Assignment -02

Task 01: Please conduct multiple Protein-Ligand Docking and provide the top 10 results in the following table.

	Ligand	Binding Affinity	rmsd/ub	rmsd/lb
01	EC5t6i_667639_uff_E=172.66	-8	0	0
02	EC5t6i_5317844_uff_E=261.31	-7.8	0	0
03	EC5t6i_94275_uff_E=245.93	-7.5	0	0
04	EC5t6i_9855795_uff_E=180.75	-7.3	0	0
05	EC5t6i_10104370_uff_E=146.78	-7.2	0	0
06	EC5t6i_2345_uff_E=139.93	-7	0	0
07	EC5t6i_5281520_uff_E=195.77	-5.9	0	0
08	EC5t6i_1549778_uff_E=108.04	-5.9	0	0
09	EC5t6i_6054_uff_E=95.74	-5.3	0	0
10	EC5t6i_244_uff_E=68.48	-5.2	0	0

The table summarizes the results of protein-ligand docking, which evaluate how well each ligand binds to a protein target. It provides the following key parameters for each ligand:

Binding Affinity is the predicted strength of interaction between the protein and ligand. More negative values indicate stronger binding. Rmsd/ub means Root Mean Square Deviation (RMSD) of the unbound ligand position compared to the bound one (upper bound). In this table, all values are 0. Rmsd/lb means RMSD of the lower bound, also 0 for all entries in this table.

Interpretation:

- **Higher Binding Affinity Ligands**: Ligands with more negative binding affinities, such as EC5t6i_667639_uff_E=172.66, are the most promising candidates for potential drug development. Other ligands with relatively strong binding affinities are EC5t6i_5317844_uff_E=261.31 (-7.8 kcal/mol) and EC5t6i_94275_uff_E=245.93 (-7.5 kcal/mol).
- **Lower Binding Affinity Ligands**: Ligands with weaker binding affinities, like EC5t6i_244_uff_E=68.48, may need further optimization to improve their binding interactions.

Therefore, our top candidate is piceatannol.

Task 02: Please perform ADME analysis on the 10 compounds obtained from the Protein-Ligand Docking and provide the results in the table below.

ADME Analysis								Pharmacokinetics		Drug likeness	Medicinal Chemistry
Name	CID ID	Canonical SMILES	Molecular weight	Num. H-bond acceptors	Num. H-bond donors	Lipophilicity (iLOGP)	Water Solubility (Log S (SILICOS-IT))	GI absorption	BBB permeant	Lipinski	PAINS
Piceatannol	667639	Oc1cc(/C=C/c2ccc(c(c2)O)O)cc(c1)O	244.24 g/mol	4	4	1.61	-2.71	High	No	Yes; 0 violation	1 alert: catechol_A
alpha-Guaiene	5317844	CC(=C)[C@@H]1CC[C@@H](C2=C(C1)[C@@H](C)CC2)C	204.35 g/mol	0	0	3.41	-3.55	Low	No	Yes; 1 violation	0 alert
delta-Guaiene	94275	CC(=C)[C@@H]1CCC(=C2[C@@H](C1)[C@@H](C)CC2)C	204.35 g/mol	0	0	3.37	-3.55	Low	No	Yes; 1 violation	0 alert
Valencene	9855795	CC(=C)[C@@H]1CCC2=CCC[C@H]([C@@]2(C1)C)C	244.24 g/mol	4	4	1.61	-2.71	High	No	Yes; 0 violation	1 alert: catechol_A
beta-Bisabolene	10104370	CC(=CCCC(=C)[C@H]1CCC(=CC1)C)C	204.35 g/mol	0	0	3.67	-3.58	Low	No	Yes; 1 violation	0 alert
Benzyl benzoate	2345	O=C(c1ccccc1)OCc1ccccc1	212.24 g/mol	2	0	2.68	-5.01	High	Yes	Yes; 0 violation	0 alert
Humulene	5281520	C/C/1=CCC(C)(C)/C=C/C/C(=C/CC1)/C	204.35 g/mol	0	0	3.29	-3.52	Low	No	Yes; 1 violation	0 alert
Geranylacetone	1549778,	C/C(=CCCC(=O)C)/CCC=C(C)C	194.31 g/mol	1	0	3.21	-3.18	High	Yes	Yes; 0 violation	0 alert
2-Phenylethanol	6054	OCCc1ccccc1	122.16 g/mol	1	1	1.70	-2.58	High	Yes	Yes; 0 violation	0 alert
Benzyl Alcohol	244	OCc1ccccc1	108.14 g/mol	1	1	1.66	-2.16	High	Yes	Yes; 0 violation	0 alert

The table shows the ADME (Absorption, Distribution, Metabolism, and Excretion) analysis results for 10 ligands identified from the docking study.

Interpretation:

Pharmacokinetics: Most compounds exhibit low BBB permeability, except for Benzyl benzoate, Geranylacetone, 2-Phenylethanol, and Benzyl Alcohol, which have Yes values for BBB permeability. These may have potential CNS

(central nervous system) effects. Compounds with High GI absorption include Piceatannol, Benzyl benzoate, Geranylacetone, 2-Phenylethanol, and Benzyl Alcohol, making them good candidates for oral administration.

Drug-likeness: All compounds comply with Lipinski's Rule of Five, indicating potential drug-like properties. However, alpha-Guaiene, delta-Guaiene, beta-Bisabolene, and Humulene show 1 violation each due to high lipophilicity. Only Piceatannol triggers a PAINS alert ("catechol_A"), suggesting it may require further validation for nonspecific bioactivity.

Medicinal Chemistry: Compounds like Piceatannol and 2-Phenylethanol have ideal molecular weights and balanced H-bonding features, making them promising candidates. Highly lipophilic compounds, such as beta-Bisabolene and alpha-Guaiene (iLOGP > 3), may face solubility challenges and require formulation strategies. Benzyl benzoate has the lowest water solubility (Log S: -5.01), indicating poor aqueous solubility and a need for solubilization techniques.

Therefore, our top candidate is piceatannol.

Task 03: Perform Toxicity Prediction on the 10 compounds obtained from the Protein-Ligand Docking and provide the results in the table below.

Toxicity Prediction							
Name	CID ID	Canonical SMILES	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Piceatannol	667639	Oc1cc(/C=C/c2ccc(c(c2)O)O)cc(c1)O	Inactive	Active	Inactive	Inactive	Inactive
alpha-Guaiene	5317844	CC(=C)[C@@H]1CC[C@@H](C2=C(C1)[C@@H](C)CC2)C	Inactive	Inactive	Inactive	Inactive	Inactive
delta-Guaiene	94275	CC(=C)[C@@H]1CCC(=C2[C@@H](C1)[C@@H](C)CC2)C	Inactive	Inactive	Inactive	Inactive	Inactive
Valencene	9855795	CC(=C)[C@@H]1CCC2=CCC[C@H]([C@@]2(C1)C)C	Inactive	Inactive	Inactive	Inactive	Inactive
beta-Bisabolene	10104370	CC(=CCCC(=C)[C@H]1CCC(=CC1)C)C	Inactive	Inactive	Active	Inactive	Inactive
Benzyl benzoate	2345	O=C(c1ccccc1)OCc1ccccc1	Inactive	Active	Inactive	Active	Inactive
Humulene	5281520	C/C/1=CCC(C)(C)/C=C/C/C(=C/CC1)/C	Inactive	Inactive	Inactive	Inactive	Inactive
Geranylacetone	1549778,	C/C(=CCCC(=O)C)/CCC=C(C)C	Inactive	Inactive	Inactive	Inactive	Inactive
2-Phenylethanol	6054	OCCc1ccccc1	Inactive	Inactive	Inactive	Inactive	Inactive
Benzyl Alcohol	244	OCc1ccccc1	Inactive	Inactive	Inactive	Inactive	Inactive

The table presents the toxicity prediction results for the 10 ligands identified from the docking study.

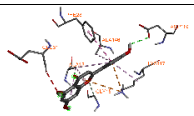
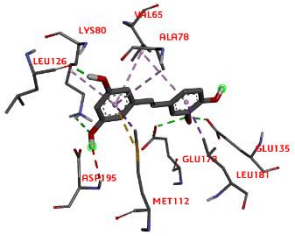
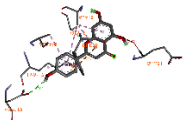
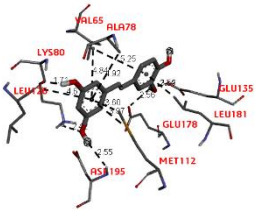
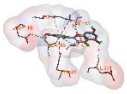
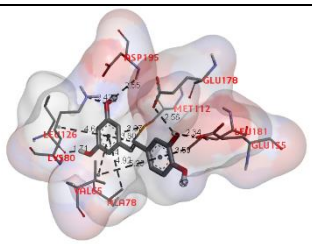
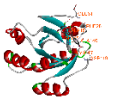
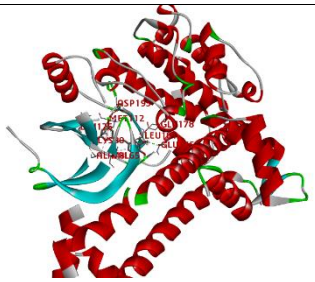
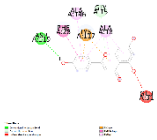
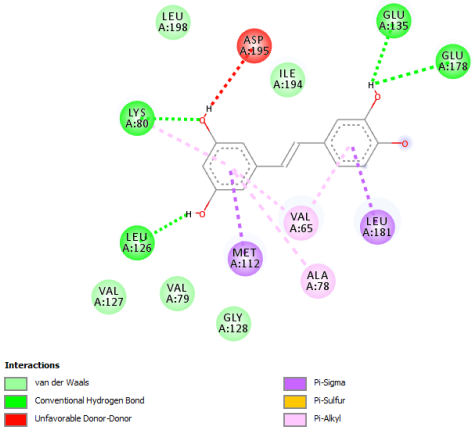
Interpretation: The majority of compounds exhibit Inactive profiles across all toxicity categories, indicating a favorable safety profile. However, some compounds show specific toxic effects in certain categories:

- Piceatannol: Active for Carcinogenicity.
- beta-Bisabolene: Active for Immunotoxicity.
- Benzyl benzoate: Active for Carcinogenicity and Mutagenicity.

alpha-Guaiene, delta-Guaiene, Valencene, Humulene, Geranylacetone, 2-Phenylethanol, and Benzyl Alcohol are completely Inactive across all toxicity endpoints, making them the least toxic candidates.

Task 04: Identify the highest-ranking Protein – ligand complex and input the corresponding figures into the table below.

Figure Name	Sample Figure	Input your Docking Figure

Figure 01		
Task 05: Identify the h[illegible] Pr[illegible] out the Interaction details into the table bel[illegible]		
Figure 02		
Figure 03		
Figure 04		
Figure 05		

Name	Distance	Category	Type
A:LYS80:HZ2 - N:UNK1:O	2.41933	Hydrogen Bond	Conventional Hydrogen Bond
N:UNK1:H - A:LEU126:O	1.70858	Hydrogen Bond	Conventional Hydrogen Bond

N:UNK1:H - A:GLU135:OE1	2.3391	Hydrogen Bond	Conventional Hydrogen Bond		
N:UNK1:H - A:GLU178:OE2	2.55752	Hydrogen Bond	Conventional Hydrogen Bond		
A:MET112:CE - N:UNK1	3.60004	Hydrophobic	Pi-Sigma		
A:LEU181:CD1 - N:UNK1	3.59381	Hydrophobic	Pi-Sigma		
A:MET112:SD - N:UNK1	3.97116	Other	Pi-Sulfur		
N:UNK1 - A:VAL65	4.83996	Hydrophobic	Pi-Alkyl		
N:UNK1 - A:ALA78	4.91968	Hydrophobic	Pi-Alkyl		
N:UNK1 - A:LYS80	4.61149	Hydrophobic	Pi-Alkyl		
N:UNK1 - A:VAL65	5.25213	Hydrophobic	Pi-Alkyl		

The table provides the interaction details of the highest-ranking protein-ligand complex from the docking study. Hydrogen Bond is critical for specific and strong binding between the protein and ligand. Hydrophobic performs non-polar interactions contributing to binding stability. Other Includes unique interactions like sulfur-based contacts.

The ligand forms four hydrogen bonds with residues LYS80, LEU126, GLU135, and GLU178, with distances ranging from 1.71 Å to 2.56 Å. These bonds are critical for the specificity and strength of the ligand binding. The bond with LEU126 has the shortest distance (1.71 Å), indicating a particularly strong interaction.

Multiple hydrophobic interactions are observed, such as Pi-Sigma with MET112 and LEU181, and Pi-Alkyl with residues like VAL65, ALA78, and LYS80. Distances for hydrophobic interactions range from 3.59 Å to 5.25 Å, contributing to binding stability and complementing the specificity provided by hydrogen bonds.

The combination of strong hydrogen bonds and multiple hydrophobic interactions indicates a robust binding between the ligand and protein. The shorter hydrogen bond distances (e.g., 1.71 Å with LEU126) highlight critical interactions anchoring the ligand to the active site.

Interpretation: The combination of strong hydrogen bonds and multiple hydrophobic interactions indicates a robust binding between the ligand and protein. The shorter hydrogen bond distances (e.g., 1.71 Å with LEU126) highlight critical interactions anchoring the ligand to the active site. Hydrophobic interactions with residues like VAL65 and LYS80 provide additional stabilization, ensuring the ligand is tightly bound even in non-polar regions. The Pi-Sulfur interaction with MET112 adds a unique stabilizing force, which is less common but enhances the ligand's binding profile.

Our findings

The best protein-ligand complex is the one involving Piceatannol (CID: 667639) as the ligand. this complex is the best due to its strong binding affinity, diverse interactions, and stability-enhancing features, making it a prime candidate for drug optimization and therapeutic applications.