

**Enasidenib:**

Enasidenib is an oral, selective inhibitor targeting mutated isocitrate dehydrogenase 2 (IDH2), a mitochondrial enzyme (Isocitrate dehydrogenase [NADP], mitochondrial) commonly mutated in adult acute myeloid leukemia (AML) patients. Mutations in IDH2 are more prevalent (8%-19%) than those in IDH1 (7%-14%) and result in increased production of the oncometabolite 2-HG, which restricts cell differentiation. Enasidenib, developed by Agios and licensed to Celgene, was approved in August 2017 for treating relapsed or refractory AML with an IDH2 mutation. The synthesis of enasidenib involves a seven-step process starting from 2-(trifluoromethyl)pyridine and culminating in the formation of enasidenib mesylate through various chemical transformations.

Based on Drug Bank and PDB Database the X-ray crystallography code of Enasidenib and Isocitrate dehydrogenase [NADP], mitochondrial has the code 5I96 and the docking is based on this data on PDB Database.

**Docking:**

X-Ray crystallography of the enzyme and the drug:



Figure 1: Isocitrate dehydrogenase [NADP], mitochondrial which is the target protein of Enasidenib.

X-ray crystallography of the protein and the modified output of AutoDockTools:

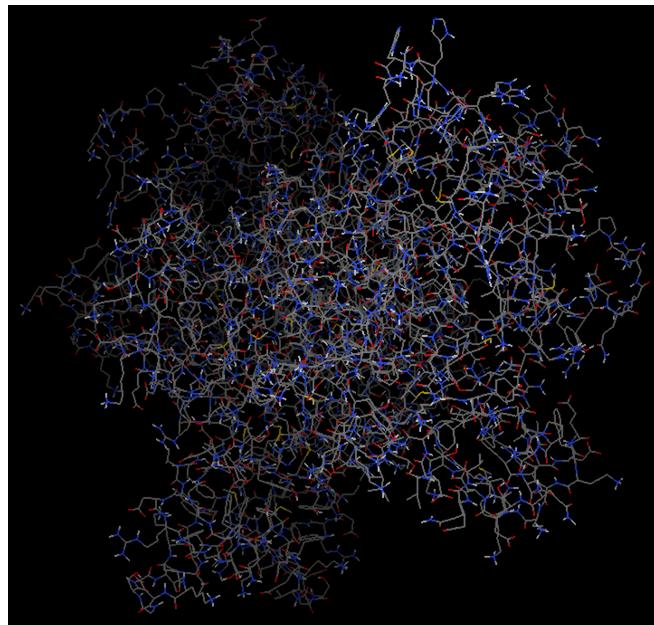
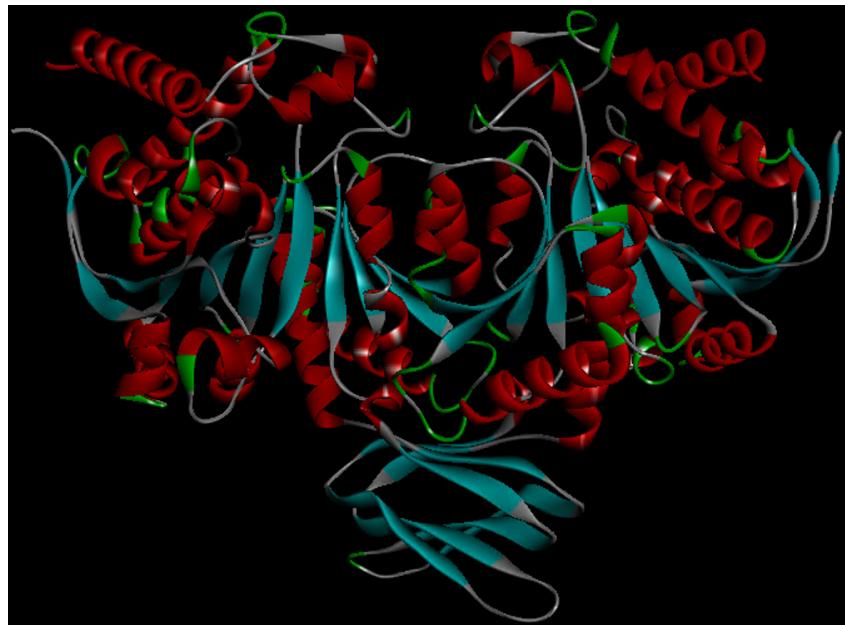


Figure 2: Left -> Protein's shape in Discovery Studio Visualizer. Right -> Protein's shape in AutoDockTools after modifications.

Docking box and it's coordinates:

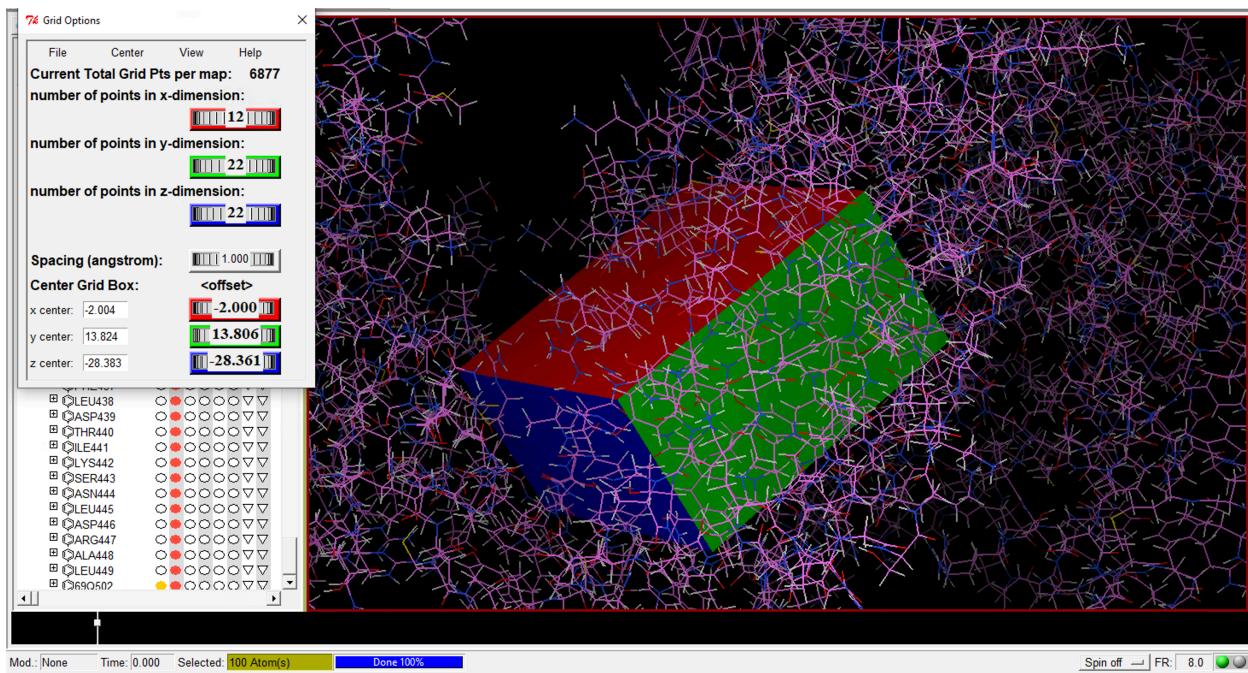


Figure 3: Docking box. The ligand (69Q502) is inside the box.

The affinities from the docking process are as follows:

| mode | affinity<br>(kcal/mol) | dist from best mode<br>rmsd l.b. | best mode<br>rmsd u.b. |
|------|------------------------|----------------------------------|------------------------|
| 1    | -14.8                  | 0.000                            | 0.000                  |
| 2    | -14.1                  | 1.595                            | 4.222                  |
| 3    | -13.1                  | 3.968                            | 6.566                  |
| 4    | -12.6                  | 1.317                            | 8.523                  |
| 5    | -12.3                  | 1.646                            | 2.237                  |
| 6    | -11.9                  | 1.943                            | 8.272                  |

Table 1: Docking output table.

This table shows the reaction is very favorable with -14.8 kcal/mol affinity.

We can see modified ligand and the docking's output overlay:

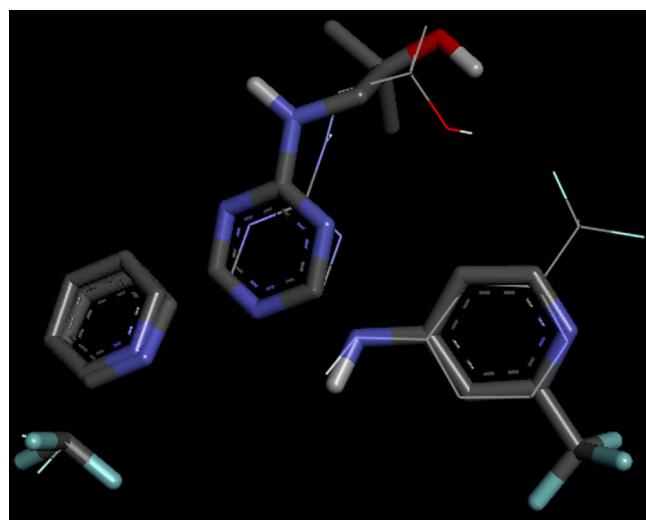


Figure 4: Tube model -> Ligand in X-ray crystallography. Wire model -> Ligand after docking.

As we can see they match pretty well which again shows the Docking was successful.

We can also see the interaction of the protein's amino acids with the ligand in the Figure 5:

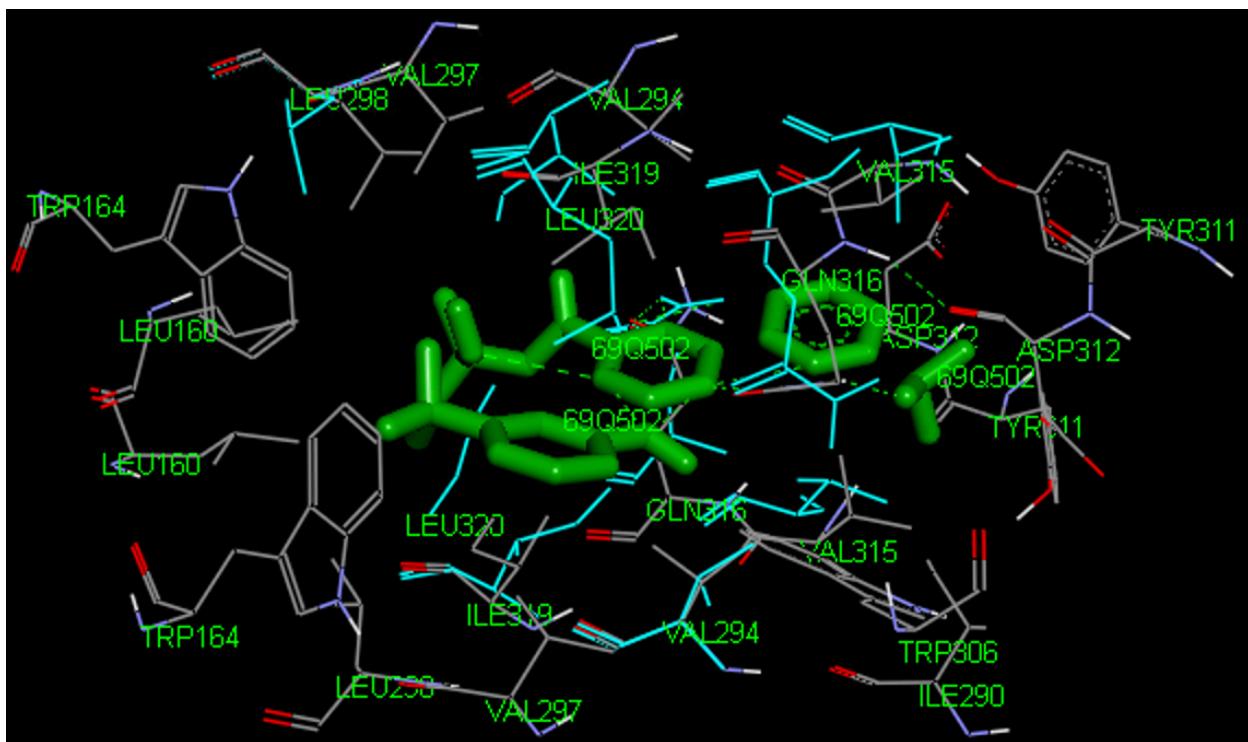


Figure 5: Tube model -> Ligand, Wire model -> Protein. Green texts -> interacting amino acids.