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ORIGINAL ARTICLE

Quantitative structure–property relationships of camptothecins in humans

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Abstract
Purpose To develop quantitative structure property relationships (QSPR) for the pharmacokinetics and the susceptibility to BCRP-mediated efflux of ten drugs in the camptothecin family of topoisomerase I inhibitors.
Methods Pharmacokinetic parameters (total and lactone clearance, total steady-state volume of distribution, and lactone:total area under the curve ratio) and IC_{50} values of cytotoxicity in both BCRP over-expressing and sensitive cell lines were extracted from the literature. Molecular descriptors were generated for both the lactone and carboxylic acid forms of the drugs using SYBYL and ACD/Labs software. A partial least squares algorithm in SAS was used to construct QSPR models for each of the properties of interest, and final models were validated using leave-one-out cross-validation.
Results The molecular descriptors calculated for the lactone forms were better correlated with the selected properties than that of the carboxylate forms. Reasonable correlations (R^2 range 0.63–0.99) and good predictive performances (Q^2 range 0.45–0.88) were obtained for all seven QSPR models. Molecular descriptors that contribute to each pharmacokinetic property and susceptibility to BCRP mediated efflux were identified.
Conclusions QSPR models were successfully constructed for the pharmacokinetics and the susceptibility to BCRP-mediated efflux of the camptothecin analogs. The identified molecular parameters may help guide the synthesis of new camptothecin analogs with improved pharmacokinetic properties and reduced potential for clinical resistance.

Keywords BCRP-mediated efflux · Camptothecins · Partial least squares · Pharmacokinetics · Quantitative structure property relationships

Abbreviations

P-gp	P-glycoprotein
MRP	Multidrug resistance-associated protein
BCRP	Breast cancer resistant protein
QSAR	Quantitative structure activity relationship
QSPR	Quantitative structure property relationship
PLS	Partial least squares
MW	Molecular weight
TOEN	Total energy
COAR	Connolly molecular surface area
MV	Molecular volume
HEFO	Heat of formation
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
logD	Octanol–water partition coefficient corrected for the ionization state of the molecule at physiological pH

Introduction

The camptothecins are a promising class of antineoplastic agents that have shown significant activity against a variety of malignancies. Topotecan is currently used as a second-line agent for advanced ovarian cancer and small cell lung

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cancer, and irinotecan is presently used for the treatment of 5-fluorouracil refractory advanced colorectal cancer. Several other synthetic campothecin analogs are in clinical trials, including 9-nitrocampothecin, lurtotecan, exatecan, diflomotecan, karenitecin, and gimatecan [8]. The camptothecins exert their pharmacological activity via binding and stabilization of the normally transient DNA-topoiosmerase I cleavable complex [18]. As the collision between a moving replication fork and the drug-stabilized cleavable complex is required for cytotoxicity, the camptothecins are far more effective in the S-phase than in the G_1 or G_2/M phases of the cell cycle [11].

The camptothecins share a basic 5-ring structure with a chiral center located at position C-20 (Fig. 1). The lactone ring is thought to be required for pharmacological activity; however, the camptothecins undergo a pH-dependent reversible hydrolysis between the lactone form and an inactive open ring carboxylate form. The lactone form predominates at acidic pH whereas the inactive carboxylate form prevails at neutral and alkaline pH. The equilibrium of this interconversion is also affected by the relative binding of the two molecular forms to serum albumin (which can be species dependant) and lipid bilayer partitioning of the lactone form [3]. Early analytical assays of the camptothecins included acidification of samples to convert the carboxylate species to the lactone form before analysis. Concentrations measured in this manner are termed "total" drug concentrations since they contain both the lactone and carboxylate forms. Techniques are now readily available for the selective detection of the intact lactone form [23, 31]. Thus, interpretation of pharmacokinetic data of the camptothecins must be done cautiously since they have been reported based on both the total and lactone concentrations in different studies.

The pharmacokinetic properties of the camptothecin analogs are diverse. Drug clearance, steady-state volume of distribution, and the area under the curve (AUC) ratio between the lactone form and total drug are variable [8]. Owing to the nature of the S-phase specific mechanism of cytotoxicity, camptothecin analogs with pharmacokinetic properties that favor prolonged exposure above a minimum threshold after administration might demonstrate clinical advantages [35].

Drug resistance represents a major challenge to chemotherapy, and various mechanisms have been proposed for the clinically observed resistance to the camptothecins [8]. One important mechanism is altered cellular accumulation and efflux transport. For example, topotecan has been determined to be a substrate of P-gp [17]. Breast cancer-resistant protein (BCRP) and multidrug resistance-associated protein (MRP) have also been associated with resistance to a number of camptothecin analogs [4, 25, 26]. Different mechanisms of camptothecin resistance, such as different efflux proteins, may be specific for certain camptothecin analogs [35].

There have been a number of quantitative structure activity relationship (QSAR) studies evaluating the relationships between camptothecin structures and topoisomerase I inhibitory activities using various statistical methods such as multiple linear regression and genetic algorithms [7, 14]. These studies have helped to improve the understanding of the structural characteristics required for good activity and have guided the development of new analogs with enhanced potency [37]. However, there is a

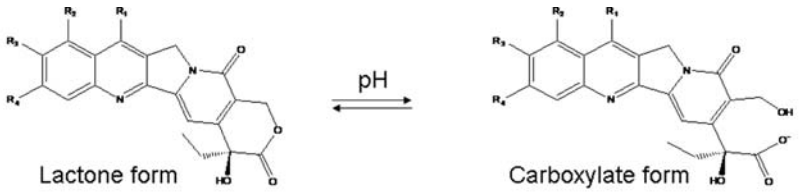
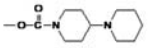
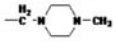


Fig. 1 Schematic of the interconversion between the lactone and carboxylate forms of camptothecins, and structures of the ten camptothecin analogs selected for this study

	CAS	R1	R2	R3	R4
Camptothecin	7689-03-4	-H	-H	-H	-H
9-amino camptothecin	91421-43-1	-H	$-NH_2$	-H	-H
Irinotecan	97682-44-5	$-CH_2CH_3$	-H		-H
SN-38	86639-52-3	$-CH_2CH_3$	-H	-OH	-H
Diflomotecan	220997-97-7	-H	-H	-F	-F
Exatecan	171335-80-1	$-CH(NH_2)-CH_2-CH_2-$		$-CH_3$	-F
Lurtotecan	149882-10-0		-H	-OCH2CH2O-	
Topotecan	123948-87-8	-H	$-CH_2N(CH_3)_2$	-OH	-H
Karenitecin	203923-89-1	-H	$-CH_2CH_2Si(CH_3)_3$	-H	-H
Gimatecan	292618-32-7	-CH=N-OBu-t	-H	-H	-H

lack of studies investigating the relationships between camptothecin physicochemical characteristics and their pharmacokinetic properties or susceptibility to efflux proteins. The purpose of this study is to utilize multivariate regression analysis to delineate the primary structural determinants of the apparent affinity of camptothecins to BCRP and their pharmacokinetic characteristics.

Materials and methods

Pharmacokinetic and BCRP affinity data

Drugs selected for this study included camptothecin, 9-amino camptothecin, irinotecan, SN-38, diflomotecan, exatecan, GI147211, topotecan, karenitecin, and gimatecan. The pharmacokinetic parameters including clearance of the total form (total CL), clearance of the lactone form (lactone CL), volume of distribution at steady-state of the total form (total V_{ss}), and the AUC ratio between the lactone form and total drug (AUC ratio), were obtained from the literature [5, 6, 10, 27, 32–34, 36, 40, 42].

Drug concentrations exhibiting 50% of maximal cytotoxicity (IC_{50}) of seven of the camptothecin analogs against both the BCRP overexpressing T8 and MX3 camptothecin-resistant cell lines and the camptothecin-sensitive IGROV1 parental cell lines were extracted from the literature [26]. Briefly, exponentially growing cells were plated and allowed to attach for 48 h. Different camptothecin analogs were then added and incubated with the cells for 5 days. Cytotoxicity was evaluated at the end of incubation using a sulforhodamine B method [26].

Molecular modeling

The molecular properties for both the lactone and carboxylate forms were calculated. The intact lactone form of the camptothecin structures were retrieved from The Department of Specialized Information Services website of the National Library of Medicine (http://chem.sis.nlm.nih.gov/chemidplus/). These structures were then imported into the SYBYL molecular modeling program (v6.9. Tripos, St. Louis, MO). The open-ring carboxylic acid forms were generated within SYBYL by modification of the ring structures. Structures were inspected using a Concord plug-in to ensure that the structures were chemically correct (Pearlman RS, Concord, distributed by Tripos Inc.). Energy minimization with the Powell method and Tripos force field was conducted in SYBYL prior to calculating molecular descriptors.

Three major types of molecular descriptors were calculated in this study including electronic, steric and hydrophobic descriptors. The electronic descriptors were the heat of formation (HEFO), energy of the lowest unoccupied molecular orbital (LUMO), energy of the highest occupied molecular orbital (HOMO), and total energy including electrostatics (TOEN) [20, 39]. These values were calculated with the MOPAC module within SYBYL using the Austin Model 1 (AM1) single point method with a time limit of 1 h and the precise option activated to improve convergence precision. HEFO represents the change of enthalpy that accompanies compound formation from its constituent elements in their standard states. The HOMO and LUMO descriptors are frequently calculated as these orbitals can influence chemical reactivity and reaction mechanisms. Theoretically, HOMO is the negative of the ionization potential, whereas the LUMO energy is directly related to the electron affinity of a molecule. Thus, HOMO features the susceptibility of a molecule toward attack by nucleophiles, and LUMO characterizes the susceptibility of the molecule toward the attack by electrophiles in chemical reactions [20]. SYBYL was also used to calculate the three steric parameters: molecular weight (MW), molecular volume (MV), and the Connolly molecular surface area (COAR), which is essentially the solvent accessible area defined as the area of the smooth outer surface of the compound generated by rolling a theoretical water molecule (1.4 Å in diameter) over the van der Waals surface of the molecule.

The octanol–water partition coefficient corrected for the ionization state of the molecule at physiological pH (log$D$) was included as the hydrophobic descriptor. Given the complexity of anticipating pK_a values (especially some camptothecin zwitterions), all log$D$ values were obtained from the program SciFinder Scholar (SciFinder, version 2007; Chemical Abstracts Service: Columbus, OH, 2007; Calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris; 1994–2008 ACD/Labs).

QSPR data analysis

Partial least squares (PLS) regression analysis was used to construct the QSPR models. PLS is a multivariate statistical method that is extensively used in QSAR/QSPR studies and can be expressed as

$$\mathbf{y} = \mathbf{V} \times \mathbf{a_{PLS}} + \mathbf{B} \quad (1)$$

where $\mathbf{y}$ is the response matrix, $\mathbf{B}$ a residual matrix, $\mathbf{a_{PLS}}$ a regression coefficient matrix, and $\mathbf{V}$ the matrix of the molecular descriptors. To avoid over-fitting the data, cross-validation to determine the number of significant components is necessary. The so-called leave-one-out method is a frequently used cross-validation technique when the number of compounds is limited. The cross-validated correlation coefficient (Q^2) is calculated as

$$Q^2 = 1 - \sum \left(y_{\text{ipred}} - y_{\text{iobs}}\right)^2 / \left(y_{\text{iobs}} - y_{\text{mean}}\right)^2 \quad (2)$$

where y_{ipred} is the predicted dependent variable, y_{iobs} the observed dependent variable, y_{mean} mean of the observed dependent variable. PLS modeling was performed using the PROC PLS procedure in SAS (v9.1, SAS Institute Inc., Cary, NC). All variables were scaled to unit variance and centered around the mean using the auto-scaling procedure, and the final number of significant components was determined by optimizing the cross-validated correlation coefficient (Q^2) using the automatic leave-one-out procedure.

Results

The pharmacokinetic parameters (CL total, CL lactone, V_{ss} total, and AUC ratio) along with the log(1/IC_{50}) of the cytotoxicity of camptothecins against BCRP over-expressing T8 and MX3 cells and the IGROV1-sensitive cell line are summarized in Table 1. Despite sharing similar backbone structures, these camptothecin analogs exhibit varying degrees of susceptibility to BCRP-mediated efflux. For example, the IC_{50} values for T8 cells ranged from 2.52 to 32,260 nM (0.42 to −4.10 after logarithm transformation of the reciprocol). Similarly, the pharmacokinetic properties are diverse, with the lactone CL for example, ranging from 6.8 to 91 L/h/m^2.

The molecular properties corresponding to the lactone and carboxylate forms were calculated. Since both forms exist in vivo after drug administration, it was not clear a priori which structural form would provide a better indicator of the activity and pharmacokinetic properties of this drug class. Thus, QSPR models were constructed separately using either sets of molecular descriptors. For each of the seven QSPR models, the lactone molecular properties (Table 2) emerged as more useful predictors of BCRP susceptibility and pharmacokinetic properties, as revealed by higher R^2 and Q^2 values of the models (data not shown). Therefore, only the results based on the lactone molecular properties are reported.

The correlation coefficients (R^2), the cross-validated correlation coefficients (Q^2) and the number of significant components determined for each of the seven PLS models

Table 1 Camptothecin pharmacokinetic parameters and BCRP mediated efflux IC_{50} values

Drug	Total CL (L/h per m^2)	Lactone CL (L/h per m^2)	Total V_{ss} (L/m^2)	AUC ratio	Log(1/IC_{50}) T8 cells	Log(1/IC_{50}) MX3 cells	Log(1/IC_{50}) IGROV1 cells
Camptothecin	0.496	–	8.62	–	–	–	–
9-amino camptothecin	3.00	24.5	9.20	0.096	−2.25	−1.37	−0.26
Irinotecan	15.3	45.6	148	0.44	−4.51	−4.10	−2.69
SN-38	–	–	–	0.51	−2.61	−1.93	−0.20
Diflomotecan	–	11.7	–	0.4	–	–	–
Exatecan	2.10	6.80	22.0	0.3	−0.40	0.42	1.05
GI147211	22.0	91.0	118	0.27	−1.36	−1.03	0.14
Topotecan	8.00	25.7	39.5	0.33	−3.00	−2.44	−0.95
Karenitecin	–	–	–	0.87	−0.65	0.03	0.35
Gimatecan	–	–	–	0.9	–	–	–

Table 2 Molecular properties of the lactone form of camptothecins

Drug	MW	Log*D*	TOEN	COAR	MV	HEFO	HOMO	LUMO
Camptothecin	348	1.90	20.2	313	268	−27.9	−9.18	−1.41
9-Amino camptothecin	363	0.70	20.8	326	280	−18.6	−9.21	−1.48
Irinotecan	588	2.85	34.4	544	493	53.5	−10.3	−4.03
SN-38	392	2.60	22.0	353	308	−79.2	−9.03	−1.38
Diflomotecan	398	2.00	22.7	336	289	−119	−9.27	−1.75
Exatecan	436	1.95	21.4	380	341	81.6	−11.7	−4.95
GI147211	520	0.40	24.3	463	420	82.8	−10.9	−4.16
Topotecan	422	0.80	25.4	383	341	93.4	−11.3	−4.56
Karenitecin	449	4.45	17.1	422	380	−74.7	−9.11	−1.32
Gimatecan	447	3.70	22.5	412	361	−11.1	−9.22	−1.59

are summarized in Table 3. These relationships all appear to show reasonable correlations (R^2 range 0.63–0.99) and predictive performances (Q^2 range 0.45–0.88). The differences between the R^2 and Q^2 values ($\sim$0.2) are moderate and indicate sufficient model predictability. A diagnostic plot showing predicted versus observed values of BCRP susceptibility and the pharmacokinetic properties is provided as online supplementary material. Good agreement for all seven models was observed.

In PLS regression, the weighted coefficients can be used to indicate the relative contributions of each descriptor in the model. The coefficients of each descriptor for the four pharmacokinetic parameters are shown in Fig. 2. The major positive contributors for total V_{ss} were MW, TOEN, COAR, and MV. These descriptors, plus HEFO, contributed positively to total CL, whereas HOMO and LUMO had a negative impact. Ionization corrected lipophilicity (log*D*) was identified as the major contributor to the AUC ratio between the lactone form and total drug. Interestingly, log*D* was a relatively large negative contributor to the lactone CL, whereas MW was a positive contributor.

The IC_{50} values of camptothecin toxicity in BCRP overexpressing cell lines (T8 and MX3) are considered to provide information on both the activity (cytotoxicity) and susceptibility to BCRP-mediated efflux for each analog. The IC_{50} values of the same analogs in a sensitive parental cell line IGROV1, which minimally express BCRP, were also used for QSPR modeling. The patterns of the contributions of each descriptor to the log(1/IC_{50}) in all three cell lines were almost identical (Fig. 3). This strongly suggests that the final QSPR models likely correspond to the susceptibility of BCRP-mediated efflux. Only the weighted PLS regression coefficients for the model of T8 cells are shown in Fig. 3 given the similarity of the patterns in the other two cell lines. The TOEN contributes negatively to this model, which suggests that TOEN of the camptothecins contributes positively to BCRP-mediated efflux. On the other hand, HOMO and log*D* were negative contributors to this property.

Table 3 Performance summary for the final camptothecin QSPR models

Parameters	Number of components	R^2	Q^2
V_{ss} total	2	0.94	0.88
CL total	1	0.63	0.45
CL lactone	4	0.99	0.74
AUC ratio	2	0.74	0.56
Log(1/IC_{50}) T8 cells	3	0.89	0.70
Log(1/IC_{50}) MX3 cells	3	0.89	0.74
Log(1/IC_{50}) IGROV1 cells	3	0.87	0.61

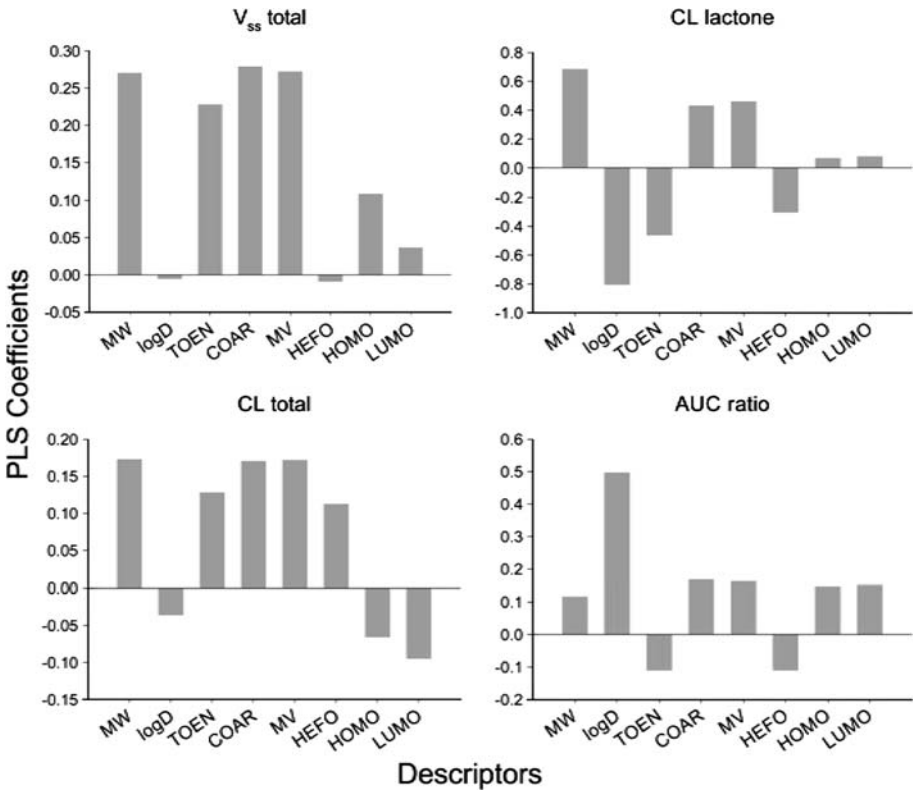


Fig. 2 Partial least squares coefficients of the molecular properties for the four camptothecin pharmacokinetic QSPR models

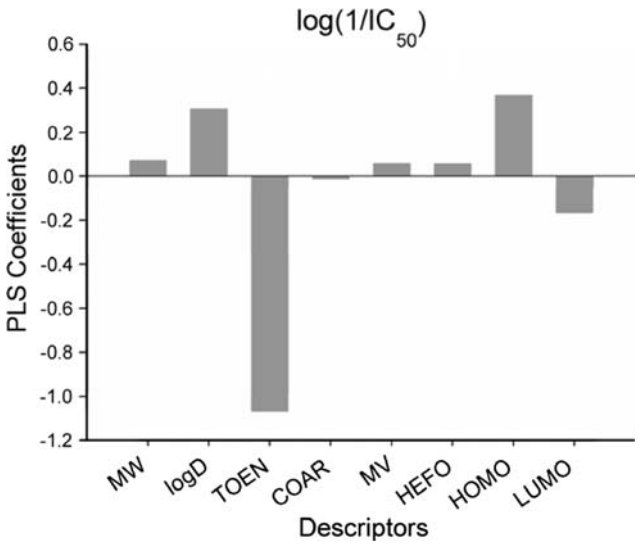


Fig. 3 Partial least squares coefficients of the molecular properties in a QSPR model of camptothecin cytotoxicity, expressed as log (1/IC_{50}), in BCRP over-expressing T8 cells

Discussion

The camptothecins remain the best characterized topoisomerase I inhibitors with potent anticancer effects. There has been considerable interest in developing new analogs with greater anticancer activity as well as better physiochemical and pharmacokinetic properties [35]. In addition, new analogs with a decreased potential for resistance would also be beneficial clinically. Thus, QSPR models that seek to correlate the pharmacokinetics and potential for drug resistance to key structural characteristics may help to guide future drug development of this class of drugs. Multivariate techniques, such as PLS regression, are now frequently utilized to construct such models [24]. Although restricted to point estimates, predictions from multivariate models may be connected with mechanism-based models to anticipate the time course of drug effects and/or toxicity [24].

Partial least squares is a robust multivariate regression algorithm that offers advantages over traditional multiple linear regression (MLR) in that it is able to accommodate co-linearity in the descriptor matrices and cases where the number of descriptors exceed the number of test compounds [9]. Van der Graaf and colleagues were the first to utilize this technique in constructing quantitative structure–pharmacokineitc relationships for several adenosine A_1 receptor agonists [38]. PLS regression was applied to global molecular descriptors of the camptothecins. Although atom fragment-based methods that relate the spatial distribution of structures to responses may provide finer details [28], global physicochemical descriptors were utilized owing to the limited number of compounds and their associated pharmacokinetic/pharmacodynamic properties. The final QSPR models demonstrated reasonable correlations and predictive performances (Table 3).

The volume of distribution at steady state (V_{ss}) of a drug can be defined as

$$V_{ss} = V_p + \sum K_{pt,i} \cdot V_{t,i} \quad (3)$$

where V_p is the plasma volume, and $K_{pt,i}$ and $V_{t,i}$ the plasma tissue partition coefficient and the physiological volume of the ith tissue. Drug lipophilicity is a major determinant of $K_{pt,i}$ values [29]. V_{ss} can also be defined according to the Gillette equation [12]:

$$V_{ss} = V_p + \frac{f_u}{f_{ut}} V_T \quad (4)$$

where f_u and f_{ut} are the free fraction of drug in plasma and tissue, and V_T the sum of all tissue volumes. Thus, plasma protein and tissue binding are determinants of the value of V_{ss} of a drug. Traditionally, the V_{ss} of free drug only has been linked with lipophilicity, particularly based on the role of this descriptor in tissue and protein binding [24]. Modern QSPR analysis frequently identifies lipophilicity as well as other steric and electronic molecular descriptors as important contributors to V_{ss} [24]. In this study, log$D$ did not emerge as an important contributor for total V_{ss} of camptothecins. The PLS coefficients for MW, COAR, and MV suggest that for camptothecins, steric properties (e.g. size and shape) are more important in terms of tissue distribution. It should be noted that COAR is related to both surface area and lipophilicity [20]; thus the contribution of lipophilicity may be reflected in this term. The V_{ss} used in this study is for the total form of camptothecins. Since the carboxylate form is more hydrophilic than the lactone form and may have different distribution properties, the total V_{ss} is likely a hybrid parameter reflecting contributions of both molecular forms. Although it might be more informative to investigate the V_{ss} of the lactone form, we were not able to extract this information for enough compounds to construct a reasonable QSPR model.

In general, clearance is more difficult to predict than other pharmacokinetic parameters due to the complexity associated with the various routes of drug biotransformation and elimination, such as the influence of active transporters and extra-hepatic metabolism. The major clearance pathways vary for the camptothecin analogs. Whereas urinary excretion plays an important role in the clearance of topotecan (30–50% urinary excretion) and 9-aminocamptothecin (30% urinary excretion), it is only of minor importance for the other analogs [8]. Metabolic biotransformation and biliary excretion are the major clearance pathways for irinotecan, whereas glucuronidation and biliary excretion are the main mechanisms of SN-38 elimination [8].

As exemplified by the β-adrenergic antagonists, renal clearance tends to decrease with lipophilicity primarily due to tubular re-absorption, whereas metabolic clearance tends to increase with lipophilicity and then plateau or slightly decrease at high log*D* values to form a parabolic or bilinear relationship [15]. Classical QSAR studies have highlighted the role of lipophilicity, hydrogen bonding, and electrostatics in the binding and metabolism of various compounds by cytochrome P450 enzymes, the major phase I metabolic enzymes [13]. However, models of other clearance processes such as biliary excretion are not fully characterized, with the molecular weight cutoff as the only major contributing molecular factor identified thus far [16].

Interestingly, lipophilicity was identified as a major negative contributor for lactone clearance (it is also negatively contributing to total clearance, but to a lesser extent), especially considering that only two of the analogs are mainly eliminated by renal excretion. Since most of these camptothecin analogs are relatively hydrophobic, it might be possible that the metabolic clearances reflect a decreasing phase of a parabolic or bilinear relationship between metabolic clearance and lipophilicity. Unknown relationships between lipophilicity and drug transport and biliary clearance complicate the interpretation of this result. In any event, this would suggest that new camptothecin analogs with relatively high lipophilicity would be preferred since it would be associated with lower clearance and thus longer half lives. However, poor absorption is likely to result from high lipophilicity as exemplified by the 'rule of 5' proposed by Lipinski and colleagues [21]. Thus, increasing lipophilicity would have to be balanced by the potential for poor absorption and complex formulation development. The steric descriptors MW, COAR, and MV are also important for the lactone and total clearance. HOMO and LUMO also influence the total clearances of these camptothecin analogs.

The AUC ratio between the lactone form and the total form after drug administration is an indicator of the stability of camptothecin drugs given that camptothecins undergo transformation and only the lactone form is assumed to be pharmacologically active. Thus, it has been a major target for chemists to synthesize new analogs with greater stability and AUC ratios. Our finding that log*D* was the most important contributor to the AUC ratio of camptothecins in a multivariate framework (Fig. 3) is in agreement with previous results [1, 2]. Lipid bilayer vesicles and erythrocytes can enhance lactone stability as the lipophilic lactone preferentially partitions into such lipid bilayers compared to the charged carboxylate forms [1]. Based on this rationale, new analogs are increasingly designed with greater lipophilicity [2].

Efflux proteins such as P-gp and BCRP might contribute to the clinical resistance of camptothecins [35]. Some camptothecin analogs are substrates of BCRP, whereas others such as exatecan and karenitecin are not effluxed by this mechanism [30]. Structural substitutions at certain positions have been linked to this differential susceptibility [30]. Yoshikawa and colleagues identified polarity as an important factor in this process, with BCRP preferentially exporting camptothecin analogs with high polarity (and thus low lipophilicity) [41]. This is consistent with the negative coefficient for log*D* in the models of susceptibility to BCRP-mediated efflux. In addition to log*D*, HOMO and TOEN were also identified as major negative and positive contributors. Electrostatic interactions might influence recognition by BCRP and interactions with substrates, but the effect of total energy of a drug is difficult to interpret. The potential energy of a molecule is a complex, multidimensional function of its 3D coordinates. The relationship between these coordinates and BCRP recognition and export is not clear. In any event, the total energy of a potential new analog could be calculated in silico before synthesis to screen for potential BCRP efflux. Total energies in this study were calculated with energy minimization methods using the Tripos force field in SYBYL. As with all energy minimization methods, local minima rather than the global minimum might confound such minimizations, and care should be taken when interpretating and applying the result for total energy.

From the QSPR models of clearance, AUC ratio, and susceptibility to BCRP efflux; analogs with high lipophilicity would be favored in all three aspects. Such compounds would likely exhibit low clearance (thus long half life), greater stability, and reduced BCRP-mediated efflux. A potential concern for these new hydrophobic analogs would be the increased potential for poor oral absorption [22]. Advanced drug delivery techniques, such as liposomal formulations, might serve to address problems associated with administering such lipophilic drugs [19]. In conclusion, several QSPR models were successfully constructed for the clinically important camptothecin anticancer drugs. This study may help to guide the synthesis of new camptothecin analogs with more favorable pharmacokinetic properties and reduced potential for clinical resistance.

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