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REPURPOSING MEBENDAZOLE FOR ITS HIDDEN POTENTIAL AS ANTI-FILARIAL DRUG: A COMPUTATIONAL DOCKING ANALYSIS

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ABSTRACT

Drug repurposing is an emerging approach in the identification of new treatments. Filarial infection is a rare-neglected disease affecting more than 150 million people in hot climatic regions. The WHO recommends albendazole and ivermectin as the line of treatment against causative agents of filariasis. Our study implements repurposing for rare disease approach with the principle of re-using anti-helmentic drug (mebendazole) to understand its hidden potential against FtsZ protein. For this, albendazole sulfone which is presently an approved drug in MDR for treating filariasis was considered as the standard reference. Filarial causative agent *W.bancrofti* has functional b-tubulin along with FtsZ (cell division protein) sequence homology. Anti-helmentic drugs have a mechanistic target against b-tubulin which is functionally similar to the FtsZ protein molecule. Therefore, FtsZ can be targeted to study the effect of mebendazole as the anti-filarial agent. An effort was made to repurpose mebendazole drugs as an anti-helmentic agent with the use of computational docking studies carried out using SeeSARbiosolve software. Surprisingly, mebendazole showed more affinity towards cell division protein as compared to standard drug molecule scores. Our future scope aims to study the affinities and potential of mebendazole through virtual screening and in-vitro techniques.

Keywords: SeeSARbiosolve, Drug Repurposing, FtsZ, Filariasis, Anti-helmentic drugs

INTRODUCTION

Filariasis is a vector transmitted worm infection declared to be a tropically neglected disease affecting more than 150 million people **[1]**. Epidemiological data revealed 81 countries as endemically affected for lympathic filariasis **[2]**. Hot climatic regions like Asia, Africa, and America are most prone to get affected. *Wucheria bancrofti*, *Brugia malagia*, *Brugia timori* are three major causative agents for lymphatic filariasis. The WHO recommends a mass-drug administration strategy for the elimination of lymphatic filariasis for the entire risk of the population. Albendazole (400mg) twice a year, Ivermectin (200 mg/ kg) with albendazole in onchocerciasis affected countries, and diethylcarbamazine citrate (6mg/kg) and albendazole combination in countries without onchocerciasis cases is the prescribed drug-regimen in the WHO strategy **[3-5]**. Drug repurposing can be used as a novel approach in designing anti-filarial drugs. The traditional drug development process is time-consuming and costly with a high risk of failure or difficulties. Re-profiling a drug with a known profile can be advantageous to avoid such losses. There are several approaches for repurposing – Repurposing oncology drugs, across different therapeutic areas, repurposing for rare diseases and the newly adopted approach is repurposing drugs for COVID-19 treatment. Our study implements repurposing for rare disease approach with the principle of re-using anti-helmentic drug (mebendazole) to understand its hidden potential against FTsZ protein. FTsZ protein functions as a cell-division initiator by assembling the cytoskeletal of the Z-ring found almost in all bacteria, archaea, mitochondria region, and chloroplasts **[6-7]**. A similar study was conducted by Garner Alamanda targeting bacterial endosymbiont *Wolbachia* (filarial parasite) investigating new inhibitors of FTsZwith an approach of controlling filarial infections and proven to inhibit the division of the bacteria as well as Mycobacterium Tuberculosis by changing the shape to long filamentous type resulting in failure to divide. Albendazole and mebendazole belong to same-line drugs and are chemically similar to benzimidazole as their backbone ring. They are mostly prescribed as Albenza (Albendazole) and Vermox (mebendazole) for intestinal worm infection. In the 2018 sub-Sahara Africa region, a randomized clinical trial was conducted to study drug regimen of single diethylcarbamazine, the single dose of ivermectin, and albendazole drug in Wucheriabancrofti-infected adults resulted in complete elimination of blood microfilaria count in 24 months **[8-9]**.

MATERIALS AND METHODS

Targeting FTsZ protein

FtsZ is a major protein that dynamically acts as cell-division machinery. Cell division is a vital process for all living beings. The composition of protein revolves around two protein domains – N-terminal GTP binding and C-terminal binding domain representing the GTP-hydrolyzing enzymes family. Filarial causative agent W.bancrofti has functional b-tubulin along with FtsZ sequence homology. Anti-helmentic drugs have a mechanistic target against b-tubulin which is functionally similar to the FtsZ protein molecule. Therefore, FtsZ can be targeted to study the effect of mebendazole as an anti-filarial agent **[10-12]**.

SeeSARBiosolve Version 10

Computational docking method using SeeSARBiosolve Version 10.2 was used to check the affinity of mebendazole with FTsZ protein. Albendazole drug used in MDB regimen of anti-filarial therapy is the standard reference for comparison of scores. Initially, the FTsZ protein structure was downloaded from the Protein Drug Bank source. The ligand was extracted and loaded in protein mode. The protein model was given a command to identify the unoccupied pockets in the protein structure. Three unoccupied pockets namely pocket A, pocket B, and pocket C were identified.

The drug mebendazole was uploaded in the protein mode. Then, the individual pockets were loaded in docking mode with drug molecules and the affinity of mebendazole with FTsZ protein was noted at different positions. For example, pocket A was loaded in docking mode. Mebendazole was docked at different positions in pocket A of FTsZ protein. The procedure was repeated with the reference molecule.

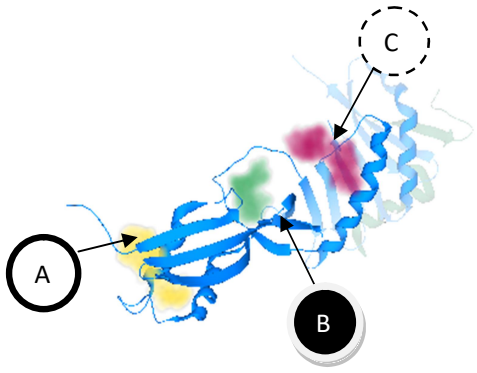


Figure 1: Three unoccupied pockets in FTsZ protein

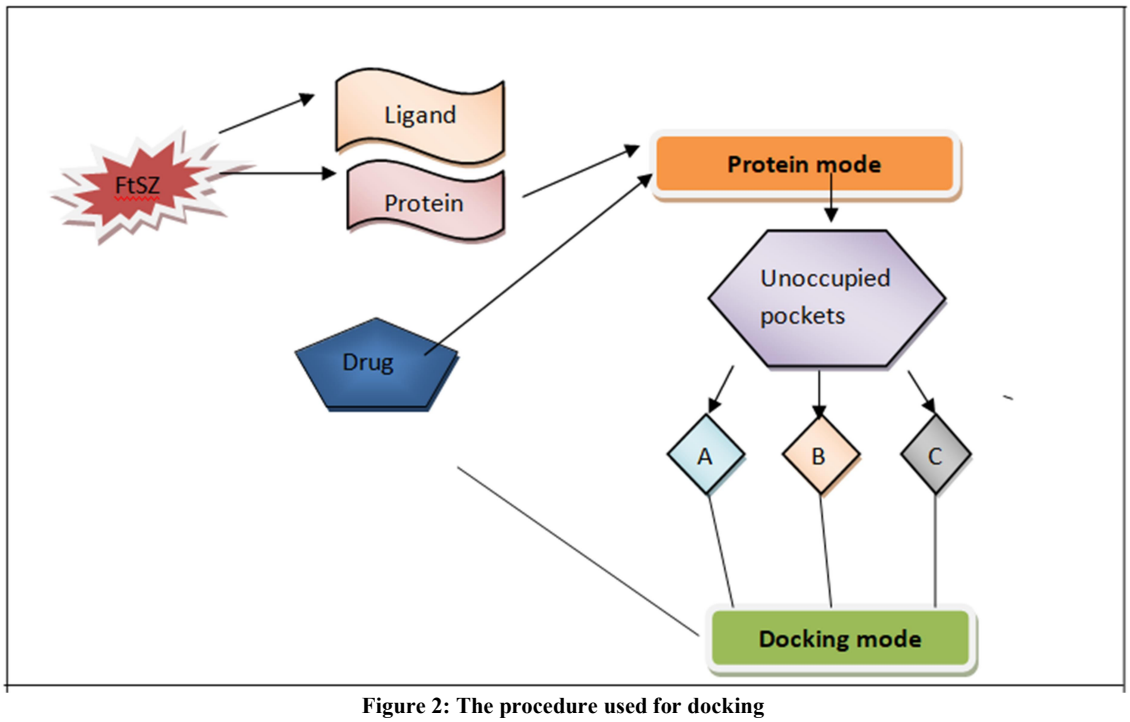


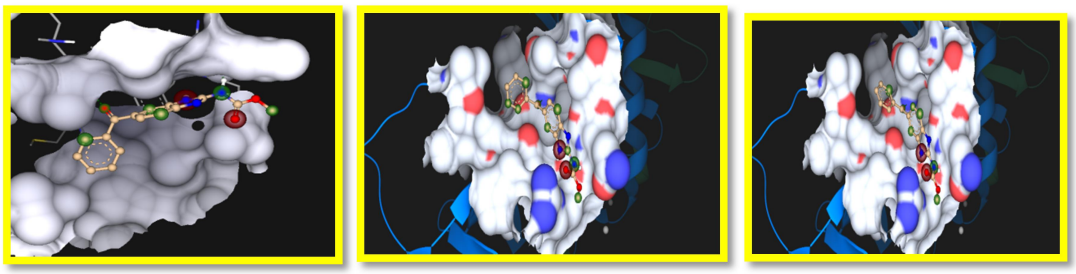
Figure 2: The procedure used for docking

RESULTS AND DISCUSSION

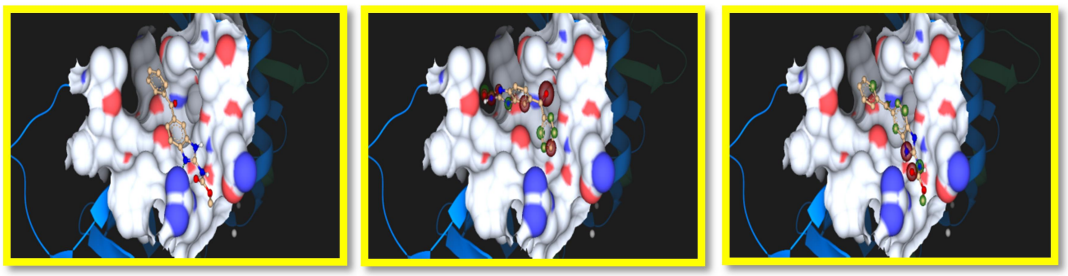
The unoccupied pocket A was placed in docking mode with the ligand (mebendazole) and no interaction was reported. Hypothetically, can be stated as the interaction between the amino acid chains at pocket A lacked pie bonds for bonding the ligand molecule. Thus, the result showed zero interaction at pocket A

For pocket B and C interaction-check, a similar method was used and the affinity was found to be good.

Albendazole was used as a standard molecule for computational studies. SeeSARbiosolve version 10 was used for standard to compare the scores. The docking interaction scores obtained for albendazole are in **(Figure 7)**.

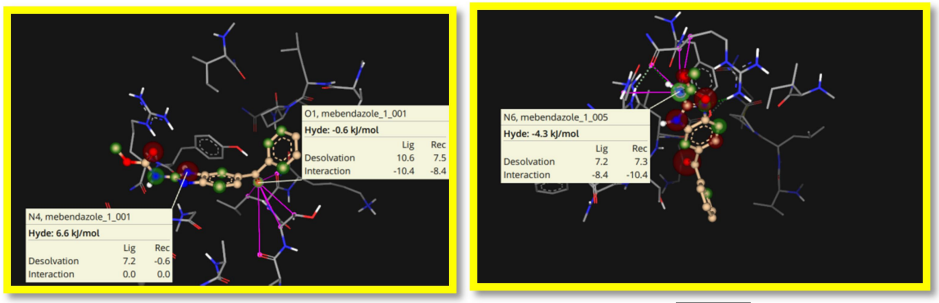


(A) (B) (C)



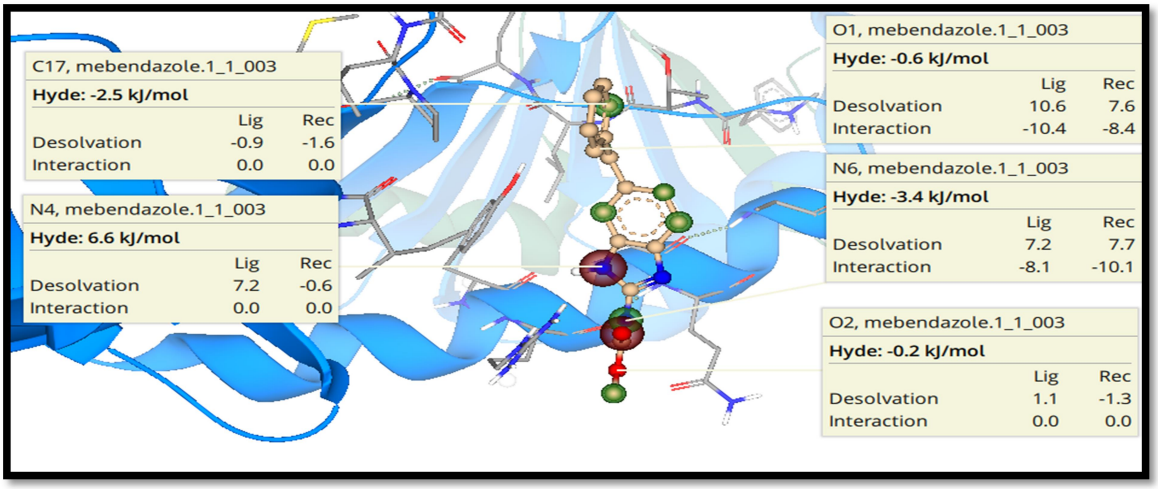
(D) (F) (G)

Figure 3: POCKET B docking of ligandat various positions (A), (B), (C), (D), (E), (F), and (G)



(H) (I)

Figure 4: POCKET B docking shows the bonding of atoms N6, O1 and N4 denoted with pink lines (H, I)



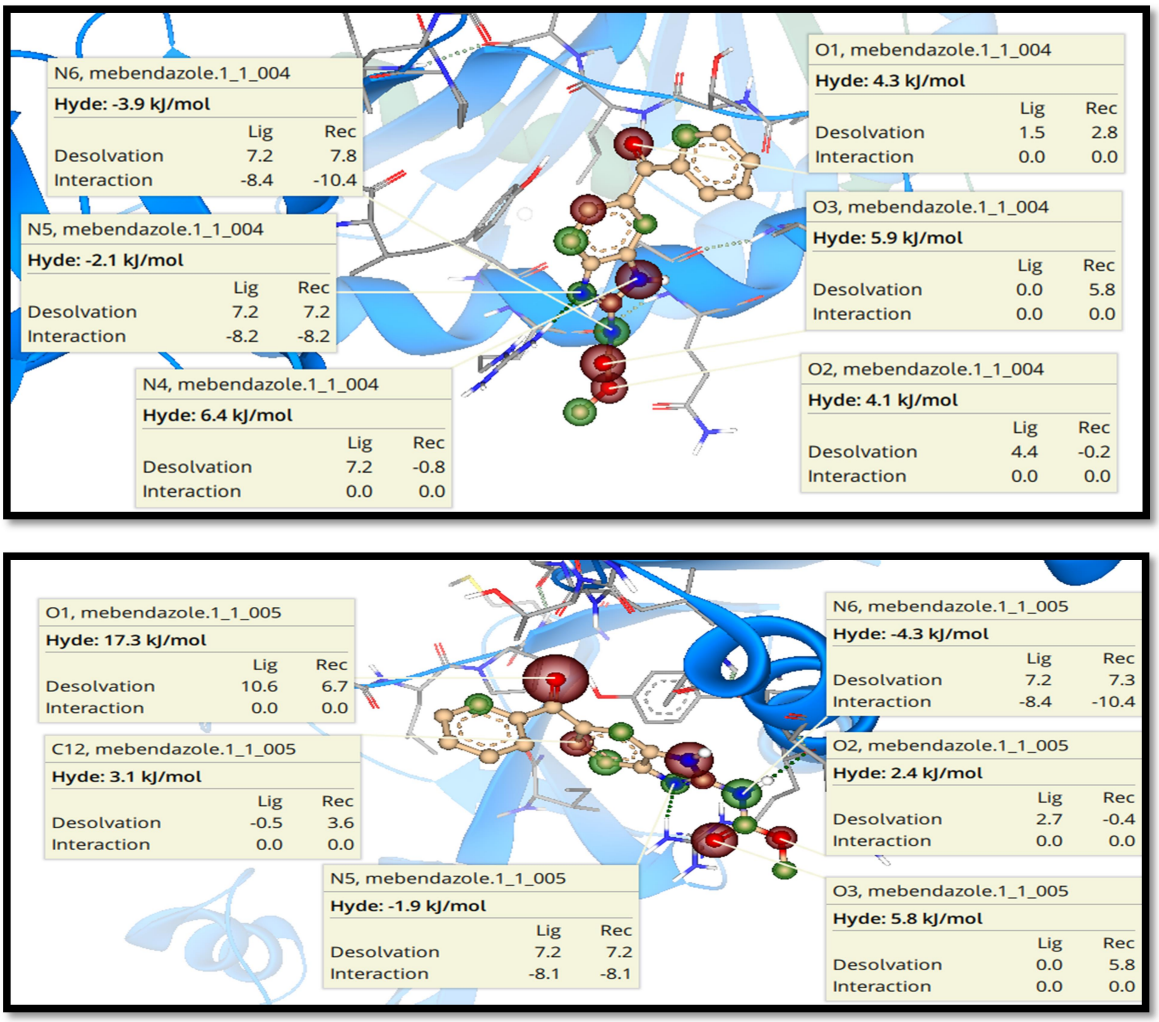
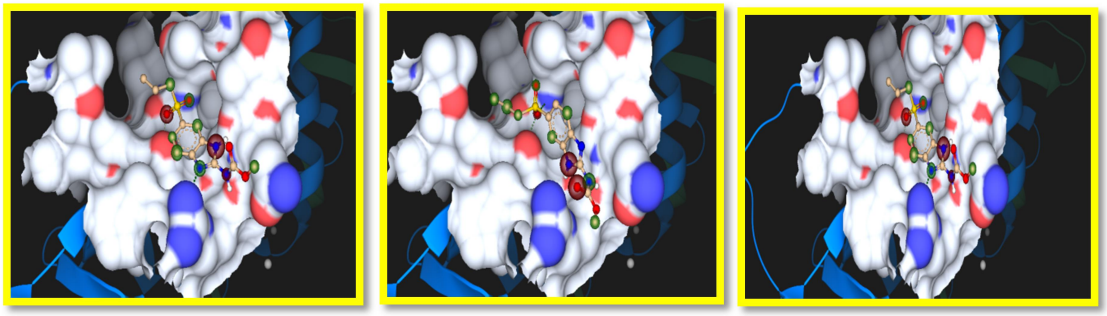


Figure 5: Desolvation and interaction scores at various atomic positions



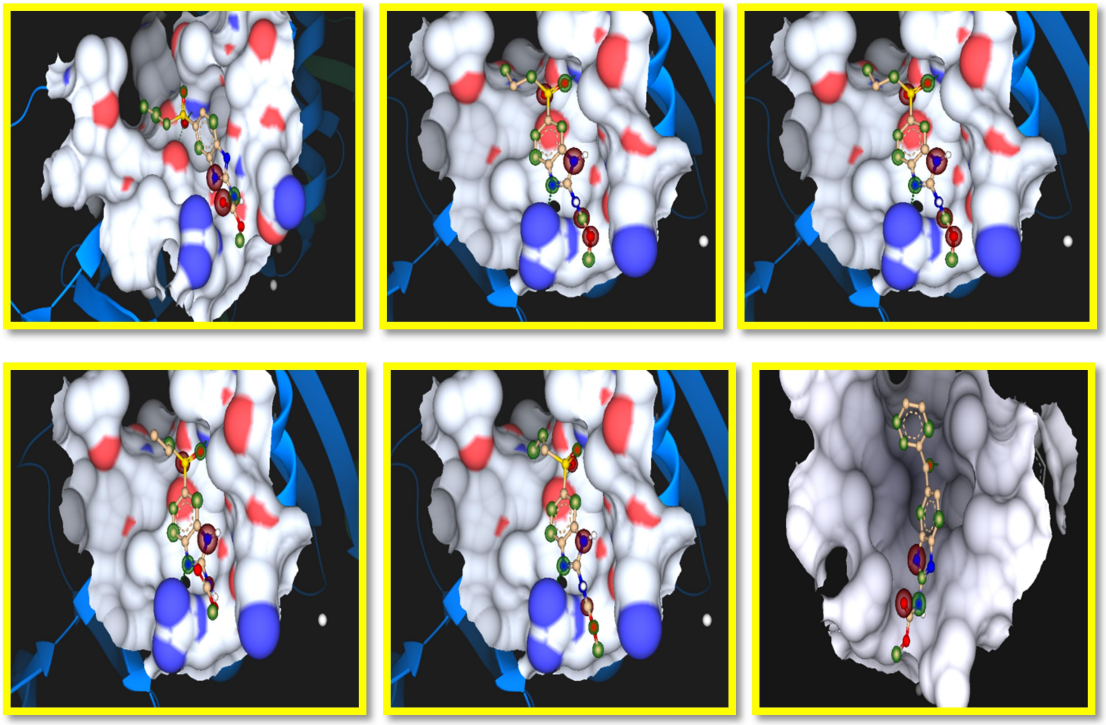
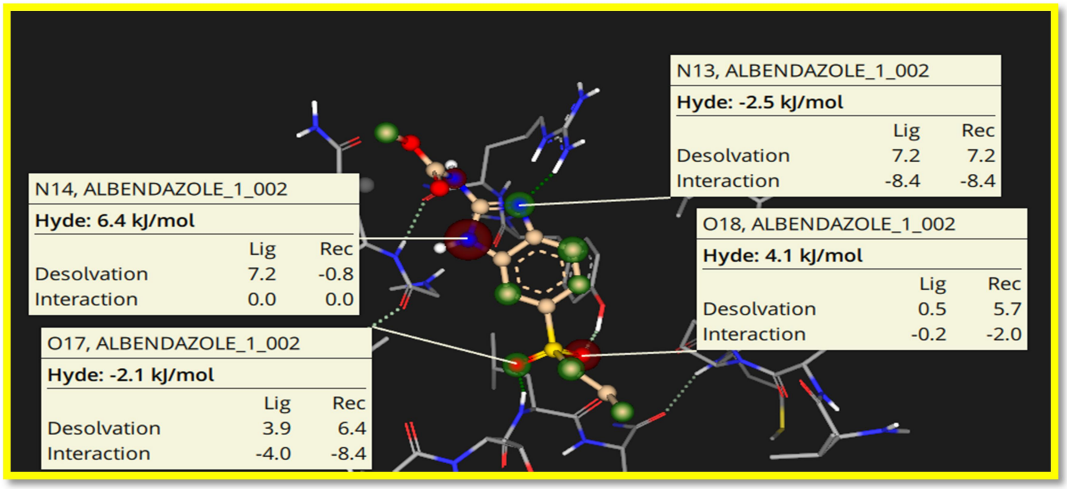


Figure 6: Albendazole docking site with FTsZprotien



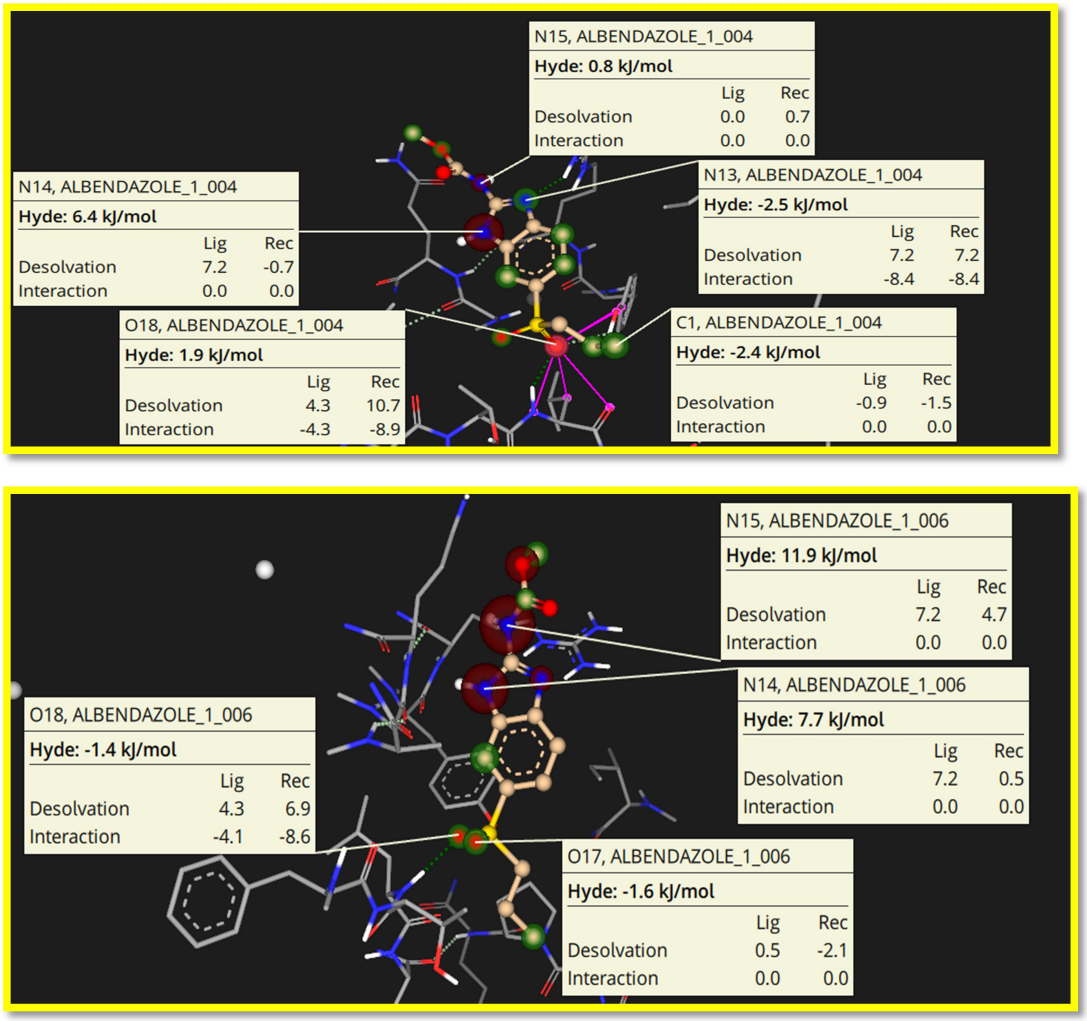


Figure 7: Docking Scores of albendazole molecule

CONCLUSION

From the above-drawn results, it can be concluded that mebendazole has good potential against FTsZ protein. This can prove to be the potential bacterial cell-division inhibiting candidate. The ligand-protein interaction and the desolvation energy were found to be greater in mebendazole than in albendazole drug molecules. The mebendazole molecule showed highest ligand-protein interaction at Oxygen atom bonded at position 1 (-10.4 & - 8.4), nitrogen atom at position 6 (-8.1 & -10.1) and position 5 (-8.1 & -8.1) respectively. Surprisingly, the albendazole molecule also showed greater interaction with protein with oxygen atoms and nitrogen atoms.

FUTURE SCOPE

Drug repurposing can overcome the limitations of drug development. Using the approach for drug designing, formulating, and research can be extended to drugs that fail out of clinical trials or even for drugs

that get withdrawn from the market. Mebendazole can be a good candidate against filarial parasites. Virtual screening of both the molecules with their derivatives is the future aspect of the study.

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