDZ 7		H	185.06

BDZ 8		Cl	185.06
BDZ 9		H	151.6
BDZ 10		Cl	151.16
BDZ 11		H	120.19
BDZ 12		H	182.26
BDZ 13		H	148.24
BDZ 14		Cl	148.24
BDZ 15		Cl	106.16
BDZ 16		Cl	131.17

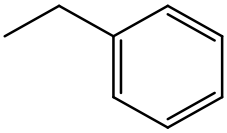
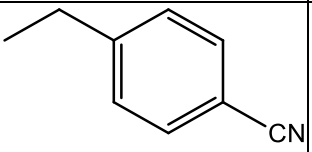
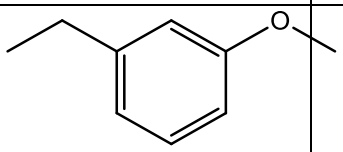
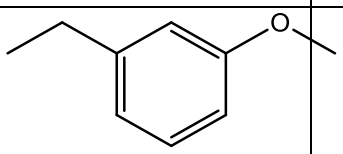
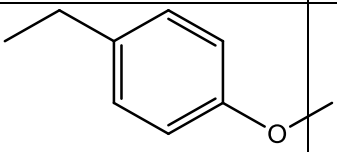
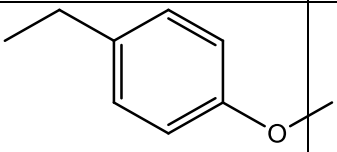
BDZ 17		H	106.16
BDZ 18		H	131.17
BDZ 19		Cl	136.39
BDZ 20		H	136.39
BDZ 21		Cl	136.39
BDZ 22		H	136.39

Table 1: Results of Bdz poses obtained from the ligand- receptor docking complex.

Compound	Moldock score	Rerank score	H-bond	Dock score	Similarity score
BDZ 1	-101.426	-72.54	0	-500.396	-398.21
BDZ 2	-104.73	-74.33	0	-503.618	-398.37
BDZ 3	-104.867	-55.90	-1.97	-495.635	-393.21
BDZ 4	-100.107	-71.99	0	-498.215	-397.38
BDZ 5	-83.276	6.38	-5.79	-498.852	-417.01
BDZ 6	-95.057	-17.20	-6.22	-506.516	-412.77
BDZ 7	-103.554	-53.88	-2.076	-494.423	-392.31
BDZ 8	-97.883	-69.83	0	-496.938	-392.31
BDZ 9	-109.089	-34.29	-4.58	-511.073	-398.31
BDZ 10	-118.65	-61.59	-4.51	-507.374	-388.31
BDZ 11	-105.329	-57.68	-1.98	-497.1.4	-394.41
BDZ 12	-115.508	-46.09	-2.36	-516.09	-400.7
BDZ 13	-120.16	-64.21	-2.27	-523.28	-404.25
BDZ 14	-124.85	-67.78	-5.06	-513.383	-386.07
BDZ 15	-105.63	14.14	-5.65	-518.35	-413.40
BDZ 16	-112.92	-67.06	-3.98	-499.831	-389.28
BDZ 17	-93.26	14.59	-5.83	-515.158	-421.53
BDZ 18	-110.172	-56.92	-2.43	-507.128	-397.6
BDZ 19	-115.677	-39.56	-6.57	-548.211	-430.90
BDZ 20	-113.495	-11.33	-6.65	-548.732	-435.19
BDZ 21	-106.404	-45.425	-1.79	-505.32	-399.51
BDZ 22	-108.83	-49.32	-1.97	-505.363	-397.22
Mefenamic acid	-96.27	-80.14	-5	-585.421	-493.73

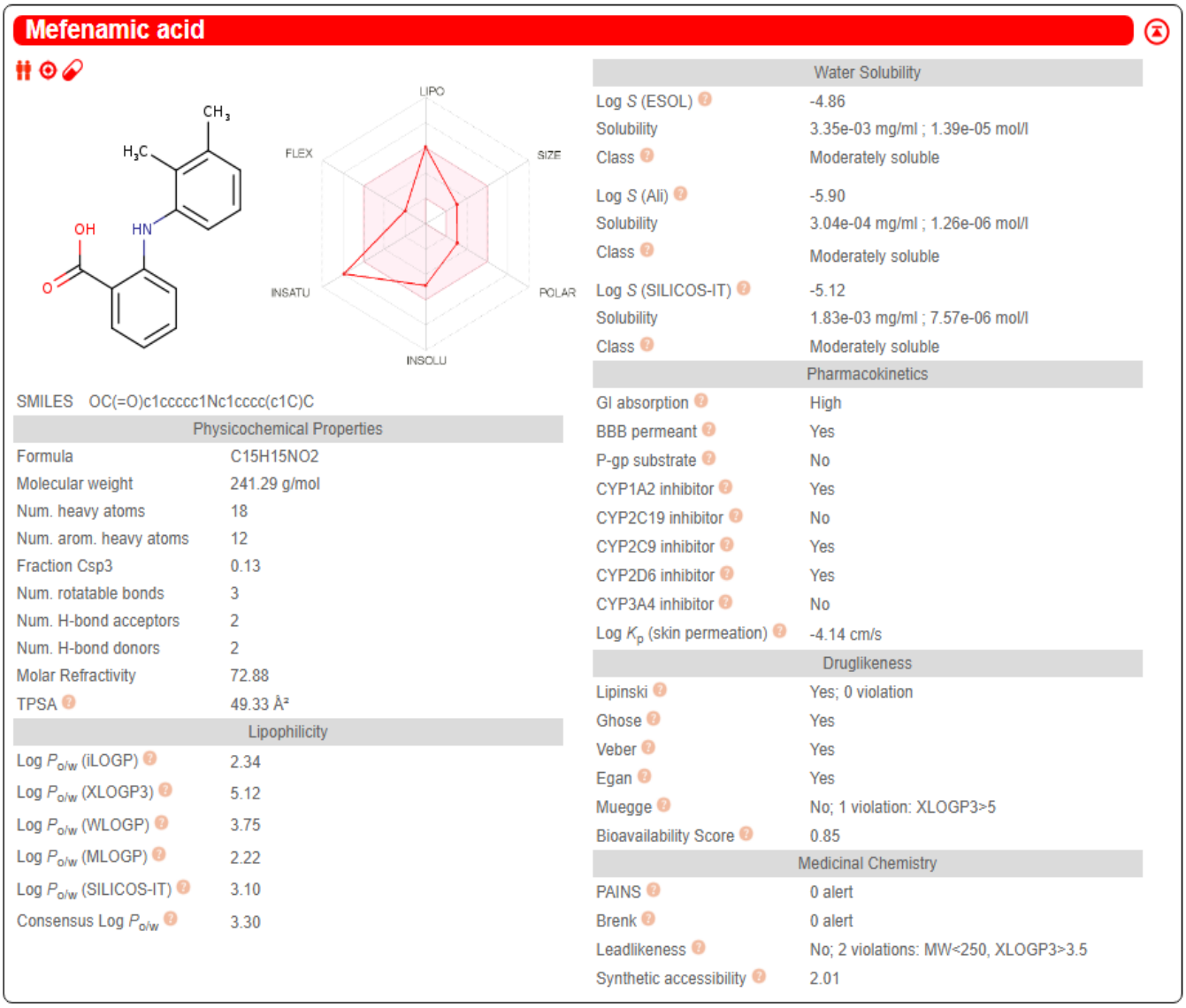


Figure 6: Physiochemical properties of the structure Mefenamic acid

The physiochemical properties of the co-crystal structure Mefenamic acid that inhibits COX-2 enzyme are indicated in a Radar (beside the Mefenamic acid structure),fig 16. The coloured zone indicates the suitable physico chemical space for oral bioavailability. The compound with the oral bioavailability properly fits the coloured space. Lipophilicity, Flexibility, Insaturation, Insolubility, Polarity and Size are observed in the Radar.

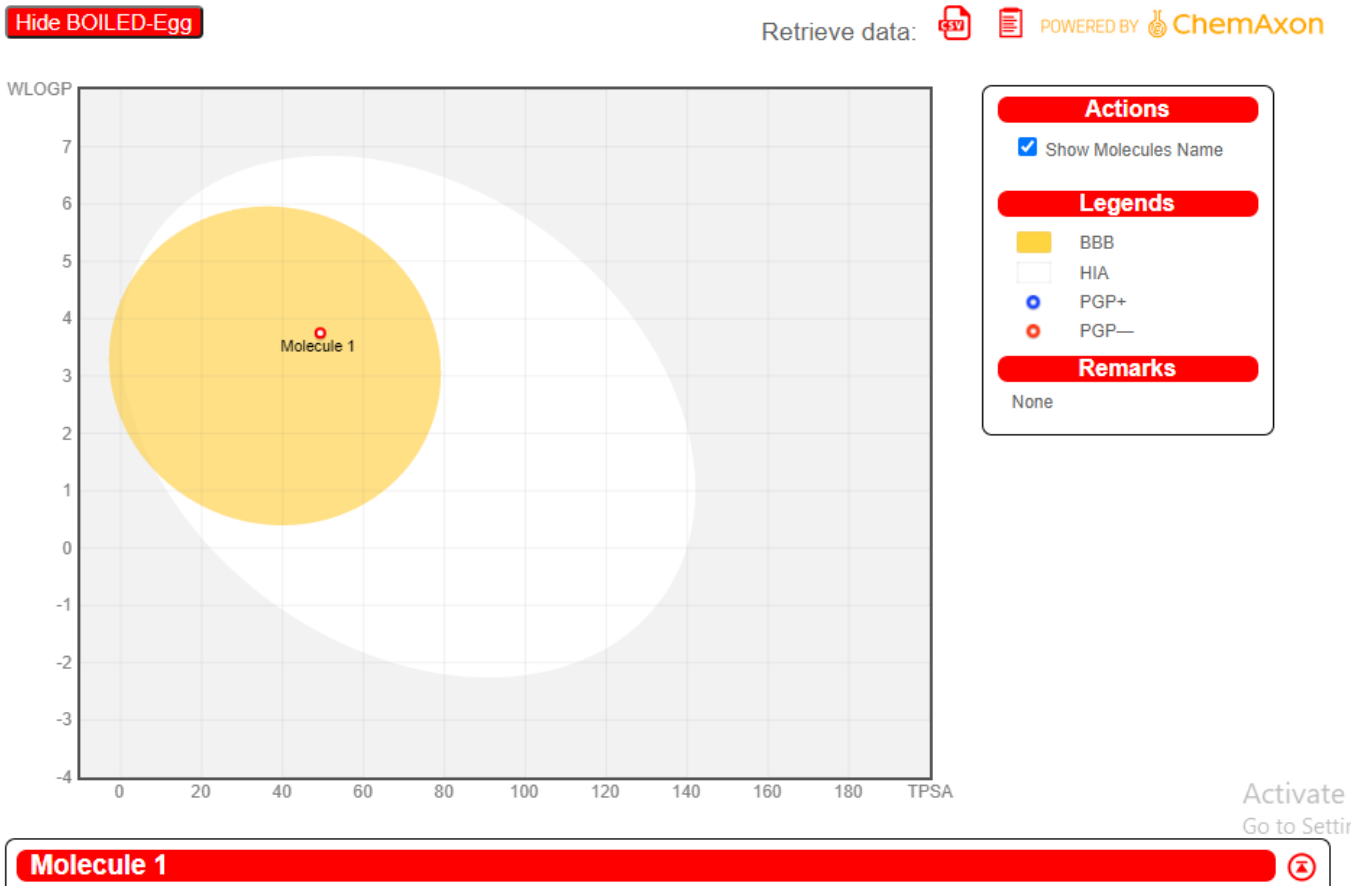


Figure 7 : Representation of BOILED-Egg that gives polarity and Lipophilicity of the drug molecule.

BOILED-Egg (Brain or Intestinal estimated Permeation method). The diagram at the X-axis shows TPSA (Topological polar surface area) and the Y-axis is observed as WLOGP,fig.17 .The white and yellow surface gives graphical representation of a Egg structure. Yellow colour region indicates the possibility of the drug to cross the Blood Brain Barrierv(BBB) due to its lipophilicity. The red dot molecule present in the yellow region is predicted not to be effluated from the central nervous system by the P-glycoprotien (PGP: drug transporter). The White part of the egg indicates the drug absorption into gastro intestinal tract .Hence, the drug present in the white region is represented in blue colour which is passively absorbed by the GI tract and the drug is effluated from the CNS. The graph of BOILED-Egg method represents the polarity and lipophilicity of the molecules and it is one of the crucial methods in various drug discovery process. In the above given, fig.17, the red dot that indicates Mefenamic acid shows that the drug can permeate through Blood brain barrier.

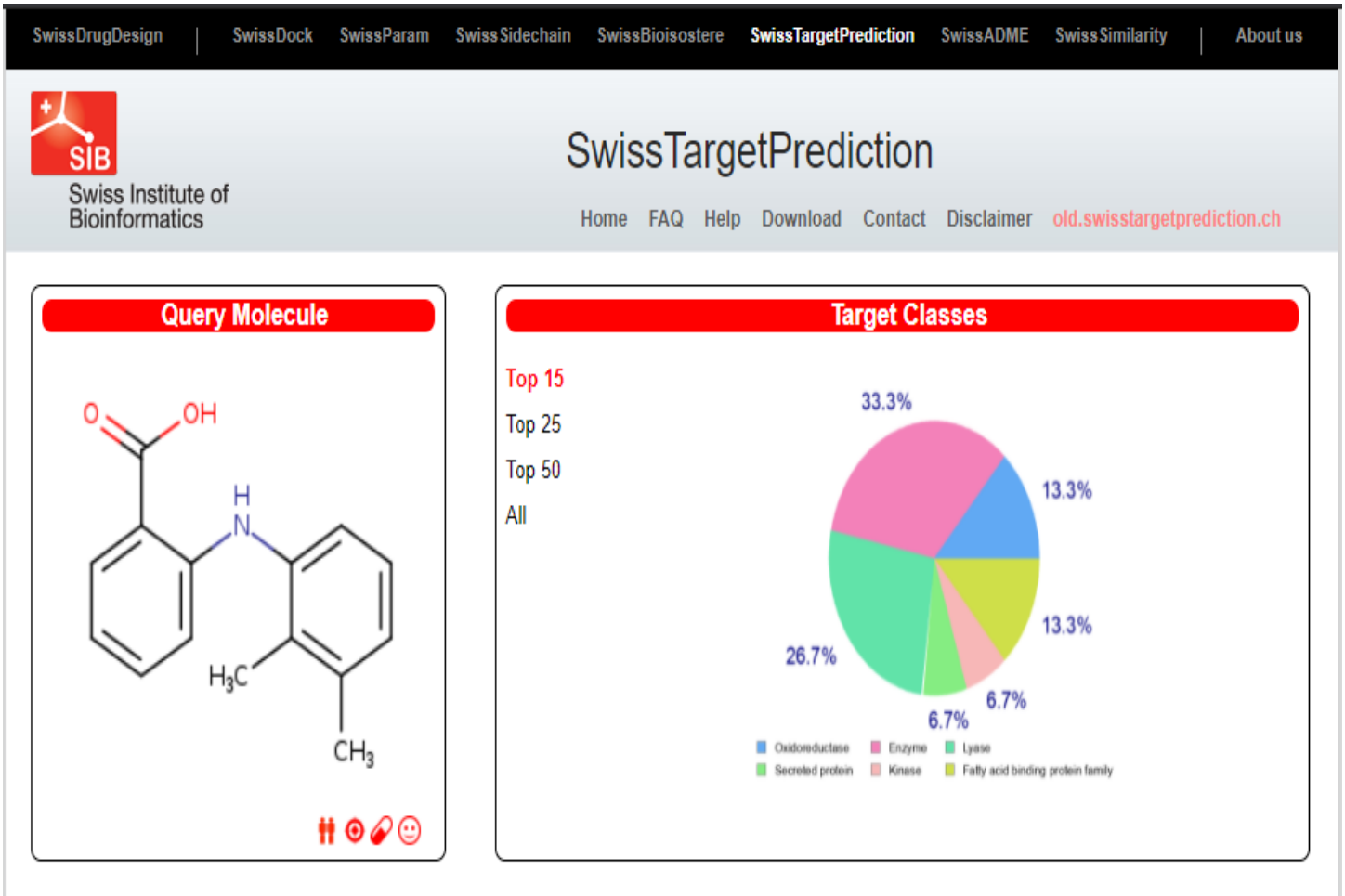


Figure 8: Swiss target prediction for enzymes by Mefenamic acid.

Swiss Target prediction gives the class of target enzymes related to the drug. The target class such as Oxidoreductase, enzyme, Lyase, secreted protein and kinase can be observed, fig.18. The probability of target prediction shows that Mefenamic acid targets Cycloxygenase-2 enzyme, fig.19.The complete target prediction for different enzymes can be analysed on Swiss target prediction.Here.in the above figure ,Mefenamic acid targets 33% of enzymes, 26.7% of secreted protein,13.3% of Oxidoreductase,13.3% of fatty acid binding protein and 6.7% of kinase. Hence, the above results show that Mefenamic acid can be a target for 33%of enzymes.

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Cyclooxygenase-1	PTGS1	P23219	CHEMBL221	Oxidoreductase		38 / 6
Cyclooxygenase-2	PTGS2	P35354	CHEMBL230	Oxidoreductase		92 / 12
Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	CHEMBL4681	Enzyme		142 / 115
Aldo-keto reductase family 1 member C2	AKR1C2	P52895	CHEMBL5847	Enzyme		56 / 68
Aldo-keto reductase family 1 member C1	AKR1C1	Q04828	CHEMBL5905	Enzyme		13 / 6
Aldo-keto reductase family 1 member B10	AKR1B10	O60218	CHEMBL5983	Enzyme		14 / 2
Carbonic anhydrase II	CA2	P00918	CHEMBL205	Lyase		34 / 9
Carbonic anhydrase I	CA1	P00915	CHEMBL261	Lyase		31 / 11
Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase		18 / 3
Carbonic anhydrase IX	CA9	Q16790	CHEMBL3594	Lyase		15 / 3
Transthyretin	TTR	P02766	CHEMBL3194	Secreted protein		8 / 5
MAP kinase ERK2	MAPK1	P28482	CHEMBL4040	Kinase		4 / 1
Fatty acid binding protein intestinal	FABP2	P12104	CHEMBL4879	Fatty acid binding protein family		2 / 1
Fatty acid-binding protein, liver *(by homology)*	FABP1	P07148	CHEMBL5421	Fatty acid binding protein family		5 / 1
Myeloperoxidase	MPO	P05164	CHEMBL2439	Enzyme		2 / 6

Showing 1 to 15 of 100 entries Previous 1 2 3 4 5 6 7 Next

*Probability for the query molecule - assumed as bioactive - to have this protein as target.

Figure 9: Swiss Target prediction of Compound Mefenamic acid for various enzymes .

Swiss target prediction was performed for all the potent Benzothiazole derivatives for the analysis of its physicochemical properties. Hence, the potent derivatives of Benzothiazole (Bdz 4, 14, 15, 17) are subjected for swiss ADME studies. The compound Mefenamic acid exhibits higher probability of target prediction towards Cycloxygenase-2 enzyme.

Physicochemical and ADME properties of potent compounds

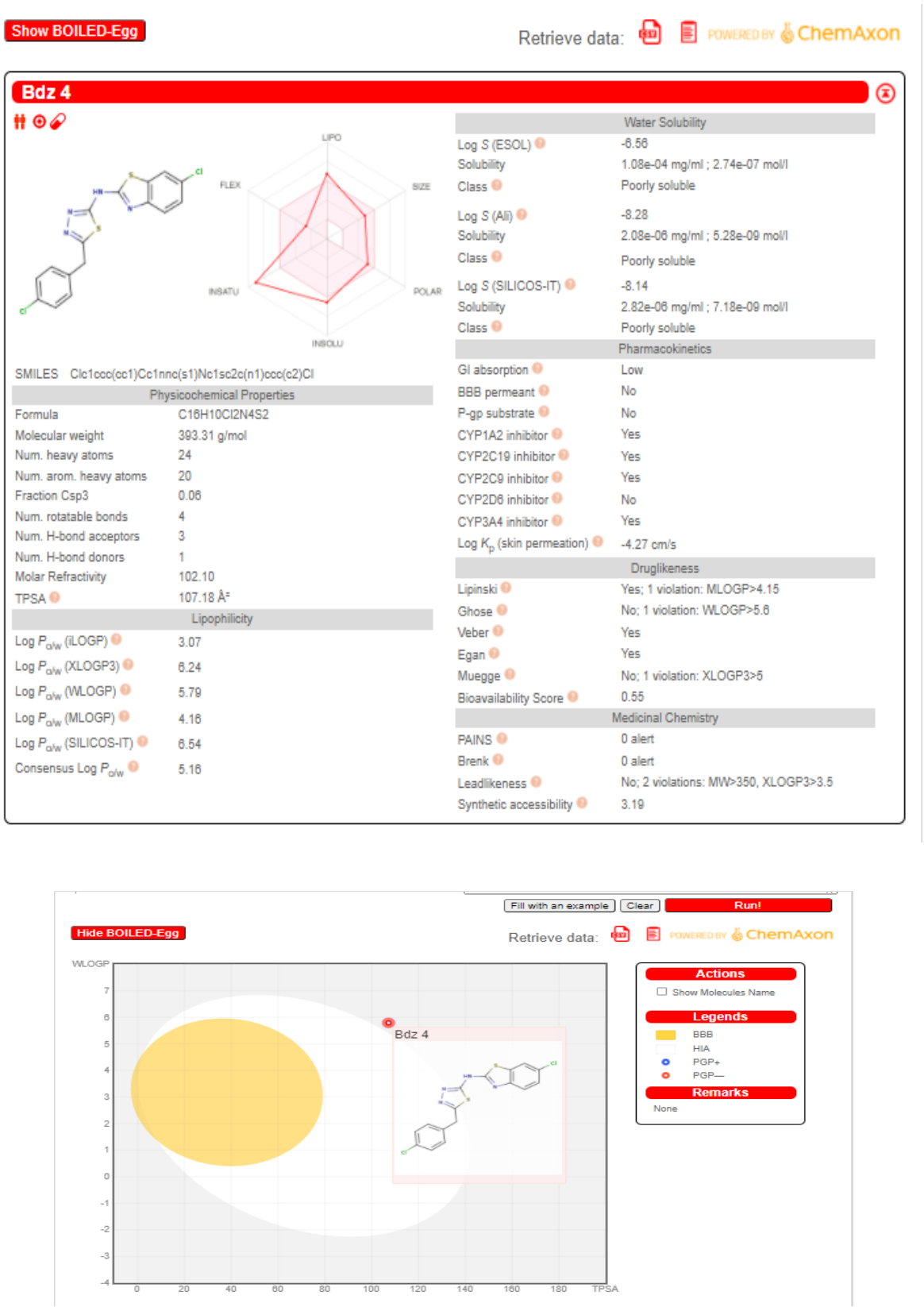
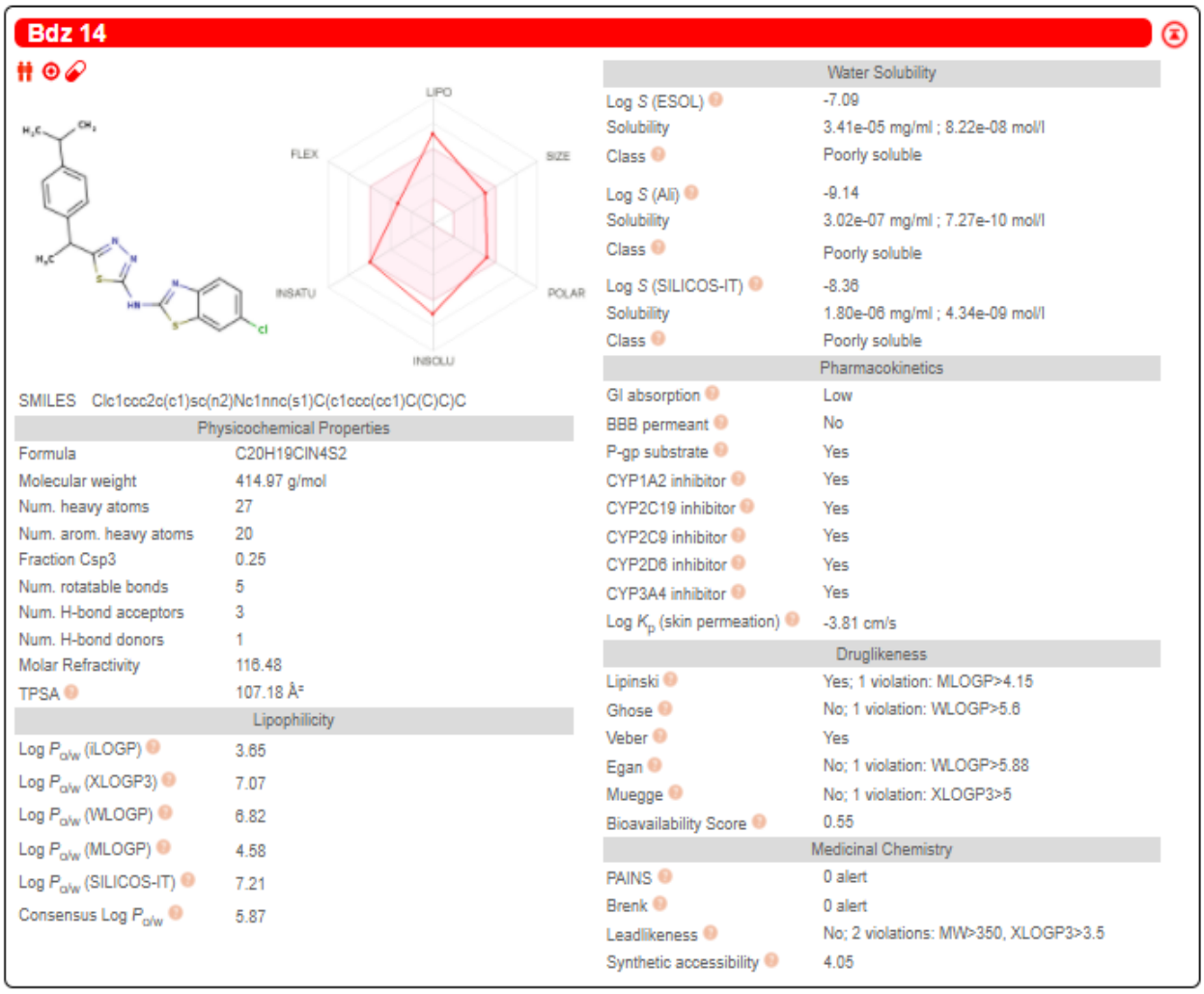


Figure 10: Computed parameter values of physicochemical properties of compound Bdz 4 is described above and the BOILED-Egg depicts that the compound Bdz 4 can be passively absorbed through gastro intestinal tract.



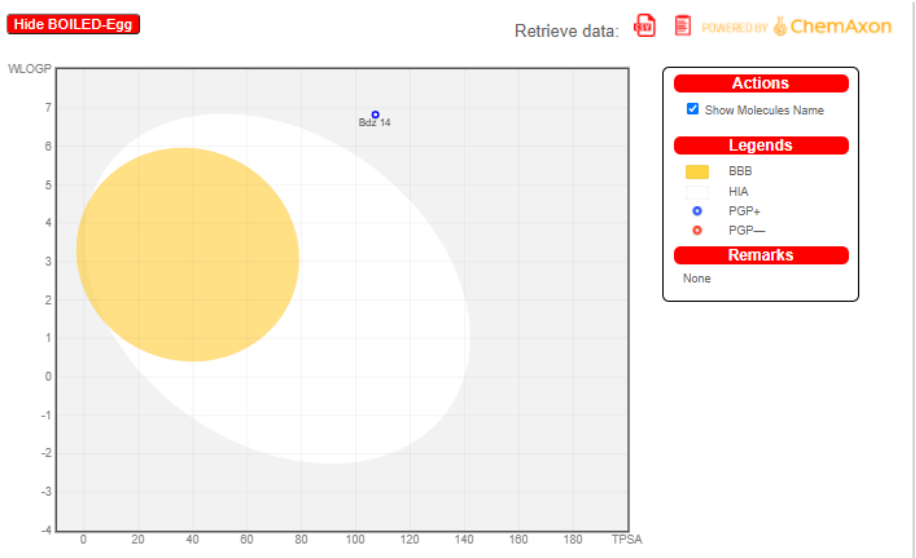
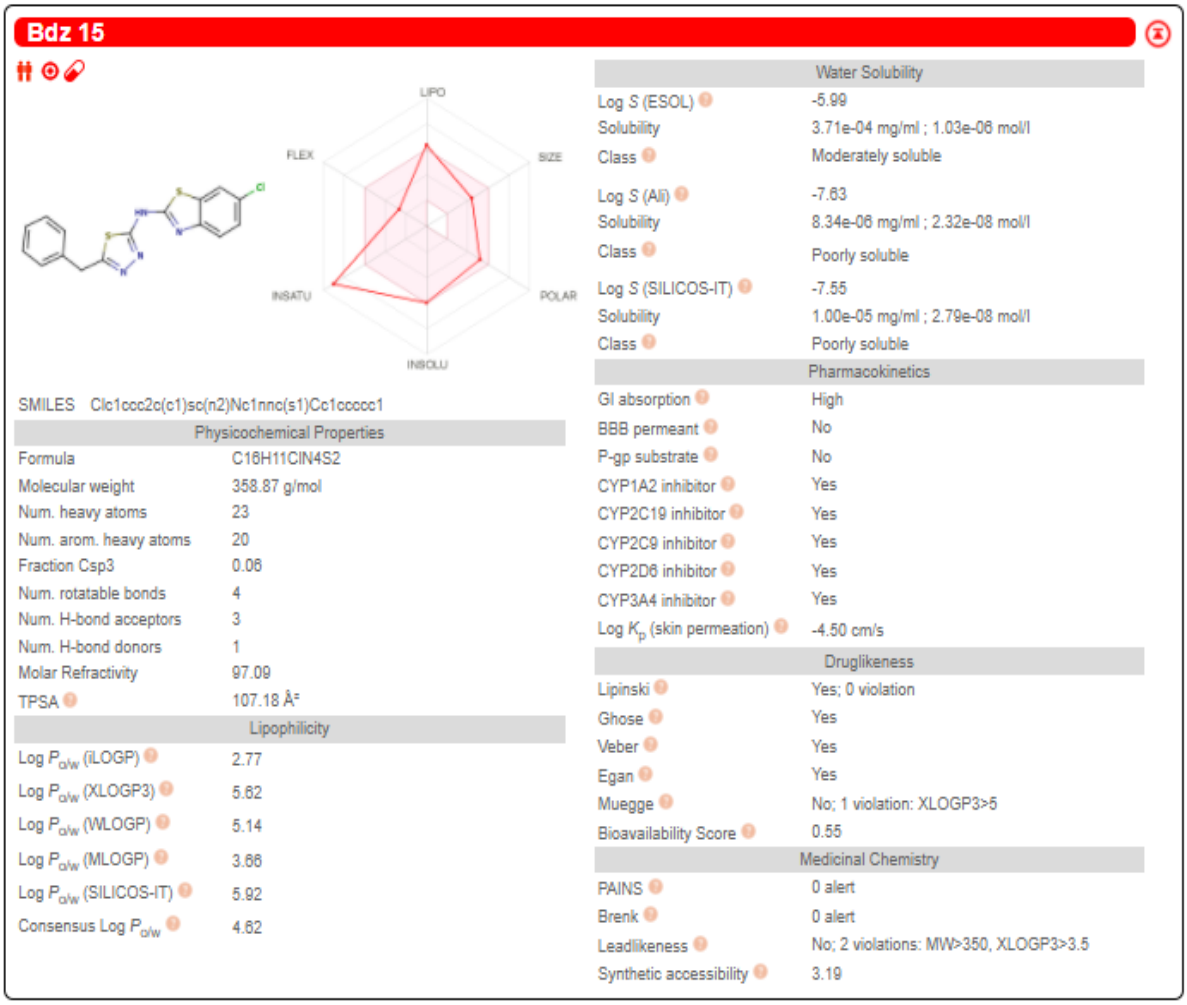
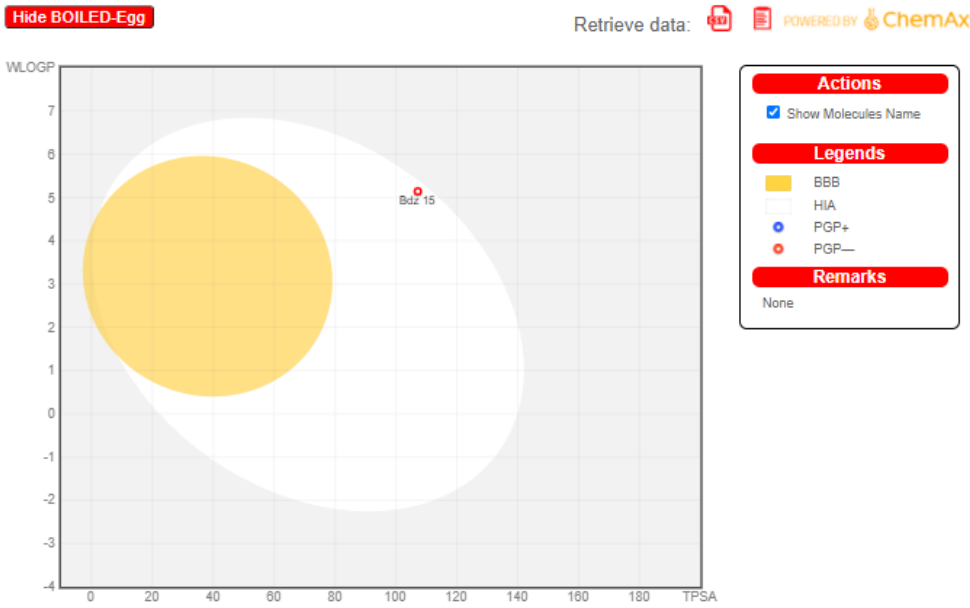


Figure 11: Computed parameter values of physicochemical properties of compound Bdz 14is described above and the BOILED-Egg depicts that the compound Bdz 14 do not have tendency of absorption in GIT.





: Figure 14: Computed parameter values of physicochemical properties of compound Bdz 15 is described above and the BOILED-Egg depicts that the compound Bdz 15 can be passively absorbed through gastro intestinal tract

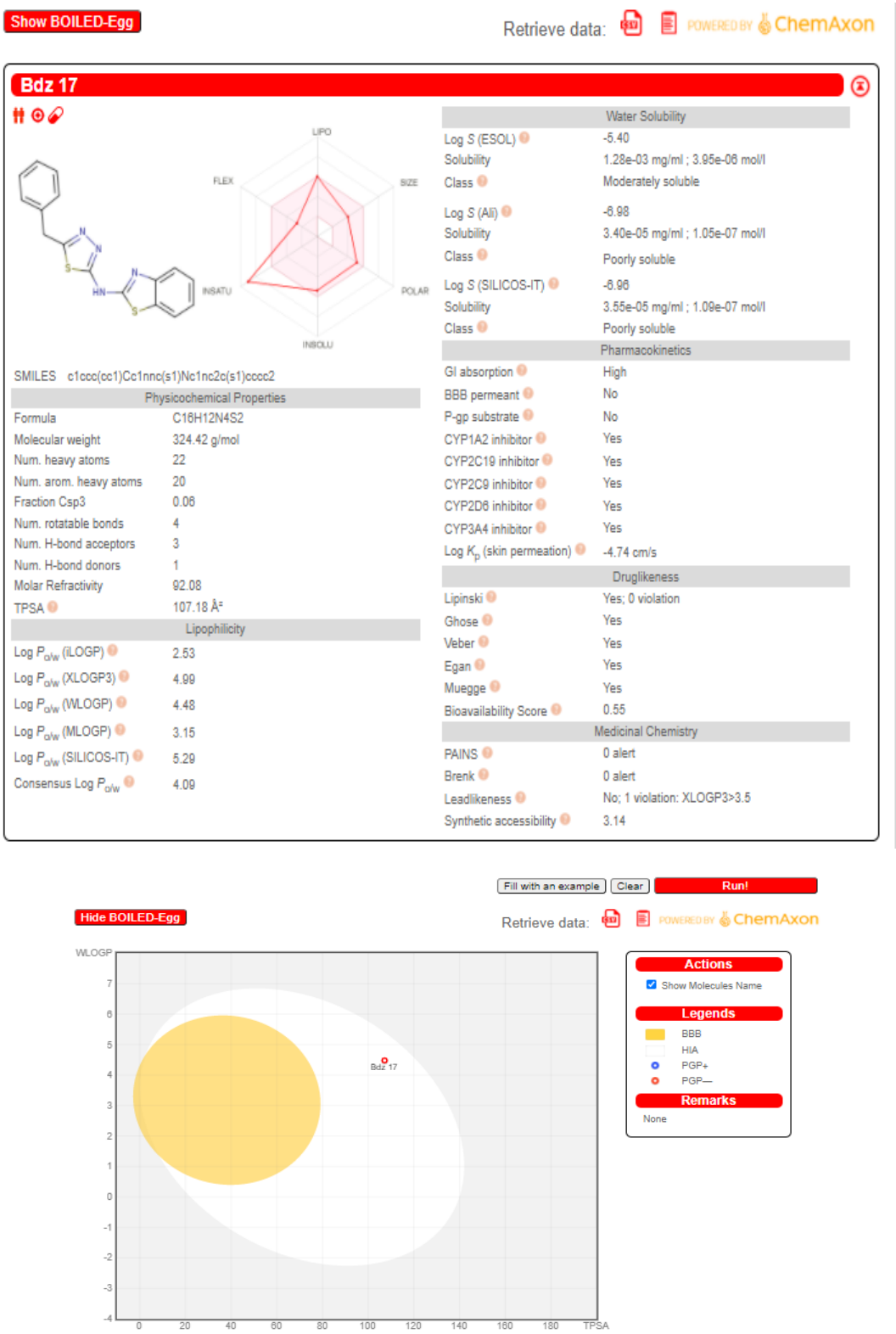
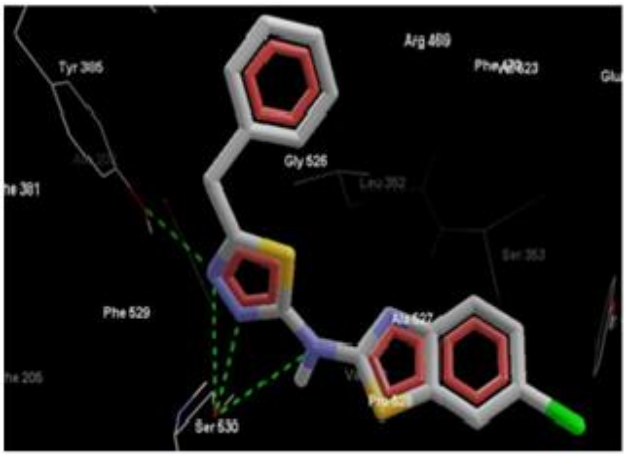


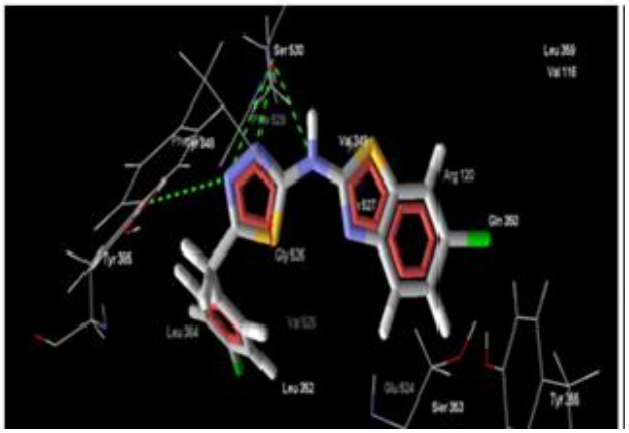
Figure 12 : Computed parameter values of physicochemical properties of compound Bdz 17 is described above and the BOILED-Egg depicts that the compound Bdz 17 can be passively absorbed through gastro intestinal tract.

The orientation and binding interactions of the selective COX-2 binding site was evaluated by Molecular docking. Results obtained from docking showed that the Pose BDZ 5, 13, 16 and 17 exhibited potent activity into the binding site of the enzyme COX-2 with the MolDock score -83.27, -124.85, -105.63 and -93.63 .Compound 4 forms hydrogen bond interactions with amino acid residues Tyr385 and Ser530. Whereas, Nitro group forms interaction with Tyr385 and amine group shows interaction with Ser530 amino acid.

The amino acids in the active site are represented by thin sticks and the ligands are represented by colour based on its element. Compound BDZ 17 has the Moldock score of -93.26 kcal/mol which is closer to Moldock score of Mefenamic acid .

Compound Bdz 14, has a Moldock score of -124.85 and Re-rank score -67.78 kcal/mol where in ,the sulphonyl groups in Benzothiazole moiety shows hydrogen bond interaction with Ser530 and nitro group forms a hydrogen bond with Tyr385 amino acid. Similarly, Bdz 15 with the highest MolDock score compared to crystal structure forms hydrogen bonds with Tyr385 and Ser530 amino acid residues linked to two nitro groups. Bdz 17 shows hydrogen bond interaction linked through amino and nitro group with the same amino acid residues Tyr385 and Ser530,fig.12.





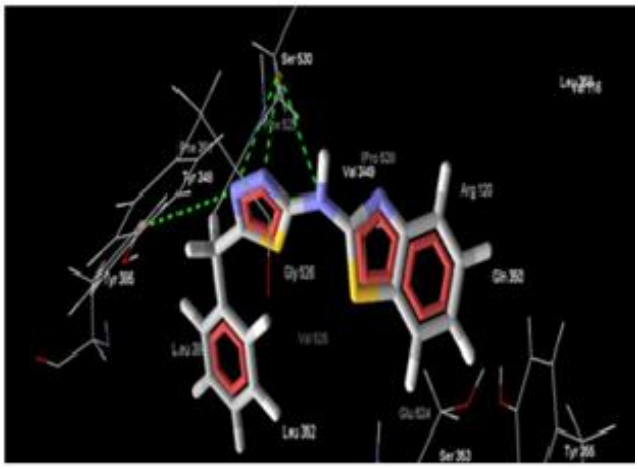
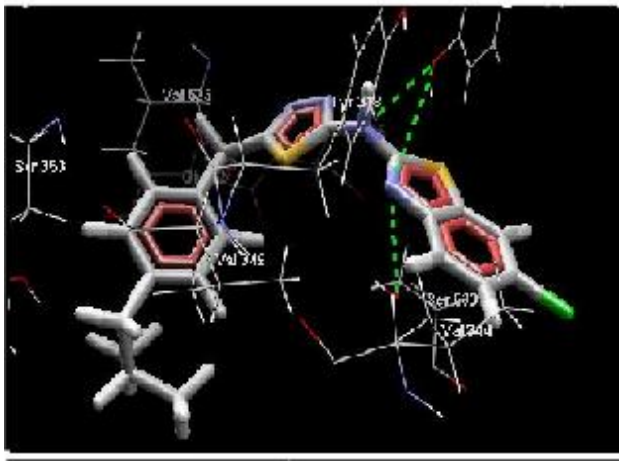


Figure 13 (a)Compound Bdz 4 (b)Bdz 14 (c) Bdz 15 and (d) Bdz 17 into the active site of COX-2 enzyme (PDB:5IKR).



IV. CONCLUSION

Current research work involves extensive Molecular docking study of Benzothiazole derivatives. A series of 21 Benzothiazole derivatives were docked into the active site of Cycloxygenase-2 for screening the anticancer activity. Structures were designed and docked into MVD software. The Results of Moldock score, Rerank score and binding interactions were analyzed in comparison with the co-crystal structure Mefenamic acid. From the docked benzothiazole derivatives Bdz 4, 14, 15 and 17 exhibited potent activity. Physicochemical and pharmacokinetic properties are analyzed by ADME studies for co-crystal structure Mefenamic acid and all the potent compounds of Benzothiazole. From the swiss target prediction results Mefenamic acid was found to target COX-2 enzyme. Benzothiazole compounds exhibited potent activity into the receptor site and hence might be used as therapeutic anticancer agents.

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