DRUG DOCKING REPORT

Of Alanine Aminotransferase (ALT)

Sumit Garai

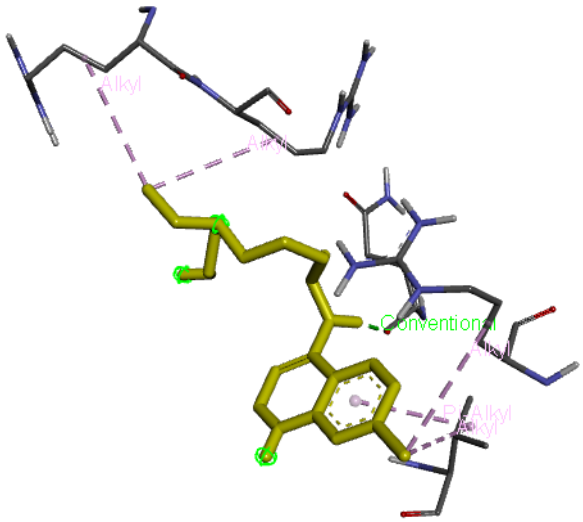
17.07.2020

ALT catalyzes the transfer of an amino group from L-alanine to α-ketoglutarate,leading to the formation of pyruvate and L-glutamate. The enzyme requires the coenzyme pyridoxal phosphate (PLP) to function.

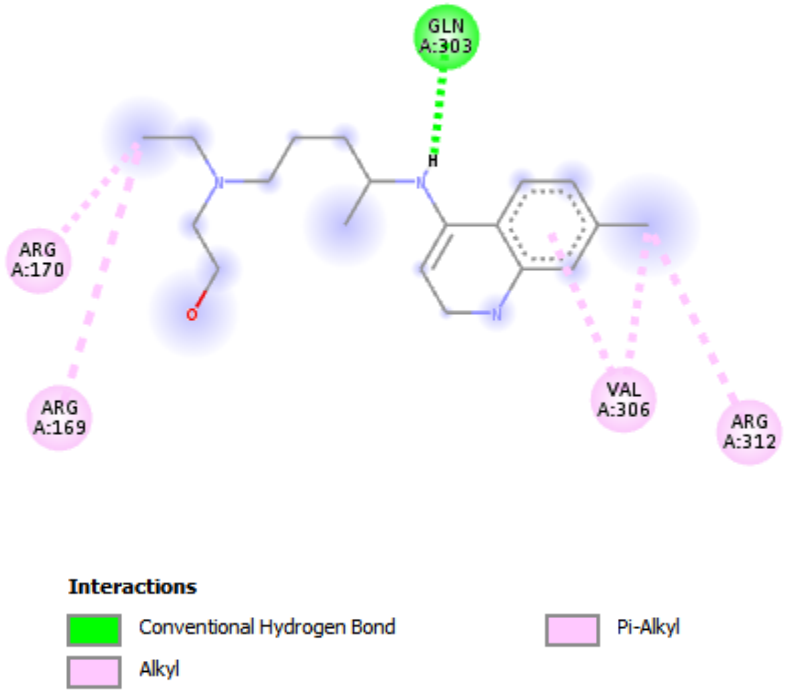
Serum ALT level, serum AST (aspartate transaminase) level, and their ratio (AST/ALT ratio) are commonly measured clinically as biomarkers for liver health.

Hydroxychloroquine

Pose	Binding Affinity (kcal/mol)
1	-5.9
2	-5.8
3	-5.8
4	-5.5
5	-5.5
6	-5.4
7	-5.4
8	-5.3
9	-5.3



The interactions formed by Hydroxychloroquine Pose-1 (yellow) with ALT (dark)



The interactions formed by Hydroxychloroquine Pose-1 with ALT (2D)

The residues of ALT involved in forming Alkyl interactions

No.	Residue	Distance (Å)
1	ARG170	4.60

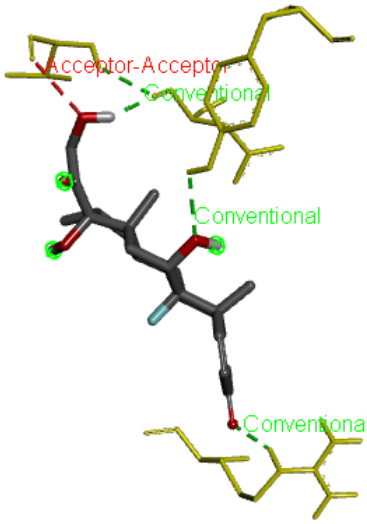
2	ARG169	4.65
3	VAL306	4.93
5	VAL306 (pi-Alkyl)	4.35
4	ARG312	4.79

The residues of ALT involved in forming hydrogen bonding interactions

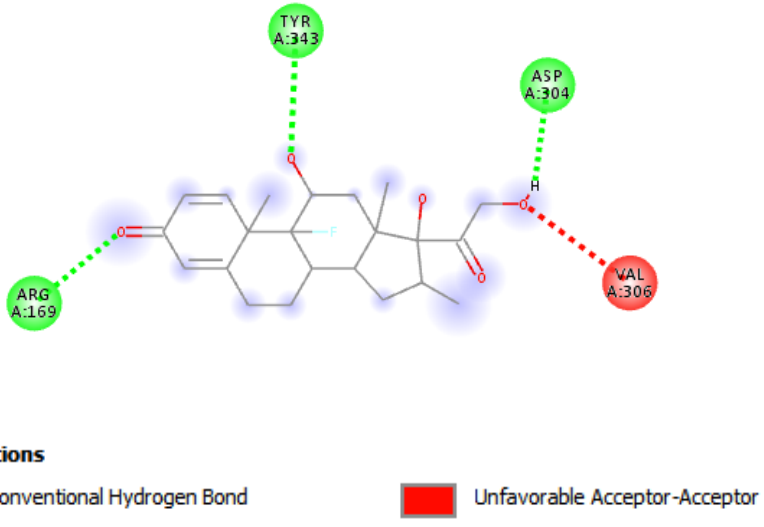
No.	**Residue**	**Distance (Å)**
1	GLN303	1.85

Dexamethasone

Pose	**Binding Affinity (kcal/mol)**
1	-8
2	-7.5
3	-7.5
4	-7
5	-7
6	-6.9
7	-6.8
8	-6.8
9	-6.7



The hydrogen bonding and acceptor -acceptor interactions formed by Dexamethasone Pose-1 (dark) with ALT (yellow)



The interactions formed by Dexamethasone Pose-1 with ALT (2D)

The residues of ALT involved in forming hydrogen-bonding interactions

No.	Residue	Distance (Å)
1	ASP304	1.83
2	ARG169	2.25
3	TYR343	2.62

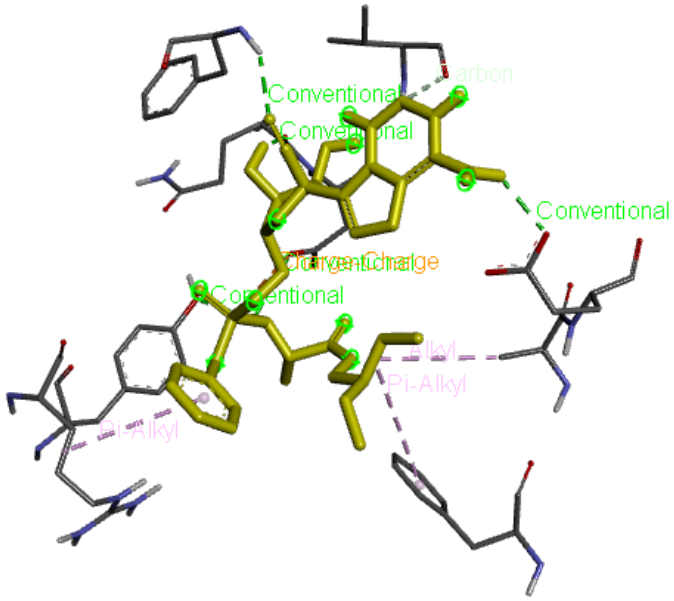
The residues of ALT involved in forming unfavourable acceptor-acceptor interactions

No.	Residue	Distance (Å)
1	VAL306	2.85

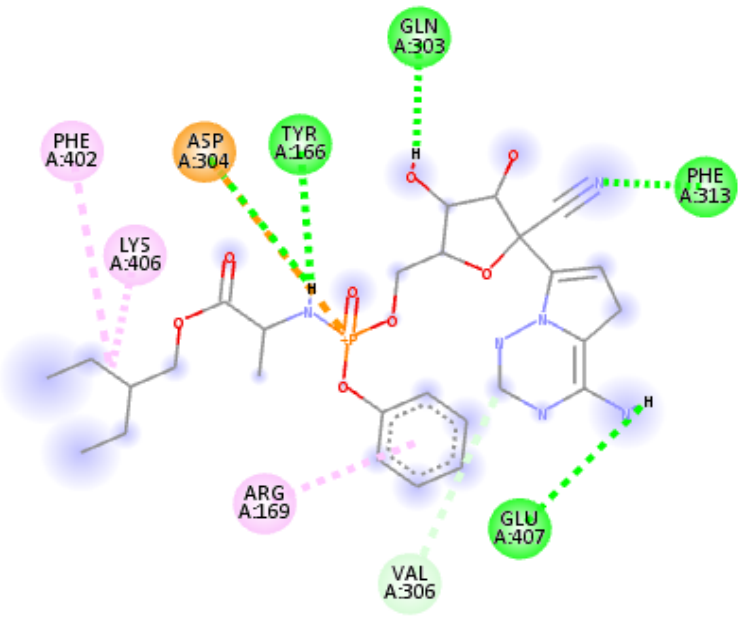
Remdesivir

Poses	Binding Affinity
1	-7.5
2	-7.3
3	-7.1
4	-6.7

5	-6.4
6	-6.4
7	-6.4
8	-6.3
9	-6.3



The interactions formed by remdesivir Pose-1 with ALT



The interactions formed by remdesivir Pose-1 with ALT (2D)

The residues of ALT involved in forming hydrogen-bonding interactions

No.	Residue	Distance (Å)
1	VAL306 (carbon H bond)	3.29
2	GLU407	2.36
3	PHE313	2.53
4	GLN303	2.17
5	TYR166	2.52
6	ASP304	2.76

The residues of ALT involved in forming electrostatic interactions

No.	Residue	Distance (Å)
1	ASP304	4.20

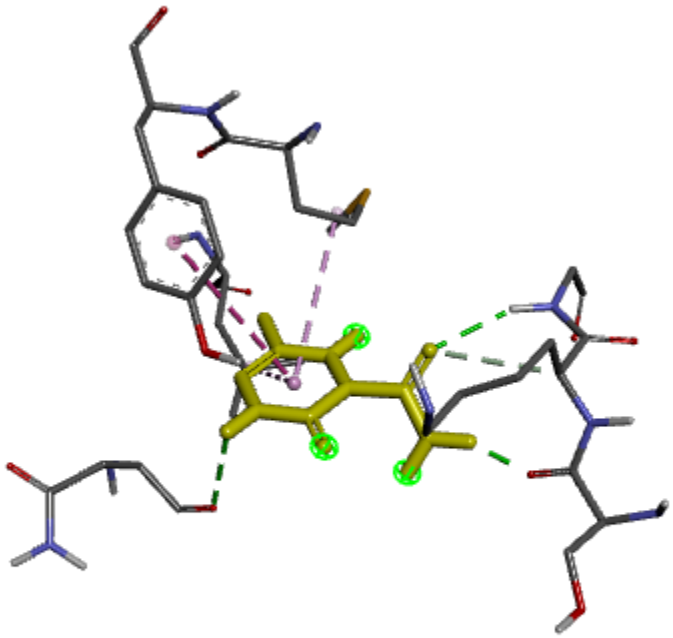
The residues of ALT involved in forming alkyl interactions

No.	Residue	Distance (Å)
1	ARG169	4.91
2	LYS406	4.55
3	PHE402	5.41

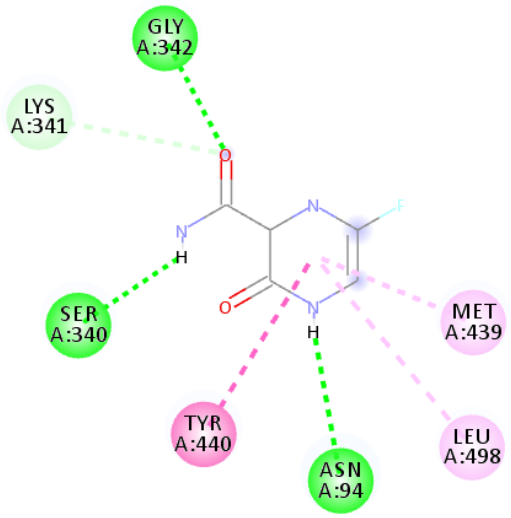
Favipiravir

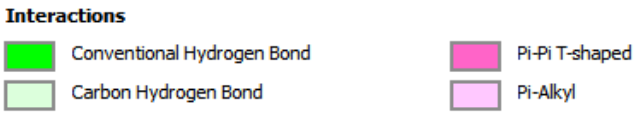
Poses	Binding Affinity
1	-5.2
2	-5.1
3	-4.9
4	-4.9
5	-4.8
6	-4.8
7	-4.6

8	-4.5
9	-4.5



The interactions formed by favipiravir Pose-1 with ALT





The interactions formed by favipiravir Pose-1 with ALT (2D)

The residues of ALT involved in forming hydrogen-bonding interactions

No.	Residue	Distance (Å)
1	GLY342	2.35
2	LYS341 (Carbon H bond)	3.53
3	SER340	1.84
4	ASN94	2.90

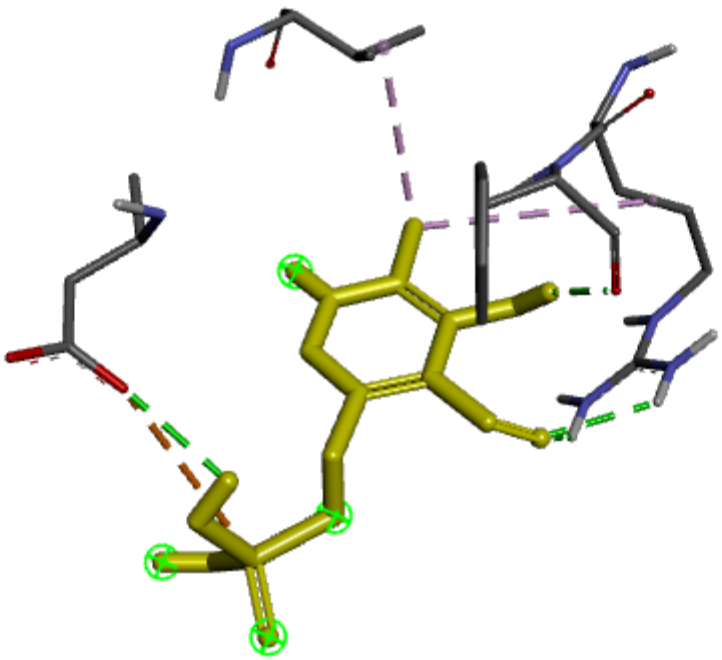
The residues of ALT involved in forming Alkyl interactions

No.	Residue	Distance (Å)
1	TYR440 (pi-pi)	5.40
2	LEU498 (pi-alkyl)	5.06
3	MET439 (pi-alkyl)	4.82

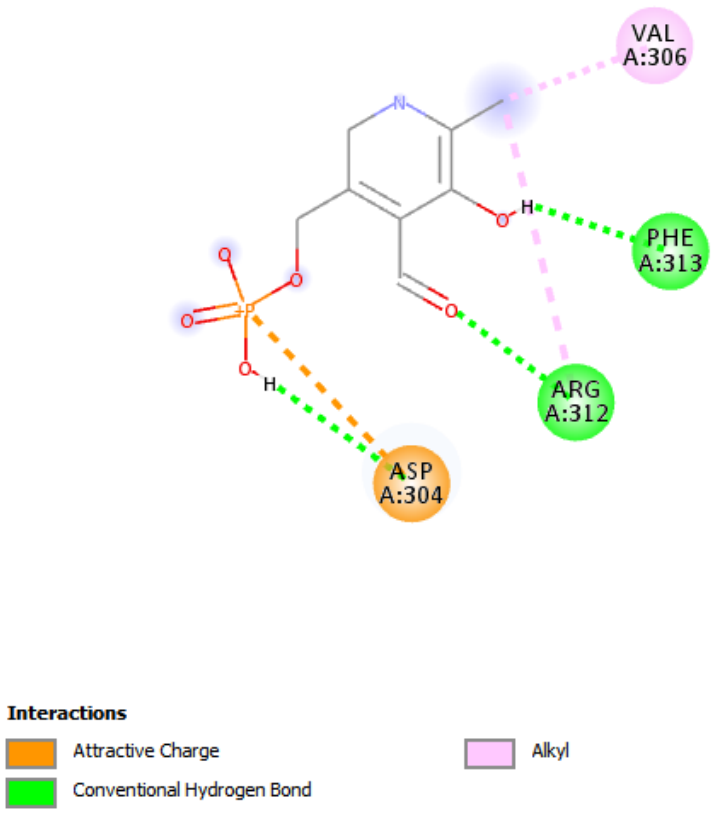
Pyridoxal phosphate - PLP - natural substrate

Poses	Binding Affinity
1	-5.5
2	-5.4
3	-5.3
4	-5.2

5	-5
6	-4.9
7	-4.9
8	-4.9
9	-4.9



The interactions formed by PLP Pose-1 with ALT



The interactions formed by PLP Pose-1 with ALT in 2D

The residues of ALT involved in forming hydrogen-bonding interactions

No.	Residue	Distance (Å)
1	ARG312	2.25, 2.48
2	PHE313	2.00
3	ASP304	2.57

The residues of ALT involved in forming Alkyl interactions

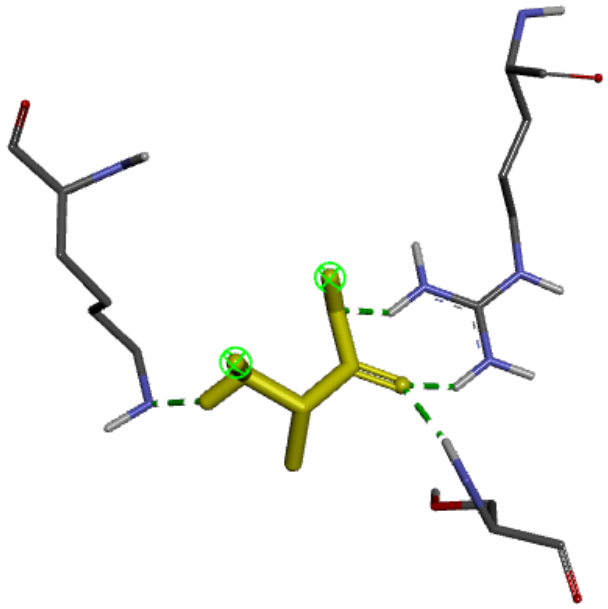
No.	Residue	Distance (Å)
1	VAL306	3.83
	ARG313	4.83

The residues of ALT involved in forming electrostatic interactions

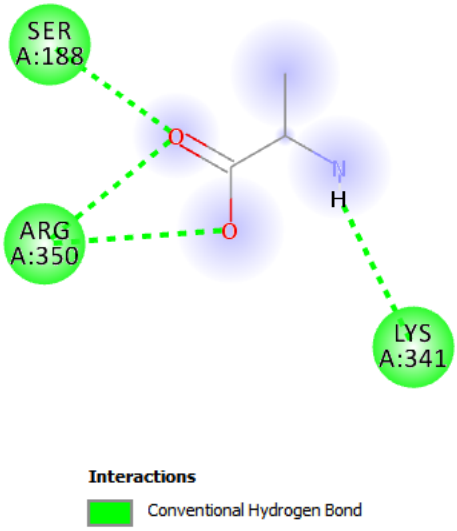
No.	Residue	Distance (Å)
1	ASP304	4.35

L - alanine - natural substrate

Pose	Binding Affinity
1	-4.1
2	-3.8
3	-3.8
4	-3.7
5	-3.7
6	-3.6
7	-3.6
8	-3.5
9	-3.5



The interactions formed by L-alanine Pose-1 with ALT



The interactions formed by L-alanine Pose-1 with ALT in 2D

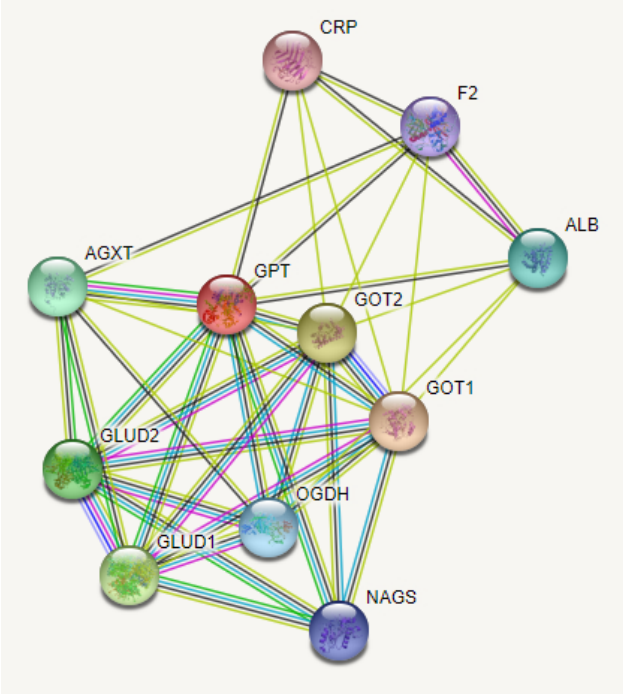
The residues of ALT involved in forming hydrogen-bonding interactions

No.	Residue	Distance (Å)
1	SER188	2.04
2	ARG350	2.18, 2.32
3	LYS341	2.16

ANALYSIS

Residues binding to natural substrates	Residues binding to Hydroxychloroquine	Residues binding to Remdesivir	Residues binding to Dexamethasone	Residues binding to Favipiravir
SER188	ARG170	ARG169	ARG169	GLY342
ARG350	ARG169	GLU407	TYR343	SER340
LYS341	GLN303	TYR166		**LYS341**
ARG312	**ARG312**	GLN303		ASN94
PHE313		**PHE313**		TYR440 (pi-pi)
ASP304		**ASP304**	**ASP304**	LEU498 (pi-alkyl)
VAL306	**VAL306**	**VAL306**	**VAL306**	MET439 (pi-alkyl)
ARG313		LYS406		
		PHE402		

ASSOCIATION NETWORK OF ALT



(GPT = ALT here)

REMARKS

We see that the amino acid residues of LYS341, ARG312, PHE313, ASP304 and VAL306 are used in the binding of both the natural substrates as well as the drugs. Thus, binding of the drug can lead to a compromise of the activity of the enzyme.

Among the drugs, dexamethasone has the lowest binding affinity, forming the strongest interaction.

Softwares and servers used:

1. AutoDock Vina
2. PyRx
3. String
4. Discovery studio
5. AutoDock Tools