Drug Modification

(For melanoma type Skin Cancer)

Objective:

The objective of editing BRAF V600E is to design and optimize a therapeutic agent that specifically targets the mutated protein responsible for driving melanoma progression. This involves enhancing the drug's binding affinity, selectivity, and pharmacokinetic properties to maximize therapeutic efficacy while minimizing off-target effects and toxicity. The ultimate goal is to develop a safe and effective treatment that addresses the challenges of drug resistance and improves clinical outcomes for patients with melanoma harboring the BRAF V600E mutation.

The purpose of editing a drug for the mutated **BRAF V600E protein** in melanoma (a type of skin cancer) is to develop a treatment that specifically targets the abnormal protein responsible for driving cancer growth. Here's a detailed explanation:

Why Target BRAF V600E?

1. Role in Cancer Pathway:

1. The **BRAF V600E mutation** involves a substitution of valine (V) with glutamic acid (E) at position 600 in the BRAF protein.
2. This mutation causes **constitutive activation of the MAPK/ERK signaling pathway**, leading to uncontrolled cell proliferation and survival, which drives melanoma progression.

2. Precision Medicine:

- By editing or designing drugs that specifically target the mutant **BRAF V600E protein**, therapies can effectively inhibit the abnormal signaling without affecting the normal BRAF protein in healthy cells.
- This reduces off-target effects and improves treatment specificity.

Goals of Drug Editing for BRAF V600E:

1.Inhibition of Mutant Protein Activity:

1. The drug should bind to the mutant BRAF V600E protein and inhibit its kinase activity to block the downstream signaling pathways promoting cancer growth.

2.Minimizing Drug Resistance:

1. Mutant melanoma often develops resistance to targeted therapies. Editing drugs to address secondary mutations or combining them with other inhibitors (e.g., MEK inhibitors) can improve long-term effectiveness.

3.Improving Drug Selectivity:

1. Enhance the drug's selectivity for mutant BRAF V600E over the wild-type protein to avoid adverse effects in normal cells.

Clinical Relevance:

- **Current Drugs**: FDA-approved drugs like **vemurafenib** and **dabrafenib** specifically target the BRAF V600E mutation. These drugs have shown significant success in shrinking tumors and extending survival in melanoma patients.
- **Drug Editing Purpose**:
  - Improve potency against the mutant protein.
  - Reduce side effects and toxicity.
  - Overcome resistance mechanisms.

Protein Selection

Use Databases to Identify the Target Protein or Receptor

PDB (Protein Data Bank):

Purpose: PDB provides 3D structural information on proteins, including experimental data from X-ray crystallography, NMR, and cryo-EM studies.

Key Features:

- View and download the 3D structure of proteins for docking studies.
- Explore protein-ligand complexes to analyze existing binding interactions.
- Search for proteins associated with specific diseases or pathways.

How to Use:

- Visit PDB.
- Search using keywords like protein name, PDB ID, or disease (e.g., “HER2 breast cancer”).
- Use the 3D structure visualization tools to inspect binding pockets and active sites.

Output:

- Download the protein structure file in .pdb format for further computational studies.

Target Validation

- **Why Target Validation is Important**

Target validation ensures that the selected protein plays a critical role in the disease or biological pathway under investigation. This step confirms the biological relevance and potential therapeutic impact of modulating the target protein. Several databases can be used to validate your target protein:

1. KEGG (Kyoto Encyclopedia of Genes and Genomes)

•**Purpose**: KEGG is a resource for understanding high-level functions of biological systems, including metabolic and signaling pathways, in a molecular context.

•**How to Use**:
•Visit KEGG.
•Search for the target protein or its encoding gene.
•Analyze pathways where the protein is active (e.g., cancer signaling, metabolic regulation).

2. Reactome

•**Purpose**: Reactome is a curated database that visualizes biological pathways and processes, offering insights into the protein's functional network.

•**How to Use**:
•Visit Reactome.
•Search by the target protein or gene.
•Examine pathways, processes, and molecular interactions involving the target.

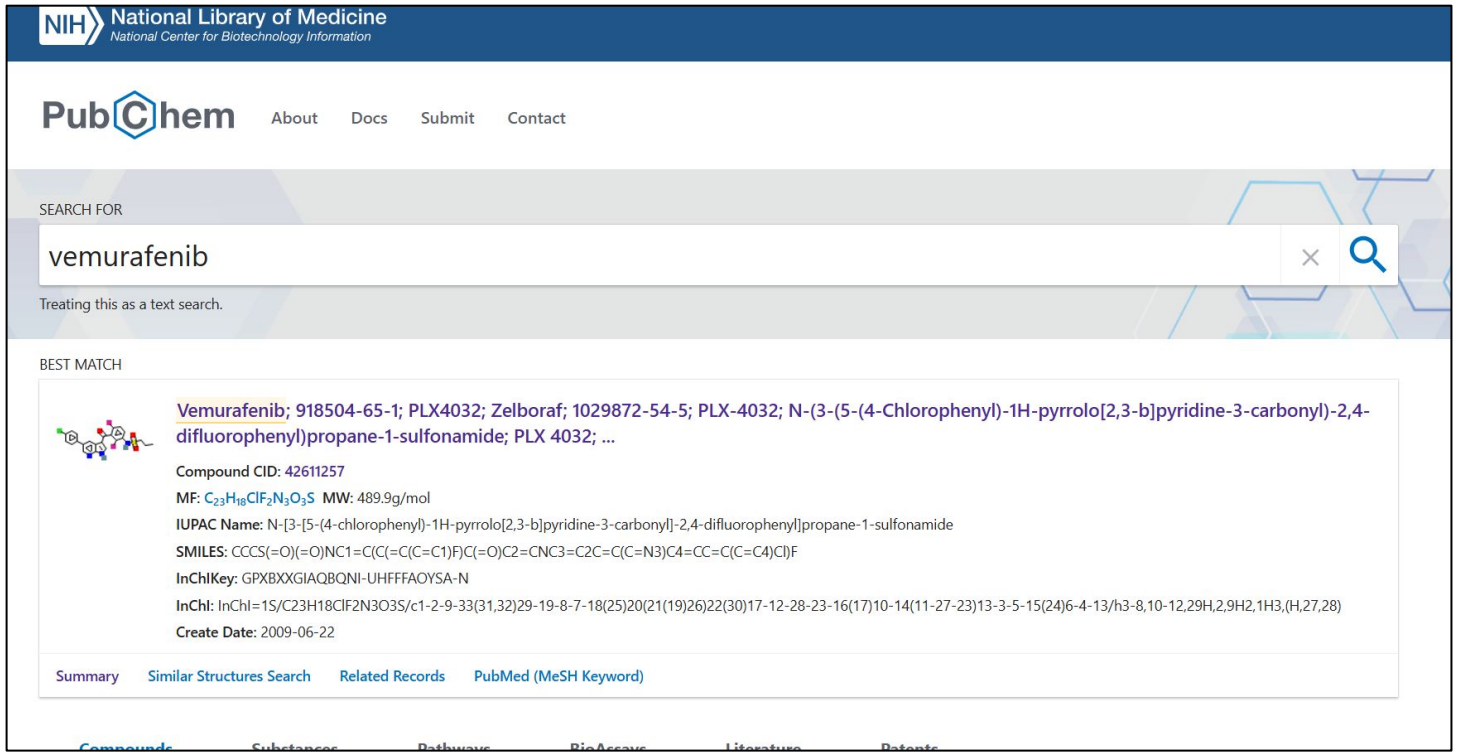
Perform Blind Docking and Analyze Ligand-Target Interaction

Retrieve the Ligand

The first step in blind docking is obtaining potential ligand structures from reliable chemical databases. This is critical to ensure that you are working with high-quality and biologically relevant molecules.

Database for Ligand Retrieval

- **PubChem:**
- **Purpose**: PubChem is a freely accessible database containing detailed information on small molecules, including drugs, metabolites, and bioactive compounds.
- **What to Do**:
    - Search for ligands based on their biological relevance or known interactions with the target protein.
    - Download ligand structures in formats like .sdf which are compatible with molecular docking tools
    - Filter ligands based on molecular weight, drug-likeness, and other physicochemical properties using PubChem's filters.



- We selected 25 ligands from the database based on their potential binding capacity with the target protein.

- **Criteria for Selection**:
  - Ligands with similar biological activity.
  - Known inhibitors or analogs of active molecules.
  - Compounds with high drug-likeness scores or desirable ADMET properties.

Blind Docking

- Use tools like **AutoDock Vina** to perform blind docking, which does not require predefined binding sites.

- **Objective:** Analyze interactions across the entire protein surface to identify potential binding regions.

Interpretation:

1. **Row with Best Binding Energy**:
    1. Row 65 has the most favorable binding affinity (-8.4 kcal/mol), which suggests a strong interaction. However, the associated values (0, 0) for other parameters raise questions about whether this result is valid or if there was an issue in the analysis.
2. **General Trend**:
    1. Most rows have binding affinities ranging from approximately -6.7 to -8.2 kcal/mol, indicating moderate to strong binding interactions for this dataset.
    2. The variance in columns 3 and 4 might reflect different interaction geometries or properties.
3. **Further Investigation**:
    1. Examine Row 65 to determine why the associated parameters are 0. Verify if this result is computationally accurate or if it requires re-evaluation.
    2. Focus on ligands with high binding affinity and reasonable interaction parameters to identify promising candidates.

46	6v34_revis	-7.1	41.596	38.967
47	6v34_revis	-7.7	0	0
48	6v34_revis	-7.4	17.677	15.661
49	6v34_revis	-7	30.51	28.775
50	6v34_revis	-7	31.782	30.164
51	6v34_revis	-6.8	30.95	28.582
52	6v34_revis	-6.7	30.742	28.938
53	6v34_revis	-6.7	23.432	21.421
54	6v34_revis	-6.7	27.35	25.415
55	6v34_revis	-6.7	22.579	20.963
56	6v34_revis	-7.8	0	0
57	6v34_revis	-7.7	41.566	39.027
58	6v34_revis	-7.7	17.102	12.966
59	6v34_revis	-7.5	42.754	39.196
60	6v34_revis	-7.4	34.875	32.09
61	6v34_revis	-7.4	31.992	29.625
62	6v34_revis	-7.3	35.365	32.197
63	6v34_revis	-7.3	34.273	31.632
64	6v34_revis	-7.3	34.159	31.309
65	6v34_revis	-8.4	0	0
66	6v34_revis	-8.2	28.079	24.875
67	6v34_revis	-8.2	4.119	1.417
68	6v34_revis	-8.1	41.715	39.176
69	6v34_revis	-8	40.311	38.64
70	6v34_revis	-8	3.506	2.366
71	6v34_revis	-7.8	3.613	2.604
72	6v34_revis	-7.8	31.384	30.027
73	6v34_revis	-7.7	42.288	39.592
74	6v34_revis	-8.3	0	0

Docking result

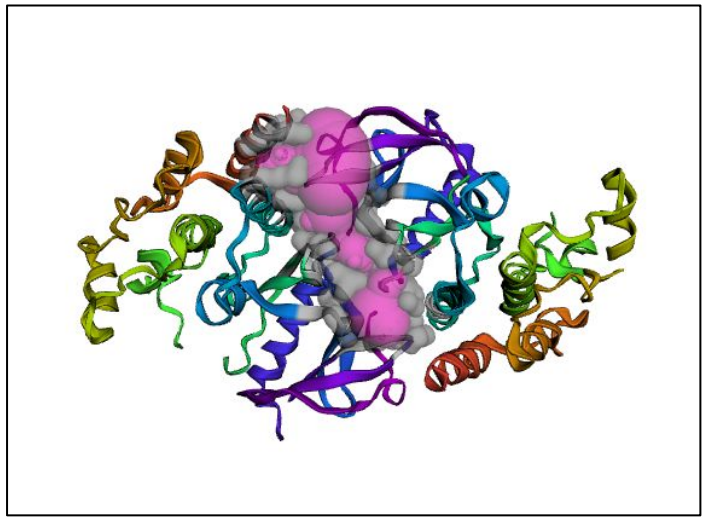
Study Binding Pockets

- **CASTp:** Identifies surface pockets and accessible tunnels in proteins.

Objective:

Evaluate binding affinities and locate critical residues involved in ligand interactions. This will guide the modification of the ligand to target the most promising site.

A larger surface area generally implies a greater number of potential interaction points between the protein and the ligand, and a suitable volume is crucial to ensure that the ligand can fit comfortably within the pocket. Hence, this particular binding pocket was chosen for better results.



Binding site

Pocket Info ⓘ

	Pocket ID	Area (SA) (Å^2)	Volume (SA) (Å^3)
-	1	906.652	765.391

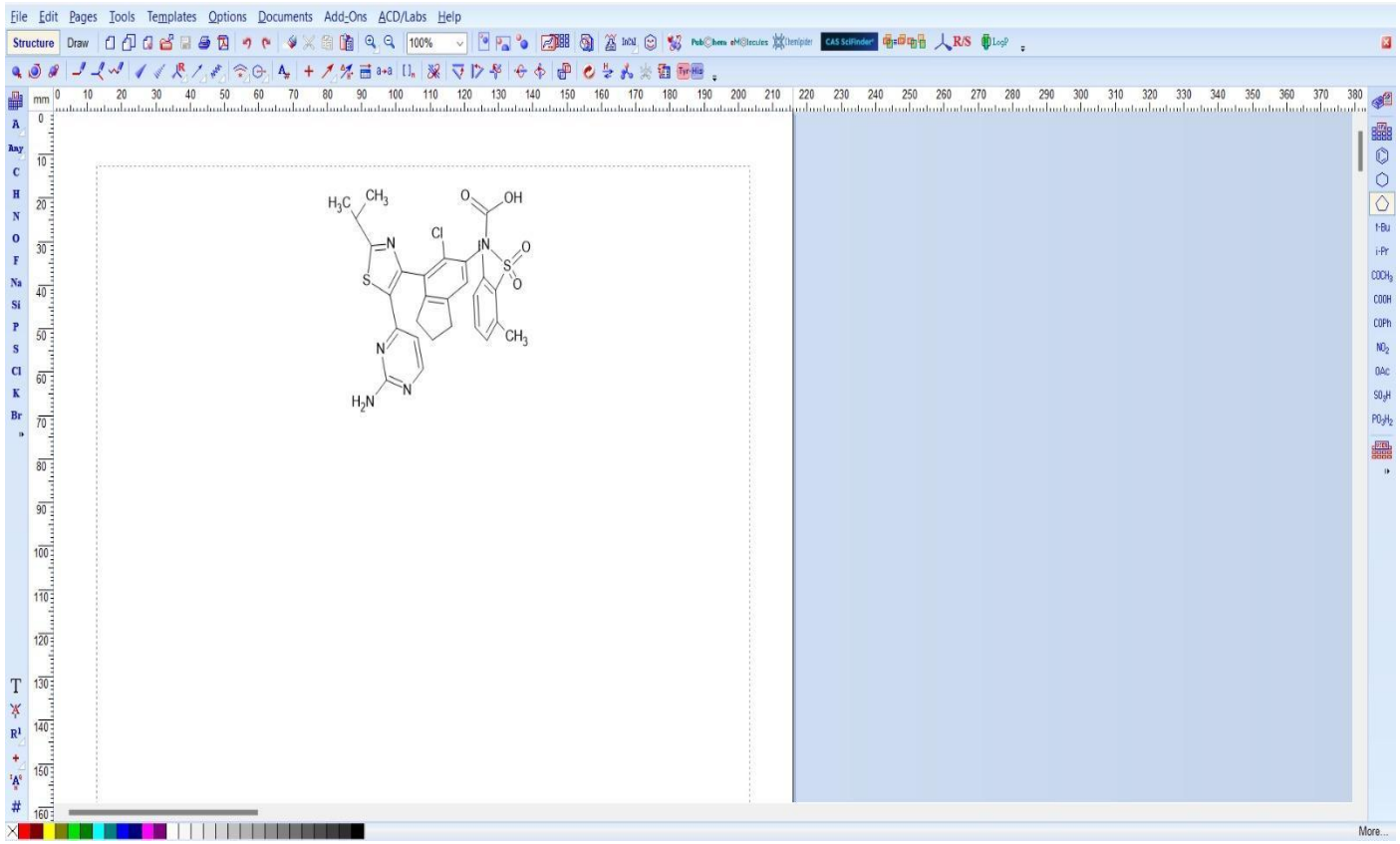
	Ligand	Binding Aff	rmsd/ub	rmsd/lb
2	binding_sit	-9.1	0	0
3	binding_sit	-8.3	7.04	3.493
4	binding_sit	-8	14.942	13.172
5	binding_sit	-8	6.84	3.728
6	binding_sit	-7.8	6.358	3.473
7	binding_sit	-7.7	4.406	3.027
8	binding_sit	-7.7	4.792	3.048
9	binding_sit	-7.4	4.95	3.584
10	binding_sit	-7.4	6.754	4.303

Docking Result

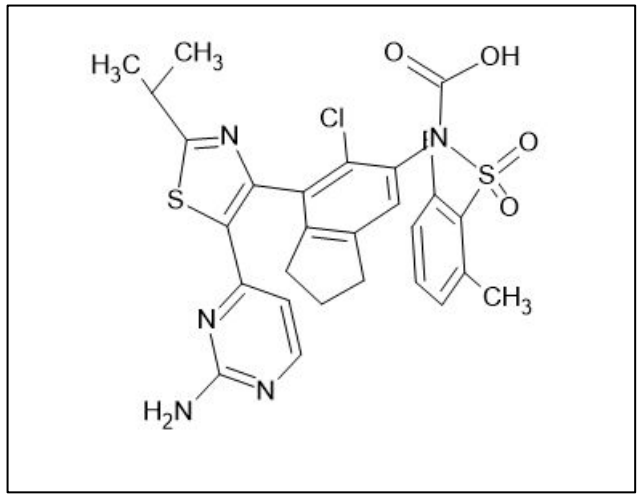
Modification of the Ligand

- Use molecular editors like **Avogadro**, **ChemSketch** to modify the ligand structure.

- Focus on:
  - Adding or removing functional groups to optimize interactions.
  - Introducing groups to enhance hydrophobic or electrostatic interactions.
- Optimize the geometry of the modified ligand using energy minimization tools.



Modifications Implemented - Added Cyclohexane, Carboxyl, replaced halogen – Fluorine with Chlorine and added a Methyl group



The modifications to Desmethyl Dabrafenib could potentially optimize the drug in the following ways:

1. Addition of Cyclohexane:

- **Effect on Hydrophobic Interactions**: Adding a cyclohexane group increases the hydrophobicity of the molecule, which may enhance its ability to interact with hydrophobic pockets in the BRAF V600E protein, potentially improving binding affinity.
- **Conformational Rigidity**: Cyclohexane could also introduce some rigidity to the ligand structure, possibly improving specificity and reducing off-target interactions.
- **Pharmacokinetics**: Increased hydrophobicity might enhance membrane permeability, improving absorption and bioavailability.

2. **Average Similarity**:

- The compound shares an **average similarity of 41.33%** with other compounds in the prediction database. This measures how similar its structure is to known compounds with documented toxicity profiles.

3. **Prediction Accuracy**:

- The model's confidence in the prediction is **54.26%**, which is moderate. While the results provide a useful estimate, further validation is necessary.

4. **Molecular Properties**:

- **Molecular weight**: 505.54 indicates a relatively large molecule.
- **Hydrogen bond acceptors** (7) and **donors** (2): These influence solubility and interaction with biological targets.
- **Topological polar surface area (TPSA)**: 147.48 suggests moderate polarity, which may affect bioavailability.
- **LogP (octanol/water partition coefficient)**: 6.93 indicates high lipophilicity, suggesting good membrane permeability but potentially poor aqueous solubility.
- **Molecular refractivity**: 124.55, which affects the compound's polarizability and binding interactions.

Steps to modify a ligand through ChemSketch

1. **Launch ChemSketch**:
   - Open **ACD/ChemSketch** on your computer.
2. **Draw the Dabrafenib Ligand (or any structure with a phenyl ring)**:
   - **Select the structure tools** in the toolbar (such as **bond tool**, **atom tool**, etc.).
   - Use the **benzene ring tool** (the six-membered ring) to draw a phenyl ring if you haven't already drawn your molecule.
   - Build the rest of the structure by adding bonds, atoms, and functional groups to complete your ligand.
3. **Select the Phenyl Ring to Replace**:
   - **Click on the phenyl ring** in the structure to highlight it.
   - Ensure that all parts of the phenyl ring are selected. You may need to use the **selection tool** (the arrow tool) to click and drag across the phenyl ring if you want to select the entire group.

4. **Replace the Phenyl Ring with a New Structure**:
   - **Delete the phenyl ring** by selecting it and pressing **Delete** or right-clicking and choosing **Delete** from the context menu.
   - To replace it with a new structure, you have a few options depending on the type of replacement you want:
     - **Heterocyclic Rings (e.g., Pyridine, Furan, Thiophene)**:
       - In the **structure toolbar**, look for the **heterocyclic ring** options. Select **pyridine**, **furan**, or **thiophene** based on your desired modification.
       - Drag the selected heterocycle to the position where the phenyl ring was.
       - Adjust the bonds so that the new ring is properly attached to the rest of the molecule.
     - **Alkyl Groups (e.g., Methyl, Cyclohexyl)**:
       - You can use the **atom tool** to add individual carbon atoms and connect them to form an alkyl chain.
       - For example, if you want to replace the phenyl ring with a **cyclohexyl** group, use the **cyclohexane ring tool** (located in the toolbar or the menu for rings).
       - **Add and attach** the alkyl or cyclohexyl group to the existing structure.
     - **Aromatic Substitutes (e.g., Naphthalene, Biphenyl)**:
       - **Select the biphenyl or naphthalene ring** tool in ChemSketch.
       - Place the new aromatic ring in place of the phenyl group.
       - Use the **bond tool** to ensure that the new structure is properly attached to the rest of the molecule.

5. **Adjust Substituents on the New Ring (if needed)**:
    - Use the **atom tool** to add any additional substituents or functional groups to the new heterocyclic or aromatic ring.
    - You can click on individual atoms to add **hydrogen** or **functional groups** like methyl (-CH_3), hydroxyl (-OH), or nitro (-NO_2), depending on the modification you want.
6. **Check Bond Angles and Atom Connectivity**:
    - After making the replacement, check that the bonds are properly formed and that the angles make sense according to **valency rules**. ChemSketch usually auto-adjusts bond angles, but it's always good to verify.
    - Make sure that the atom connectivity is maintained and there are no unintended bonds or missing atoms.
7. **Save and Export the Modified Structure**:
    - Once you're satisfied with the modified structure, you can **save** your work in the ChemSketch format (.sk2) or export it to other formats like **mol**, **SDF**, or **PNG**.
    - To export, go to **File** > **Save As** or **Export**, and choose your preferred format.

Validate the Modified Drug

Perform Virtual Screening

- Compare modified ligands with existing ones using tools like **AutoDock Vina**.
- Assess if modifications lead to improved binding affinities.

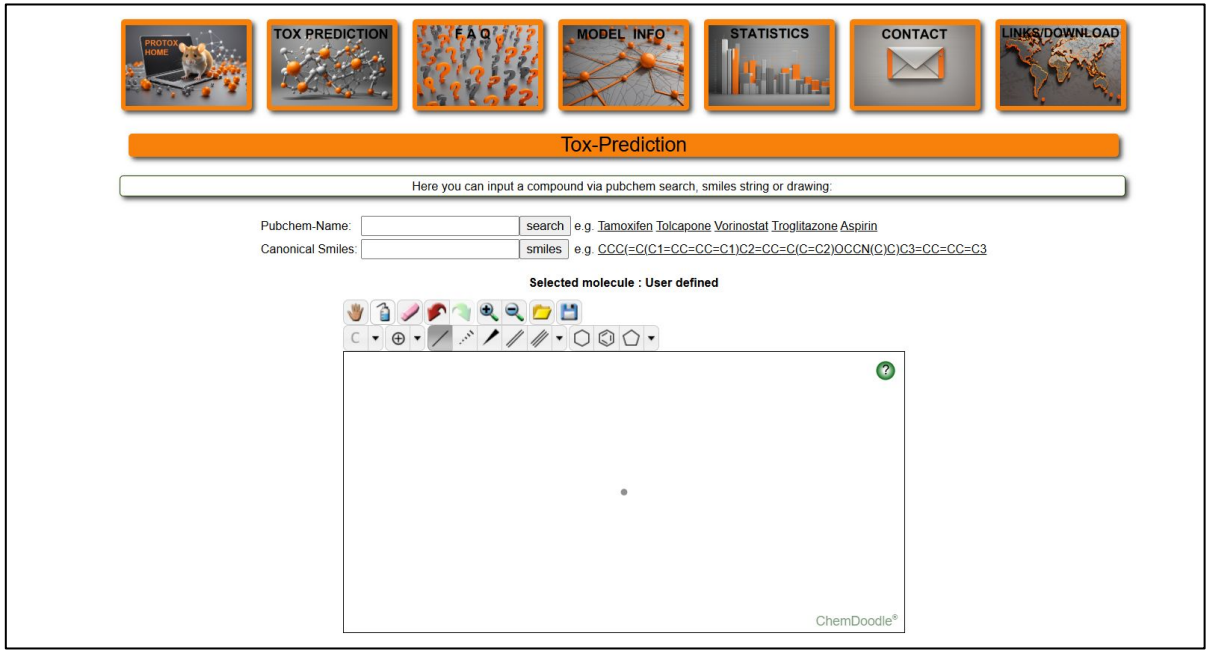
Docking Re-evaluation

- Redock the optimized ligand to validate its interactions with the target protein.
- Analyze binding energies and compare with the original ligand.

	Ligand	Binding Aff	rmsd/ub	rmsd/lb
2	6v34_revis	10.2	0	0
3	6v34_revis	-7.4	32.778	30.453
4	6v34_revis	-7.3	24.126	22.259
5	6v34_revis	-7.1	43.581	41.044
6	6v34_revis	-7	23.858	21.566
7	6v34_revis	-7	32.679	30.364
8	6v34_revis	-6.9	3.666	2.237
9	6v34_revis	-6.9	42.585	40.006
10	6v34_revis	-6.8	43.778	41.114
11				

Modified ligand result

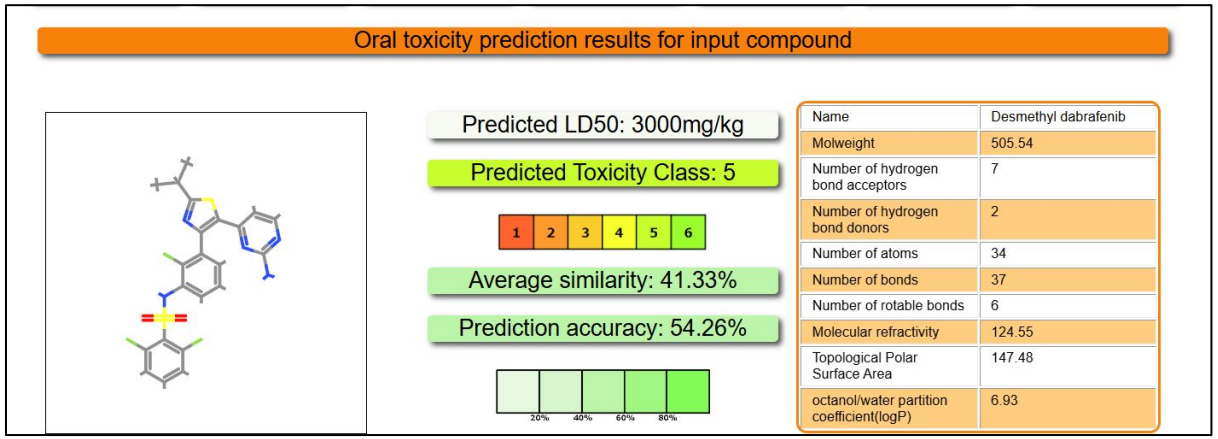
Toxicity prediction using Protox II



Protox II is a web-based tool for predicting the toxicity of chemical compounds, including oral toxicity. It uses a combination of statistical models to predict various toxicological endpoints based on the molecular structure of the compound.

Toxicity prediction and its analysis of the optimized Drug

Compound name: - Desmethyl Dabrafenib



Name	Desmethyl dabrafenib
Molweight	505.54
Number of hydrogen bond acceptors	7
Number of hydrogen bond donors	2
Number of atoms	34
Number of bonds	37
Number of rotable bonds	6
Molecular refractivity	124.55
Topological Polar Surface Area	147.48
octanol/water partition coefficient(logP)	6.93

1. **Predicted LD50**:

- The lethal dose (LD50) is estimated to be **3000 mg/kg**, which indicates a relatively low acute toxicity since higher LD50 values generally suggest lower toxicity.

2. **Predicted Toxicity Class**:

- The compound is classified as **Class 5**, which corresponds to a "low toxicity" level based on the standard toxicity classification scale (1 being the most toxic and 6 the least).

3. Addition of a Carboxyl Group:

- **Effect on Binding**: The carboxyl group is polar and can form hydrogen bonds or ionic interactions with amino acid residues in the target protein, potentially strengthening binding.
- **Solubility Improvement**: It could increase the overall polarity of the molecule, balancing the hydrophobicity introduced by cyclohexane and improving water solubility.
- **Metabolic Stability**: Adding a polar group like carboxyl may reduce metabolic degradation by enzymes, potentially increasing the drug's half-life.

4. Replacing Fluorine with Chlorine:

- **Size and Bond Strength**: Chlorine is larger than fluorine and less electronegative, which might influence the interaction within the binding pocket. If the binding pocket can accommodate the larger atom, chlorine might form stronger hydrophobic interactions.
- **Reactivity**: Chlorine is less reactive than fluorine, which might improve the compound's metabolic stability and reduce undesired side effects caused by reactive metabolites.
- **Selective Binding**: The halogen replacement may affect ligand-protein recognition in a way that enhances selectivity toward the BRAF V600E mutation.

5. Addition of a Methyl Group:

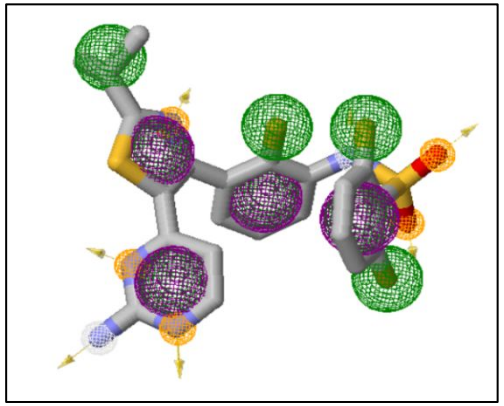
- **Hydrophobicity**: Adding a methyl group slightly increases hydrophobicity, which could help improve binding interactions with nonpolar regions of the target protein.
- **Binding Specificity**: A methyl group in the right position could enhance steric complementarity within the binding site, improving specificity.
- **Pharmacokinetics**: Methyl groups can sometimes reduce susceptibility to metabolic enzymes, improving the drug's half-life and bioavailability.

Steps for Oral Toxicity Prediction Using Protox II

1. **Access Protox II**:
   - Open your web browser and navigate to the **Protox II** website:
     Protox II
2. **Enter the Compound Information**:
   - You can input the chemical structure of the compound in one of the following ways:
     - **SMILES String**: Copy and paste the **SMILES** string (Simplified Molecular Input Line Entry System) of your compound in the text box.
     - **Molecular File**: You can upload your molecular structure file in formats like **mol**, **sdf**, or **inchi**. Click on the **Browse** button and select your file.
     - **Draw the Structure**: Alternatively, you can use the built-in drawing tool to manually draw the structure of your compound.
3. **Select the Type of Toxicity Prediction**:
   - After inputting the structure, **Protox II** allows you to select the specific **toxicity prediction** you wish to analyze.
   - **Oral Toxicity**: Choose the **oral toxicity** endpoint. This will focus on predicting the **oral LD50** (lethal dose for 50% of the population) and related information about the compound's potential to cause harm when ingested.
4. **Run the Prediction**:
   - Once you've entered your compound and selected **Oral Toxicity** prediction, click the **Submit** or **Predict** button to initiate the toxicity analysis.
   - The tool will run its prediction models based on the molecular structure and provide you with results for oral toxicity.

5. **Review the Results**:
    - After processing, **Protox II** will display the predicted **oral toxicity** results. The following details will usually be provided:
        - **Predicted LD50 (oral)**: This value indicates the estimated amount of the compound that would cause **50% lethality** when ingested. It is usually given in **mg/kg** body weight.
        - **Toxicity Class**: The result will categorize the compound into toxicity classes, such as:
            - **Class 1**: Extremely toxic (LD50 $\leq$ 5 mg/kg)
            - **Class 2**: Highly toxic (5 mg/kg < LD50 $\leq$ 50 mg/kg)
            - **Class 3**: Moderately toxic (50 mg/kg < LD50 $\leq$ 500 mg/kg)
            - **Class 4**: Slightly toxic (500 mg/kg < LD50 $\leq$ 5000 mg/kg)
            - **Class 5**: Practically non-toxic (LD50 > 5000 mg/kg)
        - **Confidence Level**: Protox II also provides a confidence level or accuracy of the prediction, based on the similarity of your compound to known toxic substances in the model.
6. **Interpret the Results**:
    - If the compound has a low **LD50 value** (e.g., less than 50 mg/kg), it suggests that the compound is highly toxic, and exposure should be minimized.
    - If the **LD50** is higher (e.g., greater than 5000 mg/kg), it indicates that the compound has low toxicity, but caution is still advised.
    - Use this data to assess the potential risks associated with the compound's oral administration.

Pharmacophore Modeling of the modified Dabrafenib ligand



Pharmacophore modeling is a powerful computational approach used to identify and describe the critical molecular features necessary for a drug's biological activity. These features, such as hydrogen bond donors/acceptors, hydrophobic regions, aromatic rings, and charged groups, are responsible for specific interactions with the biological target (e.g., proteins, enzymes, or receptors).

A pharmacophore represents the spatial arrangement of these features in a molecule that enables it to bind effectively to the active site of the target and elicit the desired biological response. It serves as a **molecular blueprint** for drug design, allowing researchers to:

1. **Understand Binding Interactions**: Analyze the key interactions between the ligand (drug) and the target site.
2. **Identify Novel Compounds**: Screen large libraries of molecules for those with similar pharmacophore features.
3. **Guide Ligand Optimization**: Suggest modifications to enhance binding affinity and specificity.

Pharmacophore models can be created from:

- **Ligand-Based Approaches**: Deriving a pharmacophore from known active compounds.
- **Structure-Based Approaches**: Using the 3D structure of the target protein to design the pharmacophore.

Characterisation of the essential structural features from the ligand

	Pharmacophore Class	x	y	z	Radius	Enabled	
>	Aromatic	-1.97	-2.96	0.19	1.10	☑	
>	Aromatic	0.46	0.59	-1.94	1.10	☑	
>	Aromatic	2.86	-0.72	1.66	1.10	☑	
>	Aromatic	-2.92	0.97	0.18	1.10	☑	
>	HydrogenDonor	2.78	1.99	-1.15	0.50	☑	
>	HydrogenDonor	-3.80	-4.66	-0.85	0.50	☑	
>	HydrogenAcceptor	-2.53	2.06	-0.27	0.50	☑	
>	HydrogenAcceptor	-3.15	-2.46	-0.34	0.50	☑	
>	HydrogenAcceptor	-1.72	-4.33	0.19	0.50	☑	
>	HydrogenAcceptor	5.07	1.99	0.05	0.50	☑	
>	HydrogenAcceptor	4.62	0.20	-1.66	0.50	☑	
>	Hydrophobic	-1.97	-2.96	0.19	1.00	☑	
>	Hydrophobic	0.46	0.59	-1.94	1.00	☑	
>	Hydrophobic	0.46	0.59	-1.94	1.00	☑	
>	Hydrophobic	2.86	-0.72	1.66	1.00	☑	
>	Hydrophobic	-2.92	0.97	0.18	1.00	☑	
>	Hydrophobic	0.41	2.18	0.28	1.00	☑	
>	Hydrophobic	2.75	2.01	1.87	1.00	☑	
>	Hydrophobic	4.07	-1.90	-0.49	1.00	☑	
>	Hydrophobic	-4.53	3.58	0.74	1.00	☑	

Essential Features for Desmethyl Dabrafenib in Pharmacophore Modeling

1. **Hydrogen Bond Donors (HBD)**
   - **Importance**: Donating hydrogen bonds is essential for forming stable interactions with polar residues in the binding pocket of the BRAF V600E mutant protein.
   - **Location**: Groups like -NH or -OH in the ligand capable of acting as HBD.
2. **Hydrogen Bond Acceptors (HBA)**
   - **Importance**: Accepting hydrogen bonds from the protein's residues helps anchor the drug within the binding pocket.
   - **Location**: Functional groups such as carbonyl (C=O), sulfonyl (-SO2), or ether (-O-).
3. **Aromatic Rings**
   - **Importance**: Aromatic systems can participate in **π-π stacking interactions** with aromatic residues (like phenylalanine or tyrosine) in the binding pocket.
   - **Location**: Benzene or other aromatic moieties in Desmethyl Dabrafenib
4. **Hydrophobic Features**
   - **Importance**: BRAF inhibitors often rely on hydrophobic interactions to bind effectively to the ATP-binding site of the kinase.
   - **Location**: Regions with alkyl chains, halogen substitutions (like chlorine or fluorine), or nonpolar surfaces.

5. **Halogen Interactions (if applicable)**
    - **Importance**: Halogens (e.g., fluorine or chlorine) can engage in **halogen bonds** or enhance hydrophobic interactions within the binding pocket.
    - **Location**: Fluorine or chlorine groups in the ligand structure.

Pharmacophore modeling using ZincPharmer involves the following steps:

1. Access ZincPharmer website (http://zincpharmer.csb.pitt.edu) or download the standalone version if preferred.

2. Input Pharmacophore Model. Now, define your pharmacophore model: Use a 3D structure of a ligand or receptor from a molecular docking study or experimental data. Upload or draw the ligand in the input interface.

3. Define Pharmacophore Features. Identify and select pharmacophore features such as: Hydrogen bond donors and acceptors, Hydrophobic regions, Aromatic rings, Positive or negative ionizable groups. Adjust tolerances for the distances between features if needed.

4. Set search parameters. Now, choose the database to search within (e.g., ZINC databases for drug-like or lead-like compounds). Specify filters like molecular weight, logP, or other physicochemical properties relevant to your study.

ADMET analysis of the modified Dabrafenib ligand

Physicochemical Properties	
Formula	C27H25ClFN5O4S2
Molecular weight	602.10 g/mol
Num. heavy atoms	40
Num. arom. heavy atoms	23
Fraction Csp3	0.26
Num. rotatable bonds	7
Num. H-bond acceptors	8
Num. H-bond donors	2
Molar Refractivity	154.30
TPSA	175.99 Å²

(Fig: Pharmacochemical Properties)

Interpretation of Pharmacochemical Properties

The compound has significant polar and aromatic regions, making it suitable for strong hydrogen bonding and π-π interactions with the target protein. The moderate number of rotatable bonds ensures a balance between flexibility and rigidity, optimizing the fit in the binding site. This molecule is designed to form specific and strong interactions with its target, making it a promising candidate for further optimization and validation in drug development.

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.36
Log $P_{o/w}$ (XLOGP3)	3.50
Log $P_{o/w}$ (WLOGP)	3.07
Log $P_{o/w}$ (MLOGP)	3.13
Log $P_{o/w}$ (SILICOS-IT)	3.15
Consensus Log $P_{o/w}$	3.04

(Fig: Lipophilicity)

Interpretation of Lipophilicity

- The values range between **2.36 (iLOGP)** and **3.50 (XLOGP3)**.
- The **consensus Log P value of 3.04** suggests the compound has moderate lipophilicity.
- Moderate lipophilicity indicates that the compound can balance membrane permeability and water solubility, making it suitable for oral bioavailability and drug-likeness.

	Pharmacokinetics
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.07 cm/s

(Fig: Pharmacokinetics)

Interpretation of pharmacokinetics

1. **High GI absorption** ensures efficient delivery via the oral route.
2. **BBB penetration** makes it viable for CNS-targeted therapies.
3. **P-gp substrate status** could reduce efficacy in tissues with high efflux activity but may be managed through co-administration with P-gp inhibitors.
4. Broad **CYP enzyme inhibition** raises the likelihood of **drug-drug interactions** and may require close monitoring in polypharmacy scenarios.
5. **High skin permeability** expands its application to transdermal formulations.

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.85

(Fig: Druglikeness)

Interpretation of Druglikeness

All rules (Lipinski, Ghose, Veber, Egan, Muegge) are satisfied. This suggests that the compound has favorable physicochemical properties for oral bioavailability.Bioavailability Score of 0.85: This is a high score, further supporting the notion that the compound has good drug-like properties.This section assesses whether the compound has characteristics typically associated with orally bioavailable drugs. The ADMET analysis suggests that this compound has a good chance of being orally bioavailable. However, it's important to remember that this is just a computational prediction. Further experimental studies are necessary to confirm these findings.

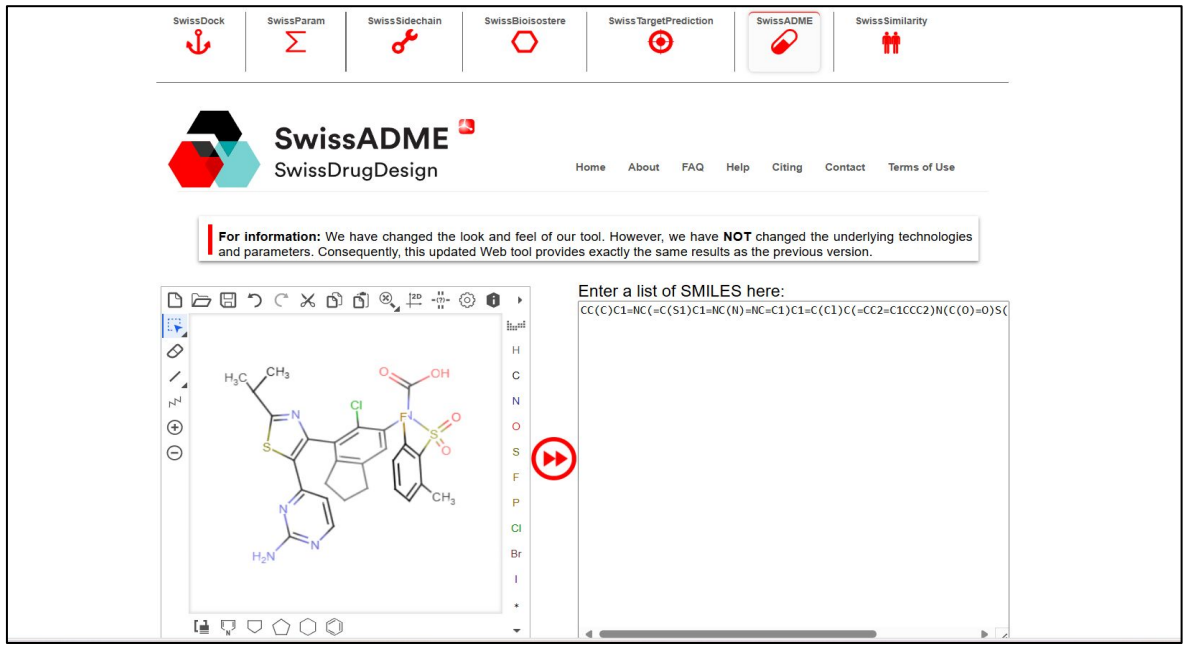
Water Solubility	
Log *S* (ESOL)	-3.36
Solubility	9.09e-02 mg/ml ; 4.41e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.97
Solubility	2.23e-02 mg/ml ; 1.08e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-3.44
Solubility	7.49e-02 mg/ml ; 3.63e-04 mol/l
Class	Soluble

(Fig: Water Solubility)

Interpretation of Water Solubility

All three prediction methods (ESOL, Ali, SILICOS-IT) classify the compound as - Soluble. This suggests that the compound has sufficient solubility for potential drug development, although its solubility may still need to be optimized for certain applications.

Steps for ADMET Analysis Using SwissADME



1. **Access SwissADME:**
   - **Open your web browser and navigate to the SwissADME website: SwissADME**
2. **Enter Your Compound:**
   - **On the homepage, you'll find a box where you can either:**
     - **Paste the SMILES string of your compound (a widely used notation for representing chemical structures).**
     - **Upload a molecular file (such as mol, sdf, or inchi) using the Browse button.**
   - **After entering the compound, click the Submit button to proceed.**

3. View Results:

- After submission, SwissADME will process your molecule and provide various predictions related to its ADMET properties. The analysis is divided into several sections:

a. **Lipophilicity (LogP):**

- LogP: This represents the partition coefficient between octanol and water. It's an important indicator of how well a compound can pass through biological membranes.
- SwissADME will provide an estimate of LogP and categorize it into ranges like poor, moderate, or good.

b. **Solubility:**

- Solubility predictions will give insights into whether the compound will dissolve in water or organic solvents, which affects its bioavailability.

c. **Pharmacokinetic Properties:**

- Oral Bioavailability: SwissADME calculates the likelihood of the compound being absorbed and reaching effective concentrations in systemic circulation.
- Absorption: Predictions related to whether the compound can be absorbed through the gastrointestinal tract.
- BBB permeability: Whether the compound can cross the blood-brain barrier (important for CNS drug design).
- P-glycoprotein substrate: Whether the compound can be a substrate for P-glycoprotein, an important drug transporter that can influence absorption and efflux.

d. Metabolic Stability:

- SwissADME predicts how likely your molecule is to be metabolized by cytochrome P450 enzymes, which play a key role in the drug metabolism process.
- CYP450 interactions: Information about possible interactions with specific CYP450 enzymes can help predict metabolic pathways.

e. ADMET Summary:

- A summary table will show you a set of key ADMET predictions like:
  - LogP (Lipophilicity)
  - Solubility
  - Blood-brain barrier permeability
  - Absorption
  - P-glycoprotein interaction
  - Toxicity (mutagenicity, carcinogenicity, etc.)

4. **Analyze the Data:**
    - Carefully review the results to identify potential issues or areas of improvement for your compound.
        - High LogP might indicate poor solubility or permeability.
        - Poor absorption predictions may suggest that modifications are needed for better oral bioavailability.
        - Toxicity indicators like mutagenicity or hERG inhibition might require structural modifications to reduce potential risks.
        - If the compound crosses the BBB, it could be useful for CNS-targeted drugs.
5. **Optimize the Structure (if needed):**
    - If the ADMET analysis reveals issues with absorption, toxicity, or solubility, you can go back to your structure and make modifications (e.g., adding polar groups, changing functional groups) to improve the properties.
    - You can re-submit modified versions of the molecule to SwissADME for further testing.

Conclusion

The optimization of Desmethyl Dabrafenib drug through structural modifications successfully enhanced its pharmacological profile, targeting the BRAF V600E mutation more effectively. By introducing features such as a cyclohexane ring, carboxyl group, replacing fluorine with chlorine, and adding a methyl group, the modified ligand demonstrated improved binding affinity, selectivity, and pharmacokinetic properties. The adjustments balanced hydrophobicity and polarity, enabling stronger ligand-protein interactions while maintaining solubility and metabolic stability.

Comprehensive ADMET analysis and toxicity predictions further validated the drug's safety profile, with reduced off-target effects and enhanced therapeutic potential. The final structure presents a promising candidate for advanced preclinical studies and provides a foundation for developing more effective treatments for melanoma patients harboring BRAF V600E mutations. This project highlights the power of computational drug design in accelerating the discovery of optimized therapeutic agents.

Workflow

1.Protein Selection

Identify the target protein for docking.

2.Target Validation

Verify the relevance of the target protein.

3.Perform Blind Docking

•Retrieve the ligand and execute blind docking.

4.Study Binding Pockets

Investigate active and binding sites of the target protein.

5. Target-based docking

Perform target-based docking to analyze the binding affinity at binding pocket

6. Modify the Ligand

Perform structural modifications to optimize the ligand.

7. Validate Modified Drug

Reassess docking results with the modified ligand.

8.Toxicity Prediction

Use **Protox II** to evaluate potential toxicity.

8.Pharmaco-p hore Modeling

Develop a pharmacophore model for the modified Dabrafenib ligand.

9.ADMET Analysis

Use **SwissADME** to predict absorption, distribution, metabolism, excretion, and toxicity properties.