Targeting KRAS^{G12C}: Repurposing of Potential Therapeutics for the Treatment of Pancreatic Ductal Adenocarcinoma (PDAC)

Final Publication Number: 440P

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BACKGROUND

- PDAC accounts for over 90% of all pancreatic malignancies.
- It is the fourth most frequent cause of cancer-related mortalities.
- Main molecular trait of PDAC is the activation of MAPK pathway caused by KRAS mutation.
- Development of drug resistance is the key factor for the failure of existing PDAC therapy. Therefore, novel therapeutic approaches are necessary for the treatment of PDAC.
- In this study, the KRAS^{G12C} protein structure has been utilized to identify a drug candidate which might be repurposed for the potential treatment of PDAC.

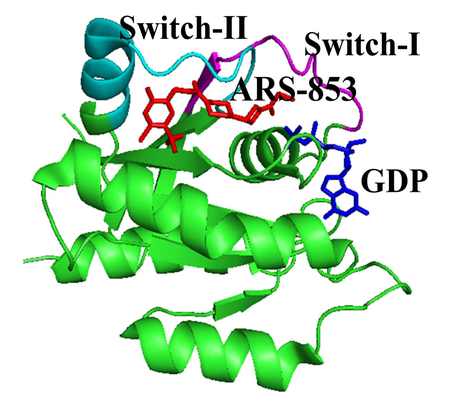


Figure 1. Structure of mutated KRAS^{G12C} (PDB ID:5F2E)

METHOD

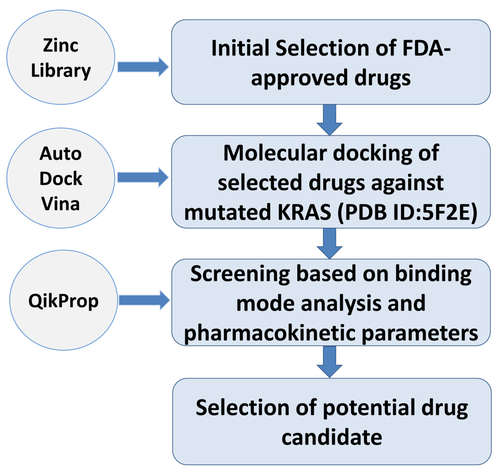


Figure 2: Screening Process

RESULTS

Molecular Docking Results

Table 1. Binding affinity values of the known inhibitor and proposed candidate with mutated KRAS

Drugs	Binding affinity (kcal/mol)
Co-crystallized Ligand (ARS-853)	-7.1
Adagrasib (FDA-approved inhibitor of KRAS^{G12C})	-10.0
Apalutamide (Androgen receptor antagonist)	-10.4

- The surface structure shows how Adagrasib (red) and Apalutamide (blue) fit into the binding pocket adjacent to Switch-II of the mutated KRAS protein.

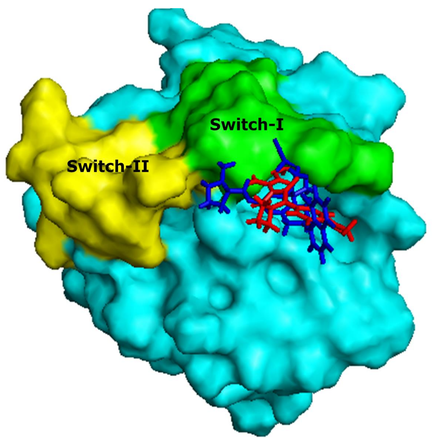
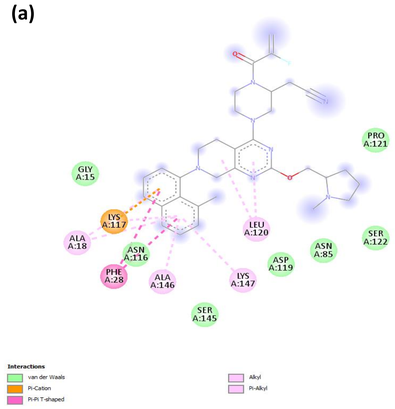


Figure 3. Binding pockets of Adagrasib (red) and Apalutamide (blue) in mutated KRAS (PDB ID: 5F2E)

Table 2. Binding interactions between the drugs and mutated KRAS

	Types of Bonds	Residue in Contact
Adagrasib	Electrostatic and others	LYS117
	Hydrophobic bond	PHE28,LEU120,ALA18,LYS117, ALA146,LYS147
Apalutamide	Types of Bonds	Residue in Contact
	Hydrogen bond	ASN116,SER145,ALA146,LYS147, GLY15,LYS117
	Halogen bond	ASP119
	Hydrophobic bond	PHE28,LYS117,LEU120,ALA18, ALA146
	Electrostatic and others	LYS117,PHE28

(a)



(b)

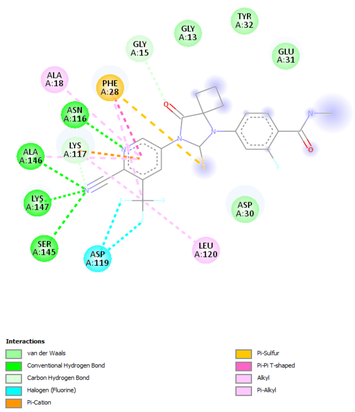
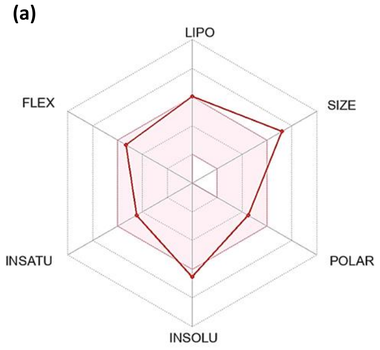


Figure 4. Ligplots showing the interactions of (a) Adagrasib, (b) Apalutamide with mutated KRAS^{G12C} (PDB ID:5F2E)

Predictions of Pharmacokinetic Parameters (ADME Profile)

(a)



(b)

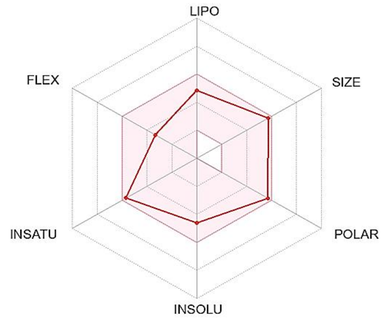


Figure 5. Schematic representation of the ADME properties of (a) Adagrasib, (b) Apalutamide

Apalutamide exhibits acceptable ADME properties.

- Based on the calculation of ADME parameters by QikProp, Adagrasib is poorly soluble and Apalutamide is moderately soluble, which is consistent with their actual solubility.
- Apalutamide has excellent GI absorption and intestinal permeability, compared to the known inhibitor.
- Apalutamide does not penetrate the CNS or the blood brain barrier as suggested by the CNS, logBB and PSA values.

CONCLUSION

- Apalutamide shows comparable binding affinity to Adagrasib.
- Apalutamide exhibits good binding interactions in the same pocket in KRAS^{G12C} as Adagrasib which might lock the protein in an inactive GDP-bound state.
- Apalutamide has acceptable ADME properties.

FUTURE WORK

- *In vitro* biological evaluation of Apalutamide against KRAS^{G12C} can be done to confirm the molecular docking results. *e.g.*, investigation of IC_{50} values and GI_{50} values in pancreatic cancer cell lines.
- Molecular dynamic simulation of Apalutamide in KRAS^{G12C} can be conducted to further investigate their interactions.
- Apalutamide can be loaded in nanocarriers for targeted cancer therapy.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest

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