Electronic Supplementary Material (ESI) for Molecular BioSystems.


**Active site analysis**

Glucose-6-phosphate isomerase (G6I) is plays a crucial role in glycolysis, gluconeogenesis and pentose phosphate pathway regulation. These pathways are important for ATP production in this parasite. Thus targeting G6I seems to promising for drug discovery and design as anti-*leishmanial* therapy. Active site analysis of human G6PI (PDB ID 1IAT) shows that it is more deep and its electrostatic potential also differs with *Leishmania* G6PI (modbase ID Q4QGN9) (Figure 1 and 2).

Phosphomannomutase (PMM) is responsible for mannose-6-phosphate to mannose-1-phosphate which helps in biosynthesis of glycoconjugates. These glycoconjugates form cell surface of prokaryote. Thus PMM consider as potential novel target in anti-*Leishmania* drug development. Kedzierski *et al* suggest that PMM inhibitors design challenging mission because of similarity between human and *Leishmania* PMM [1]. Human PMM (PDB ID 2FUC) probable active site has Asp12, Ser47, Lys189, Asp218 residues (Figure 3A) and *L. mexicana* PMM (PDB ID 2AMY) shows the presence of Asp10, Lys188, Ser46 residues (Figure 3B) respectively both the results are according to uniprot database and experimental result of Handman *et al.* [1, 2]. *L. mexicana* PMM active site volume is larger and deeper than human Phosphomannomutase (Figure 4A and 4B). There electrostatic potential difference is clearly visible in Figure 4C and 4D.

**Binding site**

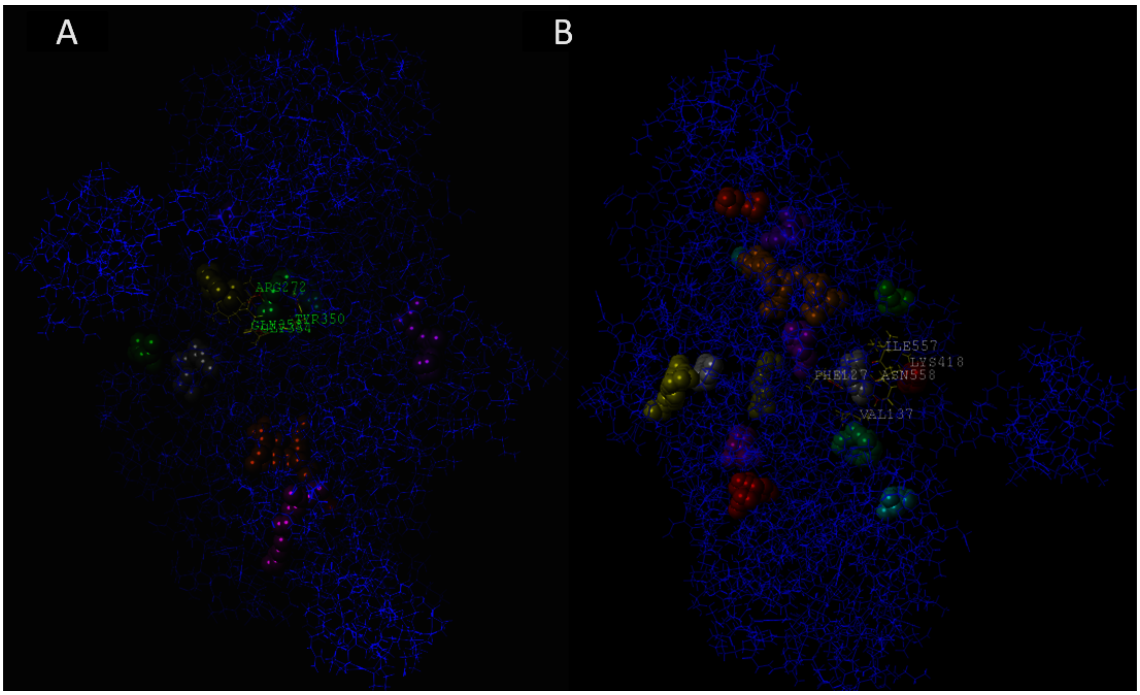


**Figure 1. Glucose 6 phosphate isomerise binding site analysis** (A) Human Glucose 6 phosphate isomerise (B) *Leishmania* Glucose 6 phosphate isomerise

**Cavity Depth and MEP analysis**

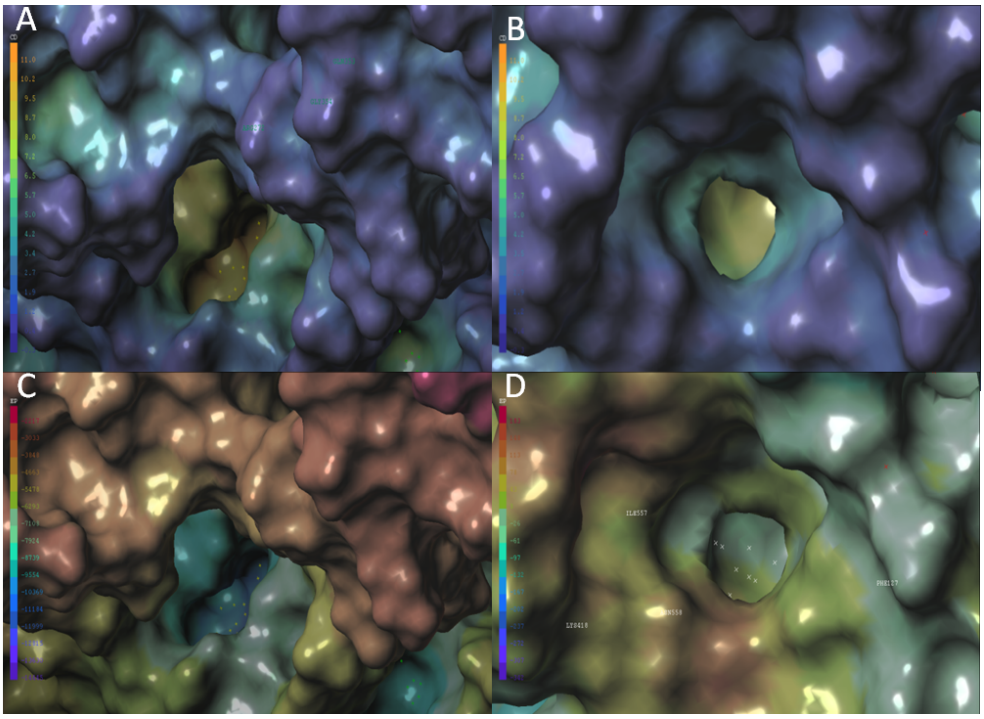


**Figure 2 Glucose 6 phosphate isomerise cavity depth and MEP analysis** (A) Human Glucose 6 phosphate isomerise cavity depth is high compare to *Leishmania* G6PI (B) *Leishmania* Glucose 6 phosphate isomerise cavity is relatively narrow (C) Human Glucose 6 phosphate isomerise MEP surface (D) *Leishmania* Glucose 6 phosphate isomerise MEP surface

**Binding site**

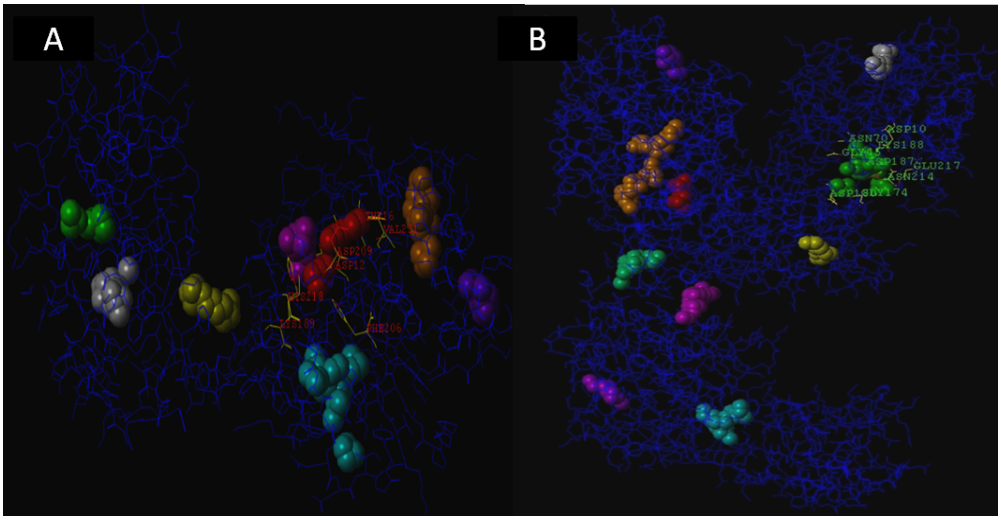


**Figure 3 Phosphomannomutase binding site analysis** (A) Analysis shows eight binding sites of Human Phosphomannomutase (B) ten binding sites are identified in *Leishmania* Phosphomannomutase

**Cavity Depth Analysis and MEP analysis**

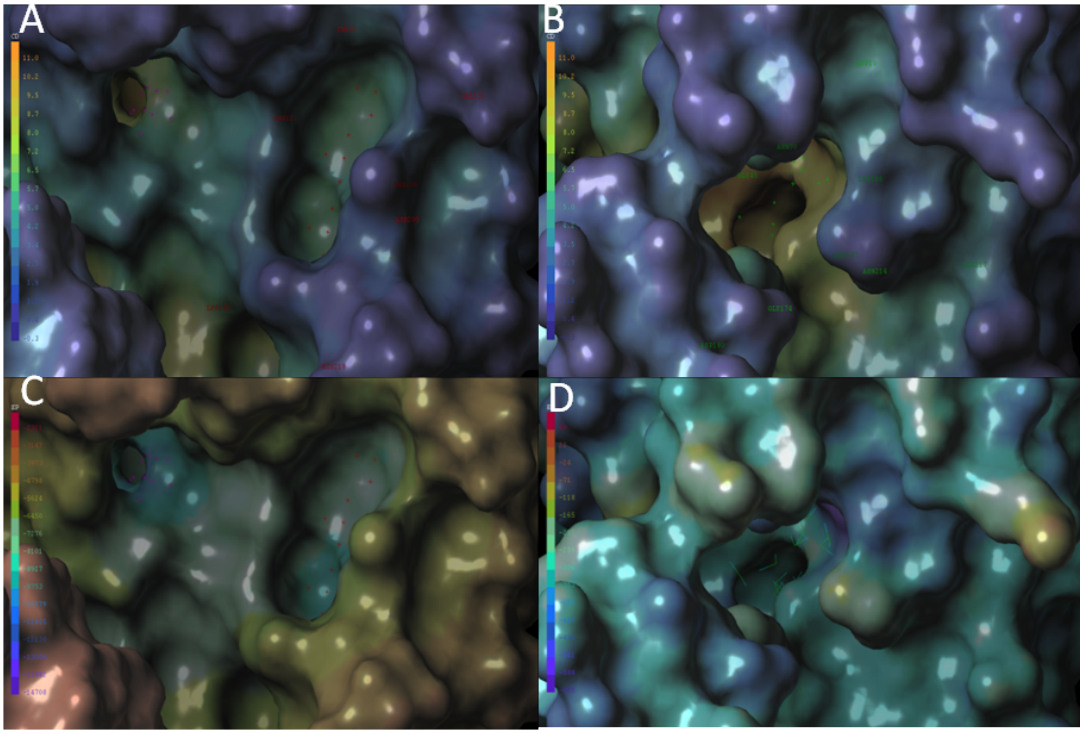


**Figure 4 Phosphomannomutase active site analysis** (A) Human Phosphomannomutase cavity depth (B) *Leishmania* Phosphomannomutase cavity depth was higher (C) Human Phosphomannomutase MEP surface (D) *Leishmania* Phosphomannomutase MEP surface

**Druggability Analysis**

**DogSiteScorer** is a new algorithm for predicting the pockets and its druggability which is highly important in pharmaceutical research. Druggability score is ranges from zero to one. The higher score indicates more druggablity of the pocket. Apart from that it also calculates the volume, surface lipo surface and depth of pocket [3].

**Results**

Druggablity results of Homoserine kinase, L-ribulokinase and Phospholipid:diacylglycerol acyltransferase are promising and gives better scope for rational drug designing (Corresponding figures 5,6 and 7). Druggability of *leishmania* targets is given in table 1 and 2.

**Table 1 Druggablity result of *Leishmania* exclusive targets**

| S. No. | Non Homologous Targets | Total No. of Pockets | Pockets | Volume [Å³] | Surface [Å²] | Lipo surface [Å²] | Depth [Å] | Drug Score |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Phospholipid: diacylglycerol acyltransferase, putative | 17 | P0 | 3787.70 | 4461.43 | 3121.12 | 38.40 | 0.81 |
| | | | P1 | 332.99 | 674.11 | 302.96 | 16.15 | 0.67 |
| 2 | Homoserine kinase, putative | 10 | P0 | 950.21 | 1324.74 | 824.22 | 25.77 | 0.82 |
| | | | P1 | 770.69 | 984.92 | 819.60 | 20.81 | 0.84 |
| 3 | L-ribulokinase, putative | 18 | P0 | 1805.85 | 2043.88 | 1310.55 | 26.71 | 0.81 |
| | | | P1 | 897.56 | 1157.53 | 822.44 | 24.99 | 0.84 |

**Table 2 Other *Leishmanial* targets druggablity analysis**

| S. No. | Non Homologous Targets | Total No. of Pockets | Pockets | Volume [Å³] | Surface [Å²] | Lipo surface [Å²] | Depth [Å] | Drug Score |
|---|---|---|---|---|---|---|---|---|
| 1 | Nucleoside diphosphate kinase B (NDKb) | 16 | P0 | 871.37 | 1168.96 | 712.42 | 18.25 | 0.57 |
| | | | P1 | 849.58 | 953.35 | 588.92 | 21.19 | 0.54 |
| 2 | Glucose-6-phosphate isomerase (G6I) | 20 | P0 | 691.20 | 765.84 | 495.81 | 24.53 | 0.38 |
| | | | P1 | 447.83 | 545.82 | 379.04 | 20.36 | 0.28 |
| 3 | Phosphomanno mutase | 11 | P0 | 365.31 | 417.08 | 231.14 | 12.33 | 0.21 |
| | | | P1 | 318.14 | 720.48 | 440.07 | 18.44 | 0.18 |

**References**


1. L. Kedzierski, R. L. Malby, B. J. Smith , M. A. Perugini, A. N. Hodder, T. Ilg, P. M. Colman, E. Handman, *J. Mol. Biol.,* 2006, **363**, 215-27.
2. The UniProt Consortium, *Nucl. Acids Res.,* 2012, **40,** D71-5
3. A. Volkamer, D. Kuhn, T. Grombacher, F. Rippmann, M. Rarey, *J. Chem. Inf. Model.,* 2012, **52**, 360-372.