Docking & QSAR studies of Camptothecin derivatives as inhibitor of DNA Topoisomerase-I

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Abstract

Camptothecin (CPT) is a cytotoxic quinoline alkaloid which inhibits the DNA enzyme Topoisomerase-I (Topo-I) and has shown remarkable anticancer activity in preliminary clinical trials. The major limitation is its low solubility and high adverse reaction. In the studied work, we performed molecular docking of CPT derivatives against Topo-I and developed the quantitative structure activity relationship (QSAR) model for anticancer activity screening. For QSAR, we used CPT and other anticancer drugs with its IC_{50} values. We used a total of forty seven anticancer drugs as training set and eight compounds as test set and thirty derivatives of CPT as query set. Total of fifty two chemical descriptors were used for the quantitative data calculation. Only four showed good correlation with the experimental activity. Forward feed regression method was used for development of multiple linear regression (MLR) QSAR model. Model showed acceptable regression coefficient (r^2) 0.89 (i.e., 89% of correlation) and cross validation coefficient (rCV^2) 0.86 (i.e., 86 % of prediction accuracy). After drug likeness test, ten compounds namely, MSB3a, MSB3b, MSB19, MSB22L, MSB22M, MSB22O, MSB22R, MSB25D, MSB37G and MSB39D, showed promising predicted anticancer activity and drug likeness properties. Out of ten, only six compounds namely, MSB19, MSB22L, MSBM, MSB22O, MSB22R and MSB37D indicate two times more activity than the parent CPT compound. In molecular docking studies, all the identified active CPT derivatives showed high binding affinity with Topo-I. QSAR study indicates that connectivity index, electron affinity, mol.wt. & ether group count highly contribute to inhibitory activity of CPT derivatives. These results can offer useful references for directing the molecular design of Topo-I inhibitor with improved anticancer activity.

Introduction

❖ In the current era, one of the leading disease related causes of death of the human population in the world is cancer and it is predicted to continue to be the same in the coming years (Gibbs JB, 2000).
❖ Topotecan is presently indicated as a second-line therapy for advanced ovarian cancer and small-cell lung cancer. Irinotecan is approved for use in the treatment of advanced colorectal cancer, both as first-line therapy in combination with 5-FU and as salvage treatment in 5-FU refractory disease, including 9-AC, 9-NC, GI-147211, exatecan mesylate, and karenitecin. A lot of CPT analogs have been synthesized and evaluated, several 3D QSAR studies of CPT were reported from laboratories, but failed in clinical trials (Carrigan SW et al., 1997).
❖ So far Yoon et al. (2003) have successfully developed the QSAR model for CPT derivatives other then present study targeting serum esterase and designed a new, easily activated SN-38 prodrug for anticancer activity (Yoon KJP et al., 2003).
❖ In the studied work, we successfully build the predictive multiple linear regression QSAR model for anticancer activity, targeting Topo-I by using CPT and other known anticancer drugs. In order to further understand the inhibition mechanism of CPT derivatives and to guide structural modification in CPT analogs, a QSAR and molecular docking studies of CPT derivatives was performed.

Method

Retrieval of Crystal structures
➢3D crystal structure of DNA Topo-I protein (PDB: 1T8I) and chemical compounds were retrieved from PDB (www.rcsb.org) and PubChem databases respectively.
Cleaning, Optimization & molecular docking of CPT derivatives
➢3D structure of CPT derivatives were designed and optimized through ChemBioOffice software. Molecular structures of target protein Topo-I and chemical molecules were prepared and docked through Scigress Explorer v7.7 (Fujitsu). Molecular docking was performed to find out the binding affinity or molecular interaction energy (kcal/mol) of docked compounds calculated by using PMF scoring scheme. Lowest energy of docked molecule indicates high binding affinity with the target protein. Binding pocket of docked CPT active derivatives were studied for selection radius 3Å.
Multiple linear regression QSAR modeling for anticancer activity targeting Topo-I
➢Calculation of 2D and 3D molecular chemical descriptors for QSAR modeling by using forward feed multiple linear regression method and drug likeness study (Lipinski et. al., 2001) was done through Scigress Explorer v7.7. The model was constructed with 45 compounds in the training set, which was validated by the remaining molecules in the test set. We employed 'leave-one-out' cross validation procedure.

Results

• MLR method was employed to generate a linear relationship that correlates changes in the computed steric and electrostatic potential fields with changes in the corresponding experimental values of the training compounds activity (IC_{50}).
• Docking results showed that all the active CPT derivatives docked on Topo-I with high binding affinity.
• 2D contour maps of CPT derivatives were compared with the crystal structure of Topo-I complex (PDB: 1T8I).
• Docking results of 10 CPT derivatives showed that the important residues of Topo-I active pocket are hydrophilic and polar.
• Asp-533, Arg-364, Gln-421, & Lys-374 are the key residues in the binding pockets responsible for molecular binding with CPT derivatives.
• QSAR results indicate that connectivity index, electron affinity, molecular weight, & ether group count highly contribute to inhibitory activity of CPT derivatives on Topo-I, followed by H-bond, hydrophobic and electrostatic factors.

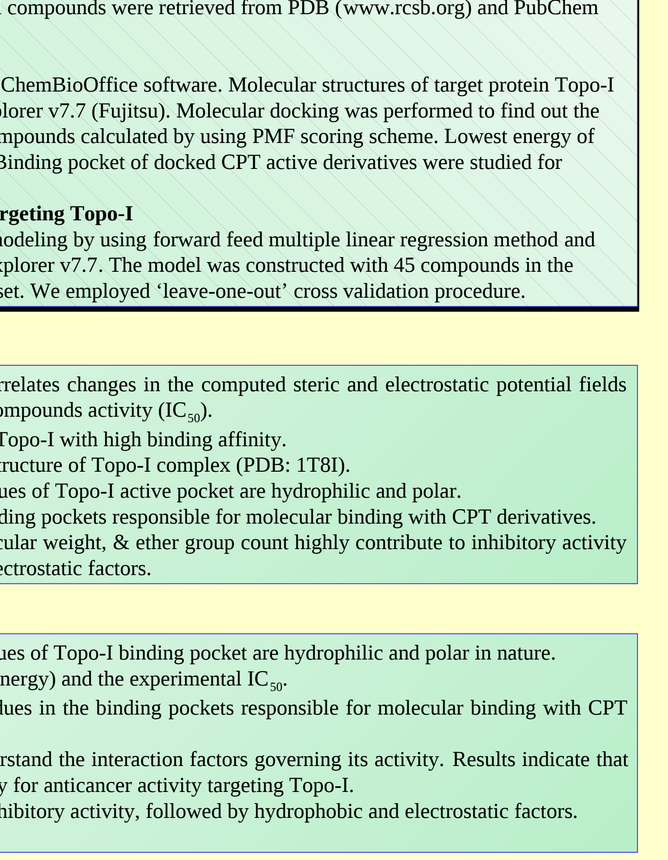
Conclusion

• The docking results of 10 CPT derivatives showed that the active residues of Topo-I binding pocket are hydrophilic and polar in nature.
• There was a significant correlation between binding affinity (docking energy) and the experimental IC_{50}.
• Moreover, Asp-533, Arg-364, Gln-421, and Lys-374 are the key residues in the binding pockets responsible for molecular binding with CPT derivatives.
• QSAR model for CPT derivatives was successfully developed to understand the interaction factors governing its activity. Results indicate that the developed QSAR model is robust and have good predictive capability for anticancer activity targeting Topo-I.
• The QSAR results indicate that hydrogen bonds highly contribute to inhibitory activity, followed by hydrophobic and electrostatic factors.
• The results of QSAR were consistent with the molecular docking.

Table 1. Comparison of experimental and predicted *in vitro* activity (IC_{50}) data calculated through developed QSAR model based on correlated chemical descriptors.

Chemical Sample	Exp. IC_{50} (nM)	Exp. log IC_{50} (nM)	Pred. log IC_{50} (nM)	Connectivity Index (order 1, std.)	Electron Affinity (eV)	Molecular Weight	Group Count (Ether)
1(CPT)	677	2.831	2.753	12.525	1.534	348.357	0
2 Topotecan	1046	3.020	3.097	13.346	1.499	378.384	0
32 (methylenedioxy)	416	2.619	2.472	17.868	1.538	504.541	2
33 (methylenedioxy)	27	1.431	1.390	13.991	1.580	392.367	2
34 (methylenedioxy)	15	1.176	1.372	13.991	1.574	392.367	2
35 (methylenedioxy)	150	2.176	2.204	14.419	1.577	426.812	2
36 (methylenedioxy)	61	1.785	1.553	14.419	1.563	407.382	2
38 (methylenedioxy)	210	2.322	2.418	17.475	1.597	489.527	2
39 (methylenedioxy)	160	2.204	1.973	15.957	1.609	445.431	2
41 (methylenedioxy)	140	2.146	2.210	17.475	1.561	486.483	2
42 (methylenedioxy)	100	2.000	2.388	18.406	1.461	519.553	2
44 (ethylenedioxy CPT)	300	2.477	2.386	18.868	1.417	532.595	2
45 (ethylenedioxy CPT)	11	1.041	1.169	14.919	1.401	420.421	2
46 (ethylenedioxy CPT)	190	2.279	2.121	18.475	1.408	517.580	2
48 (ethylenedioxy CPT)	180	2.255	2.470	18.475	1.552	514.537	2
50 (ethylenedioxy CPT)	600	2.778	2.565	19.406	1.426	547.607	2
MSB3a			2.516	12.525	1.457	348.357	0
MSB3b			2.517	12.525	1.458	348.357	0
MSB19			2.112	13.957	1.481	392.410	1
MSB 22L			1.846	15.439	1.539	438.436	2
MSB 22M			1.849	16.350	1.430	466.490	2
MSB 22O			0.977	16.905	1.420	480.516	3
MSB 22R			0.977	15.939	1.537	452.463	2
MSB 25D			0.536	10.298	1.118	245.349	0
MSB 37G			1.279	18.963	1.464	526.501	2
MSB39 D			1.559	14.419	1.565	407.382	2

Figure 1. Multiple linear regression curve for CPT QSAR modeling showing comparison of experimental logIC_{50} and predicted logIC_{50}.



Predicted logIC_{50} (nM) (C) =
-0.591058 x Connectivity Index (order 1, standard) (H)
+3.0669 x Electron Affinity (eV) (N)
+0.0312332 x Molecular Weight (Z)
-1.00655 x Group Count (ether) (AH)
-5.42856
[rCV^2=0.869478; r^2=0.899566]

Matrix used for QSAR modeling= d x n
Chemical descriptors used for forward feed multiple linear regression(d)=52
No. of reference/known drugs (n) = 45
No. of test compounds used for the prediction of activity = 4

S. No.	Compound	DNA Topo-I protein PDB ID	Docking energy (Kcal/mol)	Binding pocket residues (4Å)	Atoms of involved in docking	Residues involved in docking	Length of H-bond (Å)	No. of H-bond
1	CPT	1T8I	-73.43	PHE—361, GLY-363, ARG-364, HIS—367, LYS-493, THR-498, , ALA-499, LYS-532, ASP-533	-	-	-	-
2	TOPOTECAN	1T8I	-77.60	PHE—361, GLY-363, ARG-364, HIS—367, LYS-493, THR-498, , ALA-499, LYS-532, ASP-533	-	-	-	-
3	MSB 3a	1T8I	-78.28	PHE-361, GLY-363, ARG-364, HIS-367, LYS-493, ALA-499, LYS-532, ASP-533	H8356-O23	ASP-533	2.137	1
4	MSB 3b	1T8I	-83.44	PHE-361, GLY-363, ARG-364, HIS-367, LYS-493, ALA-499, LYS-532, ASP-533	H6954-O22	ARG-364	2.177	1
5	MSB 19	1T8I	-81.50	ASN-352, GLU-356, ARG-364, ARG-488, LYS-532, ASP-533, ILE-535,, HIS-632, GLN-633, ALA-715, THR-718	H8045-O21	ARG-488	1.912	1
6	MSB 22L	1T8I	-90.71	GLU-356, PHE-361, GLY-363, ARG-364, HIS-367, LYS-374, LYS-425, LYS-493, THR-498, ALA-499, LYS-532, ASP-533, SER-534	H8356-O23	ASP-533	1.928	1
7	MSB 22M	1T8I	-94.15	PHE-361, ARG-362, GLY-363, ARG-364, LYS-374, GLN-421, LYS-425, LYS-493, THR-498, ALA-499, THR-501, LYS-532, ASP-533	H7045-O23	LYS-374	2.169	1
8	MSB 22O	1T8I	-92.51	GLU-356, PHE-361, GLY-363, ARG-364, HIS-367, LYS-374, ILE-420, GLN-421, SER-423, LYS-425, LYS-493, THR-498, ALA-499, LYS-532, ASP-533	H7437-O32 H8356-O23	GLN-421 ASP-533	2.137 2.076	2
9	MSB 22R	1T8I	-94.96	GLU-356, PHE-361, PHE-361, GLY-363, ARG-364, HIS-367, THR-498, ALA-499, LYS-532, ASP-533, SER-534	H8356-O23	ASP-533	2.036	1
10	MSB 25D	1T8I	-79.62	ARG-488, LYS-532, ASP-533, ILE-535, LYS-587, ARG-590, ASN-631, HIS-632, GLN-633, THR-718	H8044-N7	ARG-488	2.016	1
11	MSB 37G	1T8I	-110.36	PHE-361, ARG-362, GLY-363, ARG-364, LYS-374, GLN-421, ARG-488, LYS-532, ASP-533, ILE-535, HIS-632, GLN-633, ALA-715, THR-718	H8354-O23	LYS-532	2.005	1
12	MSB 39D	1T8I	-82.62	ASN-352, GLU-356, PHE-361, GLY-363, ARG-364, HIS-367, LYS-374, GLN-421, LYS-425, ALA-499, LYS-532, ASP-533	H8356-O23 H6954-O18	ASP-533 ARG-364	1.816 2.061	2

Table 2. Details of binding affinity of CPT derivatives and its binding pocket residues docked on Topo-I.

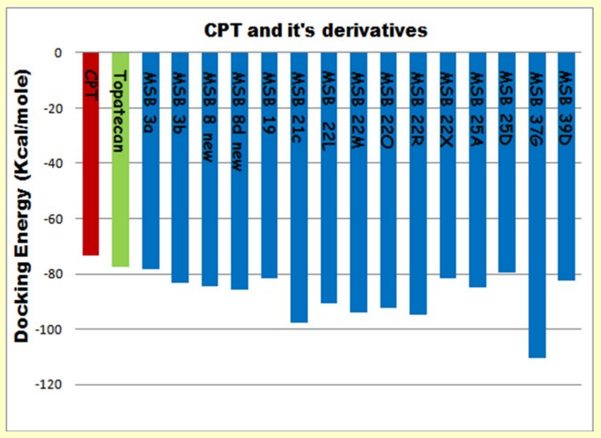


Figure 2. Docking score of CPT derivatives with anticancer human target DNA Topo-I.

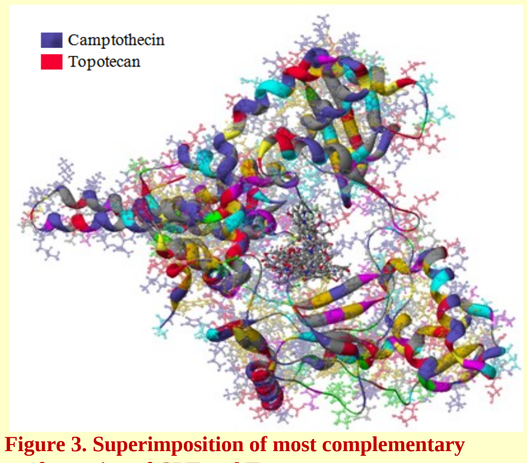
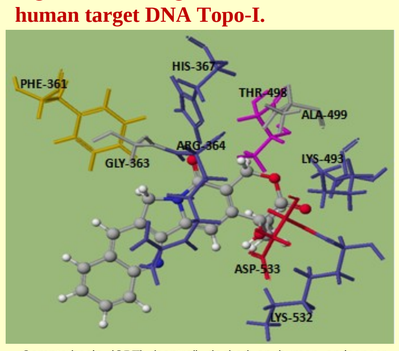
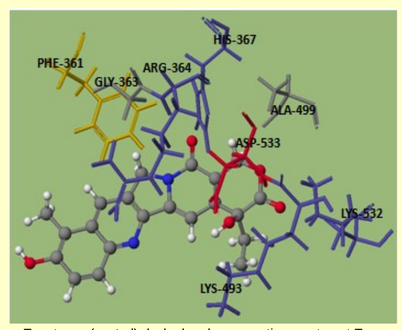


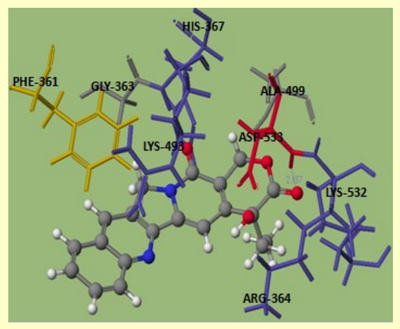
Figure 3. Superimposition of most complementary conformation of CPT and Topotecan.



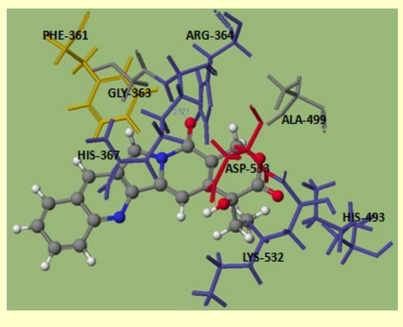
Camptothecin (CPT) (control) docked on human anticancer target enzyme DNA Topoisomerase-I (Topo-I) (1T8I) with docking score -73.43 kcal/mol.



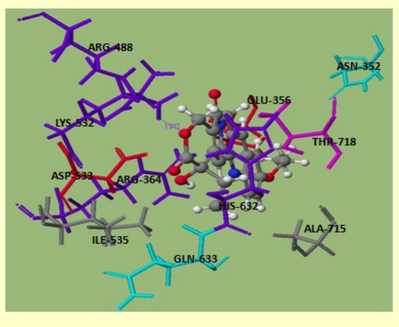
Topotecan (control) docked on human anticancer target Topo-I (1T8I) with docking score -77.60 kcal/mol.



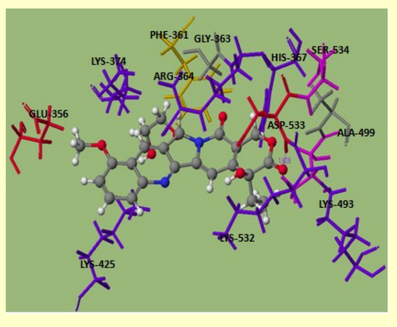
CPT derivative (3a MSB) docked on Topo-I anticancer receptor with docking score -73.28 kcal/mol.



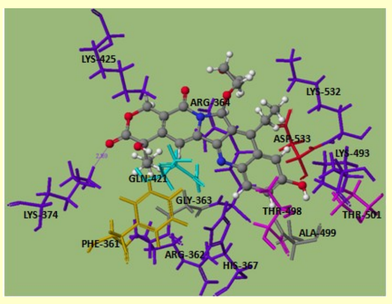
CPT derivative (3b MSB) docked with high affinity on Topo-I with docking score -73.44 kcal/mol.



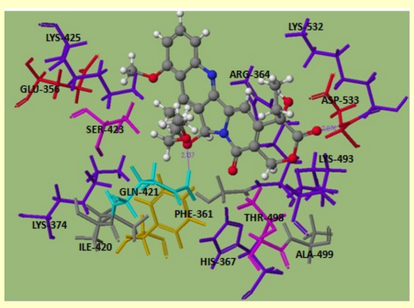
CPT derivative (19 MSB) docked with high affinity on Topo-I with docking score -81.50 kcal/mol.



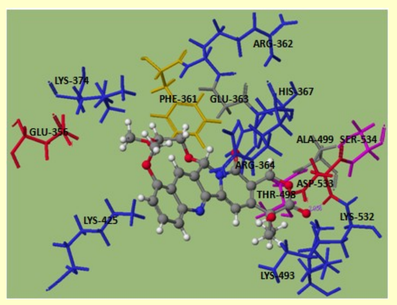
CPT derivative (22L MSB) docked with high affinity on Topo-I with docking score -90.71 kcal/mol.



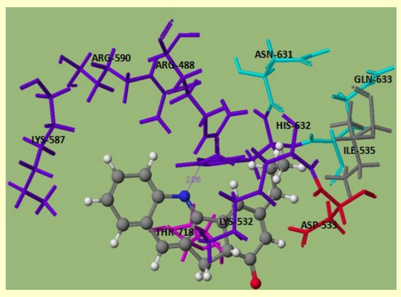
CPT derivative (22M MSB) docked with high affinity on Topo-I with docking score -94.15 kcal/mol.



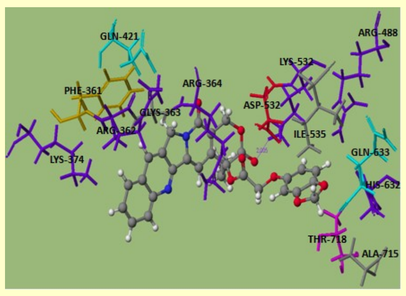
CPT derivative (22O MSBDK) docked with high affinity on Topo-I with docking score -92.51 kcal/mol.



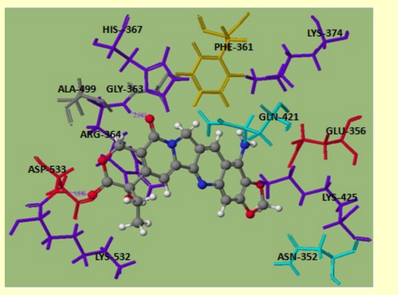
CPT derivative (22R MSBDK) docked with high affinity on Topo-I with docking score -94.96 kcal/mol.



CPT derivative (25D MSB) docked with high affinity on Topo-I with docking score -79.62 kcal/mol.



CPT derivative (27G MSB) docked with high affinity on Topo-I with docking score -110.36 kcal/mol.



CPT derivative (39D MSB) docked with high affinity on Topo-I with docking score -82.62 kcal/mol.

Figure 4. Molecular insight of CPT derivatives docked on human anticancer target DNA Topomerase-I showing binding site pocket residues comparable to Camptothecin and Topotecan.

Acknowledgment

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References

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