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

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ABSTRACT: Inosine Monophosphate Dehydrogenase (IMPDPH) plays a very important role in Guanosine Monophosphate (GMP) biosynthesis. Type I hIMPDPH 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 hIMPDPH (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 O₂' and O₃' 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 O₂' and O₃' ribose oxygen), which can also effectively interact with the residues of the mononucleotide binding pocket and may thought to act as inhibitor for IMPDPH. The drug-likeness and drug score of the modeled compounds are observed to be better.

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

Among the two isoforms of hIMPDPH, 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 hIMPDPH-II attracts new interest as an excellent potential target for the design of antileukemic agent.

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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 hIMPDPH- 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 interactions⁴. 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 enzyme⁵. 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 protocol⁶.

The simulation of IMPDPH 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 N₁/C₂/N₃ atoms of adenine moiety, O₂' and O₃' 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 IMPDPH complexes, few inhibitors have already been designed^{7,8}. However, the presence of a few other water molecules (during the dynamics of IMPDPH-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 Bank⁹, 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 field¹². 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 distance¹³ 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 field¹⁹ within the Visual Molecular Dynamics v. 1.8.5 program¹⁹. Topology and parameter files of ligands were generated using SwissParam server²⁰, and MD Simulation was performed using Auto -

Interactive Molecular Dynamics²¹ 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 ns²⁵.

After critical analysis of different snapshots (of the simulated structures), we have found few conserved hydrophilic centers (occupied by water molecules) near IMP (N₁, C₂, N₃ position of adenine and O₂' , O₃' 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 stereochemical quality, binding affinity/energy and the theoretical drug relevant properties were calculated by Vadar²⁸ Pearl BIDD²⁹ 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 N₁, C₂, and N₃ atoms of purine moiety and at O₂' and O₃' 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 (ns)	Water molecules (id.)	Adenine moiety			Ribose hydroxyl group		
		N ₁	C ₂	N ₃	O ₂ '	O ₃ '	
1	809	3.18	3.37	2.74	3.28	2.88	
	613		3.14				
	791		3.38				
	960	3.20	3.48	3.41	3.19		
	649						3.17
	797						
5	864	3.19	3.16	3.41	3.17		
	791						
	649	3.37	3.29			3.42	3.50
	799						
	797						
10	809	3.48	3.22	3.50	2.84		
	792					3.44	
	864						
	799	3.37	3.29	3.42	3.17		
	649						
	797						
15	809	3.48	3.22	3.50	2.84		
	954						
	792						

	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

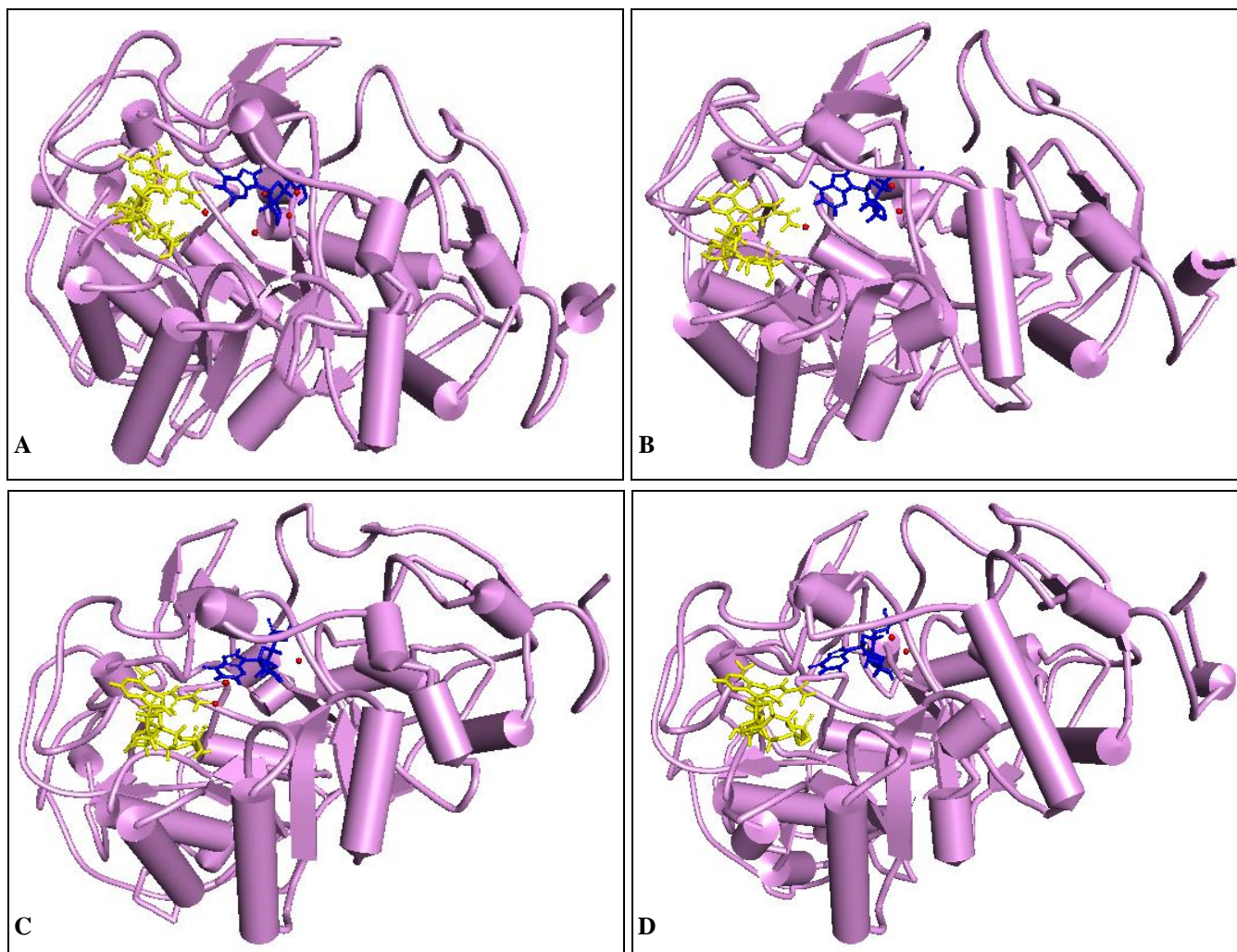


FIG. 1: THE SIMULATED STRUCTURE OF SOLVATED 1B30 AFTER DOCKING WITH (A) NAD AND IMP, (B) NAD AND COMPOUND A, (C) NAD AND COMPOUND B AND (D) NAD AND COMPOUND C

From these results, it is observed that the hydration frequency of those sites in IMP, especially at the O₂' and O₃' hydroxyl oxygen atoms seems to be high. In the simulated structure (up to 25 ns) the O₃' atom seem to be more solvated compared to O₂' and few water molecules are also observed to be conserved (with reasonable occupation frequency) around the ribose hydroxyl groups.

The water molecules W₇₉₉, W₇₉₂, W₇₉₁, and W₉₆₀ are interacting with ribose O₂' 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 W₇₉₂ seems high (~15 ns) and the other is W₇₉₉, ~10 ns, W₇₉₁ ~5ns, and W₉₆₀ is less than ~2 ns.

The O₃' of ribose hydroxyl interacts with W₇₉₇, W₆₂₅ and W₆₄₉ 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 W₇₉₇, W₆₂₅ and W₆₄₉ are 25, 10 and 25 ns respectively. So, during O₃'.....W interaction, the occupation factor of W₇₉₇ and W₆₄₉ water molecules are high, and those hydrophilic positions/centers are thought to be conserved. But in the case of O₂'.....W interaction, W₇₉₂ hydrophilic position is also nearly conserved.

Moreover, during the simulation, W₇₉₇ (interacting at O₃') and W₇₉₁ (interacting with O₂' with low ~5 ns residential time) have also observed to interact with the N₃ and C₂ 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 O₂' and O₃' 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 O₂' AND O₃' ATOMS OF RIBOSE HYDROXYL GROUPS) WITH THE DIFFERENT RESIDUES OF IMP-BINDING SITES OF hIMPDPH-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		
05	Met385 (SD)/(Ob)						*/2.83	
	Gly326 (Nb)		3.21					
	Ser327 (Nb)/(Ob)/(OG)		*/3.26/*					
	Asp364 (OD1)/(OD2)					2.62/3.24		
	Arg322 (NH1)/(NH2)					*/2.96		
10	Met385 (SD)/(Ob)						*/2.50	
	Met386 (Nb)						3.37	
	Gly324 (Ob)		3.24					
	Gly326 (Nb)		3.22					
	Ser327 (Nb/Ob)/(OG)		3.40/3.17/*					
15	Asp364 (OD1)/(OD2)					2.55/3.17		
	Met385 (SD)/(Ob)					3.39/*	*/2.80	
	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
20	Met385 (SD)/(Ob)						*/2.95	
	Gly326 (Nb)			2.93				
	Ser327 (Nb)/(Ob)/(OG)			2.93/*/*				
	Cys331 (SG)			3.23				
	Asp364 (OD1)/(OD2)					2.94/2.78		
25	Arg322 (NH1)/(NH2)					*/2.81		
	Met385 (SD)/(Ob)					3.49/*	*/2.67	
	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 O₂' bound W₇₉₂ 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.....W₇₉₂ interaction, this water molecule also forms H-bond with Gly 326 (2.93-3.26Å) and Ser 327 (2.70-3.50Å). Again, the O₂' bound W₇₉₉ has also formed H-bonds with Gly 326 and Ser 327. However, W₇₉₁ and W₉₆₀ (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 W₇₉₂ not at all forms H-bond with those residues. From **Table 2**, no O₃' bound water molecule seems to form H-bond with Cys 331. In the case of O₃' bound water molecules, the conserved W₆₄₉ 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 W₇₉₇ is only forming H-bond with Met 385 (~2.50-2.95Å), and the low occupancy W₆₂₅ water interacts with Ser 68 (OG).

On analyzing the water-mediated recognition of the O₂' and O₃' to the mono nucleotide-binding residues, specially the H-bonding pattern/distances of the water molecules around the O₂' and O₃' 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.

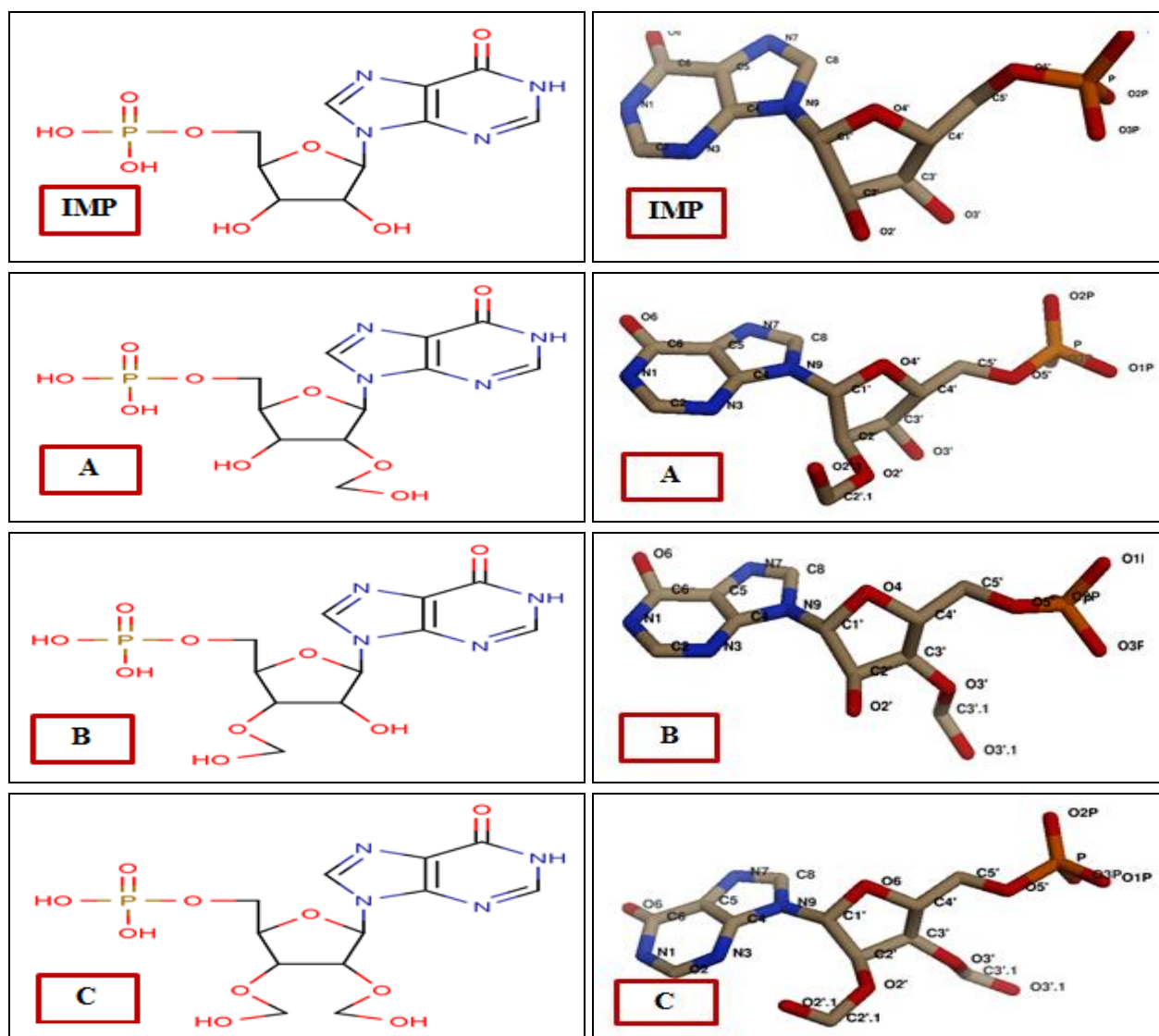


FIG. 2: THE CHEMICAL STRUCTURES (LEFT) AND NUMBERING SCHEMES (RIGHT) OF IMP AND MODIFIED-IMPS (A, B AND C COMPOUNDS)

Subsequently, we have successively modified the hydroxyl (OH) groups of O₂' and O₃' positions by adding the hydroxymethyl (-CH₂OH) group by replacing the conserved water molecules **Fig. 2**.

Here we have replaced (used) only one conserved molecular water center which interacts with the O₂' or O₃' hydroxyl oxygen atom. In the first case (compound A), keeping the O₃'-H intact, we have chosen the position of water molecule W₇₉₂ and replaced it by oxygen O₂'₁ atom so that the ribose hydroxyl (O₂'-H) group is modified as (IMP)-O₂'-CH₂-O₂'₁-H. Similarly, in compound B, keeping the O₂'-H intact, the position of W₇₉₇ is replaced by O₃'₁ oxygen atom so that the IMP is modified as compound (IMP)-O₃'-CH₂-O₃'₁-H. For the design

of compound C, we have replaced both the H-atoms of ribose hydroxyl groups (O₂'-H and O₃'-H) and replaced it by O₂'-CH₂-O₂'₁-H and O₃'-CH₂-O₃'₁-H by replacing the conserved water molecules W₇₉₂ and W₇₉₇.

Further docking the compound A, B and C in hIMPDPH-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 O₂', O₂'₁, O₃' AND O₃'₁ 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 hIMPDPH-II STRUCTURE (1B30) 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
2	649						3.18
	864		3.39				
	792				2.92		
5	797					2.83	3.06
	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 N₁, C₂ and O₃' atoms has decreased in all the three cases compared to IMP bound structure whereas increased in case of O₂' 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 (-CH₂-O₂'₁-H / -CH₂-O₃'₁-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 O₃'₁ oxygen atom seems to have higher hydrophilic surrounding compared to O₂'₁. Moreover, it is also noticed that when the hydration susceptibility of ribose/modified ribose is increased, though it decreased at the N₁, C₂ and N₃ 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 hIMPDPH-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 (-CH₂OH) at either O₂' or O₃' 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 (-CH₂OH) group at the O₂' and O₃' 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 IMPDPH or other proteins.

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CONFLICT OF INTEREST: Nil

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