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Structure based prediction of functional sites with potential inhibitors to Nudix enzymes from disease causing microbes

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Abstract:
The functional sites were predicted for Nudix enzymes from pathogenic microorganisms such as *Streprococcus pneumonia* (2B06) and *Enterococcus faecalis* (2AZW). Their structures are already determined, however, no data is reported about their functional sites, substrates and inhibitors. Therefore, we report prediction of functional sites in these Nudix enzymes via Geometric Invariant (GI) technique (Construct different geometries of peptides which remain unchanged). The GI method enumerated 2B06: RA57, EA58, EA61, EA62 and 2AZW: RA62, EA63, EA66, EA67 as putative functional sites in these Nudix enzymes. In addition, the substrate was predicted via Molecular docking (Docking of substrates against whole structure of Nudix enzymes). The substrate ADP-Ribose was docked with the Nudix enzymes, 2B06 (Docking energy -15.68 Kcal/mol) and 2AZW (Docking energy -10.86 Kcal/mol) with the higher affinity and the lower docking energy as compared to other substrates. The residues EA62 in 2B06 and RA62 in 2AZW make hydrogen bonds with the ADP-ribose. Furthermore, we screened 51 inhibitor compounds against structures of 2B06 and 2AZW. The inhibitor compounds AMPCPR and CID14258187 were docked well as compared to other compounds. The compound CID14258187 was also in agreement with Lipinski rule of 5 for drug likeness properties. Therefore, our findings of functional sites, substrates and inhibitors for these Nudix enzymes may help in structure based drug designing against *Streprococcus pneumonia* and *Enterococcus faecalis.*

Keywords: Functional sites, Nudix proteins, SG target proteins, substructures, Molecular Docking, Geometric Invariant.

Background :
Nudix (nucleoside phosphatase linked to x) enzymes are found in several diverse types of organisms such as viruses **[1],** bacteria **[2]** archaea **[3],** and eukaryotes **[4].** They catalyze the hydrolysis of nucleoside and deoxynucleoside triophosphate attached functional groups or chemical species, referred to as x **[5, 6].** Nudix enzymes remove mutation inducing nucleotide such as 8-oxy-dGTP from the cell, which tends to interfere DNA replication process causing several thousand fold increase in AT-CG transversion mutation rate **[7].** In addition, these enzymes catalyze the catabolism of cellular toxic compounds so that their cytotoxic effects on the bacterial cell can be removed **[8-10].** Thus, the Nudix enzymes perform a key role in protecting the cells from oxidative damage by radiation and from toxic effects of accumulated metabolites **[11-12].** Moreover, these enzymes are implicated in cell signaling **[11-12],** maintaining the level of signaling compounds inside the cell **[5].** Due to their protective roles in cell survival, the Nudix enzymes can be potential targets for antimicrobial drugs in pathogenic organisms such as African Swine Fever Virus **[1],** *Streprococcus pneumonia* and *Enterococcus faecalis.* These enzymes are characterized by a highly conserved *Nudix box* sequence motif **G-X(5)-E-X(7)-R-E-U-X-E-E-X-G-U**, where the conserved residues are separated by **X** (any residues) and **U**, a bulky hydrophobic residue. The Nudix box acts as a catalytic centre **[13]** and is often found in loop-alpha-helix-loop **[9].**

Due to key role of Nudix enzymes in bacterial cell survival, we targeted these enzymes from pathogenic microorganisms such as *Streprococcus pneumonia* (2B06) and *Enterococcus faecalis* (2AZW) for the functional sites, substrates and inhibitors prediction. Their structures have been determined and submitted in RCSB protein data bank. However, no data has been reported about their functional sites, substrates and inhibitors. Although, several biochemical techniques have been used to predict the functional sites, however, these techniques are time consuming and not cost effective. Therefore, we used combined computational approach of Geometric Invariant (GI) and Molecular docking methods for functional sites, substrates and inhibitor prediction in Nudix enzymes 2B06 and 2AZW.

Methodology:
Input files :
Dataset creation:
We obtained structures of Nudix enzymes, 2B06 and 2AZW, from RCSB protein data bank. Then, these structures were further subjected to Geometric Invariant calculator and enumerated putative substructures (amino acid patterns of 4-6 residues obtained from whole protein structures) based on their geometric properties such as area, volume, and perimeter. Please refer the following paper for detail of GI method **[14, 15] (Table 1 See Supplementary material).**

Library of functional sites:
The library of functional sites was constructed using 10751 non-redundant proteins from the PDB as available in level 2 of NCBI's molecular modeling database (MMDB). It contains 959 clusters of amino acid patterns of size 4-6 residues covering 136 GO terms. Each substructure is described with a number of descriptors that are invariant upon rotation and

translation transformations and hence are called as geometric invariant (GIs). For instance, we used 27, 45 and 72 descriptors to represent four, five and six sized substructures. The example descriptors are distance between two vertices, perimeter, volume, and surface area of geometric objects **[15].**

Comparison of functional sites:
The substructures from 2B06 and 2AZW were compared with the library of functional sites reported earlier and having compatible amino acid composition. The geometric similarity between a certain substructure and the site leads to declaration of that substructure as a putative functional site **(Table 5 see Supplementary material) [15].**

Substrate prediction:
We used molecular docking method for prediction of substrates and their binding sites in 2B06 and 2AZW. The substrates were selected from pdb files and literature of the template proteins present in the matched cluster (from GI method). The SMILES strings of substrates were obtained from PUBCHEM database (http://pubchem.ncbi.nlm.nih.gov/) and converted in to 3D via using CORINA server (www.molecular-networks.com/ online_demos/corina_demo.html*)*. The substrates were docked against the Nudix target 2B06 and 2AZW in two settings: (i) Blind docking and (ii) Refined docking. The blind docking considers the whole structure of the Nudix enzymes as docking target, while in refined docking, we specifies the functional sites (predicted by our GI method) as docking target and generates the grid map with grid points spacing at 0.375A. The docking experiments were performed via using AUTODOCK4.0 **[16]**. All docking parameters were set to be default (**Figure 1**).

Binding site analysis:
The substrates were ranked based on the lowest docking energy of the blind docking by including residues with in $6A^0$ radius from the substrate (as center).

Inhibitor Prediction:
The inhibitor compounds for the 2B06 and 2AZW Nudix enzymes were obtained from the literature and searched in the PUBCHEM database for finding of similar compounds. The SMILES strings of all the inhibitor compounds were downloaded and converted in to 3D structures via CORINA server. The compounds were further docked against the whole structures of 2B06 and 2AZW via PATCHDOCK software **[17]** and ranked based on the Docking score. Top ranked inhibitor compound was selected for analysis of drug likeness properties via MOLINSPIRATION server *(*www.molinspiration.com).

Results:
We divided our research work results in three parts: (1) Functional site prediction in 2B06 and 2AZW, (2) Substrates prediction and (3) Inhibitor prediction. Here we described the details of our predictions:

Functional site prediction:
Nudix enzymes from *Streptococcus pneumoniae (2B06)* and *Enterococcus faecalis (2AZW):*
Streptococcus pneumoniae, or pneumococcus, is a gram-positive anaerobic bacterium from genus *Streptococcus*. It causes bacterial meningitis in both adults and children. It also causes various pneumococcal infections like acute sinusitis, otitis media, sepsis, endocarditis etc. On the other hand, the *Enterococcus faecalis* is a gram positive facultative anaerobic bacterium homing gastrointestinal tracts of human. It causes sever infections such as endocarditis as well as infections in gal bladder, prostate and epididymal surface in Humans. The Nudix enzymes 2B06 and 2AZW may participate in the cell survival of *Streptococcus pneumoniae* and *Enterococcus faecalis* bacteria's in adverse environment.

We predicted following functional sites in the 2B06: RA57, EA58, EA61, EA62 and 2AZW: RA62, EA63, EA66, EA67 Nudix enzymes via GI method based on a match with cluster DDDK-1 in the library. The cluster DDDK-1 contains functional sites of four known Nudix enzymes: (i) MutT Nudix from *Caenorhabditis elegans* (1KTG: E.C.3.6.1.17: RA51, EA52, EA55, EA56), (ii) Nudix enzyme from *Escherichia coli* (1VHZ: E.C.3.6.1: RA94, EA95, EA98, EA99) and (iii) Nudix enzyme from *Deinococcus radiodurans* (1NQZ: E.C.3.6.1.9: RA85 EA86 EA89 EA90 and 1SU2: RA64 EA65 EA68 EA69) **(Table 1 see Supplementary material)**. All these template proteins are known to perform Hydrolase activities. Note that the 2B06 and 2AZW Nudix enzymes share very low sequence identity (less than 25%) with the template proteins. The predicted sites share the following sequence pattern: R-X-E-X (3)-E-X-E and are present in the Nudix box motif.

We also analyzed performance of the state of art methods for functional sites predictions in 2B06 and 2AZW Nudix enzymes. The sequence (BLAST) and structure (DALI) comparison of the Nudix targets against known proteins in the PDB database strongly establish homology with our template proteins of the cluster DDDK-1. PROSITE server detects Nudix hydrolase signature motif: G-x(5)-E-x(4)-[TAGCV]-[LIVMACF]-x-R-[EL]-[LIVMFGSTA]-x-[EA]-E-x-[GNDTHR] (PS:00893) for 2AZW and 2B06. However, the PINTS and CSA are unable to predict functional sites in these Nudix proteins. PROFUNC and PatchFinder, on the other hand, predicted functional sites in all the SG targets with varying degree of confidences as well as with large number of residues match (**Table 2 see Supplementary material).** These results are in agreement with residues from GI method.

Substrate prediction:
The docking of the substrates against whole structures of 2B06 and 2AZW revealed that the substrate, ADP-Ribose binds the Nudix enzymes in their cavities with the lower docking energies of -15.68 Kcal/mol (2B06) **(Figure 2(a))** and -10.86 Kcal/mol (2AZW) **(Figure 2(b))** as compared to other substrates **(Table 3 see Supplementary material).**

When we performed refined docking of the ADP-Ribose against putative functional sites of 2B06 and 2AZW (predicted by GI method), we able to obtain lower docking energies of -16.20 Kcal/mol (2B06) and -10.96 Kcal/mol (2AZW) than that of blind docking **(Table 3 see Supplementary material).** The docking analysis established the fact that ADP-Ribose is the most preferred substrate for 2B06 and 2AZW Nudix enzymes. We observed that ADP-Ribose binds the targets 2B06 and 2AZW in their cavities made up of active site residues predicted by our GI method. The amino acid residue EA62 in 2B06 and RA62 in 2AZW makes hydrogen bond with the substrate ADP-Ribose **(Figure 2(a, b)).**

Substrate binding site analysis:
We found that the residues, T10, I12, N26, R28, W35, P41, G42, G43, H44, RA57, EA58, E62, KS76, W78, YR86, V88, E105, A122, Y123, D124, L128, Y142 and W150 present in the binding cavity of 2B06 surrounding the substrate ADP-Ribose within $6A^0$ radius. On the other hand, in case of 2AZW, the following residues are surrounding ADP-Ribose substrate with in $6A^0$ radius: GA7, RA18, NA40, FA44, GA48, EA49, EA51, RA62, EA63, EA66, EA67, EA83, YA84, FA85, YA86, SA87, HA89, RA90, KA132, RA133, GA134 and RA137.

Functional mechanism:
We propose the following functional mechanism for 2B06: One of the catalytic residues, RA57, may form a hydrogen bond interaction with the nearest water molecules. The two glutamate residues, EA58 and EA61, may be involved in making coordination complex with a magnesium ion. Additionally, these glutamate residues may make hydrogen bonds with surrounding water molecules (W403, W373 and W304), while the water molecule, W318, may share a hydrogen bond with EA58 and EA62 **(Figure 3(a)).** On the other hand, in 2AZW: We found that the residues RA62 and EA63 are very close to magnesium ion and may form a coordination complex. These residues make hydrogen bonds with the nearest water molecules. For instance, RA62 makes a hydrogen bond with W314, while EA63 makes a hydrogen bond with W275. Similarly, the glutamate residue, EA66, makes hydrogen bonds with two nearest water molecules W204 and W336. The water molecule W259 shares a hydrogen bond between residues RA62 and EA63 **(Figure 3b).**

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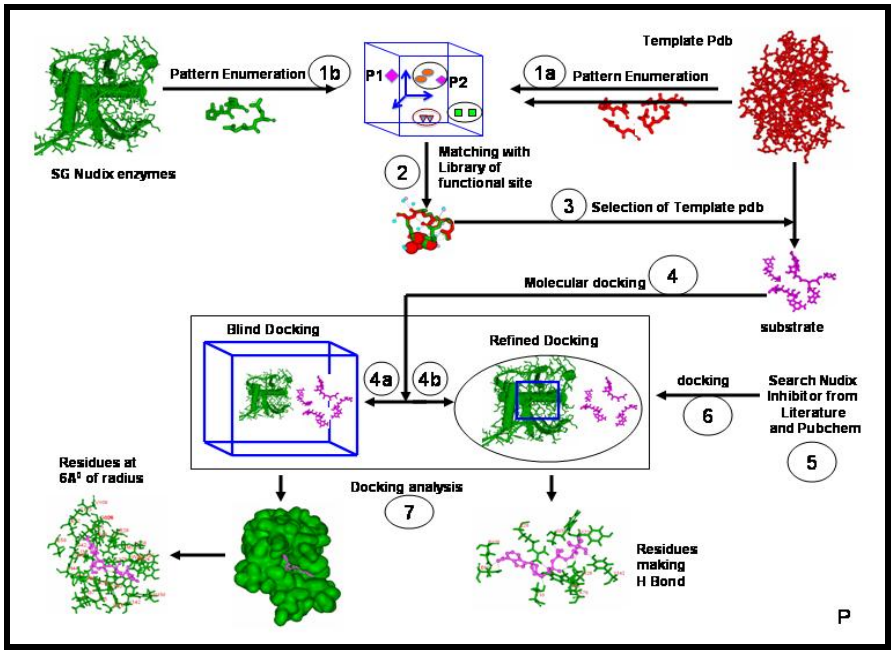

Figure 1: Overall schematic for prediction of functional sites, substrates and inhibitors for Structural Genomics Nudix enzymes 2B06 and 2AZW from *Streptococcus pneumoniae* and *Enterococcus faecalis*. It can be broadly divided into the following steps: (1a) Building library of functional sites from known proteins (templates), (1b) Enumeration of substructures from Nudix enzymes 2B06 and 2AZW and mapping them to space spanned by Geometric Invariants (GIs), (2) Matching substructures of enzymes with functional sites in the library to obtain putative functional site, (3) Based on matching templates, obtain a list of potential substrates for docking analysis, (4) Molecular docking of substrates against Nudix targets: (4a) Blind docking of substrates against the target and (4b) Refined docking of substrates against the target, (5) Search putative inhibitors of Nudix enzymes from literature and similar compounds from PUBCHEM database, (6) Docking of these inhibitors (7) Docking analysis that includes (i) Analysis of substrate and inhibitor binding in the cavity of Nudix targets, (ii) Extraction of active site residues with in 6A0 radius around the substrate binding site and (iii) hydrogen bond analysis at the predicted functional site.

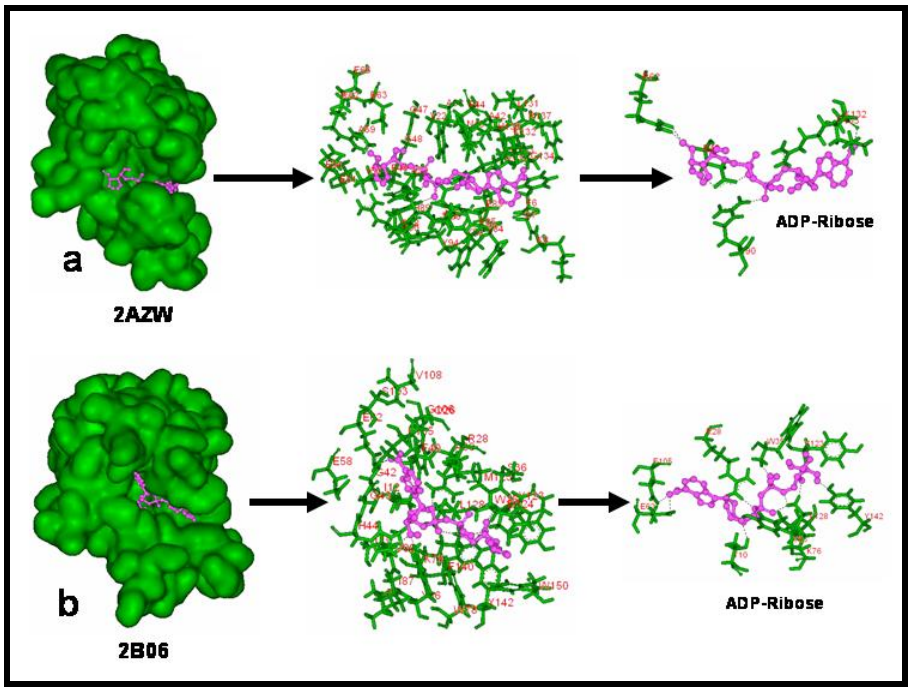

Figure 2: Docking of putative substrates with Structural Genomics Nudix targets (a) The substrate ADP-Ribose (magenta) bound at cavity of 2AZW (green) with docking energy of -10.86 Kcal/mol and residues surrounding the bounded substrate at 6 A0 of radius. Here, the residue EA62 makes a hydrogen bond with ADP-Ribose. (b) The substrate ADP-Ribose (magenta) bound at cavity of 2B06 (green) with docking energy of -15.69 Kcal/mol and residues surrounding bounded substrates at 6 A0 of radius. The docking has been performed by AUTODOCK 4.0 software. The docking analyses are performed by using Discovery Studio (http://accelrys.com/products/discovery-studio/).

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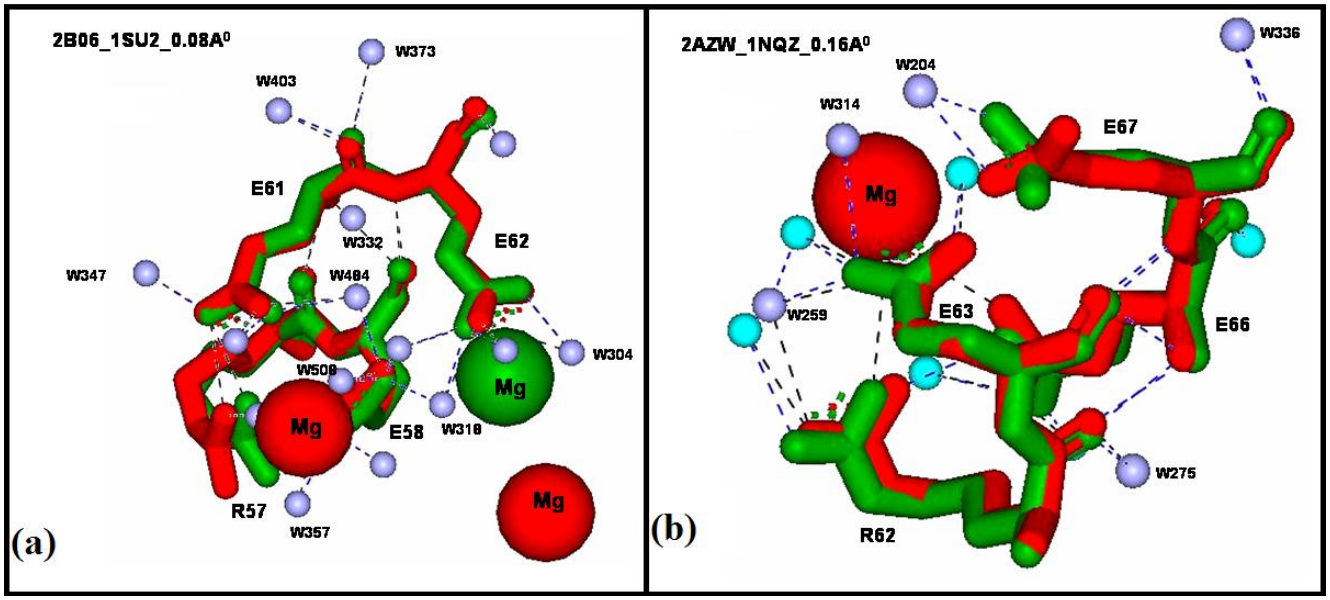

Figure 3: Superimposition of predicted functional sites with the matching templates: **(a)** The putative functional site of 2B06 (green) is superimposed with the residues of known Nudix protein 1SU2 (red) (RMSD 0.08 A0). The EA58 and EA61 make hydrogen bonds (blue) with surrounding water molecules (W403, W373 and W304). The water molecule W318 shares a hydrogen bond between glutamate residues at position 58 and 62. **(b)** The putative functional site of 2AZW (green) is superimposed with the residues of known Nudix protein 1NQZ (red) (RMSD 0.16A0). The RA62 and EZ63 make hydrogen bond with W314 and W275 respectively. The glutamate residue EA66 is involved in making hydrogen bonds with two nearest water molecules W204 and W336. The water molecule W259 is sharing the hydrogen bonding between residues RA62 and EA63. The superimposition of patterns is performed by Discovery Studio (http://accelrys.com/products/discovery-studio/).

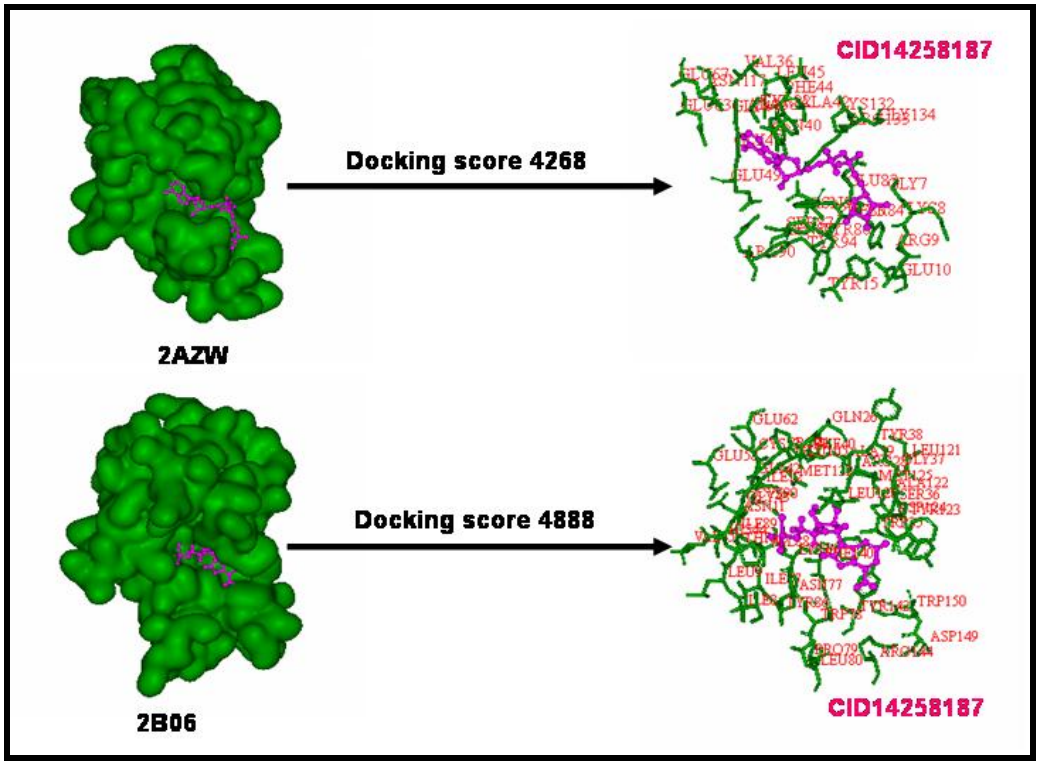

Figure 4: Docking of predicted inhibitor compound within the Cavities of Nudix enzymes. The compound CID14258187 (2R, 3R, 4S, 5R)-2-(6-aminopurin-9-yl)-5-(dichlorophosphoryloxymethyl) oxolane-3, 4-diol) was selected for analysis as it is in agreement of drug likeness properties. (a) The compound CID14258187 (magenta) bound at the cavity of 2AZW (green) with docking score of 4268. Here, the residues R62, E63, E66 and E67 surround the compound CID14258187 at the pocket (b)The compound CID14258187 (magenta) bound at the cavity of 2B06(green) with docking score 4888. The residues R57, E62 and E58 surround the compound CID14258187. These analyses are performed by using Discovery Studio software (http://accelrys.com/products/discovery-studio/).

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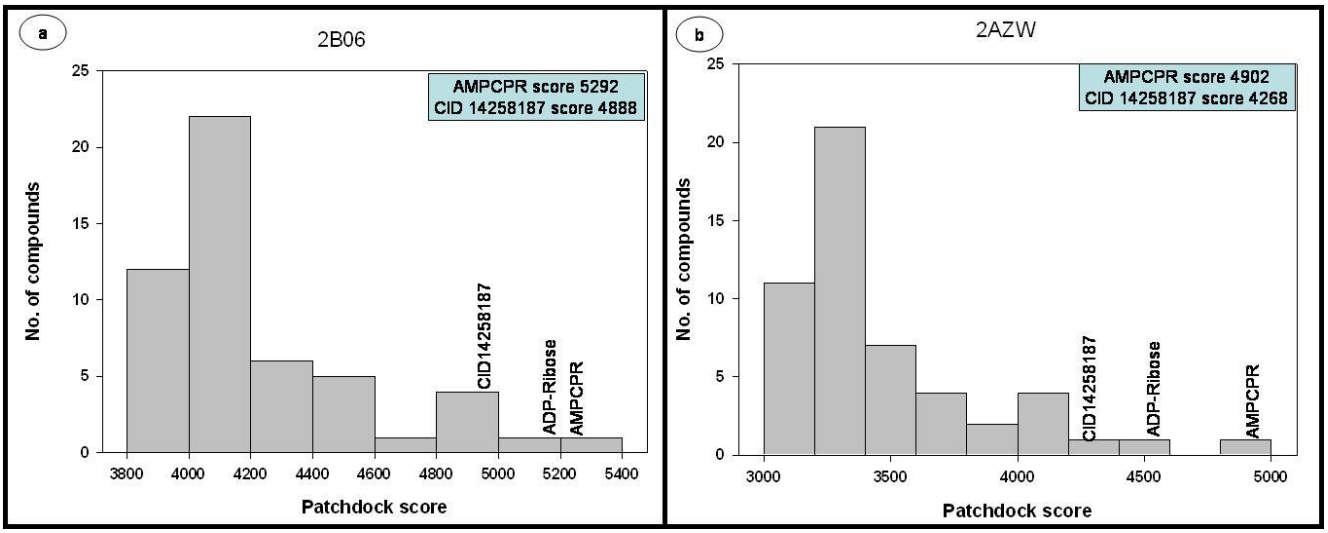

Figure 5: It shows the distribution of the Nudix inhibitors based on their docking score against the whole structure of the 2B06 and 2AZW Nudix enzymes. The inhibitors AMPCPR and CID14258187 show more affinity for **(a)** the 2B06 with score of 5292 and 4888 and **(b)** for 2AZW with higher docking score of 4902 and 4268. The docking is performed by Patchdock software.

Inhibitor prediction:

Docking of 51 inhibitor compounds revealed that the compounds AMPCPR and CID14258187 show more affinity for the 2B06 and 2AZW as compared to other inhibitor compounds. The compound AMPCPR is produced Patchdock score of 5292 and CID14258187 of 4888 in case of 2B06, which is higher than other compounds (**Figure 5(a)) (Table 6 see Supplementary material)** On the other hand for 2AZW, AMPCPR produced score of 4902 and CID14258187 of 4268 (**Figure 5(b)).** The compounds AMPCPR and CID14258187 bind within the binding site pockets of these Nudix enzymes and surround by RA57, EA62 ,EA58 (2B06) and RA62, EA63, EA66, EA67 (2AZW) binding sites residues **(Figure 4).** Furthermore, drug likeness properties analyses revealed that the compound CID14258187 shows no violation for the Lipinski rule of 5 (rules for selecting a compound as a potential drug) **(Table 4 see Supplementary material).** On the other hand, the compound AMPCPR is not in agreement of rule of 5 **(Table 4 see Supplementary material).** Therefore, we predict CID14258187 (2R, 3R, 4S, 5R)-2-(6-aminopurin-9-yl)-5-(dichlorophosphoryloxymethyl) oxolane-3, 4-diol) as potential inhibitor of the Nudix enzymes 2B06 and 2AZW.

Discussion:

In this work, we predict functional sites, substrates and inhibitors for 2B06 and 2AZW Nudix enzymes from disease causing micro-organisms such as *Streptococcus pneumoniae* and *Enterococcus faecalis*. These enzymes may act as potential drug targets in these micro-organisms because of their key roles in cell survival. Their structures are already reported, however functional sites and substrates are still unknown. Therefore, we target these enzymes for our computational study. We report functional sites in these Nudix enzymes via GI method. Our predicted sites are also matching with the residues detected by PROFUNC and Patchfinder servers. However, these servers produced large number of amino acid residues.

Furthermore, we also determine the substrate for the 2AZW and 2B06 via docking study. We find that the substrate ADP-Ribose shows more affinity for these Nudix enzymes as well as the residues EA62 (2B06) and RA62 (2AZW) interact with the ADP-ribose by making the hydrogen bonds. Note that these residues are also report by our GI method. The residues in the predicted sites for 2B06 and 2AZW are also make hydrogen bonds with nearby water molecules, leading to more convincing specificity of our functional site prediction. In addition, we determine the inhibitor compounds for these Nudix enzymes via docking. Our study finds that the compounds AMPCPR and CID14258187 may act as potential inhibitors of 2B06 and 2AZW. These compounds also bind within the same binding site pockets and residues of these Nudix enzymes, as shared by the substrate ADP-Ribose. In addition, the drug likeness properties analysis reveal that the compound CID14258187 (2R, 3R, 4S, 5R)-2-(6-aminopurin-9-yl)-5-(dichlorophosphoryloxymethyl) oxolane-3, 4-diol) is in agreement with Lipinski rule of 5 and can be act as potential drug against *Streptococcus pneumoniae* and *Enterococcus faecalis* pathogenic microorganisms.

Conclusion:

Our work concludes that the functional site residues predicted by GI method are putative substrate binding site residues for Nudix enzymes 2B06 and 2AZW. We also find that ADP-Ribose is their substrate, which infer that these Nudix enzymes may catalyze the catabolic reaction of ADP-Ribose in to AMP. Our study also determines that the AMPCPR and CID14258187 may act as inhibitor compounds for these Nudix enzymes. As these Nudix enzymes are from pathogenic microorganisms *Streptococcus pneumoniae* and *Enterococcus faecalis*, therefore these inhibitor compounds can be used as drug compound against these microorganisms. Analysis of drug likeness properties also confirm that the compound CID14258187 (2R, 3R, 4S, 5R)-2-(6-aminopurin-9-yl)-5-(dichlorophosphoryloxymethyl) oxolane-3,4-diol) is capable to act as potential drug compound. These studies may help in designing new drugs against *Streptococcus pneumoniae* and *Enterococcus faecalis.* This is the most important contribution of this work given that the Nudix enzymes are potentially important drug targets due to their key role in these organisms survival.

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Supplementary material:

Table 1: Functional site predictions in Structural Genomics (SG) unknown function proteins from Nudix family and their representative proteins.

SG Nudix PDB	Cluster ID	Predicted Functional Site	Representative PDB and Functional Site
2AZW	DDDK-1	RA62 EA63 EA66 EA67	1NQZ A:RA85 EA86 EA89 EA90
2B06	DDDK-1	RA57 EA58 EA61 EA62	1SU2 A:RA64 EA65 EA68 EA69

Table 2: Prediction of functional sites in Structural Genomics Nudix proteins

SG Targets	Predicted Functional Site	PINTS	PROFUNC	PatchFinder
2AZW	RA62 EA63 EA66 EA67	E51 G48 E49	Reverse Template Match: YA22 GA48 YA101; YA22 GA47 EA63 Ligand Binding: EA48 EA63 EA66 EA67	GA47 GA48 EA54 RA62 EA63 EA66 EA67
2B06	RA57 EA58 EA61 EA62	None	Reverse Template Match: CA13 GA42 KA92; LA65 GA98 WA110; CA13 PA41 EA62; PA41 EA62 SA103; CA13 GA42 HA44 Ligand Binding: HA44 GA43 EA58 EA62 EA105	NA11 GA42 GA43 DA48 EA49 RA57 EA58 EA61 EA62 GA64

Table 3: Docking analysis of substrates against Structural Genomics Nudix SG targets

	Blind Docking	
Substrates	DE (-Kcal/mol)	
	2AZW	2B06
ADP-RIBOSE	-10.86	-15.69
AMP	-7.68	-10.51
Apr	-10.79	-13.8
ATP	-9.2	-11.2
CTP	-8.92	-11.07
dATP	-8.36	-11.56
dGTP	-10.16	-11.99
dTTP	-10	-12.23
dUTP	-8.91	-10.97
GTP	-10.46	-13.37
TTP	-9.46	-11.1
.8-OXY-dGTP	-10.04	-12.57
	Refined docking	
Substrates	DE (-Kcal/mol)	
	2AZW	2B06
ADP-RIBOSE	-10.96	-16.2
.8-OXY-dGTP	-10	-10.1

Table 4: Comparisons of Drug likeness properties of selected inhibitor compounds

Molecular Properties		
Parameter	CID 14258187	AMPCPR
miLogP	0.274	-3.355
TPSA	145.628	282.307
natoms	23	36
MW	384.116	557.346
nON	10	18

nOHNH	4	9
nviolations	0	3
nrotb	4	9
volume	274.916	424.322

Drug Likeness

Parameter	CID 14258187	AMPCPR
GPCR ligand	0.08	-0.1
Ion channel modulator	-1.14	-1.08
Kinase inhibitor	0.36	-0.25
Nuclear receptor ligand	-2.38	-1.79

Table 5: Matching cluster and template proteins for SG Nudix enzyme

Cluster member	No.	Pattern	EC number	Function	
DDDK-1	4			hydrolase activity|1.00	
1KTG	EEER	EA52 EA55 EA56 RA51		bis(5'-nucleosyl)-tetraphosphatase activity ,hydrolase activity	Nudix
1NQZ	EEER	EA86 EA89 EA90 RA85		hydrolase activity	Nudix
1VHZ	EEER	EA95 EA98 EA99 RA94		hydrolase activity	Nudix
1SU2	EEER	EA65 EA68 EA69 RA64		hydrolase activity	Nudix
DDDK-2	3			hydrolase activity|1.00	
1VHZ	EEER	EA86 EA95 EA98 RA94		hydrolase activity	Nudix
1VK6	EEER	EA165 EA174 EA177 RA173	3.6.1.22	hydrolase activity	Nudix
1KTG	EEER	EA43 EA52 EA55 RA51		bis(5'-nucleosyl)-tetraphosphatase activity,hydrolase activity	Nudix
DDDK-3	3			hydrolase activity|1.00	
1VK6	EEER	EA174 EA177 EA178 RA173	3.6.1.22	hydrolase activity	Nudix
1KTG	EEER	EA52 EA55 EA56 RA51		bis(5'-nucleosyl)-tetraphosphatase activity,hydrolase activity	Nudix
1VHZ	EEER	EA95 EA98 EA99 RA94		hydrolase activity	Nudix

Table 6: Docking analysis of the Inhibitors with Nudix enzyme

Pubchem compound	**2B06**	**Pubchem compound**	**2AZW**
CID ID	**Docking score**	**CID ID**	**Docking score**
AMPCPR_pdb	5292	AMPCPR_pdb	4902
ADP-Ribose	5174	ADP-Ribose	4512
14258187.pdb	4888	14258187.pdb	4268
18657710.pdb	4876	18657710.pdb	4038
18950508.pdb	4876	18950508.pdb	4038
44442324.pdb	4818	46192071.pdb	4036
46192071.pdb	4790	44442324.pdb	4012
CID44299525.pdb	4512	CID44299525.pdb	3806
CID46875160.pdb	4512	CID46875160.pdb	3806
4131.pdb	4454	44442322.pdb	3786
445093.pdb	4454	16678017.pdb	3766
44574756.pdb	4408	44574718.pdb	3698
16678017.pdb	4364	21724899.pdb	3602
44442322.pdb	4312	4131.pdb	3576
21724899.pdb	4260	445093.pdb	3576
44574718.pdb	4258	44574756.pdb	3576
6338568.pdb	4202	22497880.pdb	3472

14185387.pdb	4202	22827299.pdb	3472
22497880.pdb	4152	21462459.pdb	3420
22827299.pdb	4152	22827300.pdb	3420
2024.pdb	4048	2024.pdb	3376
101812.pdb	4048	101812.pdb	3376
2735269.pdb	4048	2735269.pdb	3376
7173835.pdb	4048	7173835.pdb	3376
25632541.pdb	4048	25632541.pdb	3376
25632546.pdb	4048	25632546.pdb	3376
25632550.pdb	4048	25632550.pdb	3376
25796534.pdb	4048	25796534.pdb	3376
CID26967481.pdb	4048	CID26967481.pdb	3376
CID46780086.pdb	4048	CID46780086.pdb	3376
CID46780087.pdb	4048	CID46780087.pdb	3376
6992262.pdb	4026	6992262.pdb	3346
7173834.pdb	4026	7173834.pdb	3346
25632540.pdb	4026	25632540.pdb	3346
25632545.pdb	4026	25632545.pdb	3346
25632549.pdb	4026	25632549.pdb	3346
25796533.pdb	4026	25796533.pdb	3346
CID26967480).pdb	4026	CID26967480).pdb	3346
21462459.pdb	4010	6338568.pdb	3340
22827300.pdb	4010	14185387.pdb	3340
16131893.pdb	3916	16131893.pdb	3330
16212025.pdb	3888	16212025.pdb	3164
23902375.pdb	3888	23902375.pdb	3164
25322946.pdb	3888	25322945.pdb	3164
25322948.pdb	3888	25322946.pdb	3164
40467852.pdb	3888	25322947.pdb	3164
44629928.pdb	3888	25322948.pdb	3164
25322945.pdb	3810	26940520.pdb	3164
25322947.pdb	3810	40467851.pdb	3164
26940520.pdb	3810	40467852.pdb	3164
40467851.pdb	3810	40467853.pdb	3164
40467853.pdb	3810	44629928.pdb	3164