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IN SILICO DOCKING AND ADMET EVALUATION OF VORASIDENIB DERIVATIVES TARGETING IDH1

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ABSTRACT

Vorasidenib is a drug that blocks mutant isocitrate dehydrogenase enzymes. It is widely used in the treatment of IDH-mutant glioma. Changing its chemical structure can improve its performance. In this study, different derivatives of Vorasidenib were designed and tested using computational methods to identify compounds with stronger binding ability and better pharmacokinetic properties against IDH1. The pkCSM tool was used to study ADMET properties such as absorption, distribution, metabolism, excretion, and toxicity. Molecular docking was carried out using PyRx to examine how these derivatives interact with the target protein. The results showed that many derivatives formed strong interactions with the protein. Some compounds even showed similar or better binding affinity than the original drug. Cyclopropane - substituted analogue showed more stable interactions, which suggests that they may be useful as lead compounds for future drug development. The ADMET analysis showed that most of the compounds had good oral absorption, proper permeability, balanced distribution in the body, and acceptable toxicity levels. A few compounds showed concerns such as mutagenicity or weaker pharmacokinetic behavior. This study identified several promising Vorasidenib derivatives with improved therapeutic potential. The findings provide support for future laboratory studies and further research on optimized Vorasidenib analogues for glioma treatment.

KEYWORDS: In silico study, Molecular docking, ADMET prediction, Drug design, Glioma, Derivative analysis.

INTRODUCTION

Gliomas are tumors that come from the central nervous system's supporting glial cells. These tumors originate from astrocytic, oligodendroglial, mixed oligoastrocytic, or neuronal-glial cells. The World Health Organization (WHO) classifies gliomas from grade 1, the lowest grade, to grade 4, the highest grade, based on features like cytological atypia, anaplasia, mitotic activity, microvascular proliferation, and necrosis. The two types of low-grade gliomas (LGGs) are grade I tumors, which do not show any of the characteristics mentioned, and grade II tumors, which show only cytologic atypia.[1] In the United States, more than 66,000 people were diagnosed with brain and central nervous system cancers in 2012. Gliomas made up almost 20,000 cases, or 30% of the total. They account for 32% of these tumors in young adults aged 20 to 34. About 28% of these are glioblastomas, and 17% are astrocytic tumor.[2&3] Because the data does not separate low-grade from high-grade tumors, it's hard to know the annual number of low-grade gliomas. Additionally, white people are more than twice as likely as black people to develop certain types of gliomas.[2] As a result, there is a need for better treatment options.

Vorasidenib

Vorasidenib simple overview is shown in Fig 1 -

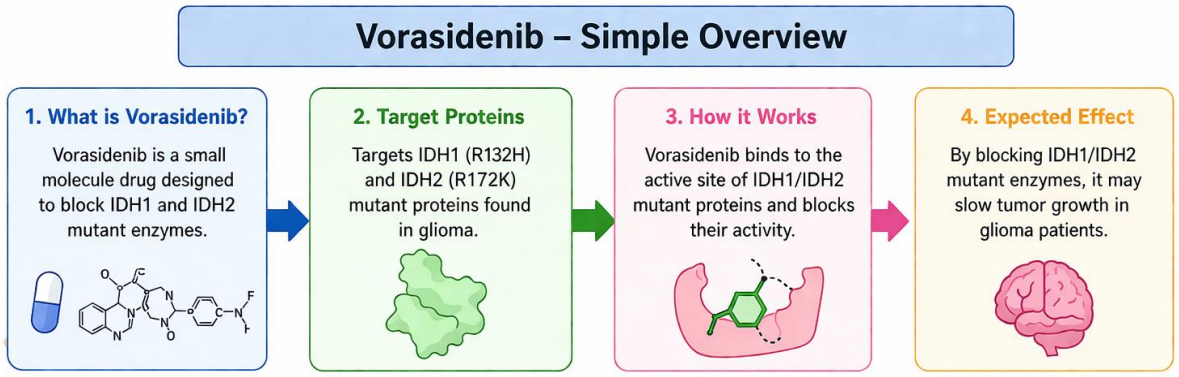


Fig. 1: Vorasidenib –Simple Overview.

The first medicine that stops both IDH1 and IDH2 enzymes from working is vorasidenib.[4] This medicine has a shape that helps it get into the brain better. It can cross the barrier that protects the brain from substances. This is good for treating brain tumors.

Research showed that vorasidenib gets into the brain easily. It also slows down tumor growth in glioma models that have IDH mutations.[5-6]

Mechanism of Action

The medicine vorasidenib gets into the brain. Stops the mutant IDH1 and IDH2 enzymes that help low-grade glioma tumors grow. By various phases its efficiency can be checked.[7] When these mutant enzymes are working they make a thing called 2-hydroxyglutarate that builds up in tumor cells. This bad thing messes with the way cells are made and how they work, which makes tumors grow faster. Vorasidenib stops the IDH1 and IDH2 enzymes from making 2-hydroxyglutarate.[8] It does this by binding to these enzymes and changing their shape so they cannot work. By making cells work normally Vorasidenib helps stop tumors from growing and spreading.[9-10] Vorasidenib is a promising treatment, for IDH-mutant gliomas because it goes after the reason tumors grow in the first place.[11-12] To make Vorasidenib work better and be safer we need to look at its derivatives. This means we need to see if we can change Vorasidenib to make it get into the brain better work better and have side effects. Looking at Vorasidenib derivatives can also help us find medicines that work better for IDH-mutant gliomas.

Pharmacokinetic

After taking vorasidenib by mouth it gets absorbed well into the body. The amount of vorasidenib in the blood increases as the dose gets higher. This happens when the dose ranges from 10 to 200 mg. At the dose of 200 mg the peak level of vorasidenib in the blood plasma is 133ng/mL. The highest concentration happens about two hours after taking the dose. Vorasidenib is available in a form that can be taken by mouth and has 34% bioavailability. It takes 28 days of taking vorasidenib every day to reach steady-state levels in the body. You can take vorasidenib with or without food. However eating food, high-fat meals helps the body absorb vorasidenib better.[13] Vorasidenib spreads out a lot in the body because it has a volume of distribution.97% Of vorasidenib binds to plasma proteins in the blood. It also gets into the brain easily which is important, for treating brain cancers. The body mainly uses CYP1A2 enzymes to process vorasidenib. Mostly vorasidenib gets eliminated in the feces. The effect of vorasidenib lasts for a time about 10 days because of its long half-life by inhiniting IDH 1/IDH2.[13-14]

Adverse effect

Although vorasidenib has some treatment-related side effects it is generally well tolerated in people with IDH- low-grade glioma.[14-16] The common side effects are fatigue, headaches, diarrhea, nausea and increased liver enzymes like AST and ALT. Some patients have reported liver problems, which can be serious. This might require stopping treatment reducing the dose or taking a break. Other common side effects include musculoskeletal pain and seizures. Vorasidenib seems to have a safety profile but it is essential to closely monitor liver function during treatment to minimize potential harm.[15] The liver function of patients, on vorasidenib should be watched closely to avoid any complications. Vorasidenib is a treatment option. Its side effects need to be managed properly.[16]

Treatment

After surgery like when they do a biopsy or remove part of the tumor vorasidenib is used to treat a type of brain cancer called grade 2 astrocytoma or oligodendroglioma in adults and kids who're 12 years old or older. This cancer has something called IDH1 or IDH2 mutations.[17-18] Vorasidenib is a medicine that you take by mouth. It works by stopping the enzymes that make a substance that helps the tumor grow. You take vorasidenib as 40 milligrams a day. When they compared vorasidenib to a treatment they found out that vorasidenib helps people live longer without their cancer getting worse. It also helps people wait longer before they need treatments like radiation or chemotherapy. This is what they learned from a study called the INDIGO trial.[18-19] Vorasidenib is an important treatment that doctors can use after surgery for people with brain cancer that has IDH mutations. It helps slow down the cancer. Reduces the bad side effects that people can get from other treatments.[19] This is especially good, for people who still have cancer left after surgery or whose cancer has come back.

MATERIALS AND METHODS

In Silico study of Vorasidenib as dual inhibitor of IDH1/IDH2 IN Glioma is shown in Fig 2

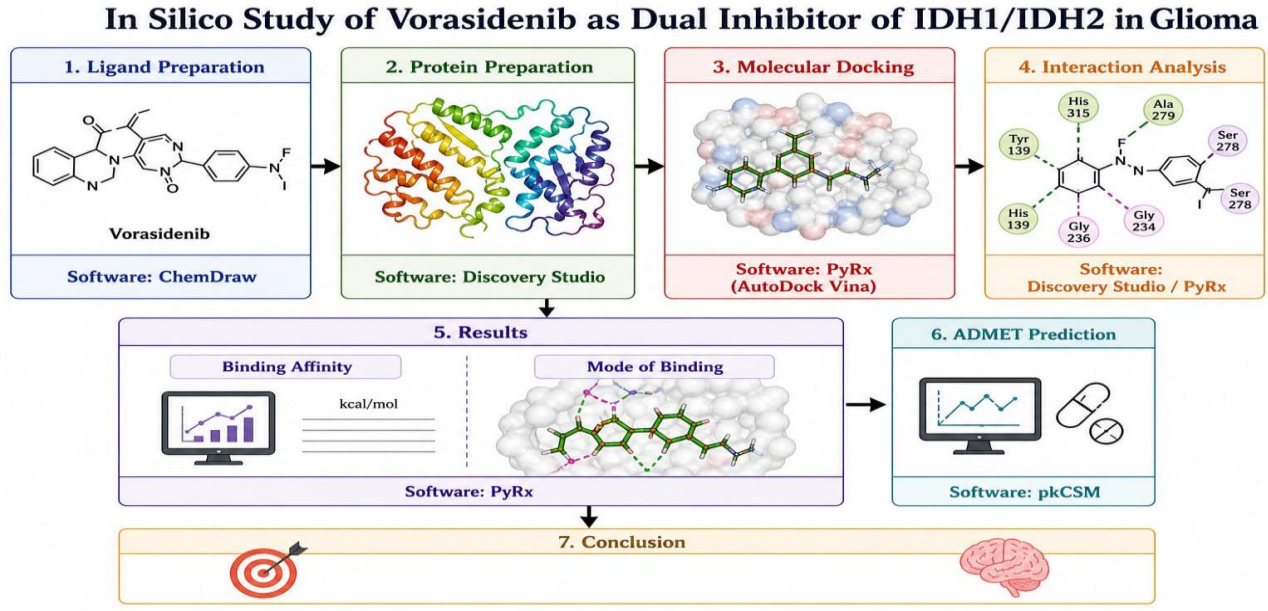


Fig. 2: In Silico Study of Vorasidenib as dual inhibitor of IDH1/IDH2 in Glioma.

Using the pkCSM tool we checked how vorasidenib behaves in the body and its potential toxicity[20] then determine ADMET parameters, which are required for understanding how the drug works in humans.[21] The ability of vorasidenib to get into the bloodstream was determined by checking its absorption characteristics, such as: How it gets absorbed in the intestine, how easily it passes through the skin, how soluble it is in water, it also passes through Caco-2 cells. To understand how vorasidenib distributed throughout the body we examined by distribution parameters like: BBB permeability, Central nervous system permeability, Fraction unbound in plasma, Volume of distribution. We also check how vorasidenib interacts with cytochrome P450 enzymes which is important for breaking down drugs. We checked its substrate or inhibitory activity to enzymes like CYP3A4, Inhibitory activity towards CYP2D6, inhibitory activity toward enzymes like CYP1A2, Substrate or inhibitory activity toward enzymes like CYP2C9. The elimination profile of vorasidenib was assessed using parameters related to excretion such as: clearance, Renal OCT2 substrate status. We also evaluated the toxicology of vorasidenib by predicting: Hepatotoxicity, AMES mutagenicity, Minnow toxicity. The highest dose that humans could tolerate. These parameters help reveal the safety profile of the drug candidate, vorasidenib.[21] We used PyRx for molecular docking studies to examine how vorasidenib binds to the target protein.[22] We get the vorasidenib structure into the program. We loaded the macromolecular target. We set

up a grid box, around the site to ensure precise docking. We ran the docking simulation. Got the binding affinities and interaction poses. We exported the outcomes for further interpretation.[23]

RESULT AND DISCUSSION

1) Absorption

The pkCSM software was used to study derivatives has good oral absorption .how absorption of vorasidenib and its derivatives takes place .Result shows most of Vorasidenib derivatives has good oral absorption. Vorasidenib itself has intestinal absorption 83-89 %. When compared with its derivatives, cyclopropyl analogue have strong intestinal absorption. It shows that modified compound enter effectively after oral intake. Some Cyclopropyl-substituted analogue has better Caco2 permeability means it can pass through intestinal cells more than Vorasidenib. Acetyl analogue showed slightly better solubility but overall water solubility remain low, as same as Vorasidenib. As drug does not dissolve easily in water, food intake affect how well it is absorbed and inhibit IDH1&2.[24]

2) Distribution

When compound bind to plasma protein at moderate level, it travel in blood effectively. Distribution studies shows that how drug reaches to body tissue easily. Vorasidenib is specially designed to cross BBB. because it’s necessary for treating brain tumors such as gliomas. Among all evaluated compounds, cyclopropane substituted derivative has most balanced distribution profile with excellent BBB penetration, moderate plasma protein binding and efficient systemic circulation. Which indicates these compounds acts on target so well. Prediction also suggest that cyclopropane analogue effectively reach in Nervous system without building up too much in brain required for safety. Vorasidenib is known to reduce 2-hydroxyglutarate level, that makes it effective for glioma treatment.[25] Therefore cyclopropyl -substituted analogue is most promising derivative of brain tumor targeting.

3) Metabolism

Most of the derivatives shows stable interaction with enzyme. Cyclopropane substituted derivatives has better compatibility with CYP450 enzyme, which makes them more suitable for body normal metabolism. On other hand tert-butyl analogue cause issue with CYP450 enzyme as it is bulky which makes it less suitable for long-term drug use. Vorasidenib mainly processed in liver and in some cases it affects liver enzyme level therefore doctors need to monitor patient during treatment.[26] Computer based studies suggest that structural changes

in Vorasidenib may improve its effectiveness and make its metabolism more predictable. Computational study shows that Cyclopropane containing derivative has ability to maintain therapeutic effectiveness.

4) Excretion

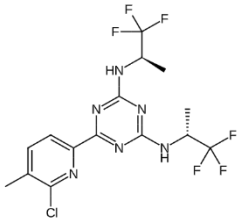
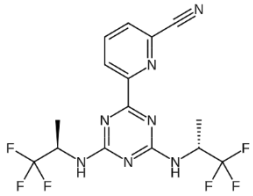
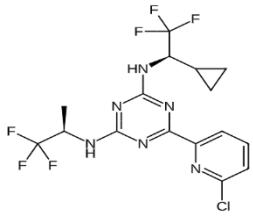
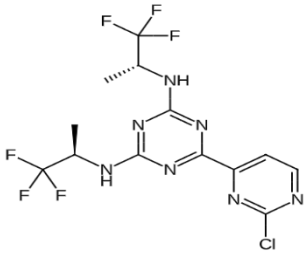
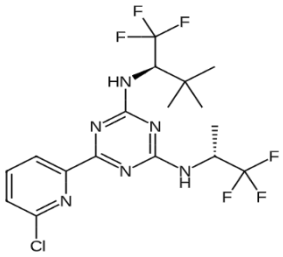
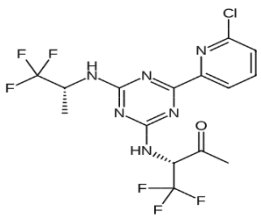
By this study we know that how body removes Vorasidenib and its related compound. The result shows that compounds leave the body in balanced way. This means they do not stay in our body for long time and don't leave too fast. The compounds are not affected by kidney transporters. This suggest some problems in way they are removed from body. Vorasidenib and its derivatives can maintain proper levels in body which helps in giving regular doses. Cyclopropane- substituted analogue has favourable excretion behaviour, which maintain appropriate systemic concentration without rapid elimination. Vorasidenib also has a long half-life and stays steady in blood, therefore it may be taken once a day .It occurs with cyclopropane substituted analogue.

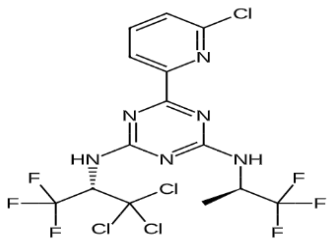
5) Molecular Docking

Molecular docking studies showed that vorasidenib and its derivatives interact strongly with target proteins.[27] The original compound had a binding affinity of -8.0 kcal/mol, while some derivatives such as cyno-substituted derivative has -8.6 Kcal/mol binding affinity and Acetyl, CCL3 -substituted analogue has -8.3kcal/mol. As these derivatives had better binding, some shows weaker ADMET properties. But cyclopropane derivative had a balance between a binding affinity of -8.2 kcal/mol, and good absorption, permeability, and the ability to cross the blood-brain barrier. Its has stable metabolic behaviour, makes it a best compound for further development.

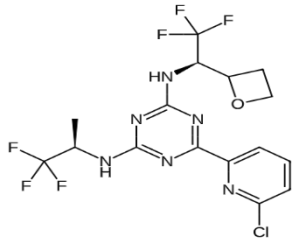
Methyl pyridine analogue, Cyno analogue, Cyclopropane- substituted analogue, Pyrimidine ring analogue, Tert butyl -substituted analogue, Acetyl -substituted analogue, Trichloromethyl-substituted analogue, Oxetane -substituted analogue, Methylthio-substituted analogue Detivatives Designs are shown in following Table 1-

Table 1: Derivatives Design.

1) Methyl pyridine analogue

2)Cyno analogue (CL is replaced by CN)

3)Cyclopropane –substituted analogue (CH3 is replaced by cylcopropyl)

4)Pyrimidine ring analogue (pyridine is replaced by pyrimidine)

5)Tert butyl –Substituted analogue (CH3 is replaced by Tert-butyl)

6)Acetyl –substituted analogue (CH3 replaced by Acetyl)

7)Trichloromethyl-substituted analogue (CH3 replaced by CCL4)



8) Oxetane-substituted analogue(CH3 replaced by Oxetane)



9)Methylthio-substituted analogue (CH3 replaced BY S-CH3)

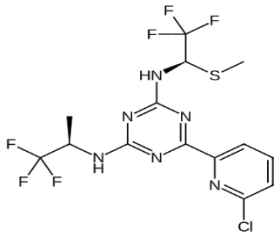


Table 2: Absorption study of designed compounds.

Property		Standard drug: Vorasidenib	1	2	3	4	5	6	7	8	9
Absorption	Water solubility	-6.147	-6.342	-5.92	-6.123	-5.636	-6.502	-5.664	-6.59	-5.529	-6.217
Absorption	Caco2 permeability	0.588	0.603	0.388	0.582	1.331	0.568	0.426	0.509	0.548	0.558
Absorption	Intestinal absorption (human)	87.725	87.186	83.815	87.903	88.054	86.87	87.623	84.04	88.71	86.83
Absorption	Skin Permeability	-3.141	-3.162	-3.138	-3.129	-3.081	-3.1	-3.036	-2.82	-3.025	-3.09
Absorption	P-glycoprotein substrate	No	No	No	No	No	No	No	No	No	No
Absorption	P-glycoprotein I inhibitor	No	No	No	No	No	No	No	No	No	No
Absorption	P-glycoprotein II inhibitor	No	No	No	No	No	No	No	No	No	No

Table No. 3: Distribution study of designed compounds.

Property		Standard drug: Vorasidenib	1	2	3	4	5	6	7	8	9
Distribution	VD ss (human)	-0.598	-0.52	-0.737	-0.454	-0.844	-0.532	-0.805	-0.72	-0.586	-0.604
Distribution	Fraction unbound (human)	0.341	0.311	0.354	0.248	0.326	0.197	0.303	0.239	0.311	0.32
Distribution	BBB permeability	-1.666	-1.645	-1.646	-1.62	-1.887	-1.576	-1.897	-2.14	-1.798	-1.854
Distribution	CNS permeability	-3.163	-3.124	-3.194	-3.127	-3.239	-3.03	-3.272	-3.16	-3.316	-3.195

Table no -4 Metabolism study of designed compounds.

Property		Standard drug: Vorasidenib	1	2	3	4	5	6	7	8	9
Metabolism	CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No
Metabolism	CYP3A4 substrate	No	No	No	Yes	No	Yes	Yes	Yes	No	Yes
Metabolism	CYP1A2 inhibitior	Yes	No	No	No	No	No	No	No	No	No
Metabolism	CYP2C19 inhibitior	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes
Metabolism	CYP2C9 inhibitior	No	No	No	Yes	No	Yes	No	No	No	No
Metabolism	CYP2D6 inhibitior	No	No	No	No	No	No	No	No	No	No
Metabolism	CYP3A4 inhibitior	No	No	No	No	No	No	No	No	No	No

Table No. 5: Toxicity study of designed compounds.

Property		Standard drug: Vorasidenib	1	2	3	4	5	6	7	8	9
Toxicity	AMES toxicity	No	No	No	No	No	No	No	No	No	No
Toxicity	Max. tolerated dose (human)	0.288	0.293	0.261	-0.063	0.548	0.058	0.334	0.223	0.112	0.29
Toxicity	hERG I inhibitor	No	No	No	No	No	No	No	No	No	No
Toxicity	hERG II inhibitor	No	No	No	No	No	No	No	No	No	No
Toxicity	Oral Rat Acute Toxicity (LD50)	2.75	2.709	2.568	2.827	2.618	2.784	2.716	2.761	2.851	2.702
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	-0.376	-0.358	-0.328	-0.101	0.963	-0.098	1.073	-0.19	0.767	-0.4
Toxicity	Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Toxicity	Skin Sensitisation	No	No	No	No	No	No	No	No	No	No
Toxicity	T.Pyriformis toxicity	0.343	0.372	0.33	0.388	0.307	0.441	0.309	0.317	0.298	0.334
Toxicity	Minnow toxicity	2.213	2.134	3.069	2.058	2.686	1.944	2.162	1.456	2.241	1.945

Table No. 6: Excretion study of designed compounds.

Property		Standard drug: Vorasidenib	1	2	3	4	5	6	7	8	9
Excretion	Total Clearance	0.205	0.157	-0.511	0.092	0.12	0.227	0.177	0.188	0.357	0.275
Excretion	Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No

Table no -7 Molecular Docking results of designed compounds.

Derivative No.	Binding Affinity
Standard drug: Vorasidenib	-8.1
1	-8.1
2	-8.6
3	-8.2
4	-7.8
5	-8.1
6	-8.3
7	-8.3
8	-8.2
9	-7.8

The docking Poses are given in following Figures

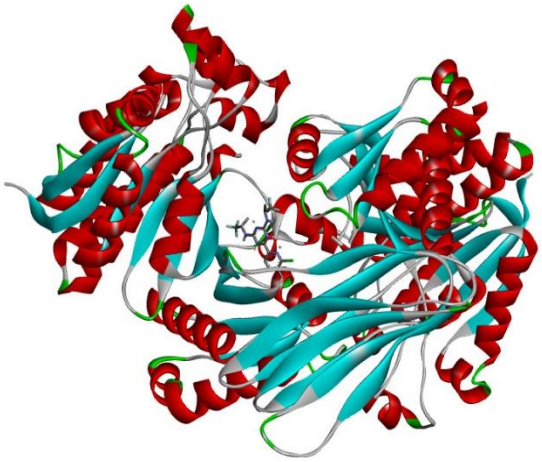


Fig. 3: Methyl pyridine analogue docking pose.

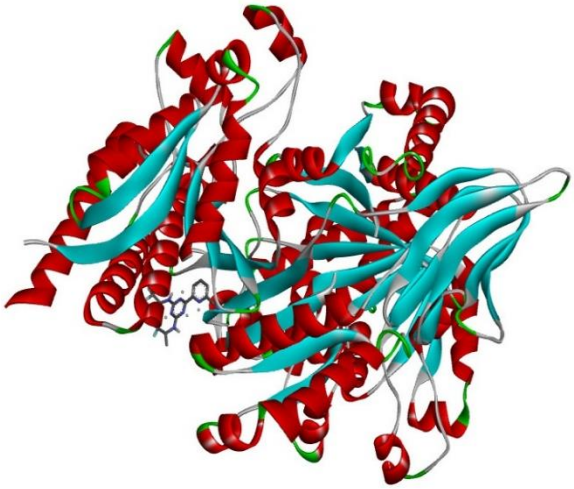


Fig. 4: Cyno analogue docking pose.

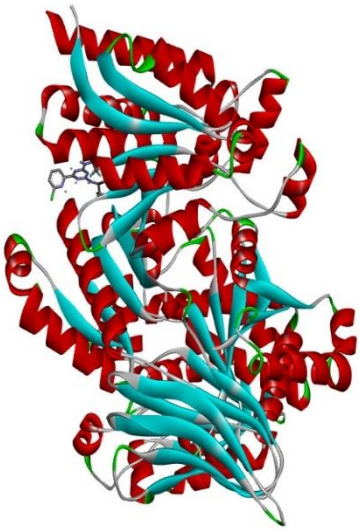


Fig. 5 : Cyclopropane Docking pose.

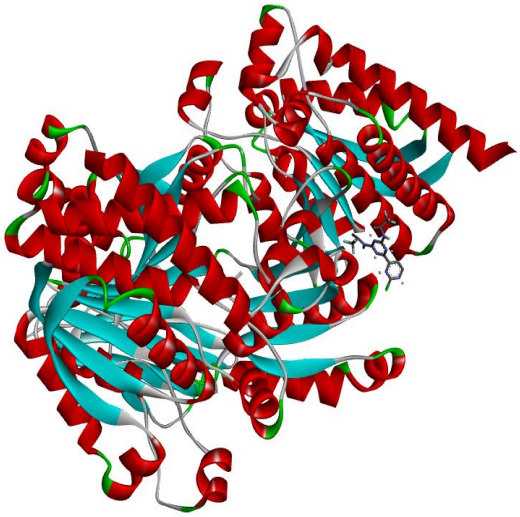


Fig. 6 :Pyrimidine ring analogue docking Pose.

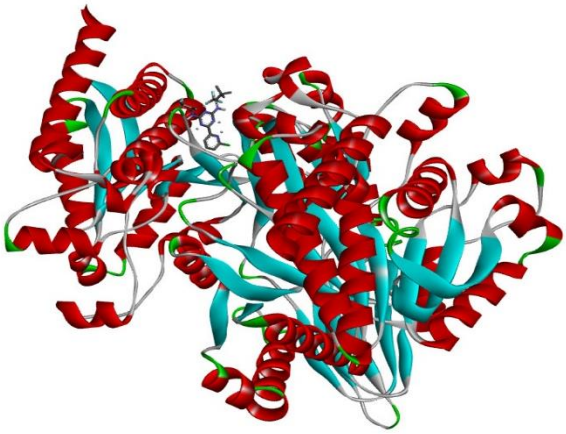


Fig. 7 : Tertbutyl analogue Docking Pose.

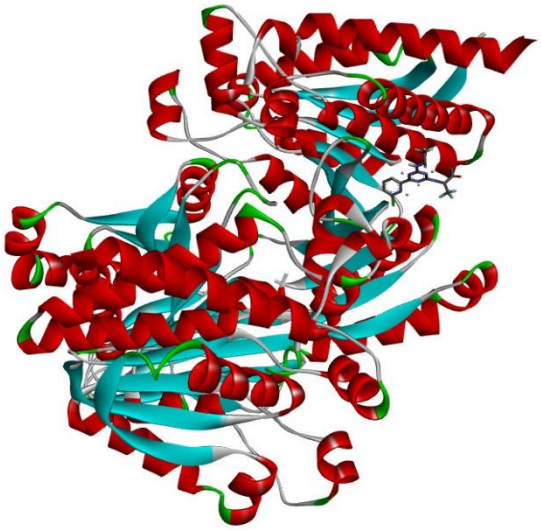


Fig. 8 :Acetyl analogue Docking Pose.

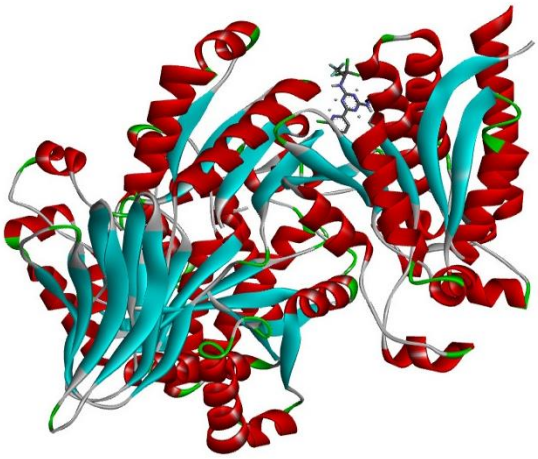


Fig. 9:Trichloromethyl analogue Docking Pose.

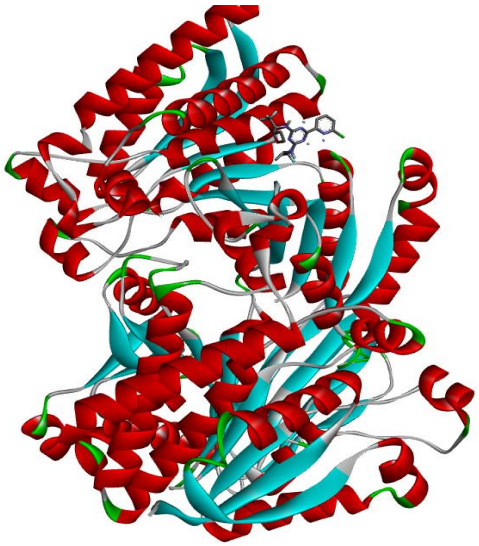


Fig. 10: Oxetane analogue Docking Pose.

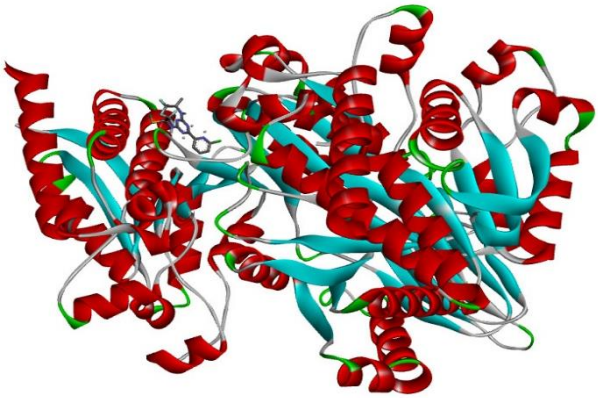


Fig. 11: Methlthio analogue Docking Pose.

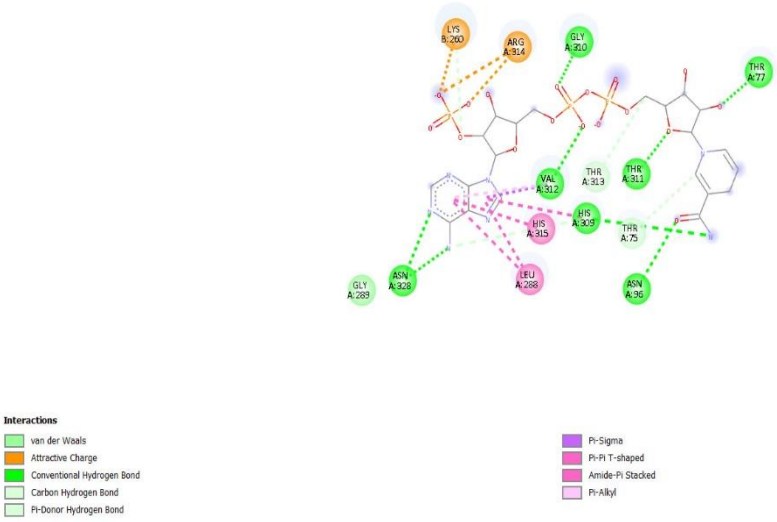


Fig 12: Cyclopropane substituted analogue (Best derivative in 2D Interaction)

CONCLUSION

To find compounds that can be used as medicines we made and tested 9 different versions of Vorasidenib are studied. We used computers to see how well these versions would work and to check if they are safe. The Cyclopropane- substituted derivative worked well. It stuck to the target strongly was absorbed well by the body and did not break down too quickly. It is not too toxic. Some other versions, like the acetyl and tert-butyl versions worked a little better in the computer tests. They had some problems, such as not being soluble enough in water being broken down by the body too quickly or not being balanced in terms of how they were absorbed and removed by the body. They were not good enough to be considered for further testing. Cyclopropane –substituted derivative of Vorasidenib is one to use for more research because it has a good balance of being able to fight the disease and being safe for the

body. We think this version should be tested further in the lab and, in living things to see if it can be used as a medicine.

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Author contributions

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Data availability

Data sharing is not applicable to this article as no new data were created or analyze in this study.

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