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# Research Article
# *In silico* Molecular Docking and ADME/Tox Study on Benzoxazole Derivatives Against Inosine 5'-Monophosphate Dehydrogenase

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## Abstract

**Background and Objective:** *Cryptosporidium parvum* (*C. parvum*) is a microscopic parasite that causes cryptosporidiosis in human. Accessible medications to treat cryptosporidiosis are ineffective and there is yet no immunization against *C. parvum*. So there is an urgent need to develop a suitable synthetic drug from available databases for suitable targets using computer aided drug designing and quantitative structure activity relationship. Present study was conducted to screen the best compound suitable for binding 5-Monophosphate dehydrogenase (IMPDH) target having optimum binding energy. **Materials and Methods:** In this regards, 38 benzoxazole derivatives were screened from PubChem compound database and docked with inosine 5-Monophosphate dehydrogenase (IMPDH) of *Cryptosporidium parvum* using the program AutoDock 4.2 from docked compound. **Results:** Four best predicted compounds CID 649646, CID 1318080, CID782217, CID1385213 with optimal binding energies -9.48, -9.39, -9.07 and -9.13 kcal $mol^{-1}$ were found with IMPDH, respectively. The biological activity of docked compounds in terms of $pIC_{50}$ was predicted based on 2D QSAR model built in our previously published work. The docked complex structures were optimized by molecular dynamics simulation with the CHARMM-22 force field using NAMD and evaluated the stability of complex structures by calculating RMSD. *In silico* ADME/Tox properties of best predicted derivatives of IMPDH were evaluated. **Conclusion:** The screened compounds showed satisfactory results for oral administration. Compounds have HIA in the range of well absorbed compounds and $P_{CaCO_2}$ value in standard range. Skin permeability of derivatives showed negative values. Derivatives lightly bind to plasma proteins. The Ames test showed compounds were mutagenic and carcinogenicity showed negative value in mouse and positive value in rat.

Key words: Benzoxazole derivatives, *Cryptosporidium parvum*, inosine 5-Monophosphate dehydrogenase (IMPDH), molecular docking, ADME/Tox, AutoDock 4.2

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Cryptosporidiosis is the most widely recognized food and waterborne infections with worldwide spread, going about as a typical reason for diarrhoea in human[1]. Among the five common *Cryptosporidium* species in people, *C. parvum* and *C. hominis* are in charge of over 90% of human instances of cryptosporidiosis[2]. *Cryptosporidium* is a standout amongst the most essential parasitic diarrheal ailments among youthful kids in developing countries and is dangerous as a sharp co-contamination with HIV because of expanded morbidity and mortality[3,4]. At present accessible medications are not successful for treating cryptosporidiosis and vaccine therapy is inadequate with regards to, so new medications are required. Genome sequencing of *Cryptosporidium parvum* revealed different choke points that might be used in drug design[5]. One such vulnerability lies in the pathway that supplies purine nucleotides for the synthesis of DNA and RNA. Inosine 5-Monophosphate dehydrogenase (IMPDH) catalyzes the transformation of inosine 5'-Phosphate to xanthosine 5'-Phosphate, the principal conferred and rate-limiting step in the *de novo* synthesis of guanine nucleotides and in this manner assumes a vital part in the regulation of cell growth[6].

Inosine monophosphate dehydrogenase (IMPDH) is an important enzyme in biosynthetic pathway of purine nucleotide. It is a key target for drug discovery in course of antibacterial, antiviral and anticancer therapeutics[7]. IMPDH is also an attractive and potent TB drug target[8]. On the basis of pharmacophore mapping, docking score, binding energy and binding interactions with the active site residues of the target protein IMPDH with potent inhibitors of PfDXR have the ability to bind with other *Plasmodium falciparum* drug targets[9].

In this study, 38 benzoxazole derivatives, screened from PubChem compound database were docked with IMPDH protein of *C. parvum* using AutoDock 4.2[10]. The $pIC_{50}$ value of docked compounds was predicted using a built 2D QSAR model having correlation coefficient $r^2$ of 0.7948[11]. Stability of docked complexes was validated by Molecular dynamics simulation. Further, the best predicted benzoxazole derivatives were subjected to ADME/Tox studies. The best predicted derivatives evaluated from ADME/TOX study optimized. The compound shows significant value for oral administration was selected for the development of new drug compound.

## MATERIALS AND METHODS

The study was carried out at Bioinformatics Lab at Department of Biotechnology, IFTM University, Moradabad and Department of Biotechnology, Noida International University, Noida, India.

**Protein target structure:** Crystal structure of the catalytic domain of the inosine 5-monophosphate dehydrogenase from *Cryptosporidium parvum* (PDB Id: 4IXH) was retrieved from protein databank[12]. This is utilized as a target model for docking. 3D structure of catalytic domain of IMPDH protein was optimized by the chimera tool[13].

**Inhibitors dataset:** About 38 benzoxazole derivatives screened from PubChem compound database[14]. The 3D structures of known 38 derivatives were downloaded in SDF format and later converted in PDB format with the help of open babel tool[15]. All the compounds were subjected to energy minimization using the HyperChem software (HyperChem (TM) Release 7.5).

**Molecular docking:** Docking of 38 benzoxazole derivatives screened from database against *C. parvum* IMPDH structure were done using molecular docking program AutoDock4.2[10]. Gasteiger charges and maximum 32 numbers of active torsions were given to the lead compounds using AutoDock tool (http://autodock.scripps.edu/resources/adt). Kollman charges and the solvation term were added to the IMPDH protein structure. The Lamarckian genetic algorithm implemented in AutoDock 4.2 was utilized for docking.

**2D QSAR:** The $pIC_{50}$ value of docked compounds was predicted using built QSAR model having correlation coefficient $r^2$ value 0.7948[11]:

$$\text{Predicted } pIC_{50} \text{ of compound} = \begin{bmatrix} 1.0291\text{-}26.7693\ (\text{Binding energy})+25.9634 \\ (\text{Intermolecular energy})+0.7866(\text{Internal} \\ \text{energy})+25.9788(\text{Torsional energy})\text{-}0.0536 \\ (\text{vdW+Hbond+desolv energy})\text{-}1.7919 \\ (\text{Electrostatic energy}) \end{bmatrix}$$

**Molecular dynamics simulations:** Molecular dynamics simulations were done using the NAMD[16] graphical interface module joined in VMD[17]. The protein-compound complex was immersed in the center of a 50 Å box of water molecules where all water molecule atoms were nearer than 1.5 Å and a CHARMM22 parameter file for proteins and lipids was used in

the force field for protein-compound complexes. The PSF was created from the initial PDB and topology files utilizing PSF gen package of VMD, which generated protein, PDB and protein PSF and by accessing these files, NAMD produced the trajectory DCD file.

**ADME and toxicological properties of compounds:** The predicted inhibitors were subjected for calculation of absorption, distribution, metabolism, excretion and toxicological properties. Physicochemical properties like molecular weight, XLogP, hydrogen bond donor count and hydrogen bond acceptor were calculated for predicted inhibitors. ADME properties like percentage of human intestinal absorption, cell permeability, skin permeability, blood brain barrier, plasma protein binding and toxicological properties like mutagenicity and carcinogenicity were calculated using PreADMET tool[18,19].

## RESULTS AND DISCUSSION

**Molecular docking:** Based on R1 group, 38 benzoxazole derivatives were screened from PubChem compound database was shown in Table 1. In docking studies of benzoxazole derivatives with IMPDH protein, lower binding affinity was used as criteria to select best conformation among 30 generated conformations by AutoDock 4.2. Results of docking between compounds and IMPDH protein were shown in Table 1. Docked complexes were visualized by Python Molecular Viewer[20] software for their interaction studies and best docked confirmation of compounds with protein was shown in Fig. 1-4. Compounds CID 649646 and CID 1318080 had no hydrogen bond with IMPDH protein. Compounds CID 782217 and CID 1385213 had one hydrogen bond with residue ASP217 and ASP252 of IMPDH protein, respectively (Fig. 3 and 4).

**Prediction of inhibitory concentration:** Thirty eight screened benzoxazole derivatives were selected for calculation of biological activity on the basis of QSAR model[21] and result was shown in Table 1.

**Molecular dynamics simulation:** Root mean square deviation (RMSD) of protein-compound complex store in RMSD dat a were accessed in Microsoft office excels. RMSD, a crucial parameter to analyze the equilibration of MD trajectories, is estimated for backbone atoms of the compounds CID649646,

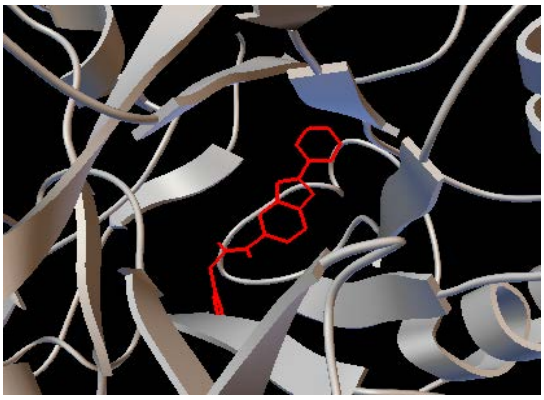


Fig. 1: Docked complex of compound CID 649646 with IMPDH protein

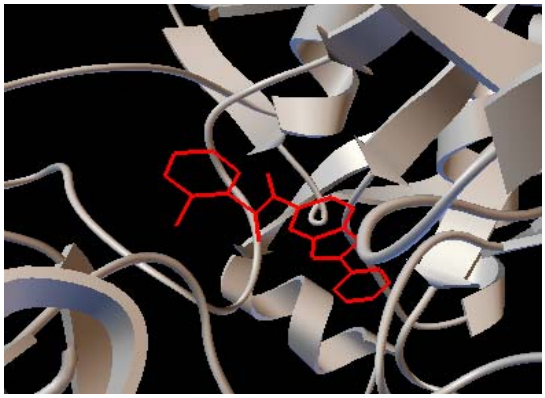


Fig. 2: Docked complex of compound CID 1318080 with IMPDH protein

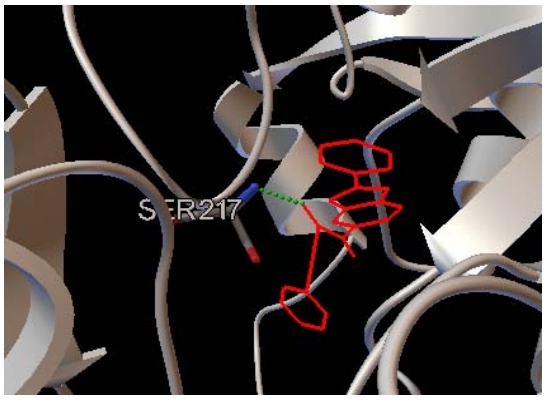
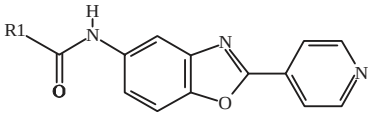



Fig. 3: Docked complex of compound CID782217 with IMPDH protein. One H-bond formed between compound and residue ASP217 of IMPDH protein. H-bond represented by green dotted sphere. Bonded residue of protein is represented by sticks and balls. Compound CID782217 is represented by red lines

Table 1: Docking results of benzoxazole derivatives with IMPDH structure with activity ($pIC_{50} = - logIC_{50}$)

Benzoxazole derivatives



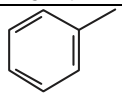
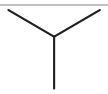
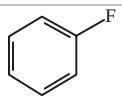
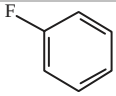
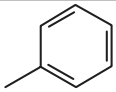
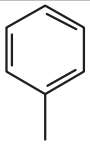
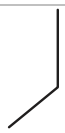
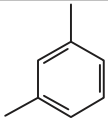
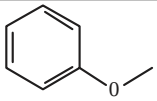
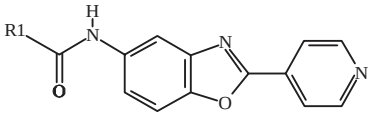
| Derivative | R1 groups | PubChem CID | Predicted $pIC_{50}$ | BE | IME | IE | TorE | VdwE | EE |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 649646 | 8.87 | -9.48 | -10.38 | -0.32 | 0.89 | -10.30 | -0.08 |
| 2 |  | 659689 | 7.70 | -8.07 | -9.27 | -0.26 | 1.19 | -9.19 | -0.07 |
| 3 |  | 659778 | 9.36 | -8.60 | -9.19 | -0.24 | 0.60 | -9.09 | -0.10 |
| 4 |  | 675056 | 8.49 | -8.59 | -9.19 | -0.17 | 0.60 | -9.08 | -0.10 |
| 5 |  | 699259 | 8.48 | -8.60 | -9.19 | -0.35 | 0.60 | -9.18 | -0.02 |
| 6 |  | 3713194 | 6.72 | -7.29 | -8.19 | -0.48 | 0.89 | -8.18 | 0.00 |
| 7 |  | 1849635 | 7.18 | -7.52 | -9.01 | -0.62 | 1.49 | -8.98 | -0.04 |
| 8 |  | 652465 | 7.09 | -7.55 | -8.74 | -0.61 | 1.19 | -8.77 | 0.02 |
| 9 |  | 659819 | 7.37 | -7.94 | -9.73 | -0.70 | 1.79 | -9.76 | 0.03 |
| 10 |  | 921484 | 8.31 | -8.44 | -9.04 | -0.41 | 0.60 | -9.05 | 0.01 |
| 11 |  | 699256 | 8.15 | -8.81 | -9.41 | -0.56 | 0.60 | -9.44 | 0.03 |
| 12 |  | 739163 | 7.27 | -7.43 | -8.32 | -0.42 | 0.89 | -8.26 | -0.07 |
| 13 | $CH_3$ | 744279 | 7.60 | -7.99 | -8.59 | -0.43 | 0.60 | -8.59 | 0.00 |
| 14 |  | 970723 | 7.82 | -8.65 | -9.55 | -0.63 | 0.89 | -9.51 | -0.03 |
| 15 |  | 1112725 | 7.22 | -8.36 | -9.85 | -1.50 | 1.49 | -9.80 | -0.05 |

Table 1: Continue

Benzoxazole derivatives



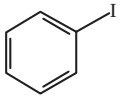
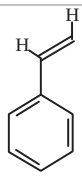
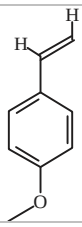
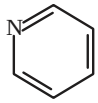
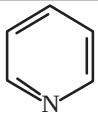
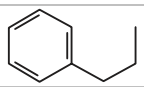
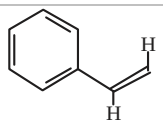
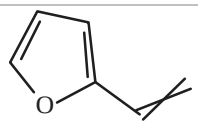
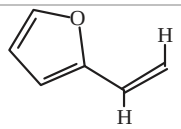
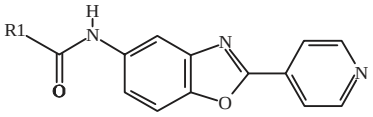
| Derivative | R1 groups | PubChem CID | Predicted $pIC_{50}$ | BE | IME | IE | TorE | VdwE | EE |
|---|---|---|---|---|---|---|---|---|---|
| 16 |  | 1318080 | 8.74 | -9.39 | -9.99 | -0.46 | 0.60 | -10.01 | 0.02 |
| 17 |  | 1727025 | 7.43 | -8.39 | -9.58 | -1.20 | 1.19 | -9.54 | -0.03 |
| 18 |  | 1975688 | 8.01 | -8.78 | -10.27 | -0.91 | 1.49 | -10.24 | -0.03 |
| 19 |  | 2880603 | 9.04 | -8.05 | -8.64 | -0.35 | 0.60 | -8.55 | -0.09 |
| 20 |  | 5345989 | 7.06 | -8.02 | -8.92 | -0.93 | 0.89 | -8.88 | -0.04 |
| 21 |  | 71662586 | 7.87 | -8.84 | -10.03 | -1.02 | 1.19 | -10.05 | 0.02 |
| 22 |  | 6457248 | 7.38 | -8.06 | -8.96 | -0.48 | 0.89 | -8.96 | 0.00 |
| 23 |  | 782217 | 8.51 | -9.07 | -10.26 | -0.51 | 1.19 | -10.26 | 0.00 |
| 24 |  | 782265 | 7.85 | -8.28 | -9.47 | -0.61 | 1.19 | -9.42 | -0.06 |
| 25 |  | 782267 | 7.70 | -8.09 | -9.28 | -0.60 | 1.19 | -9.22 | -0.06 |

Table 1: Continue

Benzoxazole derivatives



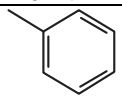
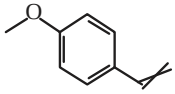
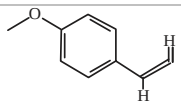
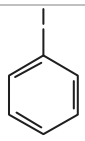
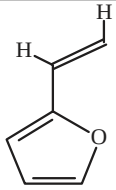
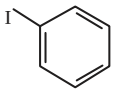
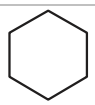
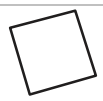
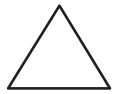
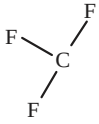
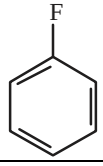
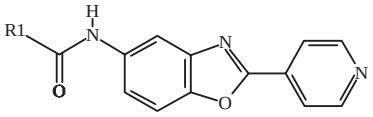
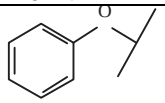
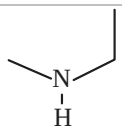
| Derivative | R1 groups | PubChem CID | Predicted $pIC_{50}$ | BE | IME | IE | TorE | VdwE | EE |
|---|---|---|---|---|---|---|---|---|---|
| 26 |  | 921482 | 8.12 | -8.61 | -9.21 | -0.42 | 0.60 | -9.22 | 0.01 |
| 27 |  | 1362353 | 8.46 | -8.98 | -10.47 | -0.70 | 1.49 | -10.38 | -0.09 |
| 28 |  | 1362355 | 7.93 | -8.85 | -10.35 | -0.72 | 1.49 | -10.34 | -0.01 |
| 29 |  | 1385213 | 9.18 | -9.13 | -9.73 | -0.28 | 0.60 | -9.45 | -0.28 |
| 30 |  | 1600325 | 7.53 | -8.49 | -9.68 | -0.99 | 1.19 | -9.74 | 0.06 |
| 31 |  | 1983747 | 8.72 | -8.94 | -9.53 | -0.39 | 0.60 | -9.53 | -0.01 |
| 32 |  | 5063740 | 7.61 | -8.48 | -9.37 | -0.65 | 0.89 | -9.52 | 0.15 |
| 33 |  | 8081249 | 7.84 | -8.35 | -9.24 | -0.54 | 0.89 | -9.24 | 0.00 |
| 34 |  | 8082264 | 7.07 | -7.26 | -8.15 | -0.50 | 0.89 | -8.07 | -0.08 |
| 35 |  | 9203582 | 6.86 | -7.16 | -8.05 | -0.56 | 0.89 | -8.03 | -0.03 |
| 36 |  | 17078851 | 7.83 | -8.38 | -8.98 | -0.37 | 0.60 | -9.06 | 0.09 |

Table 1: Continue

| Derivative | Benzoxazole derivatives<br>  <br>R1 groups | PubChem CID | Predicted $pIC_{50}$ | BE | IME | IE | TorE | VdwE | EE |
|---|---|---|---|---|---|---|---|---|---|
| 37 |  | 30308174 | 7.68 | -9.00 | -10.19 | -1.42 | 1.19 | -10.22 | 0.03 |
| 38 |  | 118261924 | 7.79 | -8.06 | -9.26 | -1.29 | 1.19 | -8.20 | -1.05 |

BE: Binding energy, IME: Intermolecular energy, IE: Internal energy, TorE: Torsional, energy, VdwE: vdW+Hbond+desolv energy, EE: Electrostatic energy

Table 2: Physicochemical properties of 4 best predicted compounds

| Derivative | PubChem CID | Molecular weight (g $moL^{-1}$) | Donor | Acceptor | XLogP |
|---|---|---|---|---|---|
| 1 | 649646 | 329.359 | 1 | 4 | 3.1 |
| 2 | 1318080 | 441.228 | 1 | 4 | 3.8 |
| 3 | 782217 | 341.370 | 1 | 4 | 3.6 |
| 4 | 1385213 | 441.228 | 1 | 4 | 3.8 |

Table 3: Absorption properties of 4 best predicted compounds

| Derivative | PubChem CID | Absorption<br>HIA (%) | $P_{CaCO_2}$ | MDCK | Skin permeability |
|---|---|---|---|---|---|
| 1 | 649646 | 96.242002 | 38.1994 | 3.966980 | -3.31018 |
| 2 | 1318080 | 97.765126 | 27.5722 | 0.378139 | -3.46741 |
| 3 | 782217 | 96.427923 | 43.7072 | 2.973880 | -3.09312 |
| 4 | 1385213 | 97.765148 | 27.5032 | 0.408973 | -3.48735 |

HIA: Percentage of human intestinal absorption, $P_{CaCO_2}$ : Cell permeability ($CaCo_2$ in nm $sec^{-1}$), MDCK: Cell permeability Maden Darby Canine Kidneyin (nm $sec^{-1}$)


Fig. 4: Docked complex of compound CID 1385213 with IMPDH protein. One H-bond formed between compound and residue ASP252of IMPDH protein. H-bond represented by green dotted sphere. Bonded residue of protein is represented by sticks and balls. Compound CID1385213 is represented by red lines

CID1318080, CID782217 and CID1385213 with IMPDH protein complex (Fig. 5a-d). Result of simulation shows that compounds were stable.

**ADME and toxicological properties:** Best predicted compounds satisfied the Lipinski rule of five to evaluate oral absorption and was shown in Table 2. Predicted compounds CID102080317 and CID16215157 have human intestinal absorption (HIA) values in the range of 96.242002-97.765148 are belong to the range of well absorbed compounds (HIA: 70 ~100%) was shown[22] in Table 3. The cell permeability *in vitro* $CaCO_2$ is an important test to assess intestinal absorption of drug compounds. It was found that the $P_{CaCO_2}$ (nm $sec^{-1}$) value of compounds were ranging from 27.5722-44 nm $sec^{-1}$ was shown in Table 3 and categorized in standard range ( $P_{CaCO_2}$ >70 nm $sec^{-1}$)[22]. *In vitro* in MDCK system is used as a tool for the rapid analysis of cell permeability. MDCK value of compounds was in range of 0.378139-3.96698 nm $sec^{-1}$ (Table 3). These values had lower MDCK value than mean

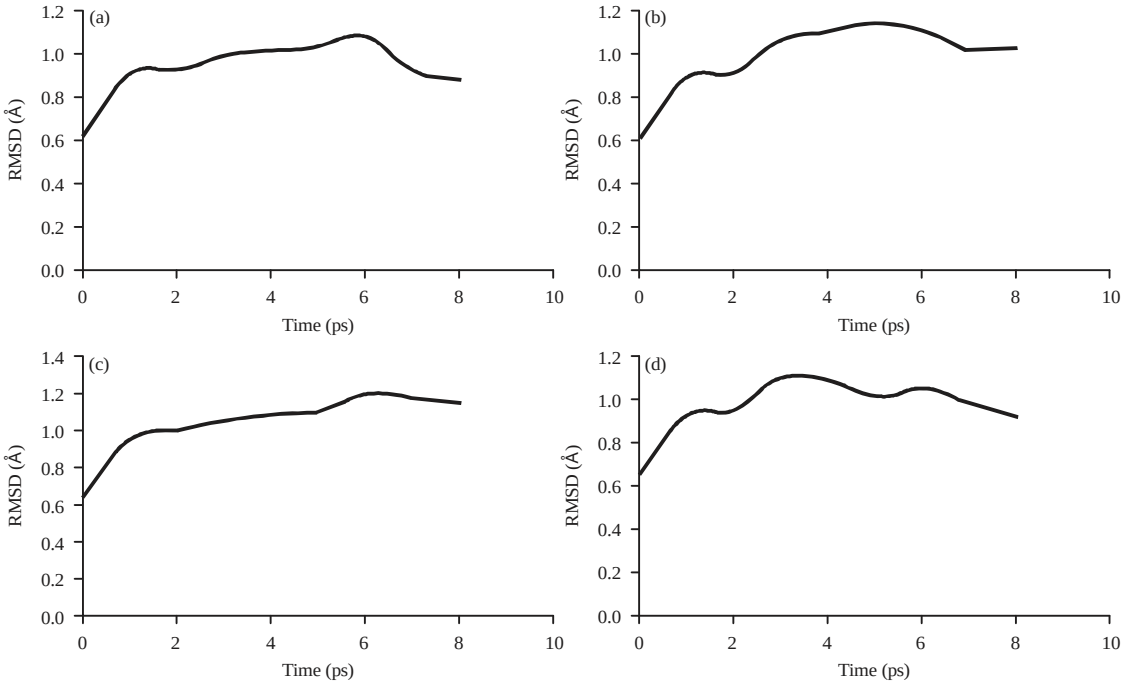



Fig. 5(a-d): RMSD of docked protein complex versus time (in Ps) (a) RMSD of compound CID 649646-IMPDH protein complex versus time (in Ps), resulted in highest peak at 1.08 Å, (b) RMSD of compound CID 1318080-IMPDH protein complex versus time (Ps), resulted in highest peak at 1.13 Å, (c) RMSD of compound CID 782217-IMPDH protein complex versus time (in ps), resulted in highest peak at 1.20 Å and (d) RMSD of compound CID 1385213-IMPDH protein complex versus time (in ps), resulted in highest peak at 1.10Å

Table 4: Distribution properties in percentage of plasma protein binding (PPB) and penetration of the blood brain barrier (BBB) for 4 best predicted compounds

| | | Distribution | |
|---|---|---|---|
| Derivative | PubChem CID | PPB (%) | BBB |
| 1 | 649646 | 91.880449 | 0.0226817 |
| 2 | 1318080 | 100.00000 | 0.0440191 |
| 3 | 782217 | 93.449146 | 0.0366843 |
| 4 | 1385213 | 91.947869 | 0.0674035 |

Table 5: Toxicological properties of mutagenicity and carcinogenicity for 4 best predicted compounds

| | | | Carcinogenicity | |
|---|---|---|---|---|
| Derivative | PubChem CID | Ames test | Mouse | Rat |
| 1 | 649646 | Mutagenic | Negative | Positive |
| 2 | 1318080 | Mutagenic | Negative | Positive |
| 3 | 782217 | Mutagenic | Negative | Positive |
| 4 | 1385213 | Mutagenic | Negative | Positive |

range[23]. Predicted compounds had negative permeability values were shown in Table 3. Skin permeability parameter is used in the pharmaceutical industry to assess the risk chemical products in case there is accidental contact with skin[24]. The binding of drug to blood and plasma proteins can alter the half-life of the drug in the body of the individual[25,26]. All the best predicted compounds strongly bind with plasma protein as shown in Table 4. Identified derivatives were belonging to inactive compound range (blood-brain barrier <1)[27]. The Ames test[28] calculated mutagenicity of the compounds. Test predicted compounds mutagenicity are enlisted in Table 5. Carcinogenicity of compounds showed negative value in mouse and positive in rat was shown in Table 5.

## CONCLUSION

Four best predicted compounds CID649646, CID1318080, CID782217, CID1385213 were found having lower binding energies -9.48, -9.39, -9.07 and -9.13 kcal $moL^{-1}$ with IMPDH protein. Inhibitory concentration in terms of $pIC_{50}$ of compounds CID649646, CID1318080, CID782217 and CID1385213 were 8.87, 8.74, 8.51 and 9.18, respectively. Molecular dynamics simulations showed that predicted compounds were stable. *In silico* ADME and toxicological properties of predicted compounds showed satisfactory results. Therefore it is predicted that benzoxazole derivatives CID649646, CID1318080, CID782217 and CID1385213 could be promising drug like compounds for IMPDH protein as drug target yet experimental studies have to confirm it. The present study may provide the information about potential derivatives of Benzoxazole for synthetic medicinal chemist as chemotherapeutic agents to fight against the increasing burden of Cryptosporidiosis infections.

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