CHAPTER 3

A comparative QSAR analysis and molecular docking studies of camptothecin derivatives as DNA-topoisomerase I inhibitor: A impartial approach to anticancer drug design

IN THIS CHAPTER-

- INTRODUCTION
- COMPUTATIONAL DETAILS
- QSAR MODELING AND ANALYSIS
- MOLECULAR DOCKING

OUTLOOK-

- ✓ DFT based reactivity descriptors in combinations with physicochemical descriptors are used to study the activity of substituted CPTs.
- ✓ Out of the various types of calculated descriptors, the hydration energy is found to be more predominant in describing the cytotoxicity of CPTs.
- ✓ Docking studies are also performed in order to ensure the binding affinity of the selected molecules against 1T8I.
- ✓ The Docking study reveals that CPT and some of its analogue are potent inhibitors of the enzyme 1T8I.

3.1 Introduction

Camptothecin is the first topoisomerase I inhibitory drug isolated from *Camptotheca acuminate*.[1,2] It is also one of the prominent leading compounds for the development of anticancer drug. Because of the marked activity of camptothecin 20-S in a number of leukemia[1] and solid tumor systems[3], it has drawn the eyes of researcher to work in this type of pentacyclic system. Camptothecin possesses a pentacyclic ring system (Figure 3.1) with an asymmetrical center at ring E having 20-S configuration. The pentacyclic ring system includes a pyrrolo-quinoline moiety (rings A, B, and C), a conjugated pyridone (ring D) and a six-membered lactone (ring E) with a α-hydroxyl group.[4,5] Under the physiological pH condition, camptothecin undergoes a reversible hydrolysis and there occurs a dynamic equilibrium between the close ring lactone and open ring carboxylic acid as shown in Figure 3.2. The lactone form predominates at acidic pH whereas the inactive carboxylate form prevails at neutral and alkaline pH.

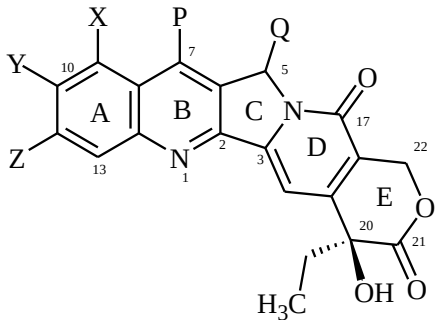
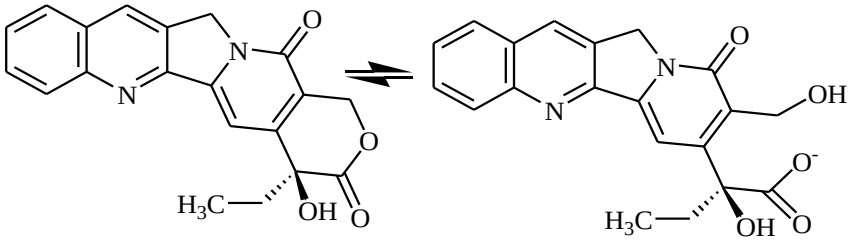


Figure 3.1 Structure of Camptothecin



Lactone form Carboxylate form

Figure 3.2 Interconversion between the lactone and carboxylic form of camptothecin

Camptothecins are generally classified into two groups, first one is water soluble Topotecan[6], and Irinotecan[7]. Topotecan is currently used as a second line agent for the clinical treatment of the ovarian and small-cell lung cancers[8,9] and Irinotecan[10,11] is presently used for the colon cancers. The second group comprises of the water insoluble, mother compound camptothecin[12] and its synthetic derivatives 9-nitro camptothecin, 9-amino camptothecin, lurtotecan, exatecan, diflomotecan, karenitecin and gimatecan[13] which are in clinical trials.

Camptothecin and some of its analogue are potent inhibitors of the enzyme DNA-topoisomerase I. The CPTs exerts their pharmacological activity by stabilizing the covalent protein DNA complex and enhancing apoptosis through blocking the advancement of replication forks. The molecules are first going to interact with the topo I-DNA cleavable complex, the collision between the complex and the replication fork occurs during S-phase which breaks the DNA double strand that eventually lead to cell death.[14,15] It has also been suggested that topo I cleaves DNA at multiple sites. However, sites of cleavage stabilized by CPT exhibit a strong preference for guanine at +1 position, while thymidine remains the preferred nucleobase at the -1 position.[16] The exact mechanism by which CPT stabilizes the DNA topo I covalent binary complex is not fully understood because the drug acts as an uncompetitive inhibitor and binds only the transient binary complex.[17]

More generally, QSAR began with the pioneering work of Hansch[18] who used multiple linear regression (MLR) to build predictive models of the biological active compounds. Quantitative Structure-Activity Relationship (QSAR) study is basically concerned with the correlation of structure with property or activity.[19] Several physicochemical descriptors, such as hydrophobicity, topology, electronic parameters and steric effects, are usually used in QSAR studies in many disciplines, with many pertaining to drug design and environmental risk assessments.[20] There have been a number of QSAR studies evaluating the relationship between camptothecin structure and topoisomerase I inhibiting activity using various statistical methods such as multiple linear regression and genetic algorithm.[21,22] However, DFT based reactivity descriptors have not been used in any of the previous QSAR study to investigate the cytotoxity of camptothecin and its

analogues. Inspired from the foregoing discussion, an attempt has been made to study QSAR on camptothecin using hydration energy and other physiochemical parameter along with DFT based descriptors for 32 camptothecin compounds substituted with various groups that inhibit different cancer cells *viz*. HL-60 leukemia cells, SN-38 resistant cells and UACC-62(melanoma) cancer cells.

3.2 Methodology

3.2.1 Computational Details

We calculated all the DFT based reactivity descriptors for the compounds using DMol^3 programme.[23] The compounds are subjected to full geometry optimization using double numerical with polarization (DNP) basis set in combination with the hybrid BLYP functional.[24-26] The DNP basis set is comparable to Gaussian 6-31G** basis set.[27-29] However, it is believed to be much more accurate than a Gaussian basis set of the same size. The physiochemical parameter namely hydration energy (HE), logP, surface area (SA), molar refractivity (MR) and polarizability (Pol), for each of the compound are computed using Hyperchem software.[30] These parameters are used to generate various QSAR equations and to calculate cytotoxity (pIC_{50}) of the compounds.

3.2.2 Docking

We have also performed molecular docking study as it has gained enormous importance in the field of drug designing. These approaches help us to recognize some potent drug candidates for some more rigorous calculations, whose target is already known. The three dimensional structure of DNA-topoisomerase I is retrieved from protein data bank having 3.00 resolution (protein id 1T8I).[31]

The docking calculation is performed using Molegro Virtual Docker (MVD) 5.0 (Molegro ApS, Aarhus, Denmark) with all the potential active site detected on 1T8I.[32] The scoring functions which reflects the binding affinity are calculated by taking into account of all hydrogen bond that is being formed between the ligand with the amino acid residues. The scoring is done by considering the numerous orientations of the ligands with respect to the target protein. We have not taken into account the water molecules in our study.[38] In order to locate the active potential interacting site, the cavity detection algorithm in MVD is used. A set of 100 runs are given for each docking study using 2000

interactions and both the Rerank score and the MolDock score are evaluated. The best fit score was obtained on the basis of the Rerank score.

3.3 Results and Discussion

The list of studied camptothecin (CPT) compounds along with their pIC_{50} values, are provided in Table 3.1. Values of the DFT based descriptors such as chemical hardness (η), chemical potential (μ) and electrophilicity (ω) computed at BLYP/DNP level for 32 CPT compounds along with the physicochemical parameters such as hydration energy, logP, surface area, refractivity and polarizability are obtained from the MM+ computations with Hyperchem software[33] are presented in Table 3.2.

Table 3.1 List of compounds with different substituents and pIC_{50} values

Compounds	**X**	**Y**	**Z**	**P**	**Q**	**pIC_{50}**
1	H	CH_3	H	OCH_3	H	7.18
2	H	CH_2CH_3	H	OCH_3	H	7.59
3	H	$(CH2)_2CH_3$	H	OCH_3	H	7.66
4	H	$(CH2)_3CH_3$	H	OCH_3	H	8.47
5	H	OH	H	CH_2CH_3	H	6.58
6	H	CH_3	H	CH_2CH_3	H	8.86
7	H	Br	H	CH_2CH_3	H	9.03
8	H	Cl	H	CH_2CH_3	H	8.67
9	H	H	Br	CH_2CH_3	H	8.54
10	H	H	Cl	CH_2CH_3	H	8.75
11	H	H	F	CH_2CH_3	H	9
12	H	H	OH	CH_2CH_3	H	6.96
13	H	Cl	Cl	CH_2CH_3	H	8.8
14	H	NH_2	H	CH_2CH_3	H	7.62
15	H	OCH_3	F	CH_2CH_3	H	8.94
16	H	OH	F	CH_2CH_3	H	7.06

17	H	CH_3	F	CH_2CH_3	H	8.82
18	H	F	F	CH_2CH_3	H	8.66
19	H	OH	H	H	CH_2COOCH_3	5.39
20	NO_2	H	H	H	CH_2COOCH_3	5.12
21	H	OH	H	H	CH_2COCH_3	6.7
22	H	H	H	H	$CH_2COOCH_2CH_2F$	7.15
23	H	H	H	H	$CH_2COOCH_2CH_2OH$	4.8
24	H	H	H	H	$CH_2COOCH_2CF_3$	7.18
25	H	H	H	H	CH_2CONH_2	7.59
26	CH_3	H	H	H	H	6.93
27	CH_3CH_2	H	H	H	H	7.11
28	$(CH_2)_2CH_3$	H	H	H	H	6.73
29	$(CH_2)_3CH_3$	H	H	H	H	6.41
30	H	OCH_3	H	H	H	6.51
31	H	H	H	H	CH_2COOCH_3	5.19
32	H	H	H	H	CH_2COCH_3	5.45

Table 3.2 Calculated values of the selected descriptors for all compounds

No	EHOMO (au)	ELUMO (au)	ENL (au)	ω (au)	HE	logP	REF ($Å^3$)	Pol ($Å^3$)	SA ($Å^2$)
1	-0.193	-0.109	-0.0823	0.2711	-10.13	5.64	49.35	40.49	507.42
2	-0.192	-0.108	-0.0819	0.2683	-9.75	6.04	53.95	42.33	528.28
3	-0.192	-0.108	-0.0816	0.2668	-9.27	6.44	58.55	44.16	570.62
4	-0.192	-0.107	-0.0814	0.266	-8.88	6.83	63.15	46	609.58
5	-0.196	-0.11	-0.0855	0.272	-14.8	6.11	48.91	40.49	482.48
6	-0.197	-0.11	-0.0835	0.2721	-7.13	6.6	52.14	41.69	507.84
7	-0.203	-0.12	-0.0922	0.3118	-7.89	7.18	54.84	42.48	513.4
8	-0.203	-0.119	-0.0917	0.3091	-7.9	6.91	52.02	41.78	503.82
9	-0.204	-0.12	-0.0913	0.3118	-7.84	7.18	54.84	42.48	515.81
10	-0.203	-0.119	-0.0907	0.3094	-7.86	6.91	52.02	41.78	506.3
11	-0.203	-0.119	-0.0881	0.3071	-7.9	6.53	47.43	39.76	481.67
12	-0.198	-0.112	-0.0807	0.2785	-14.94	6.11	48.91	40.49	485.34
13	-0.205	-0.123	-0.0951	0.3298	-7.63	7.54	56.52	43.71	539.77
14	-0.187	-0.104	-0.08	0.2538	-13.16	5.42	50.86	41.2	475.44
15	-0.197	-0.111	-0.0847	0.2744	-9.25	6.29	53.86	42.23	531.01
16	-0.199	-0.114	-0.0875	0.2885	-13.71	6.36	48.82	40.4	492.61

17	-0.2	-0.115	-0.0854	0.2899	-6.95	6.85	52.04	41.6	517.68
18	-0.205	-0.122	-0.0933	0.3198	-7.69	6.78	47.34	39.67	492.27
19	-0.197	-0.111	-0.0872	0.2773	-18.77	7.3	52.1	43.05	550.6
20	-0.211	-0.143	-0.1223	0.4597	-16.36	7.51	56.71	44.13	570.71
21	-0.198	-0.112	-0.0874	0.2793	-16.18	7.44	50.93	42.41	524.77
22	-0.204	-0.116	-0.0893	0.2918	-11.15	7.63	55.32	44.16	567.92
23	-0.201	-0.113	-0.0866	0.2822	-17.35	7.03	57.01	44.88	569.38
24	-0.206	-0.118	-0.0916	0.2981	-11.37	8.45	56.17	43.97	579.96
25	-0.202	-0.112	-0.0857	0.2763	-15.48	6.84	47.62	41.29	477.52
26	-0.199	-0.1142	-0.0856	0.2875	-8.58	5.89	42.93	38.02	445.62
27	-0.1993	-0.1133	-0.0854	0.2839	-8.16	6.28	47.53	39.85	467.18
28	-0.1992	-0.1128	-0.0851	0.2819	-7.76	6.68	52.13	41.69	506.12
29	-0.1989	-0.1124	-0.0846	0.2801	-7.43	7.08	56.73	43.52	535.86
30	-0.1952	-0.1121	-0.0855	0.2839	-11.08	5.33	44.74	38.66	481.18
31	-0.202	-0.114	-0.0875	0.2853	-12.01	7.47	50.72	42.41	534.23
32	-0.202	-0.115	-0.088	0.2884	-9.42	7.62	49.55	41.77	508.14

3.3.1 QSAR analysis

Based on the DFT calculations, different descriptors are selected for QSAR modeling such as the energy of highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), energy of the next lowest unoccupied molecular orbital (E_{NL}), electorphilicity (ω) etc. The HOMO and LUMO descriptors are frequently calculated as these orbitals can influence the chemical reactivity and hence the reaction mechanism. The HOMO features the susceptibility of a molecule towards attack by nucleophile, whereas LUMO characterizes the susceptibility of a molecule towards the attack by electrophiles in chemical reactions.[34]

In addition, molecular mechanics (MM) parameters such as hydration energy, molecular refractivity index (MR), surface area (SA), hydrophobicity (logP) of the compounds are also selected. The biological activity data (pIC_{50}) of compounds (1-32) against various cancer cells are taken from the results reported in the literature.[35-37] At the first step, we perform the simple linear regression for twenty seven camptothecins by considering the pIC_{50} as dependent variable and other descriptors as single independent variable. However, the correlations of pIC_{50} with all the individual descriptors are found to be very much insignificant except in case of hydration energy and there exists auto correlation among the various parameters. From simple linear regression analysis descriptors having greater correlation to cytotoxicity (pIC_{50}) are selected out to perform the stepwise multiple linear regression (MLR). In MLR analysis, hydration energy is kept fixed as one of the independent variable and then MLR equations are generated utilizing the pool of all calculated descriptors. The autocorrelation values of the parameters are shown in Table 3.3. The predictability of the models is determined using the "leave one out (LOO)" cross-validation method.

The QSAR modeling with absolute values of statistical parameters are initially developed for twenty seven CPT derivatives (compound 1-25, 31 and 32) against the cytotoxicity (pIC_{50}) values. The values of the correlation coefficient (R^2) when calculated by considering the cytotoxicity (pIC_{50}) as dependent variable and other physical descriptors as independent variable (keeping hydration energy fixed in every case) are

found to be in the range of 0.627-0.69. However, on swapping of the compounds 31 and 32 improve the value of R^2 to an acceptable one.

The QSAR equations after deleting compounds 31 and 32 with significant statistical quality are presented in Table 3.3. The positive coefficients of the hydration energy in all the equations in Table 3.3 suggest that higher hydration energy favours the biological activity of compounds. In equation E_1 the negative coefficients of logP suggests that lower value of logP (Octanol-water partition coefficients) favours the inhibitory action of camptothecins. The molecular refractivity (MR) index of a compound is a combined measure of its size and polarizability.[38] Surface area (SA) is mainly the size of a molecule. The QSAR equations E_2, E_3 and E_4 results from the inclusion of these parameters gives high significant correlation coefficient (R^2) indicating that the inhibitory activity of the camptothecins is related to the above three parameter. The positive coefficient of MR in equation E_2 brings about no steric effect of the substituents at various positions. The negative coefficients of the parameters in E_3 and E_4 suggest that an increase in the polarizability and size of the molecule will reduce the cytotxic activity of the compounds. It has been proposed that the lactone carbonyl oxygen, oxygen and the H-atom of the 20-OH group of CPT are involved in the hydrogen bonding with the topo I-DNA.[39-42] This type of interaction involves the nucleophillic attack at this site. The nucleophillic attack at a particular site of a system represents the sites with maximum values of Fukui function, f^+ and the electroophillic attack at a particular site of a system represents the sites with maximum values of Fukui function f^-. The negative coefficients of the f^- in equation E_5 and E_6 of the lactone carbonyl oxygen and oxygen of 20-OH group in the E-ring of camptothecin indicates that these two position of the ring are less susceptible to electrophillic attack. However, the negative coefficient of f^+ in equation E_7 and and positive coefficient in E_8 suggest that the lactone carbonyl oxygen and oxygen of 20-OH group sites are more susceptible to nucleophillic attack which is in good agreement with the reported results[43] and theses two positions of the E-ring are favourable site for interacton with topo-DNA complex. So, increasing value of f^+ at

these sites will increase the inhibitory action of the compounds. Similar to this, the negative coefficients Fukui functions (f^+ and f^-) at H-20 (hydrogen 20-OH group) of the CPT in equation E_9 and E_{10} demonstrate that increasing either of the Fukui functions at H-20 of 20-OH group would retard the inhibitory action of these compounds. Experimentally, it has also been proposed that the replacement of 20-OH group by amino or halogens reduces the activity[16] of the camptothecins.[43] The high negative coeffecients of the descriptor ω in equation E_{11} suggest that electrophilicity, ω has negative effect on the cytotoxicity of the CPTs. The D/E ring of CPT derivatives with respect to their involvement in hydrogen bonding with the topo I-DNA complex, the four oxygen serve as the hydrogen bond acceptor and the mechanism involves the nucleophilic attack at this site. In this type of interaction E_{LUMO} and E_{NL} play an important role. The lower values of these parameters increases the capacity of the molecules to accept electrons from DNA making the system stable. We found that coefficient of E_{NL} and E_{LUMO} in E_{12} and E_{13} are positive suggesting that lower value of E_{NL} and E_{LUMO} will highly favour the intermolecular interaction between the topoI-DNA complex and camptothecin molecule, thus, enhanced the cytotoxity. The positive value of the coefficient of E_{HOMO} in E_{14} indicates that during the part of interaction with the cancer cell, the increase in the energy of the HOMO orbital will favour the intermolecular interaction of camptothecin with the topo-DNA complex. The negative coefficient of fukui function in equation E_{15}, E_{16}, E_{17} and E_{18} suggest that substitution at 10 and 11 position of the A-ring makes these two sites less prone for both nucleophillic and electrophillic attack and an increase in either values f^+ or f^- will have negative effect on the biological activities of camptothecins. Similarly, the negative coefficient of f^- in E_{19} suggests substitution at 9 position of B-ring of camptothecins makes it less favourable site for electrophillic attack. However, the positive coefficient of f^+ in equations E_{20} and E_{21} suggest that substitution at 9 position of B-ring and substitution at 5 position of C-ring favours the nucleophillic attack at these two positions and increase the anticancer activity of camptothecins.

Table 3.3 Results of MLR with different set of compounds using various descriptors

No	QSAR equations	N	R^2	SE	F	Auto correlation	Q
E_1	12.46404 – 0.20691 logP + 0.313714 HE	25	0.81	0.597	47.24	0.01	1.5
E_2	10.6538 + 0.00783 MR + 0.3146 HE	25	0.80	0.614	44.1	0.01	1.45
E_3	11.7188 – 0.00124 SA + 0.314771 HE	25	0.80	0.613	44.29	0.01	1.46
E_4	11.8357 – 0.01813 Pol + 0.31476 HE	25	0.80	0.614	44.1	0.01	1.45
E5	11.33047–14.6824 f^-_{LAC} +0.31673 HE	25	0.80	0.61	43.99	0.07	1.46
E_6	11.24046 – 11.2336 f^-_{OXY} + 0.317 HE	25	0.80	0.614	44.03	0.04	1.45
E_7	10.20972 + 0.31704 HE – 65.76119 f^+_{LAC}	25	0.80	0.61	44.67	0.00	1.46
E_8	10.7525 + 0.321431 HE + 67.026 f^+_{OXY}	25	0.80	0.61	44.59	0.10	1.46
E_9	11.49275 – 31.5481 f^-_{H} +0.317751 HE	25	0.80	0.613	44.131	0.05	1.45
E_{10}	11.11185 + 0.315718 HE – 3.5269 f^+_{H}	25	0.80	0.614	43.96	0.00	1.45
E_{11}	11.66484 + 0.3149 HE – 2.01309 ω	25	0.80	0.609	44.98	0.00	1.47
E_{12}	12.13551 + 12.3595 E_{NL} + 0.3125 HE	25	0.80	0.605	45.64	0.01	1.48
E_{13}	12.20541 + 9.73146 E_{LUMO} +0.31627 HE	25	0.80	0.609	44.87	0.00	1.47
E_{14}	13.98112 +14.4838 E_{HOMO} + 0.31677 HE	25	0.80	0.609	45.01	0.00	1.47
E_{15}	12.50915 – 53.1668 $f^-_{C\ 10}$+ 0.283735 HE	25	0.82	0.583	49.92	0.29	1.55
E_{16}	11.35084 – 6.51125 $f^+_{C\ 10}$ + 0.313771 HE	25	0.80	0.613	44.3	0.02	1.46
E_{17}	12.26247 – 63.1134 $f^-_{C\ 11}$+0.280777 HE	25	0.82	0.588	49.08	0.36	1.54
E_{18}	11.85845 + 0.297141 HE – 25.254 f^+_{C11}	25	0.81	0.6	46.561	0.23	1.50
E_{19}	11.15184 – 4.3445 $f^-_{C\ 9}$ +0.312822 HE	25	0.80	0.613	44.126	0.09	1.45
E_{20}	11.0386 + 1.072752 f^+_{C9} + 0.315376 HE	25	0.80	0.614	43.96	0.07	1.45
E_{21}	8.88612 + 0.254651 HE + 165.75 f^+_{C5}	25	0.84	0.546	58.56	0.41	1.68

In order to check the model predictivity, the compounds (1-25) are considered as a training set and other seven compounds (26-32) are treated as test set. It is found that the calculated values for the test set compounds fits well into E_7, confirming the validation of our developed models. The predicted pIC_{50} values of the compounds in the test set are presented in Table 3.4

Table 3.4 Experimental and predicted pIC_{50} values of compounds in the test set

Compound	Observed pIC_{50}	Calculated pIC_{50}	Residual
26	6.93	6.56	0.36
27	7.11	6.70	0.40
28	6.73	6.82	-0.09
29	6.41	6.93	-0.52
30	6.51	5.77	0.73
31	5.19	5.48	-0.29
32	5.45	6.30	-0.85

Further, in order to investigate the relative importance of the variable appeared in the final models obtained by multiple regression analysis (MLR), the P-values using the F statics in each equation for each variable are compared. The P-value reflects the importance of variable in multiple regression. A regression model or a QSAR descriptor is significant only if its P-value is <0.05. The P-values for each variable in the studied models are presented in Table 3.5. From the Table 3.5, it can be observed that in all cases the P-value for the hydration energy descriptor is <0.05. On the other hand, the P-values for the other molecular descriptors are found to be more than 0.05 and hence contribute less to QSAR model in determining the cytotoxicity of the studied camptothecins. Thus, the influence of hydration energy parameter is very much prominent than the other parameters. The more positive the hydration energy coefficient more is the cytotoxiciy.

Table 3.5 P-values for each independent variables used in the studied model

Equation	Independent variable		P-values	
	X_1	X_2	X_1	X_2
E_1	logP	HE	0.264	2.6×10^{-9}
E_2	MR	HE	0.810	4.6×10^{-9}
E_3	SA	HE	0.718	4.0×10^{-9}
E_4	Pol	HE	0.813	4.5×10^{-9}
E_5	f^-_{LAC}	HE	0.913	6.9×10^{-9}
E_6	f^-_{OXY}	HE	0.864	5.4×10^{-9}
E_7	f^+_{LAC}	HE	0.599	3.4×10^{-9}
E_8	f^+_{OXY}	HE	0.621	6.7×10^{-9}
E_9	f^-_{H}	HE	0.794	5.3×10^{-9}
E_{10}	f^+_{H}	HE	0.983	3.9×10^{-9}
E_{11}	ω	HE	0.538	3.4×10^{-9}
E_{12}	E_{NL}	HE	0.420	3.9×10^{-9}
E_{13}	E_{LUMO}	HE	0.552	3.2×10^{-9}
E_{14}	E_{HOMO}	HE	0.524	3.1×10^{-9}
E_{16}	f^-_{C10}	HE	0.137	1.9×10^{-9}
E_{17}	f^+_{C10}	HE	0.715	5.0×10^{-9}
E_{18}	f^-_{C11}	HE	0.166	5.6×10^{-7}
E_{19}	f^+_{C11}	HE	0.318	7.2×10^{-8}
E_{20}	f^-_{C9}	HE	0.797	1.1×10^{-8}
E_{21}	f^+_{C9}	HE	0.972	7.5×10^{-9}

The calculated pIC_{50} values of the camptothecins derived from the best fit QSAR model is presented in Table 3.6. The correlation plot between experimental and calculated pIC_{50} for the best fit QSAR model is shown in Figure 3.3.

Table 3.6 Observed and calculated values of pIC_{50} using E_{21}(best fit model)

No.	Observed pIC_{50}	Calculated pIC_{50}
1	7.18	8.12
2	7.59	8.06
3	7.66	8.18
4	8.47	8.28
5	6.58	6.94
6	8.86	8.89
7	9.03	8.53
8	8.67	8.53
9	8.54	8.54
10	8.75	8.54
11	9.01	8.69
12	6.96	6.73
13	8.8	8.6
14	7.62	7.35
15	8.94	8.18
16	7.06	7.21
17	8.82	8.77
18	8.66	8.75
19	5.76	5.1
20	5.39	5.54
21	5.12	5.76
22	6.7	7.04
23	6.7	5.46
24	7.15	6.98
25	4.8	5.93

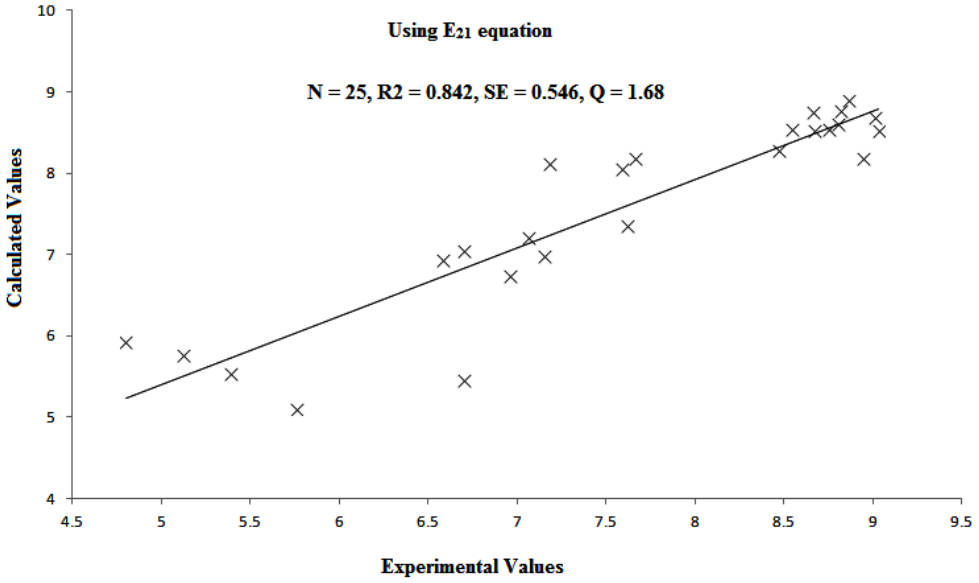


Figure 3.3 Correlation plot between experimental and calculated values using E_{21} (best fit model)

3.3.2 Docking Study

The various CPTs that we have used to build our QSAR models are docked with the target protein 1T8I with 2000 iterations and 100 runs. The results obtained from the study are given in the Table 3.7 for the best six docked scores. Once the docking is over, pose generation is done on the basis of Rerank scores for each ligand. Though the Rernk score are computationally more expensive compared to the other scoring functions used in docking stimulations but it gives better result compared to that of others in determining the relative orientation of the ligand with respect to the target system. Therefore, we have focused on the Rerank score in order to evaluate the best binding pose with respect to the receptor system.

From our study it is clear that compound 30 exhibited a better Rerank score of -87.6607 and Moldock score of -107.397 against all other compounds under study. The amino acid residues which interacted with the ligands are Arg 488, Asn 491, Thr 501, Asp 533, Ser 534, His 367, Arg 364, Gln 421 and Gly 490 (Figure 3.4). The bond distances of

the interacting residues are found to be 2.20 Å, 3.13 Å, 3.20 Å, 3.42 Å, 2.95 Å, 3.03 Å, 2.01 Å, 3.23 Å and 3.78Å, respectively.

Table 3.7 Docking score using Molegro Visual Docker (best six molecules)

Ligand	MolDock Score	Rerank Score	H-Bond
Compound 30	-107.397	-87.6607	-8.41995
Compound 23	-104.472	-80.6461	-4.73333
Compound 28	-108.419	-78.5982	-8.93445
Compound 20	-107.111	-77.3923	-13.3444
Compound 26	-100.3	-77.3462	-9.52696
Compound 15	-92.4565	-77.0328	-8.40256

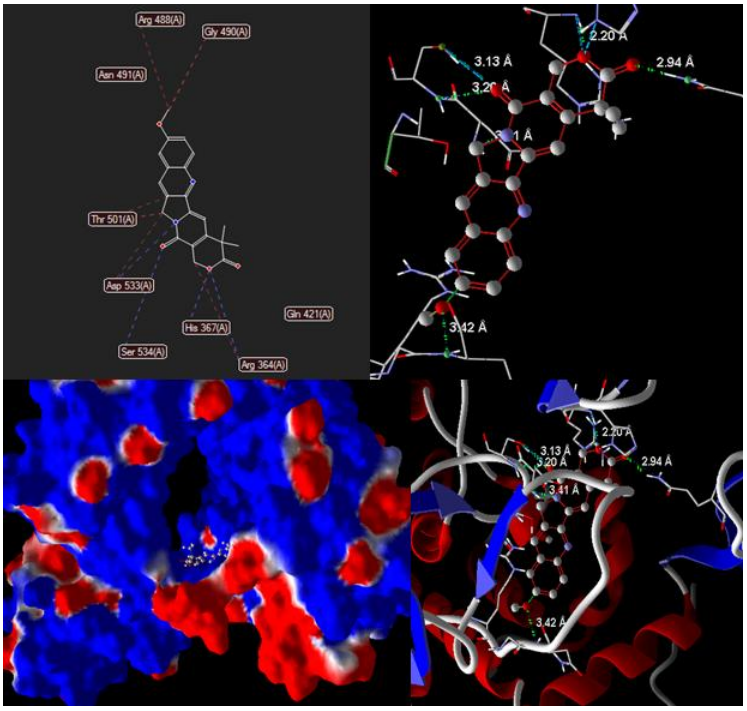


Figure 3.4 Compound 30 at its highest bond cavity of 1T8I

3.4 Conclusion

A systematic theoretical calculation of CPTs has been carried out in order to build quantitative structure activity relationship between pIC_{50} values of camptothecins with their physiochemical parameter and DFT based descriptors. Out of the various types of calculated descriptors, the hydration energy parameter is found to be more predominant in finding the correlation between the cytotoxicity of camptothecin. Different QSAR models reveal that the DFT based reactivity descriptors, electrophilicity and Fukui function has significant impact on the cytotoxicity of camptothecin compounds. The findings of the correlation of the these descriptors with the cytotoxicity (pIC_{50}) of camptothecin compounds lead us to conclude that our calculated DFT based reactivity descriptors are very powerful in investigating quantitative structure and activity relationship of biologically active compounds. The docking result signifies the inhibitory activity of CPT for the target protein. Thus, these class of compound is capable of prohibiting the protein 1T8I.

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