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Research Article

Computational docking studies of Noscapines: A potential bioactive agent

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ABSTRACT

Computer docking provides the necessary data for biochemists, chemists, and pharmacologists to design and study ligands for various proteins and identifying the ligands that bind effectively in the active site of these protein structures. There are varieties of docking strategies which are based different algorithms but herein authors used genetic algorithms. Herein, Estrogen sulfotransferase (1AQU), Q251Q8 DESHY protein taken from Desulfitobacterium hafniense (3IPF), anti-apoptotic protein Bcl-xL (2O1Y) and β-catenin (1JDH) have been chosen to interact with noscapines via docking method. Standard docking approach was used for docking calculations based on the generic algorithms. Scoring of ligands was done which is based on the fitness score, which is basically the total energy docking interaction. The most fit noscapine derivative for each protein was reported.

Keywords: Noscapines, Docking, Modelling, Inhibitors.

INTRODUCTION

Noscapines are benzyl isoquinoline alkaloid and extracted from the plants of poppy family. It is primarily, used for its anti-tussive effect. Recently, it has been introduced as an anti-mitotic agent. It has mild analgesic property and exerts its mitotic effect by binding to tubulin, resulting in disturbance of microtubule assembly dynamics and then, the cell death occurs. Therefore, noscapine and its derivatives have great potential to act as anti-cancer agents[1-7].

Recent advances in protein structure determination, via nuclear magnetic resonance, X-ray crystallography, or computer modeling, are providing the necessary data for biochemists, chemists, and pharmacologists to design and study ligands/substrates for these proteins. Docking is basically a method which predicts the suitable orientation of ligands that bind in the active site of these protein structures, which has led to the development of a variety of potent molecules. Generally, molecular docking is one of the most preferred methodologies in designing the structure based drug like molecules. Docking has predicted the conformation of ligand molecule to appropriate target binding site of protein based on the several interactions like hydrogen bonding, steric etc[8-12]. On the basis of these interactions a score is developed and with the help this score one can screen the ligand molecule as potent one.

Estrogen sulfotransferase is a small enzyme available in cytoplasm as well it is found soluble in water and its PDB ID is 1AQU. It is generally used as a cofactor and very important in the transfer a sulfonated group to the steroid that is estrogen. This chemical reaction of the path involved is used to stop or prevent the activity of the estrogen via increasing its solubility[13,14]. Anti-apoptotic protein Bcl-xL is a complex formed by the acyl-sulfonamide-based ligand. It is a transmembrane molecule and available in the mitochondria (2O1Y). It is basically acts as an anti-apoptotic protein and used to prevent or stop the release of mitochondrial contents. It may be cytochrome c and it leads to caspase activation. Finally, it causes the programmed cell death[15,16]. β-catenin (1JDH) is a protein present in the humans and it is encoded by the *CTNNB1* gene. β-catenin is a dual function protein and it has been involved in regulation. It is also involved in the coordination of cell–cell adhesion and gene transcription. β-catenin mutations is observed as one of the important step in the progression of a subset of colon cancer, melanoma, hepatocellular carcinoma, ovarian cancers and suggesting an important role in the control of cellular proliferation or cell death[17,18]. Q251Q8 DESHY protein is obtained from the bacteria Desulfitobacterium hafniense and its PDB ID is 2O1Y. It has the ability to dechlorinate the compounds having halogens in the absence of oxygen[19,20].

In this paper, used four PDB files have been chosen based on their relevance discussed above, to find the different potential of noscapine. Ligands were optimized using suitable force field and docked against the protein. Standard docking protocol was used

for all docking calculations. The docked ligands available in PDB crystal structure have been removed prior to study the protein. Also the preparation of protein has been performed if there was some missing like hydrogen atom, charges etc.

EXPERIMENTAL PROCEDURE

Ligand preparation

Noscapine is invoked from the database of research literature and all derivatives have been drawn on Cambridge Soft ChemDraw Ultra V 7.0 and saved in suitable format. The change in noscapine molecule gives three parent molecule given in Table 1. Further the side chain (R-group) are changed, which finally gives total eleven derivative from one parent molecule, which are given in Table 1. These structures have been optimization on applying the molecular mechanics as a force field (MM2) and the energy minimization were performed, where the minimum RMS were set at 0.100.

Protein preparation

Protein preparation were done with the help of Molagro Molecular Viewer V 2.5 (MMV), which are the freeware and obtained from www.clcbio.com. Where, the assigning of missing bonds, assigning of missing bond order and hybridization, assigning of missing explicit hydrogen, assigning of missing charges always, assigning of flexible torsion in ligands always and assigning of tripos type atoms if missing were performed. Finely the prepared protein is used for molecular docking.

Molecular docking of noscapines

The docking of all derivatives of noscapine derivatives into the binding site of the above protein (PDB ID-1AQU, 3IPF, 2O1Y and 1JDH) was performed using iGEMDOCK (Generic Evolutionary Method for molecular Docking) software, which was a program for computing a ligand conformation and orientation relative to the active site of the target protein. To validate the molecular modeling programs, the docking accuracy of GEMDOCK was first evaluated by docking three known PI3K inhibitors, wortmannin, triciribine and LY294002 into the binding site (Arcaro and Wymann, 1993; Dieterle et al., Gharbi et al., and Yano et al.. The binding pockets of the 1AQU, 3IPF, 2O1Y and 1JDH was defined to include the amino acid residues within an 8˚A radius sphere centered on the binding site of proteins. In the present study, the GEMDOCK parameters included the population size (n=200), generations (g=70) and number of solutions (s=2). (http://gemdock.life.nctu.edu.tw/dock/) [21,22].

Finally, interaction profile of all docked poses was generated for the interaction analysis of ligand with proteins. Three main types of ligand– protein interactions were generated; electrostatic (E), hydrogen-bonding (H), and van der Waals (V) interactions.

The interaction data was short out by applying the default parameters as energy and the highly potent derivative were reported so that lead out will be most potent one. The values of total energy, vander

Walls, H-bonding and electrostatic interactions of protein and noscapine derivatives are given in Table 2.

E_{total} = VDW + Hbond + Elec.

Modeling of noscapines with PDB (1AQU, 1JDH, 2O1Y and 3IPF)

Modeling of noscapines derivatives with sulfotransferase (PDB 1AQU), β-catenin, (PDB 1JDH) anti-apoptotic protein Bcl-xL (PDB 2O1Y) and Desulfitobacterium hafniense (PDB 3IPF) respectively have been performed using Molegro Molecular Viewer 2.5. Rendering of protein and ligand, labeling of amino acids of proteins residues of highest potent one were also performed for better visualization. The modeling results are shown in Figure 1.

RESULTS AND DISCUSSION

Now-a-days it remains difficult the diagnosis of delirium because it's many presentations. Consequently, it remains underdiagnosed and sub treated in the most different patient scenarios – ward, ICU, PLC, community. The earlier it is diagnosed, less complications are linked to the patient, with substantial reduction in the its morbidity and mortality and with lower direct and indirect health costs. Non-pharmacological and pharmacological strategies are eligible, specially the first ones. Haloperidol is the most used drug, with a good safety profile.

Interaction of noscapines (1a-1k, 2a-2k and 3a-3k) with sulfotransferase (PDB 1AQU), β-catenin, (PDB 1JDH) anti-apoptotic protein Bcl-xL (PDB 2O1Y) and Desulfitobacterium hafniense (PDB 3IPF) respectively have been performed. We obtained the total energy based on Vander Waal, hydrogen bonding and electrostatic interaction and it tells how stronger the bonding is between them. Lesser the energy obtained by interaction indicated effective binding between noscapines and the PDB. Based in the interaction of noscapines (1a-1k, 2a-2k and 3a-3k) with sulfotransferase (PDB 1AQU), it indicates the compound 1k has the strongest binding as it has lowest energy and the manor contribution is from van der Waal interaction and hydrogen bonding. It shows total 15 H-bonding interaction with the amino acids viz., with Thr 227, Tyr 193, Arg 103, Ser 138, Gly 259, Lys 258, Thr 52, Arg 257, Thr 51. Ser 49, Gly 50 and Lys 48. Based in the interaction of noscapines (1a-1k, 2a-2k and 3a-3k) with β-catenin, (PDB 1JDH), it indicates the compound 1f has the strongest binding as it has lowest energy and the manor contribution is from van der Waal interaction and hydrogen bonding. It shows total 04 H-bonding interaction with the amino acids viz., with Gly 268, Asn 34 and Lys 270. Based in the interaction of noscapines (1a-1k, 2a-2k and 3a-3k) with anti-apoptotic protein Bcl-xL (PDB 2O1Y), it indicates the compound 1h has the strongest binding as it has lowest energy and the manor contribution is from van der Waal interaction and hydrogen bonding. It shows total 1 H-bonding interaction with the amino

acids Asn 140. Based in the interaction of noscapines (1a-1k, 2a-2k and 3a-3k) with Desulfitobacterium hafniense (PDB 3IPF), it indicates the compound 1j has the strongest binding as it has lowest energy and the manor contribution is from van der Waal interaction and hydrogen bonding. It shows total 04 H-bonding interaction with the amino acids viz., Gly 30, Arg 23, Asn 22 and Ser 32.

CONCLUSION

It has been observed that effective or potential noscapines are 1k, 1f, 1h and 1j only and their structures are given in Figure 2. They are potent inhibitor of sulfotransferase, β-catenin, anti-apoptotic protein Bcl-xL and Desulfitobacterium hafniense. Further, it has been observed that unreduced noscapines are biologically most potent candidates and it is in correlation with the literature.

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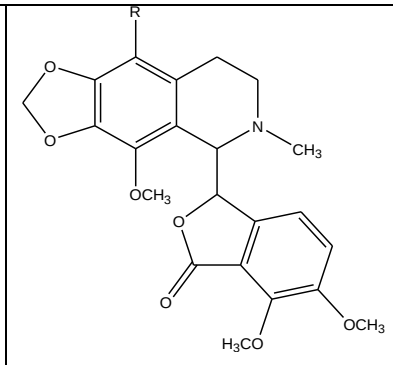
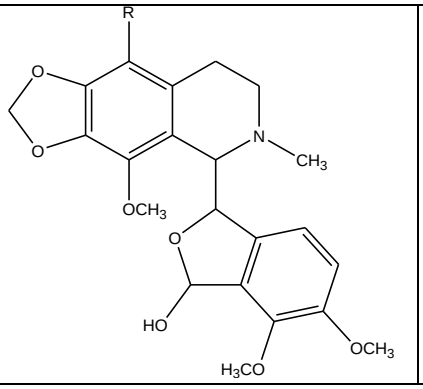
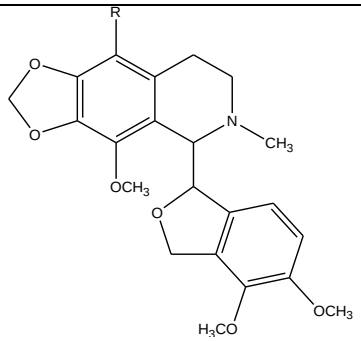
Table 1. Library of the noscapines (1a-1k, 2a-2k and 3a-3k).

Structure			

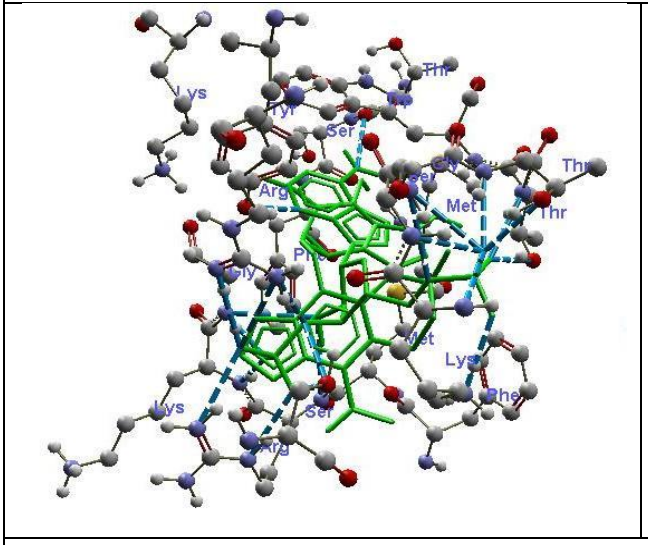
C. No.	1	2	3
	-H (1a); -NH_2 (1b); -Br (1c), -CHO (1d); -COCl (1e); -COOH (1f); Cl (1g); -CH_2Cl (1h); -F (1i); -CH_2OH (1j), -NO_2 (1k)	-H (2a); -NH_2 (2b); -Br (2c), -CHO (2d); -COCl (2e); -COOH (2f); Cl (2g); -CH_2Cl (2h); -F (2i); -CH_2OH (2j), -NO_2 (2k	-H (3a); -NH_2 (3b); -Br (3c), -CHO (3d); -COCl (3e); -COOH (3f); Cl (3g); -CH_2Cl (3h); -F (3i); -CH_2OH (3j), -NO_2 (3k)

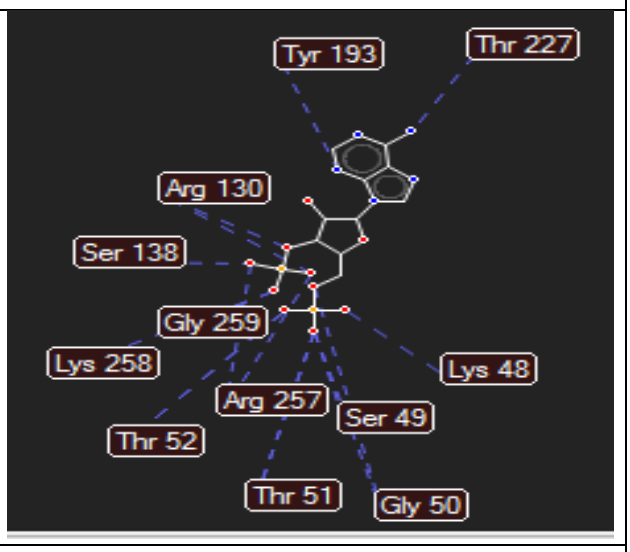
Table 2. The values of total energy, van der Walls, H-bonding and electrostatic interactions.

	PDB 1AQU				**PDB 1JDH**			
C. No.	**Total Energy**	**VDW**	**H-Bond**	**Elec**	**Total Energy**	**VDW**	**H-Bond**	**Elec**
1a	-144.340	-106.022	-38.318	0	-95.8871	-77.6831	-18.204	0
1b	-129.237	-89.9523	-39.2847	0	-95.2379	-67.6298	-27.6081	0
1c	-105.719	-91.0774	-14.6416	0	-98.18	-83.849	-14.331	0
1d	-127.290	-103.029	-24.2604	0	-90.4484	-71.7621	-18.6863	0
1e	-131.195	-97.734	-33.4607	0	-94.7625	-86.6901	-8.07244	0
1f	-136.279	-78.8077	-53.7415	-3.7293	-110.792	-98.4293	-12.3258	-0.0372
1g	-129.786	-100.452	-29.3349	0	-90.9812	-87.4812	-3.5	0
1h	-128.033	-104.841	-23.1924	0	-90.0943	-69.9646	-20.1297	0
1i	-120.326	-81.3852	-38.9405	0	-91.9815	-81.5721	-10.4094	0
1j	-125.629	-83.6214	-42.0078	0	-103.152	-80.66	-22.4918	0
1k	-152.404	-119.953	-33.4673	1.01583	-104.042	-69.9573	-33.4147	-0.6703
2a	-144.752	-106.576	-38.1764	0	-95.1747	-84.603	-10.5717	0
2b	-125.310	-97.4459	-27.8637	0	-91.3604	-80.3926	-10.9678	0
2c	-120.365	-85.7952	-34.5696	0	-92.6127	-74.4258	-18.1869	0
2d	-142.082	-108.728	-33.3539	0	-91.168	-78.4355	-12.7325	0
2e	-131.879	-91.9245	-39.9541	0	-93.6748	-72.7874	-20.8874	0
2f	-135.159	-101.757	-31.4764	-1.9260	-90.467	-76.1821	-14.2849	0
2g	-132.871	-105.779	-27.0919	0	-85.993	-70.3098	-15.6832	0
2h	-136.476	-94.2188	-42.257	0	-100.14	-84.0249	-16.1152	0
2i	-126.378	-91.4138	-34.9644	0	-89.4934	-80.4953	-8.99811	0
2j	-144.253	-109.753	-34.5005	0	-96.8235	-82.2751	-14.5484	0
2k	-135.393	-82.5376	-52.8558	0	-100.791	-74.8528	-27.9086	1.97063
3a	-139.073	-112.873	-26.2003	0	-95.9147	-82.497	-13.4178	0

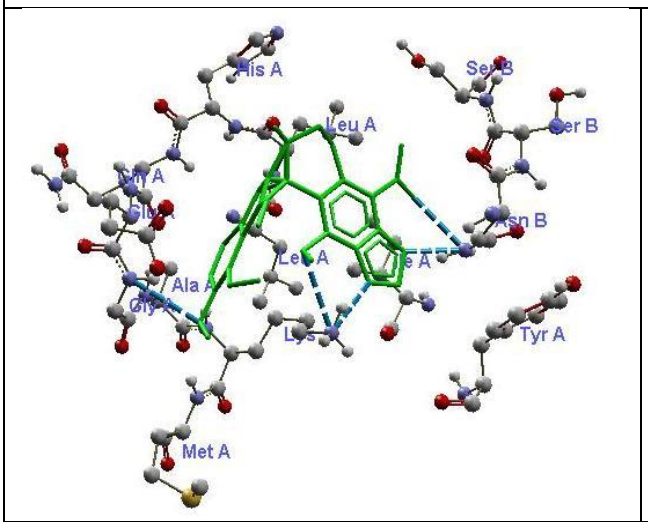
3b	-122.820	-100.199	-22.6213	0	-103.944	-90.0158	-13.9278	0
3c	-130.767	-113.386	-17.3816	0	-89.6292	-79.5149	-10.1143	0
3d	-138.284	-117.29	-20.9935	0	-99.0961	-88.2947	-10.8014	0
3e	-122.732	-93.3149	-29.4169	0	-106.02	-99.0705	-6.94953	0
3f	-144.548	-101.707	-38.4503	-4.3905	-109.603	-89.1661	-18.3111	-2.1259
3g	-118.082	-90.0261	-28.0559	0	-91.9895	-84.8848	-7.10469	0
3h	-130.808	-114.768	-16.0393	0	-88.8877	-74.1578	-14.7299	0
3i	-123.350	-107.771	-15.5785	0	-94.8115	-68.608	-26.2035	0
3j	-130.450	-110.18	-20.2698	0	-93.9163	-85.4655	-8.45079	0
3k	-139.351	-81.4563	-58.1679	0.27350	-96.2045	-69.8049	-28.5322	2.13259
	PDB 2O1Y				**PDB 3IPF**			
C. No.	**Total Energy**	**VDW**	**HBond**	**Elec**	**Total Energy**	**VDW**	**HBond**	**Elec**
1a	-104.683	-96.7774	-7.90571	0	-85.2101	-71.4996	-13.7106	0
1b	-100.983	-91.645	-9.33757	0	-92.5057	-77.8467	-14.6591	0
1c	-109.136	-100.96	-8.17686	0	-82.8429	-78.0002	-4.84269	0
1d	-105.215	-96.0824	-9.13298	0	-88.684	-74.9235	-13.7606	0
1e	-105.38	-77.1536	-28.2265	0	-95.5461	-77.3223	-18.2248	0
1f	-112.883	-103.051	-9.83187	0	-90.7656	-79.3311	-11.4345	0
1g	-103.899	-100.057	-3.84141	0	-87.8122	-82.5464	-5.2658	0
1h	-117.505	-107.719	-9.78623	0	-97.212	-76.7822	-20.4298	0
1i	-105.108	-96.3203	-8.78745	0	-87.3488	-81.101	-6.24787	0
1j	-111.321	-98.3192	-13.0021	0	-98.5649	-80.0997	-18.4652	0
1k	-112.623	-105.641	-6.98246	0	-96.9521	-72.3891	-24.563	0
2a	-105.238	-98.2382	-7	0	-85.4814	-74.8028	-10.6786	0
2b	-113.737	-106.108	-7.62935	0	-84.7097	-71.1099	-13.5998	0
2c	-115.175	-104.444	-10.7309	0	-79.3136	-75.9886	-3.32502	0
2d	-102.575	-81.2726	-21.3026	0	-95.012	-74.5822	-20.4298	0
2e	-108.626	-87.2318	-21.3943	0	-87.0675	-70.5612	-16.5063	0
2f	-111.243	-105.758	-5.48498	0	-79.9192	-69.5104	-10.4088	0
2g	-101.938	-87.6562	-14.2814	0	-89.9021	-82.272	-7.63006	0
2h	-105.156	-101.656	-3.5	0	-91.1738	-70.8585	-20.3153	0
2i	-109.204	-107	-2.20337	0	-94.2659	-79.9272	-14.3386	0
2j	-106.848	-88.0412	-18.8065	0	-93.5014	-81.076	-12.4254	0
2k	-113.134	-94.6919	-18.6806	0.2388	-85.9488	-62.3001	-23.6487	0
3a	-107.072	-100.072	-7	0	-79.2136	-70.3928	-8.82076	0
3b	-98.8745	-98.8745	0	0	-89.3617	-72.0853	-17.2765	0
3c	-99.2075	-99.2075	0	0	-84.5205	-72.4586	-12.0619	0

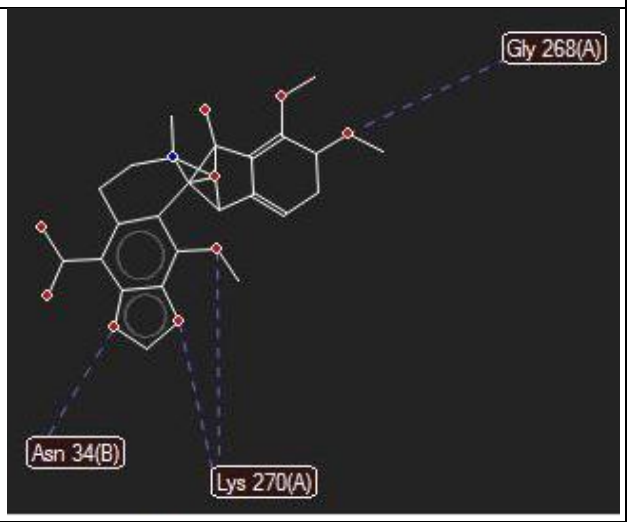
3d	-101.45	-94.557	-6.89327	0	-80.0748	-65.3022	-14.7726	0
3e	-108.471	-102.517	-5.95442	0	-84.1256	-70.7871	-13.3385	0
3f	-99.8357	-86.4555	-13.3803	0	-86.1584	-66.1995	-19.9589	0
3g	-104.598	-103.835	-0.76250	0	-87.0243	-73.5839	-13.4404	0
3h	-100.599	-94.9077	-5.69163	0	-93.1741	-84.6108	-8.56333	0
3i	-99.8786	-92.945	-6.93363	0	-77.4645	-68.1514	-9.31316	0
3j	-113.566	-100.569	-12.9971	0	-85.9349	-72.0677	-13.8673	0
3k	-105.061	-102.724	-2.33669	0	-86.3756	-77.7105	-8.66519	0



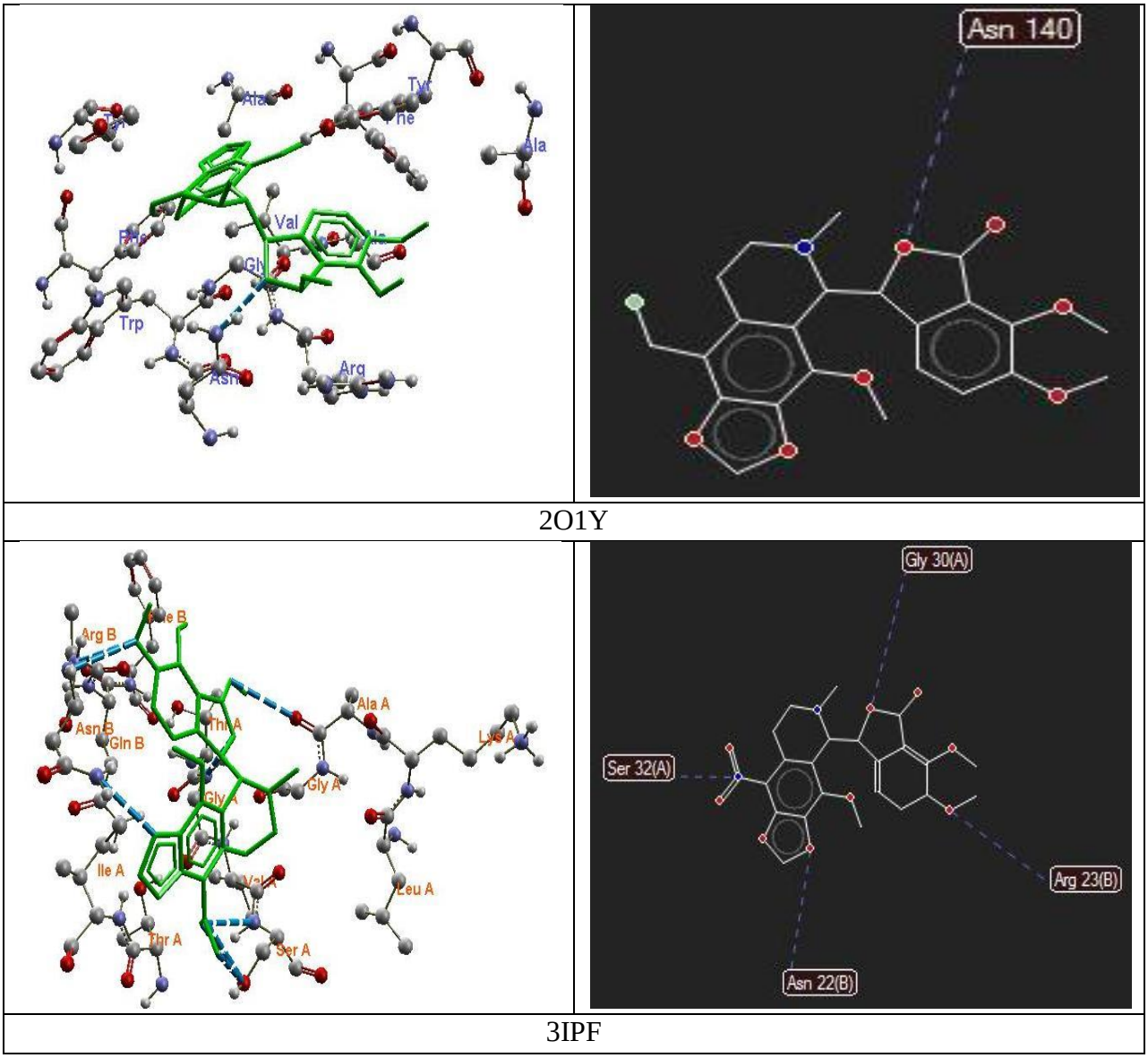


1AQU





1JDH



2O1Y

3IPF

Figure 1. Showing the modeled structure of ligand-protein in which the H-bonding interactions are shown as dashed lines in blue color. Column 1 shows the ligand inside the cavity of protein, where the amino acid recedues labeled, where as in column 2 shows the clear picture of H-bonding interaction with amino acid recedues labeled with their sequence no and chain

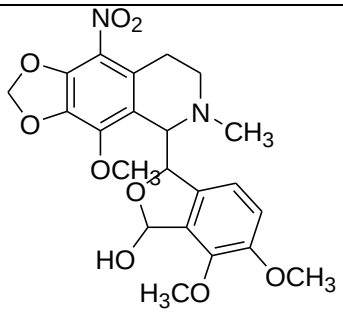
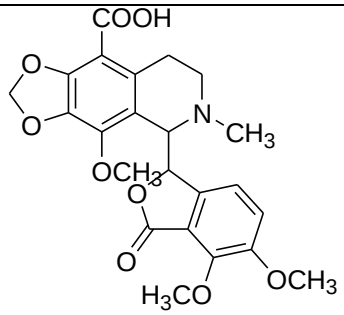
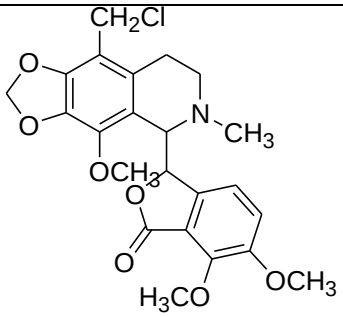
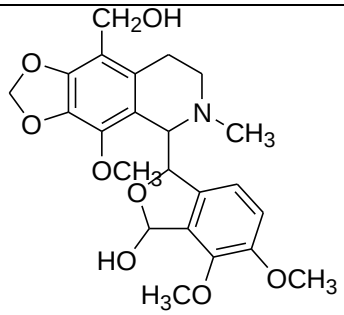
	
1k	1f
	
1h	1j

Figure 2. Structures of noscapines 1k, 1f, 1h and 1j as potentials inhibitor for sulfotransferase (PDB 1AQU), β-catenin, (PDB 1JDH) anti-apoptotic protein Bcl-xL (PDB 2O1Y) and Desulfitobacterium hafniense (PDB 3IPF) respectively.