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Biopharma Hypothesis

Design and computational analysis of a derivative of camptothecin

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ABSTRACT

Camptothecin (CPT) as anti-tumor quinoline alkaloid drug is demonstrated. In this research, a derivative of camptothecin, Diol camptothecin, was designed. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were computed to achieve appreciate bioavailability and computational chemistry studies performed using AM1 semi-empirical method to establish the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), electrostatic potential map, virtual fourier transform infrared (FTIR), statistical thermodynamics parameters and chemometrics calculations of Diol CPT in terms of pharmacokinetic and physicochemical descriptors relationships. The obtained results showed that Diol CPT has optimum pharmacological parameters including lack of CYP450 inhibitory and low toxicity.

***Keywords*:** Quinoline alkaloid, camptothecin, bioavailability, ADMET

INTRODUCTION

Camptothecin is a highly potent, naturally occurring anticancer alkaloid that acts by inhibiting both DNA topoisomerase I and HIF-1α activities [1,2]. However, its systemic delivery is due to its low aqueous solubility and nonspecific toxicity. In addition, its anticancer activity of CPT is derived only from its lactone form. The

inactive ring-opened carboxylate form is favored at physiological pH. Furthermore, the carboxylate form binds to human serum albumin (HSA) leading to further CPT ring opening and deactivation [3]. The Food and Drug Administration (FDA) approved CPT derivatives of Irinotecan and Topotecan are used to treat solid tumors in a variety of cancers, but numerous toxicities remain problematic and play a significant role in their clinical efficacy and safety [4,5]. CPT is conjugated to various polymers and is currently evaluated in clinical trials for the treatment of solid tumors [6-9]. All of these molecular conjugates and nanoparticles seek to exploit the enhanced permeability and retention (EPR) effect that causes the preferential accumulation of macromolecules/nanoparticles in solid tumors [10]. Active targeting can be gained by functionalizing the surface of nanoparticles with ligands against over-expressed or specific receptors on tumor cell surfaces. The studies present that active targeting improves the efficacy of nanoparticle therapeutics by increasing the cellular uptake of the targeted nanoparticles compared with non-targeted nanoparticles with similar size and surface charge [11-13]. Moreover, CPT derivatives with low solubility and severe side effects could decrease white blood cells and red blood cells count. Moreover, cytotoxicity, chemical instability of the hydroxylactone ring and multi drug-resistance (MDR) are some of other limitations of CPT applications. So many attempts have been done to manipulate and design the CPT analogues to reduce to toxicity, dose-limiting side effects and improving pharmacokinetics properties, which consequently could increase activity [14]. In this research, we design a new bioisoester of Camptothecin which physicochemical and pharmacologic properties were evaluated.

MATERIALS AND METHODS

The Diol CPT structure was designed by Avogadro and Chemdoodle 7.0.2 software. thermo physical parameters including the heat of formation, zero-point energy (ZPE), enthalpy, entropy using the AM1 semi-empirical by wave function spartan version .16. Pharmacologic parameters were predicted using ChemAxon and Swiss-ADME software. Principal component analysis (PCA) as chemometrics analysis of CPT analogues was done by XLSTAT 2018 version statistical package.

RESULTS

The designed derivative of Camptothecin is shown in figure 1 and electrostatic potential

map and HOMO-LUMO molecular orbitals are presented in figure 2 and figure 3.

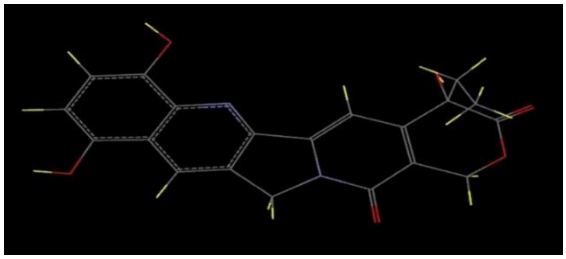

Figure 1. Optimized structure of Diol CPT by Avogadro software.

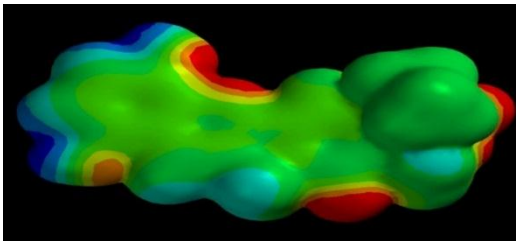

Figure 2. Electrostatic potential map of Diol CPT.

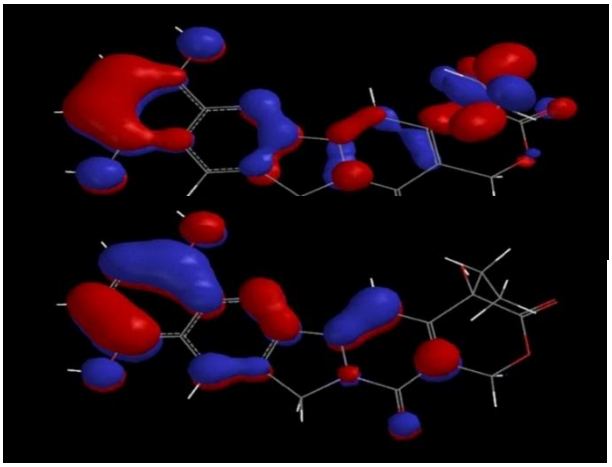

Figure 3. HOMO-LUMO molecular orbitals in Diol CPT.

In fact, electrostatic potential map in figure 2 illustrates distribution of molecule charge in three dimension which could be used to predict CPT interactions and identification of nucleophilic and electrophilic zones with DNA topoisomerase I so that red zones illustrate low potential areas which is electron enrichment sites and blue zones have high potential with absence of electrons. As in the figure 3 is shown the most important HOMO and LUMO molecular orbitals of CPT molecule that play key role in intermolecular interactions between CPT and DNA topoisomerase I.

Actually, hydroxylation of C-9 and C-12 that modified Camptothecin A ring, which made a new bioisostere of CPT. calculated pharmacokinetics and physicochemical parameters are displayed in table 1. furthermore, radar chart optimality, carcinogenicity and toxicity probability of Diol CPT are described in table 1 and table 2, also optimality of physicochemical properties are shown in figure 4.

Table 1. Pharmacokinetics and physicochemical parameters of Diol CPT

Physicochemical properties	
TPSA	121.88 A^2
Molar refractivity	99.36
Consensus Log o/w	1.45
Log S	-3.20
Monoisotopic Mass	380.100
Polarizability	38.10
Pharmacokinetics properties	
Gastrointestinal (GI)	High
BBB permanent	No
P-gp Substrate	No
Log Kp(Skin Permeation)	-7.89 cm/s

Table 2. Toxicity and carcinogenicity probability of Diol CPT

Rat Acute Toxicity	**3.0860**	**LD50, mol/kg**
AMES Toxicity	**Non AMES toxic**	0.5559
Carcinogens	**Non-Carcinogens**	0.8392
Acute Oral Toxicity	**II**	0.5511
Carcinogenicity (Three-class)	**Non-required**	0.5216

Table 3. Calculated thermophysical parameters of CPT using semi-empirical method

Term	**ZPE (kJ/mol)**	**Enthalpy(kJ/mol)**	**Entropy(J/mol.K)**	**Cv (J.mol.E)**
Total Vibrations	847.2510	46.9935	264.73181	274.1960
Ideal Gas		2.4789	-	-
Translation		3.7184	182.8411	12.4716
Rotation		3.7184	150.6888	12.4716
Total		904.1602	598.2679	299.1393

Figure 4. Radar chart optimality of physicochemical parameters of Diol CPT.

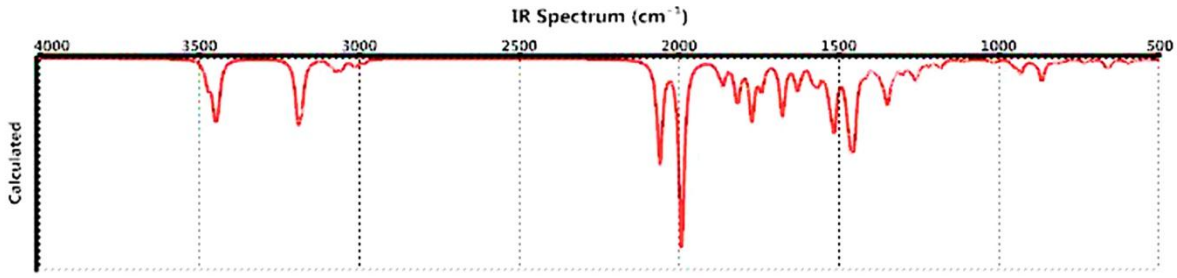

Figure 5. Virtual FTIR of Diol CPT.

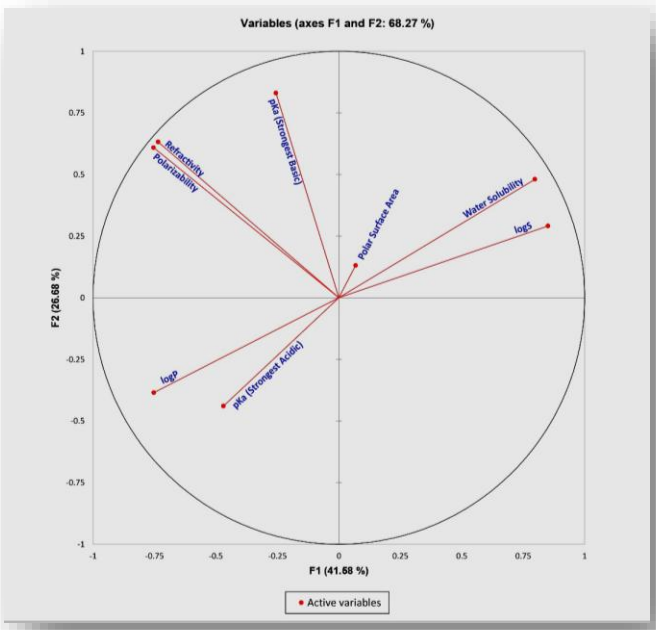

Figure 6. Correlation circle for active descriptor.

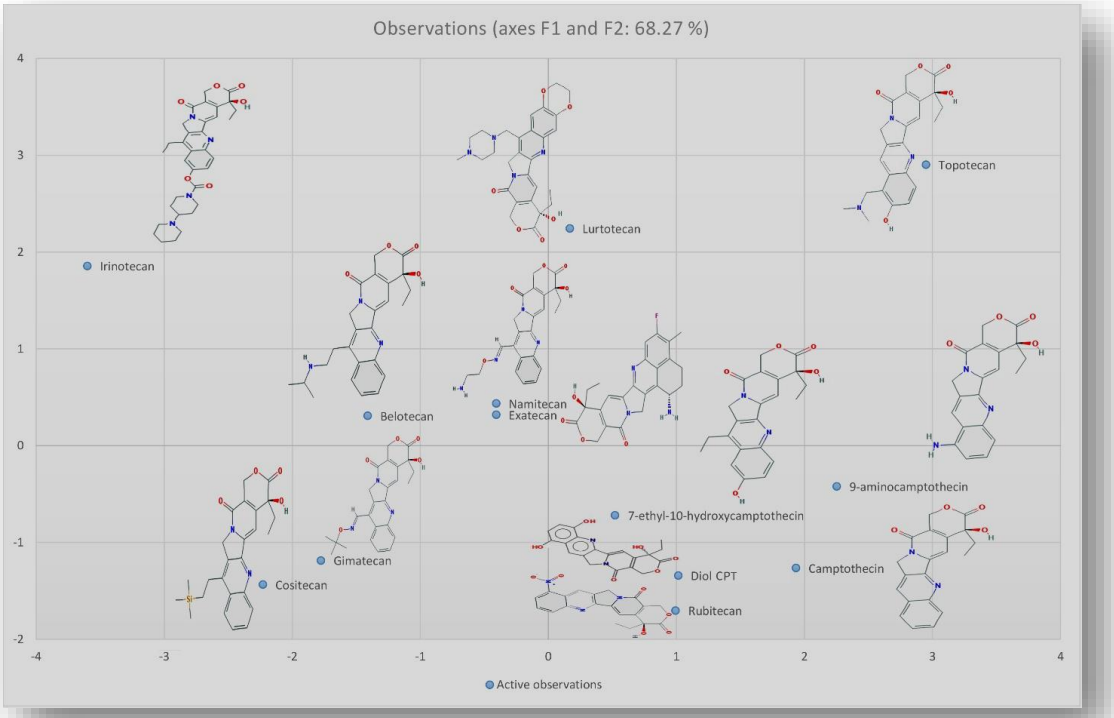

Figure 7. PCA analysis of CPT derviatives and Diol CPT.

DISCUSSION

Basically, drugs which cause CYP450 metabolic interactions are referred to as either inducers or inhibitors, so that inhibitors block the metabolic activity one or more enzymes of CYP450. Calculated pharmacokinetics parameters of Diol Camptothecin showed that there is no inhibitory for CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 which is in contrary with Camptothecin conventional structure, so that CYP1A2, CYP2C9 and CYP3A4 are inhibited by CPT. Moreover, physicochemical parameters including TPSA, water solubility and polarizability parameters are enhanced in accepted range of Lipinski rule to demonstrate virtual A ring. Virtual FTIR spectra of Diol CPT structure in the 4000-400 cm^{-1} is calculated in figure 5. Actually, a peak near 3500 cm^{-1} refers to hydroxyl group (OH stretching vibration) which demonstrated hydroxyl modifications which shows in figure 5. A peak appeared after 3000 cm^{-1} refers to C-H stretching vibration and the peaks in the range of 2000-2100 cm^{-1} belong to C=C and CN functional groups and a peak around 1700 cm^{-1} related to C=O stretching vibration.

Standard thermo physical parameters were computed using AM1semi empirical method at 287.15 K and 1 atm including zero-point energy (ZPE), enthalpy, entropy and volume constant heat of capacity (Cv) in translational, vibrational and rotational frequency modes of CPT molecule are shown in table 4.

Mulliken atomic charge and bond orders could be characterized charge distribution and prediction of polarizability of CPT. Based on Chemometrics computations, results of the correlation circle is shown in figure 6, the best distribution of data was done according to the measured descriptors (table1) and the CPT derivatives, which had 12 CPT derivatives and the Diol CPT which are shown in figure 7. The highest significant percentage for correlation between descriptors (water solubility and log p) was 67.28 %. After plotting the correlation circle, the magnitude of each of the parameters measured in the designed drug is shown according to the two specified attributes. The first descriptor accounted for 41.58 % and the second attribute was 26.66 % of the total share of the data. The results of the distribution of descriptors in the correlation circle showed that the distribution of the

descriptors was normal due to their relationship. The closeness of the distance between the two lines of the descriptor to each other indicates a high correlation and a significant correlation between these two descriptors compared to other descriptors.

Structure activity relation (SAR) studies indicated replacement at C-7, C-9, C-10 positions could have positive effect on ADMET properties, so that presence of CH2 unit in lactone ring could enhance its ability and metabolic processing. Alkyl addition reaction such as ethyl or chloromethyl groups at C-7 increased cytotoxicity [15]. Also nitrogen in carbon chain made more hydrophilic and water-soluble such as CKD-602 derivate which is potent topoisomerase inhibitor with high hydrophilicity and cytotoxicity [16]. Researches showed modification of C-9 and C-10 by hydroxylation have been made considerable activity using electron-withdrawing groups hydrophilicity was occurred. Previous studies indicated replacement in rings made much less potent of CPT. Fundamentally rings are crucial for activity of CPT [14,17].

Previous reports about rings manipulations represented limit opportunity to get sufficient activity [18]. It seems enhancement of polarizability via hydroxylation of Diol CPT leads to stabilize topo I-CPT complex and make it promising candidate to higher potent activity.

CONCLUSION

In this project, Diol Camptothecin was designed as pentacyclic CPT bioisostere via hydroxylation of C-9 and C-12 position of a ring to improve ADMET parameters and overcome restrictions of Camptothecin derviatives. Results showed that modification leads to improve solubility, eliminate inhibitory of CYP450 enzymes and theoretical computations indicated higher polarizability, which is probable more DNA top I-CPT complex stabilization that make the Diol CPT as an efficient drug.

REFERENCES

[1]. Hsiang YH, Hertzberg R, Hecht S, Liu LF. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J Biol Chem,* 1985; 260(27): 14873-78.

[2]. Rapisarda A, Uranchimeg B, Scudiero DA, Selby M, Sausville EA, Shoemaker RH, et al. Identification of small molecule inhibitors of hypoxia-inducible factor 1 transcriptional activation pathway. *Cancer Res*, 2002; 62(15): 4316-24.

[3]. Mi Z, Burke TG. Marked interspecies variations concerning the interactions of

camptothecin with serum albumins: a frequency-domain fluorescence spectroscopic study. *Biochemistry,* 1994; 33(42): 12540-45.

[4]. Xu Y, Villalona-Calero MA. Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. *Ann Oncol,* 2002; 13(12): 1841-51.

[5]. Tian Q, Zhang J, Chan SY, Tan TM, Duan W, Huang M, et al. Topotecan is a substrate for multidrug resistance associated protein 4. *Curr Drug Metab*, 2006; 7(1): 105-18.

[6]. Svenson S, Wolfgang M, Hwang J, Ryan J, Eliasof S. Preclinical to clinical development of the novel camptothecin nanopharmaceutical CRLX101. *J Control Release*, 2011; 153(1): 49-55.

[7]. Homsi J, Simon GR, Garrett CR, Springett G, De Conti R, Chiappori AA, et al. Phase I trial of poly-L-glutamate camptothecin (CT-2106) administered weekly in patients with advanced solid malignancies. *Clin Cancer Res,* 2007; 13(19): 5855-61.

[8]. Yurkovetskiy AV, Fram RJ. XMT-1001, a novel polymeric camptothecin pro-drug in clinical development for patients with advanced cancer. *Adv Drug Deliv Rev,* 2009; 61(13): 1193-202.

[9]. Scott LC, Yao JC, Benson AB, 3rd, Thomas AL, Falk S, Mena RR, et al. A phase II study of pegylated-camptothecin (pegamotecan) in the treatment of locally advanced and metastatic gastric and gastro-oesophageal junction adenocarcinoma. *Cancer Chemother Pharmacol,* 2009; 63(2): 363-70.

[10]. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release,* 2000; 65(1-2): 271-84.

[11]. Kirpotin DB, Drummond DC, Shao Y, Shalaby MR, Hong K, Nielsen UB. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. *Cancer Res,* 2006; 66(13): 6732-40.

[12]. Bartlett DW, Su H, Hildebrandt IJ, Weber WA, Davis ME. Impact of tumor-specific targeting on the biodistribution and efficacy of siRNA nanoparticles measured by multimodality in vivo imaging. *Proc Natl Acad Sci,* 2007; 104(39): 15549-54.

[13]. Choi CH, Alabi CA, Webster P, Davis ME. Mechanism of active targeting in solid tumors with transferrin-containing gold nanoparticles. *Proc Natl Acad Sci,* 2010; 107(3): 1235-40.

[14]. Li F, Jiang T, Li Q, Ling X. Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as

their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? *Am J Cancer Res,* 2017; 7(12): 2350-94.

[15]. Zunino F, Dallavalleb S, Laccabuea D, Berettaa G, Merlinib L, Pratesi G. Current status and perspectives in the development of camptothecins. *Curr Pharm Des,* 2002; 8(27): 2505-20.

[16]. Virupaksha B, Alpana G. CoMFA QSAR models of camptothecin analogues based on the distinctive SAR features of combined ABC, CD and E ring substitutions. *Comput Biol Med,* 2012; 42(9): 890-97.

[17]. Malgorzata ND, Agma K, Wakelin L, Pommier Y, Griffith R. Exploring DNA topoisomerase I ligand space in search of novel anticancer agents, *Plos One,* 2011, 6(9): 1-12.

[18]. Pommier Y. Topoisomerase I inhibitors: camptothecins and beyond. *Nat Rev Cancer,* 2006; 6(10):789-802.