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CONSERVED WATER MIMIC INHIBITOR DESIGN FOR hIMPDH (INOSINE MONOPHOSPHATE DEHYDROGENASE): MD SIMULATION AND DOCKING STUDIES OF IMP-ANALOGS

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ABSTRACT: Inosine Monophosphate Dehydrogenase (IMPDH) plays a very important role in Guanosine Monophosphate (GMP) biosynthesis. Type I hIMPDH is expressed at lower levels in all cells, whereas type II is especially observed in acute myelogenous leukemia, chronic myelogenous leukemia cancer cells, so it is thought to be an active target for leukemic drug design. MD-simulation studies of the solvated modeled structure of hIMPDH (PDB Id: 1B3O) in the presence of NAD^+ have revealed some interesting feature on the role of some conserved water molecules in the binding of IMP to the enzyme. Based on H-bonding interaction of IMP with Asp 364, Arg 322, Asp 274, Cys 331 and Asn 303 residues in the X-ray and simulated structures, and the recognition dynamics of O_2' and O_3' ribose hydroxyl groups (of IMP) with the conserved water molecules, we have modified the hydroxyl group of IMP and modeled a few number of derivatives. Optimization of ligand structures, followed by docking in enzyme, solvation, energy minimization of the protein-ligand complexes and their successive all atoms simulation studies have been made up to 5 ns. After critical investigation of different snapshots, the stereochemical quality, binding affinity/energy of the modified ligand is calculated and have screened three IMP-analogs (modified at O_2' and O_3' ribose oxygen), which can also effectively interact with the residues of the mononucleotide binding pocket and may thought to act as inhibitor for IMPDH. The drug-likeness and drug score of the modeled compounds are observed to be better.

INTRODUCTION: IMPDH involves in the de novo biosynthesis pathway for the formation of guanine nucleotides by converting inosine monophosphate (IMP) to xanthosine 5′-monophosphate (XMP) [1].

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Among the two isoforms of hIMPDH, type I is found at lower levels in all cells, whereas type II is selectively upregulated in neoplastic fast replicating lymphocytes and tumor cells.

Moreover, isoform II is especially observed in cases of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and CML–blast crisis (BC) blood cancer patients [2, 3]. Nowadays, the hIMPDH-II attracts new interest as an excellent potential target for the design of antileukemic agent.

Several ligands like 6-chloropurine riboside 5′-monophosphate (CPR), ribavirin (RVP), mizoribine 5′-monophosphate (MZP), tiazofurin adenine dinucleotide (TAD), benzamide adenine dinucleotide (BAD), and 2-β-D-ribofuranosyl-selenazole-4-carboxamide (SAD) have been developed as inhibitors of the hIMPDH- II and few of them are in clinical uses as immunosuppressive and antileukemic agent. Water molecules are known to play an important role in mediating protein-ligand interactions [4]. Especially, the conserved water molecules at the ligand-binding sites (in the enzyme-inhibitor complex) may have some rational importance toward the interaction of ligands to the binding residues of the enzyme [5]. Those conserved water molecular (hydrophilic centers) positions could be useful for designing the analog compounds (through covalent modification of existing drug/inhibitor) by water mimic inhibitor/drug design protocol [6].

The simulation of IMPDH with known and potential ligands (*e.g.*, IMP) and cofactors (NAD^+) in the presence of water molecules may provide some insights on the geometrical and electronic consequences of inhibitor-protein interaction. The topology of conserved water-mediated interaction around the $N_1/C_2/N_3$ atoms of adenine moiety, O_2' and O_3' hydroxyl group of ribose in IMP and their H-bonding stereochemistry may provide some information on the integrated role of a water molecule in the function of that enzyme. Based on these interactions of conserved molecules with the ligands, especially with the phosphate group of IMP and carboxamide group of NAD^+ in the IMPDH complexes, few inhibitors have already been designed [7, 8]. However, the presence of a few other water molecules (during the dynamics of IMPDH-IMP-NAD^+ complex) around the purine nucleotide insist us to design few IMP-analogs using water mimic inhibitor design protocol.

MATERIALS AND METHODS: The crystallographic structure of 1B3O having 104 missing residues were obtained from the Protein Data Bank [9], and B-chain was selected (excluding ligands and water molecules) using Swiss PDB Viewer program [10, 11].

Missing residues were covalently added one by one in the respective five gaps within the X-ray structure using Swiss PDB Viewer program. Each residue was refined after incorporating in the protein structure by implementing GROMOS 96 force field [12]. Energy minimization was performed (500 steps of steepest descent followed by 1000 steps of the conjugate gradient) without assigning any constraint. Finally, the modeled structure (containing the entire sequence) was again energy minimized with a 10 Å cut-off distance [13] for the non-bonded interaction and distance-dependent dielectric constant. The final RMSD of modeled protein was 0.73Å (backbone) and 0.84Å (C_α) with the template X-ray structure 1B3O. Then the ligand IMP (Inosine monophosphate) and NAD^+ (Nicotinamide adenine dinucleotide) were parameterized and were successively docked in the mono and dinucleotide binding pockets of the enzyme.

Ligands Preparation: All the structures were built by Marvin Sketch software version 5.11.5 and the optimization were performed using Hyperchem program TM Release 7.52 for Windows TM program (HyperChem, 1996).

Protein Docking with Ligands: Protein-ligand docking was done using Autodock 4.2.3 with MGL Tools 1.5.4 plugin [14, 15, 16] where total grid points per map took was 64000 with a spacing of 0.375 Å and center grid box of 65, 55 and 10 Å in x, y and z-axis respectively (from Q-Site Finder server) [17]. In our entire docking experiments, the Lamarckian genetic algorithm was used with the default parameters.

Solvation of Energy Minimized and Docked Structure: Solvation of energy minimized docked structures was done using the program CHASA (Conditional Hydrophobic Accessible Surface Area) [18]. The TIP3P model of water molecules was used with a probe radius of 1.4 Å.

Molecular Dynamics Simulation: Solvated PDB structure (with their respective ligand and cofactor) was converted to the Protein Structure File (PSF) by using the tool Automatic PSF Generation Plugin - 1.0 v by applying the CHARMM27 force field [19] within the Visual Molecular Dynamics v. 1.8.5 program [19]. Topology and parameter files of ligands were generated using SwissParam server [20,] and MD Simulation was performed using Auto -

Interactive Molecular Dynamics [21] connected between the visualization program Visual Molecular Dynamics v. 1.8.5 and the molecular dynamics program Nanoscale Molecular Dynamics v. 2.6 [22, 23, 24]. Initially, water dynamics of 1 ns was performed to equilibrate the water molecules followed by all atoms Molecular dynamics simulation up to 25 ns (with time step 2 fs) at 300 K, 1atm. and Periodic Boundary Condition. The fluctuations in potential energy, kinetic energy, and total energy were monitored at the regular interval of 2 ps. Dynamics of 25 ns was performed since the structure get stabilized between 20-25 ns [25].

After critical analysis of different snapshots (of the simulated structures), we have found few conserved hydrophilic centers (occupied by water molecules) near IMP (N_1, C_2, N_3 position of adenine and O_2', O_3' position of ribose hydroxyl group) which play some role in recognition of mononucleotide to the enzyme. Based on this study, we have built a few IMP-analogs and did their docking in the 25 ns simulated IMPDH-II structure and performed further 5 ns MD simulation with each enzyme-ligand complex.

Search of Conserved/Hydrophilic (Water Molecular) Centers: The conserved water molecules in the simulated IMPDH-II structures were identified by a standard least-square fitting algorithm using Swiss PDB Viewer program. The 1 ns simulated structure was taken as a template on which the other prerecorded snapshots at the interval of 100 ps were successively superimposed to identify conserved hydrophilic water molecular center.

The fit was initially optimized on the backbone – backbone atoms of the template – reference structures. Those water molecules that were found to be within 1.5Å [26, 27] between the two snapshots (MD simulation) were taken as conserved.

Binding Free Energy/Drug Property: After critical investigation of different snapshots of the protein-ligand docked structures, the stereo-chemical quality, binding affinity/energy and the theoretical drug relevant properties were calculated by Vadar [28] Pearl BIDD [29] and OSIRIS server.

RESULTS AND DISCUSSIONS: The simulated structures of solvated 1B3O after docking with different compounds are shown in **Fig. 1**.

During the simulation of solvated IMPDH-II structure (PDB Id: 1B3O) containing IMP and NAD^+, the interaction of different water molecules at the N_1, C_2, and N_3 atoms of purine moiety and at O_2' and O_3' of the ribose hydroxyl group of IMP is given in **Table 1**.

TABLE 1: DISTANCES (Å) OF THE DIFFERENT WATER MOLECULES FROM IMP IN THE SIMULATED STRUCTURE OF SOLVATED 1B3O (CONTAINING NAD^+)

Snapshots	Water molecules	Adenine moiety			Ribose hydroxyl group	
(ns)	(id.)	N_1	C_2	N_3	O_2'	O_3'
1	809	3.18	3.37			
	613		3.14	2.74		
	791		3.38	3.28		
	960				2.88	
	649					3.08
	797					2.77
5	864	3.20	3.48			
	791	3.19	3.16			
	649					3.19
	799				2.71	
	797					2.74
10	809		3.41			
	792	3.37	3.29			
	864		3.42	3.41		
	799				3.17	
	649					3.37
	797					2.84
15	809	3.48	3.22	3.50		
	954	3.44	3.27			
	792				2.85	

	791			3.06	3.05	
	649					3.46
	625					2.94
	797					3.50
20	864	3.98				
	792				2.94	
	649					3.76
	797					2.86
25	864	3.17	3.46			
	649					3.41
	792				3.34	
	625					3.43
	797					2.69

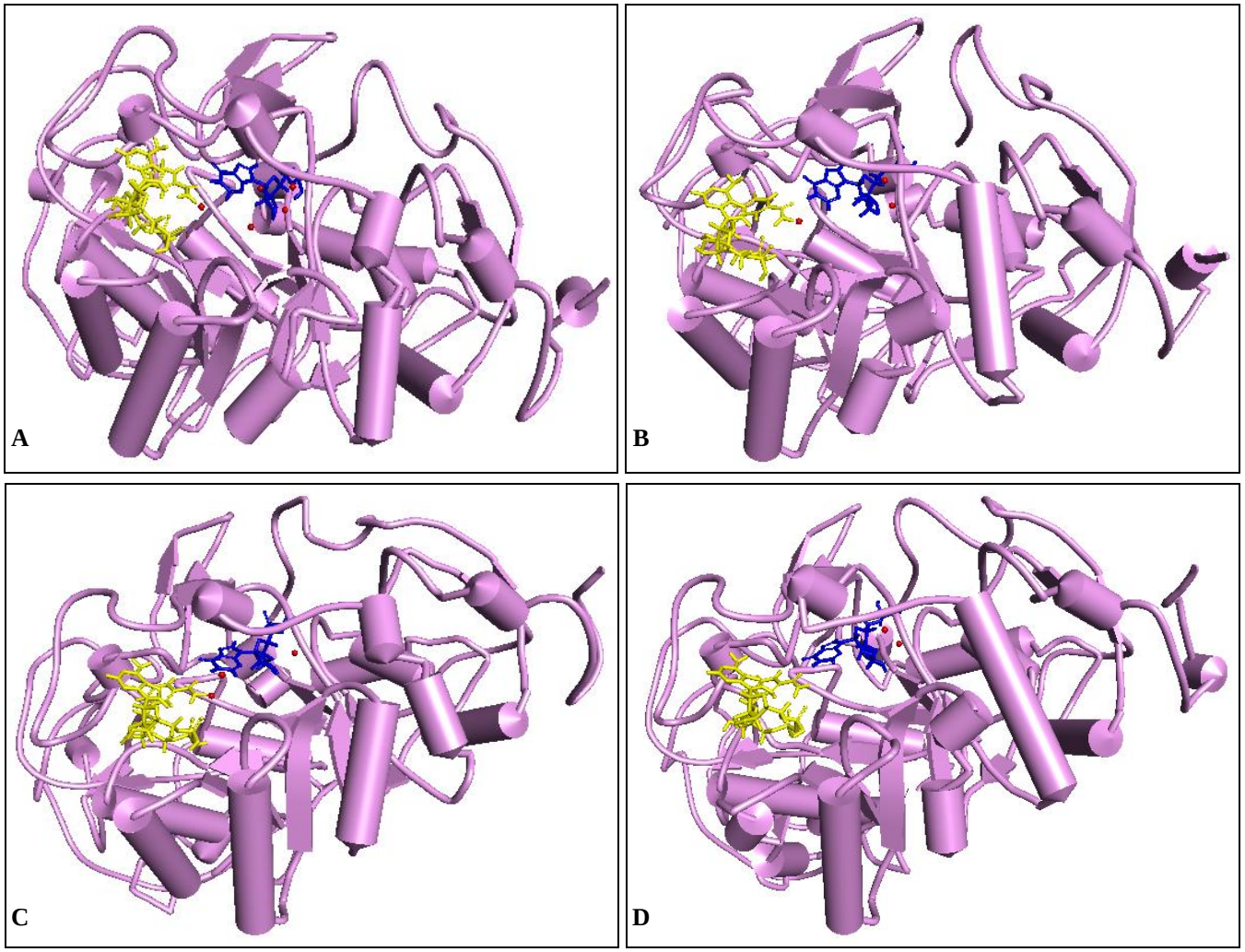

FIG. 1: THE SIMULATED STRUCTURE OF SOLVATED 1B3O AFTER DOCKING WITH (A) NAD AND IMP, (B) NAD AND COMPOUND A, (C) NAD AND COMPOUND B AND (D) NAD AND COMPOUND C

From these results, it is observed that the hydration frequency of those sites in IMP, especially at the O_2' and O_3' hydroxyl oxygen atoms seems to be high. In the simulated structure (up to 25 ns) the O_3' atom seem to be more solvated compared to O_2,' and few water molecules are also observed to be conserved (with reasonable occupation frequency) around the ribose hydroxyl groups.

The water molecules W_{799}, W_{792}, $W_{791,}$ and W_{960} are interacting with ribose O_2' atom and the H-bonding distances are varying from 2.71-3.17, 2.85-3.34, 3.05-3.38 and 2.88Å respectively. However, among those interacting water molecules, the residential time of W_{792} seems high (~15 ns) and the other is W_{799}, ~10 ns, W_{791} ~5ns, and W_{960} is less than ~2 ns.

The O_3' of ribose hydroxyl interacts with W_{797}, W_{625} and W_{649} water molecules and the H-bonding distances are varying 2.69-3.50, 2.94-3.43 and 3.08-3.76Å. During the 25 ns simulation, residential time of W_{797}, W_{625} and W_{649} are 25, 10 and 25 ns respectively. So, during O_3'…..W interaction, the occupation factor of W_{797} and W_{649} water molecules are high, and those hydrophilic positions/centers are thought to be conserved. But in the case of O_2'…..W interaction, W_{792} hydrophilic position is also nearly conserved. Moreover, during the simulation, W_{797} (interacting at O_3') and W_{791} (interacting with O_2' with low ~5 ns residential time) have also observed to interact with the N_3 and C_2 atoms of IMP.

During the simulation, the H-bonding interaction of some important residues of the IMP binding pocket Asp 364, Asn 303, Arg 322 and the catalytic Cys 331 with the O_2' and O_3' bound water molecules are observed, and they are summarized in **Table 2**.

TABLE 2: THE H-BONDING DISTANCES (Å) OF PSEUDO CONSERVED WATER MOLECULES (WHICH ARE INTERACTING WITH O_2' AND O_3' ATOMS OF RIBOSE HYDROXYL GROUPS) WITH THE DIFFERENT RESIDUES OF IMP-BINDING SITES OF hIMPDH-II STRUCTURE

Snap shots (ns)	Residues	Interacting water molecules at O_2'				Interacting water molecules at O_3'		
		W_1	W_2	W_3	W_4	W_1'	W_2'	W_3'
		960	799	792	791	649	797	625
01	Gly326 (Nb)	2.90						
	Asp364 (OD1)/(OD2)	*/3.26				2.57/3.03		
	Asn303 (OD1)/(ND2)	*/3.44						
	Arg322 (NH1)/(NH2)					*/3.03		
	Ser68 (OG)					3.19		
	Met385 (SD)/(Ob)						*/2.83	
05	Gly326 (Nb)		3.21					
	Ser327 (Nb)/(Ob)/(OG)		*/3.26/*					
	Asp364 (OD1)/(OD2)					2.62/3.24		
	Arg322 (NH1)/(NH2)					*/2.96		
	Met385 (SD)/(Ob)						*/2.50	
	Met386 (Nb)						3.37	
10	Gly324 (Ob)		3.24					
	Gly326 (Nb)		3.22					
	Ser327 (Nb/Ob)/(OG)		3.40/3.17/*					
	Asp364 (OD1)/(OD2)					2.55/3.17		
	Met385 (SD)/(Ob)					3.39/*	*/2.80	
15	Gly326 (Nb)			3.26				
	Ser327 (Nb)/(Ob)/(OG)			3.50/*/*				
	Cys331 (SG)			3.47				
	Asp364 (OD1)/(OD2)				*/2.78	2.63/3.28		
	Asn303 (OD1)/(ND2)				3.11/*			
	Arg322 (NH1)/(NH2)				*/2.93	*/3.13		
	Ser68 (OG)					2.57		3.20
	Tyr411 (OH)							3.24
	Met385 (SD)/(Ob)						*/2.95	
20	Gly326 (Nb)			2.93				
	Ser327 (Nb)/(Ob)/(OG)			2.93/*/*				
	Cys331 (SG)			3.23				
	Asp364 (OD1)/(OD2)					2.94/2.78		
	Arg322 (NH1)/(NH2)					*/2.81		
	Met385 (SD)/(Ob)					3.49/*	*/2.67	
25	Gly326 (Nb)			2.94				
	Ser327 (Nb)/(Ob)/(OG)			2.95/2.70/ 3.45				
	Cys331 (SG)			3.10				
	Asp364 (OD1)/(OD2)					2.95/2.85		
	Arg322 (NH_1) /(NH_2)					*/2.92		
	Ser68 (OG)					2.96	3.29	3.26
	Met385 (SD)/(Ob)						*/2.94	

Among those conserved or partially conserved water molecules, only the O_2' bound W_{792} having a residential frequency of 0.60 is interacting with the SG atom of Cys 331, and the distances are ranging from 3.10-3.47Å. During this Cys 331…..W_{792} interaction, this water molecule also forms H-bond with Gly 326 (2.93-3.26Å) and Ser 327 (2.70-3.50Å). Again, the O_2' bound W_{799} has also formed H-bonds with Gly 326 and Ser 327. However, W_{791} and W_{960} (whose residential frequencies are ~0.20 or lower) have seen to interact with the residues Asp 364 (2.78-3.26Å), Asn 303 (3.11-3.44Å) and Arg 322 (2.93-3.70Å), though the Cys 331 bound W_{792} not at all forms H-bond with those residues. From **Table 2**, no O_3' bound water molecule seems to form H-bond with Cys 331. In the case of O_3' bound water molecules, the conserved W_{649} forms H-bond with Asp 364 (2.55-3.28Å), Arg 322 (2.92-3.13Å) and sometimes interact with Met 386 (Nb atom).

However, the other conserved water molecule W_{797} is only forming H-bond with Met 385 (~2.50-2.95Å), and the low occupancy W_{625} water interacts with Ser 68 (OG).

On analyzing the water-mediated recognition of the O_2' and O_3' to the mono nucleotide-binding residues, specially the H-bonding pattern/distances of the water molecules around the O_2' and O_3' hydroxyl groups of ribose, we are interested on the water mimic inhibitor design using conserved water molecular dynamics at the inhibitor/IMP binding pocket of protein.

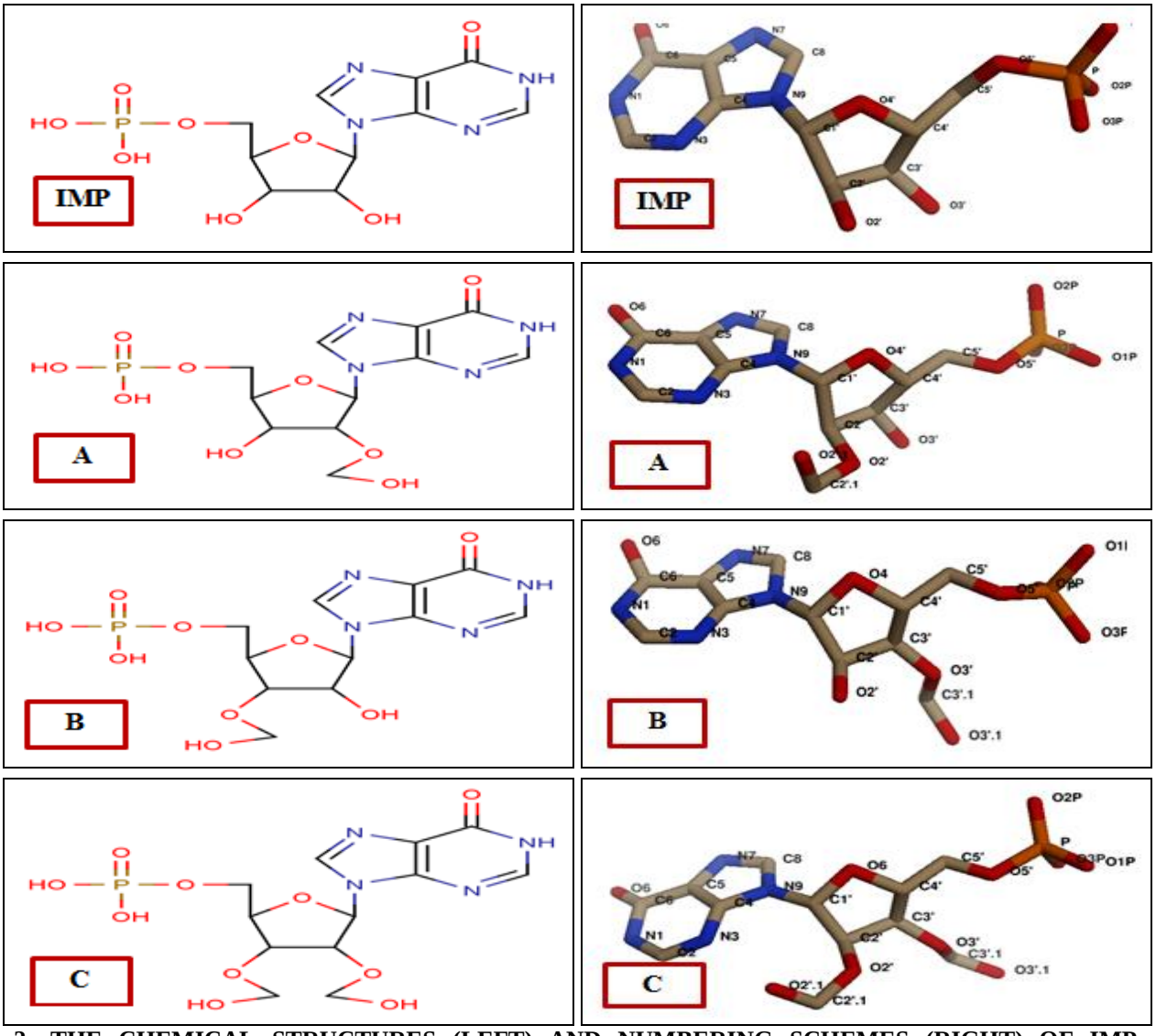

FIG. 2: THE CHEMICAL STRUCTURES (LEFT) AND NUMBERING SCHEMES (RIGHT) OF IMP AND MODIFIED-IMPS (A, B AND C COMPOUNDS)

Subsequently, we have successively modified the hydroxyl (OH) groups of O_2' and O_3' positions by adding the hydroxymethyl (-CH_2OH) group by replacing the conserved water molecules **Fig. 2**.

Here we have replaced (used) only one conserved molecular water center which interacts with the O_2' or O_3' hydroxyl oxygen atom. In the first case (compound A), keeping the O3'-H intact, we have chosen the position of water molecule W_{792} and replaced it by oxygen $O_2'_1$ atom so that the ribose hydroxyl (O2'-H) group is modified as (IMP)-O_2'-CH_2-$O_2'_1$-H. Similarly, in compound B, keeping the O_2'-H intact, the position of W_{797} is replaced by $O_3'_1$ oxygen atom so that the IMP is modified as compound (IMP)-O_3'-CH_2-$O_3'_1$-H. For the design of compound C, we have replaced both the H-atoms of ribose hydroxyl groups (O_2'-H and O_3'-H) and replaced it by O_2'-CH_2-$O_2'_1$-H and O_3'-CH_2-$O_3'_1$-H by replacing the conserved water molecules W_{792} and W_{797}.

Further docking the compound A, B and C in hIMPDH-II structure and subsequent simulation (5 ns) of the docked structures have shown the recognition susceptibility of these designed compounds to protein.

During the simulation, the H-bonding interactions of all the three IMP-analogs (A, B, and C) with water molecules are shown in **Table 3**.

TABLE 3: INTERATOMIC H-BOND DISTANCES (Å) OF THE WATER MOLECULES FROM THE O_2', $O_2'_1$, O_3' AND $O_3'_1$ ATOMS OF THE RIBOSE MOIETY PRESENT IN THE DIFFERENT MODIFIED IMP ANALOGS (COMPOUNDS A, B AND C) DURING THE SIMULATION OF THEIR SOLVATED COMPLEX OF hIMPDH-II STRUCTURE (1B3O) IN PRESENCE OF NAD^+

Time (ns)	Water molecules (Id. no.)	Distances of water molecules from the different atoms of compound A					
		N_1	C_2	N_3	O_2'	$O_2'_1$	O_3'
1	864	3.35					
	649				3.48		2.94
	625						3.02
	792				3.18	2.95	
2	649				3.25		3.09
	792					2.81	
	625						2.94
5	799	3.46					
	792				3.12	2.71	
	625						2.68

Time (ns)	Water molecules (Id. no.)	Distances of water molecules from the different atoms of compound B					
		N_1	C_2	N_3	O_2'	$O_2'_1$	O_3'
1	864	3.21					
	792				3.27		
	797					3.19	2.81
	649						3.18
2	864		3.39				
	792				2.92		
	797					2.83	3.06
5	688	3.47					
	988	3.09					
	625						3.04

Time (ns)	Water molecules (Id. no.)	Distances of water molecules from the different atoms of compound C						
		N_1	C_2	N_3	O_2'	$O_2'_1$	O_3'	$O_3'_1$
1	792				3.33			
	797							2.88
2	864	3.10						
	792				2.87	3.08		
	797						3.27	2.73
5	792				2.96	3.00		
	797							3.21

Through this analysis, it is observed that the five molecular water center in case of IMP bound 1B3O of 25 ns simulated structure is replaced by 3, 3 and 2 water molecular center in case of IMP-analogs bound enzyme (Compound A, B, and C) of 5 ns respectively.

Again the hydration susceptibility of N_1, C_2 and O_3' atoms has decreased in all the three cases compared to IMP bound structure whereas increased in case of O_2' atom.

The reasonable aquation frequency of the modified ribose moiety of A, B, and C compounds have been observed in the simulated docked structures.

The oxygen atom of the newly added hydroxyl methyl groups (-CH_2-O_2'$_1$-H / -CH_2-O_3'$_1$-H) can form H-bonds with the different water molecules ranging from 2.71-3.18Å. However, in compound C (where both the hydroxyl groups of IMP were modified), the O_3'$_1$ oxygen atom seems to have higher hydrophilic surrounding compared to O_2'$_1$. Moreover, it is also noticed that when the hydration susceptibility of ribose/modified ribose is increased, though it decreased at the N_1, C_2 and N_3 sites of adenine moiety of the compound A, B, and C. The binding energy of IMP and the modified compounds (in the presence of NAD^+) have given in **Table 4**.

The binding energy of compound A, B, and C have observed to be higher compared to IMP. The binding energy of compound A and C are nearly the same, and they are higher than the others. The drug properties of IMP and modified compound A, B, and C have been evaluated by theoretical, computational methods which are included in **Table 5**.

TABLE 4: THE BINDING ENERGY OF IMP (AFTER 25NS) AND MODIFIED- IMP, COMPOUNDS (A, B, AND C) IN THE DOCKED STRUCTURES OF hIMPDH-II (PDB CODE: 1B3O) AFTER 5 NS SIMULATION

S. no.	Structures	Binding energy (Kcal/mol)
1	Protein + NAD + IMP	-2.80
2	Protein +NAD + IMP modified at O_2' position (compound A)	-18.68
3	Protein +NAD + IMP modified at O_3' position (compound B)	-16.60
4	Protein +NAD + IMP modified at O_2' and O_3' position (compound C)	-18.70

TABLE 5: SOME THEORETICAL DRUG PROPERTIES OF IMP AND MODIFIED- IMP (COMPOUNDS A, B, AND C)

Drug properties	IMP	IMP modified at O_2' Position (Compound A)	IMP modified at O_3' position (Compound B)	IMP modified at O_2' and O_3' position (Compound C)
Mutagenic	Yes	Yes	Yes	Yes
Tumorogenic	No	No	No	No
Irritant	No	No	No`	No
Reproductive effective	No	No	No	No
Drug likeness	-20.12	-16.46	-16.35	-16.57
Drug score	0.28	0.27	0.27	0.26

All the compounds having nearly similar drug score, however, the modified-IMP have higher drug-likeness property.

All the results may suggest that adding the hydroxymethyl group (-CH_2OH) at either O_2' or O_3' or at both sites of the ribose in IMP (by replacing few H-bonded conserved water molecules) may affect the binding affinity of parent ligand.

CONCLUSION: Our computational results may provide some light on the conserved water mimic inhibitor modification protocol. Using this conserved hydrophilic (water molecular) positions near the hydroxyl group of IMP (indicated in MD-studies), we have modified the ligand by covalent addition of new hydroxymethyl (–CH_2OH) group at the O_2' and O_3' position(s) of ribose (in IMP) by replacing conserved water molecules. This computational water mimic inhibitor design protocol based on the H-bonding dynamics of conserved or partially conserved water molecules (which have an affinity towards the hydrophilic sites of ligand) may put forward a new strategy in the forthcoming substrate-structure based inhibitor design for IMPDH or other proteins.

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CONFLICT OF INTEREST: Nil

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