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Cytotoxicity of Organic Compounds against Ovarian Cancer Cells: A Quantitative Structure−Activity Relationship Study

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Abstract: The interest in the application of structure−activity relationships has steadily increased in recent decades. In the present paper, we have discussed the cytotoxicity of various sets of organic compounds against ovarian cancer cells by the formulation of a total number of 11 QSARs. Hydrophobicity is found to be one of the most important determinants of activity followed by steric parameters. Parabolic correlation with hydrophobicity is an encouraging example, where the optimal hydrophobicity is well-defined. We believe that this may be the predictive model to narrow the synthetic challenges in order to yield very specific OVCAR-3 inhibitors. On the basis of this model, we can predict three compounds that may be the next synthetic target. Cross-validation and Y-randomization tests were used to validate all the QSAR models.

Keywords: Cytotoxicity; hydrophobicity; molar refractivity; polarizability; QSAR

Introduction

Ovarian cancer remains the deadliest gynecological malignancy and is the leading cause of death due to cancer in women. The American Cancer Society estimates every year the number of new cancer cases and deaths expected in the United States and compiles the most recent data on cancer incidence, mortality, and survival based on incidence data from the National Cancer Institute and mortality data from National Center for Health Statistics. A total number of 22 220 new cases and 16 210 deaths are expected from ovarian cancer in the United States in 2005.[1] This is mainly due to the fact that the successful clinical management of patients with ovarian cancer is limited by the lack of reliable and specific methods for early detection, and the frequent recurrence of chemoresistance disease.[2] Significant progress has been made in understanding the molecular biology of ovarian cancer and the role that single-nucleotide polymorphisms, tumor suppressor genes, and oncogenes play in promoting tumor cell growth and proliferation. Strategies have been developed to correct gene defects or single out ovarian cancer cells for destruction. Molecular-based therapies are now under development to specifically target receptors and signal transduction pathways that control cell proliferation and apoptosis, angiogenesis, cellular adhesion, and cell motility in ovarian tumors.[3]

Tumor necrosis factor related apoptosis-inducing ligand (TRAIL) is known to induce apoptosis in many malignant cells without any known detrimental effects to normal cells. Recently, it has been established that ovarian cancer cells are sensitive to TRAIL-induced cell death when treated with TRAIL alone or in combination with chemotherapeutic agents. Results suggested that the presence of interleukin-8 (IL-8) regulates cell-surface expression of TRAIL receptors in ovarian cancer cell lines in vitro. There may be a possible

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Table 1. Biological and Physicochemical Parameters Used To Derive QSARs 1 and 2 for the Inhibition of CH1 and SKOV-3 Human Ovarian Carcinoma Cells, Respectively, by 3,6-Disubstituted Acridines (**I**)

		log1/*C* (Eq **1**)			log1/*C* (Eq **2**)				
No	X	Obsd.	Pred.	Δ	Obsd.	Pred.	Δ	Clog *P*	MgVol
1	$N(C_2H_5)_2$	5.61	5.37	0.24	5.65	5.58	0.07	5.47	3.82
2	$N(CH_3)_2$	5.01	4.97	0.04	5.60	5.56	0.04	3.36	3.25
3	Piperidinyl	5.65	5.43	0.22	6.27[a]	5.59	0.68	5.77	3.88
4	Morpholinyl	4.82	4.97	-0.14	4.89[a]	5.30	-0.41	3.35	3.72
5	Pyrrolidinyl	5.09	5.22	-0.13	5.59	5.57	0.01	4.66	3.60
6	2-C_2H_5-Piperidinyl	5.66	5.80	-0.15	5.41	5.58	-0.17	7.74	4.44
7	1-CH_3-Piperidinyl	5.64	5.60	0.04	5.47	5.57	-0.10	6.68	4.16
8	4-CH_3-Piperidinyl	5.69	5.60	0.09	5.62	5.57	0.05	6.68	4.16
9	3-CH_3-Piperidinyl	5.66	5.60	0.06	5.55	5.57	-0.03	6.68	4.16
10	2-CH_2OH-Piperidinyl	4.98	5.19	-0.21	5.15	5.16	-0.01	4.51	4.28
11	2-$(CH_2)_2$OH-Piperidinyl	4.96	5.27	-0.31	4.98	5.07	-0.09	4.94	4.56
12	4-OH-Piperidinyl	4.82	4.61	0.22	4.89	4.84	0.05	1.47	4.00
13	Cyclo-$N(CH_2)_6$	5.73	5.64	0.09	5.60	5.61	0.00	6.89	4.16
14	Cyclo-$N(CH_2)_7$	5.66	5.85	-0.20	5.64	5.62	0.02	8.01	4.44
15		6.27	6.12	0.15	5.66	5.48	0.17	9.38	5.07

[a] Not included in the derivation of QSAR 2.

Table 2. Biological and Physicochemical Parameters Used To Derive QSAR 3 for the Inhibition of CH1 Human Ovarian Carcinoma Cells by Thiadiazinoacridines (**II**)

			log1/*C* (eq 3)				
no.	X	Y	obsd	pred	Δ	CMR	$C\pi_Y$
1	OCH_3	$(CH_2)_2N(CH_3)_2$	5.70	5.83	−0.13	10.53	0.96
2	OCH_3	$(CH_2)_3N(CH_3)_2$	5.70	5.52	0.17	10.99	1.23
3	OCH_3	$(CH_2)_2N(C_2H_5)_2$	5.72	5.58	0.14	11.46	2.02
4	H	$(CH_2)_2N(CH_3)_2$	6.66	6.48	0.18	9.91	0.96
5	H	$(CH_2)_3N(CH_3)_2$	6.17	6.17	0.00	10.38	1.23
6	H	$(CH_2)_2N(C_2H_5)_2$	6.18	6.23	−0.05	10.84	2.02
7	H	$(CH_2)_2$-piperidinyl	5.54[a]	5.94	−0.40	11.13	2.04
8	CH_3	$(CH_2)_2N(CH_3)_2$	5.85	5.99	−0.14	10.38	0.96
9	CH_3	$(CH_2)_3N(CH_3)_2$	5.64	5.69	−0.05	10.84	1.23
10	CH_3	$(CH_2)_2N(C_2H_5)_2$	5.62	5.74	−0.12	11.30	2.02
11	CH_3	$(CH_2)_2$-piperidinyl	5.46	5.45	0.00	11.59	2.04

[a] Not included in the derivation of QSAR 3.

role for the p38 mitogen-activated protein kinase (MAPK) pathway in TRAIL-induced apoptosis of the ovarian cancer cell.[4]

Hormonal therapy has limited efficacy in ovarian cancer. However, considering the mild toxicity of these drugs may be useful.[5] Reduction of ovarian steroids at menopause leads to significant changes in the urogenital tract. These changes often worsen with time, particularly in nonsmokers, affecting up to 38% of menopausal women. Urogenital symptoms that clearly respond to estrogen therapy include atrophic vaginitis, dryness, and accompanying dyspareunia. Estrogen reduces urinary tract infections in women plagued by frequent recurrence. Options for estrogen therapy include native, synthetic, or biological derived estrogens delivered by cream, gel, insert (pessary), ring, or tablet.[6]

The relationship between the use of nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, and the risk of ovarian cancer has been controversial. But the meta-analysis findings from a recent publication do not support that NSAID use plays a role in the chemoprevention of ovarian cancer.[7] The primary chemotherapy of ovarian cancer is the combination chemotherapy using paclitaxel and carboplatin.[8] The management of advanced ovarian cancer consists of cytoreductive surgery followed by combination chemotherapy. Gemcitabine is a deoxytidine-analogue antimetabolite that has established in vitro and in vivo activity against ovarian carcinoma resistant to paclitaxel and platinum compounds. Recently, clinical studies on sequential single and/or combined use of gemcitabine with various other effective agents such as etoposide, topotecan, and vinorelbine as well as novel platinum and taxane compounds are increasing.[9]

The quantitative structure−activity relationship (QSAR) paradigm may be helpful in the discovery and development of new chemotherapeutic agents for ovarian cancer. In a QSAR study on paclitaxel analogues versus ovarian carcinoma 1A9 cells, the quantitative structure−activity relationship described by eq i was obtained.[10]

$$\log 1/IC_{50} = 2.09(\pm 0.95)\,MR_m - 1.60(\pm 0.53)\,MR_m^2 - 0.96(\pm 0.38)\sigma_m^2 + 0.66(\pm 0.27)N_m - 0.97(\pm 0.33)I_p - 0.75 \quad (\pm 0.86) \quad \text{(i)}$$

$$n = 25, \quad r = 0.94, \quad \text{SEE} = 0.29$$

In this equation, MR_m is the molar refractivity of meta substituents on the phenyl ring (with respect to the ester

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Table 3. Biological and Physicochemical Parameters Used To Derive QSAR 4 for the Inhibition of CH1 Human Ovarian Carcinoma Cells by 9,10-Anthraquinones (**III**)

		log1/*C* (eq 4)					
no.	X	obsd	pred	Δ	Clog *P*	MgVol	*I*
1	1,4-NHCO$(CH_2)_2$-piperidinyl	6.59	6.55	0.04	4.29	4.00	1
2	1,4-NHCO$(CH_2)_2$-pyrrolidinyl	7.72[a]	6.83	0.89	3.17	3.71	1
3	1,4-NHCO$(CH_2)_2$-morpholinyl	5.71	5.92	−0.21	1.86	3.83	1
4	1,4-NHCO$(CH_2)_2N(CH_3)_2$	7.40	7.21	0.19	1.87	3.37	1
5	1,4-NHCO$(CH_2)_2N(C_2H_5)_2$	6.59	6.59	0.00	3.99	3.93	1
6	1,5-NHCO$(CH_2)_2$-piperidinyl	6.38[a]	5.43	0.95	4.29	4.00	0
7	1,5-NHCO$(CH_2)_2$-pyrrolidinyl	6.44[a]	5.72	0.72	3.17	3.71	0
8	1,5-NHCO$(CH_2)_2N(CH_3)_2$	6.43	6.10	0.33	1.87	3.37	0
9	1,5-NHCO$(CH_2)_2N(C_2H_5)_2$	6.49[a]	5.48	1.01	3.99	3.93	0
10	1,8-NHCO$(CH_2)_2$-piperidinyl	5.71	5.43	0.28	4.29	4.00	0
11	1,8-NHCO$(CH_2)_2$-pyrrolidinyl	5.89	5.72	0.17	3.17	3.71	0
12	1,8-NHCO$(CH_2)_2$-morpholinyl	4.67	4.81	−0.14	1.86	3.83	0
13	1,8-NHCO$(CH_2)_2N(CH_3)_2$	5.87	6.10	−0.23	1.87	3.37	0
14	1,8-NHCO$(CH_2)_2N(C_2H_5)_2$	5.28	5.48	−0.20	3.99	3.93	0
15	2,6-NHCO$(CH_2)_2$-piperidinyl	5.23	5.43	−0.20	4.29	4.00	0
16	2,6-NHCO$(CH_2)_2$-pyrrolidinyl	4.31[a]	5.72	−1.41	3.17	3.71	0
17	2,6-NHCO$(CH_2)_2$-morpholinyl	4.85	4.81	0.04	1.86	3.83	0
18	2,6-NHCO$(CH_2)_2N(CH_3)_2$	5.74	6.10	−0.36	1.87	3.37	0
19	2,6-NHCO$(CH_2)_2N(C_2H_5)_2$	5.50	5.48	0.02	3.99	3.93	0
20	2,7-NHCO$(CH_2)_2$-piperidinyl	5.50	5.43	0.07	4.29	4.00	0
21	2,7-NHCO$(CH_2)_2$-pyrrolidinyl	5.74	5.72	0.02	3.17	3.71	0
22	2,7-NHCO$(CH_2)_2$-morpholinyl	5.12	4.81	0.31	1.86	3.83	0
23	2,7-NHCO$(CH_2)_2N(C_2H_5)_2$	5.34	5.48	−0.14	3.99	3.93	0

[a] Not included in the derivation of QSAR 4.

linkage on the C-2 position of the taxane skeleton). Similarly, σ_m is the Hammett electronic parameter of meta substituents, N_m is a dummy parameter denoting number of meta substituents, and I_p is an indicator variable representing the presence or absence (value 1 or 0 respectively) of para substituents on the phenyl ring with respect to the ester linkage on the C-2 position of the taxane skeleton. *r* is the correlation coefficient, and SEE is standard error of estimate.

In the present paper, we would like to demonstrate the QSAR (quantitative structure−activity relationship) studies on various sets of compounds with respect to their cytotoxic activities against ovarian cancer cells. In the past 43 years, the use of QSAR, since its advent,[11] has become increasingly helpful to understand the chemical−biological interactions in the drug-design process and pesticide research as well as

Table 4. Biological and Physicochemical Parameters Used To Derive QSAR 5 for the Inhibition of OVCAR-3 Human Ovarian Carcinoma Cells by Antibiotic Brefeldin A Derivatives (**IV**)

		log1/*C* (eq 5)				
no.	X	obsd	pred	Δ	MgVol	*I*
1	$SCH_2CH(OH)CH_3$	4.43[a]	6.39	−1.96	2.94	1
2	$S(CH_2)_4OH$	4.33[a]	5.83	−1.50	3.08	1
3	SCH_2-(4-OCH_3-C_6H_4)	4.20	4.53	−0.33	3.41	1
4	S-(4-NH_2-C_6H_4)	5.50	5.49	0.01	3.17	1
5	S-(3-NH_2-C_6H_4)	5.45	5.49	−0.04	3.17	1
6	S-(2-NH_2-C_6H_4)	5.43	5.49	−0.06	3.17	1
7	S-(4-Br-C_6H_4)	5.56	5.19	0.37	3.24	1
8	S-(2-$COOCH_3$-C_6H_4)	4.51	4.47	0.04	3.42	1
9	$SO(CH_2)_3OH$	6.59[a]	7.45	−0.86	3.00	0
10	$SOCH_2CH(OH)CH_3$(S)	7.60	7.45	0.15	3.00	0
11	$SOCH_2CH(OH)CH_3$(R)	7.52	7.45	0.07	3.00	0
12	$SO(CH_2)_4OH$	6.55	6.89	−0.34	3.14	0
13	$SOCH_2$-(4-OCH_3-C_6H_4)	5.83	5.59	0.24	3.47	0
14	SO-(4-NH_2-C_6H_4)	6.40	6.55	−0.15	3.22	0
15	SO-(3-NH_2-C_6H_4)	6.52	6.55	−0.03	3.22	0
16	SO-(4-Br-C_6H_4)	6.31	6.25	0.06	3.30	0

[a] Not included in the derivation of QSAR 5.

in the areas of toxicology.[12] It is useful in elucidating the mechanisms of chemical−biological interaction in various biomolecules, particularly enzymes, membranes, organelles, and cells.[12,13] It has also been utilized for the evaluation of absorption, distribution, metabolism, and excretion (ADME) phenomena in many organisms and whole animal studies.[14] The QSAR approach employs extra-thermodynamically derived and computational-based descriptors to correlate biological activity in isolated receptors, in cellular systems, and in vivo. QSAR models can stand alone, augment other graphical approaches, or be examined in tandem with equations of a similar mechanistic genre to establish authenticity and reliability.[15]

Materials and Methods

All the data used in this paper have been collected from the literature (see individual QSAR for respective references). *C* is the molar concentration of a compound, and log 1/*C* is the dependent variable that defines the biological parameter

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Table 5. Biological and Physicochemical Parameters Used To Derive QSAR 6 for the Inhibition of SKOV-3 Human Ovarian Cancer Cells by Camptothecin Derivatives (**V**)

				log1/*C* (Eq **6**)			
No.	R_1	R_2	R_3	Obsd.	Pred.	Δ	CMR
1	H	H	H	7.55	7.88	-0.33	10.79
2	C_2H_5	H	H	7.85	7.42	0.43	11.72
3	H	CH_3	H	7.59	7.72	-0.14	11.26
4	C_2H_5	CH_3	H	6.85	6.98	-0.13	12.19
5	H	C_2H_5	H	7.72	7.42	0.30	11.72
6	H	CH_2CN	H	7.49	7.41	0.08	11.74
7	H	$(CH_2)_2NH_2$	H	6.27[a]	7.08	-0.81	12.09
8	H	H		4.98	5.04	-0.07	13.46
9	H	H	$CH_2N(CH_3)_2$	5.06[a]	6.53	-1.46	12.55
10	Camptothecin			7.70	7.60	0.10	9.52
11	SN-38			7.96	7.91	0.05	10.60
12	Topotecan			7.32	7.62	-0.31	11.43

[a] Not included in the derivation of QSAR 6.

for QSAR equations. Physicochemical descriptors are autoloaded, and multiregression analyses (MRA) used to derive the QSARs were executed with the C-QSAR program.[16] The parameters used in this paper have already been discussed in detail along with their application.[12] Briefly, Clog *P* is the calculated partition coefficient in *n*-octanol/water and is a measure of hydrophobicity, and π is the hydrophobic parameter for the substituents usually measured for substituents attached to benzene. CMR is the calculated molar refractivity for the whole molecule. MR is calculated from the Lorentz−Lorenz equation and is described as follows: $[(n^2 - 1)/(n^2 + 2)](MW/\delta)$, where *n* is the refractive index, MW is the molecular weight, and δ is the density of a substance. MR is dependent on volume and polarizability. It can be used for a substituent or for the whole molecule. MR is thus a means of characterizing the bulk and polarizability of a substituent/compound. Although it contains no information about the shape, it has found considerable usage in biological QSARs where intermolecular effects predominate. MR is usually scaled at 0.1 to make it equiscalar with π. A new, rapid, easily calculable polarizability parameter, NVE, was recently developed and shown to be effective at delineating various chemico−biological interactions.[17−19] NVE represents the total number of valence electrons and is calculated by simply summing up the valence electrons in a molecule, that is, H = 1, C = 4, Si = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. It may also be represented as $NVE = n_\sigma + n_\pi + n_n$, where n_σ is the number of electrons in σ-orbitals, n_π is the number of electrons in π-orbitals, and n_n is the number of electrons in lone pairs. It has shown an excellent correlation with molecular polarizabilities, α (n = 146, r^2 = 0.987), as well as molar refractivity (n = 146, r^2 = 0.992).[19] MgVol is the molar volume for the whole molecule and calculated by the C-QSAR program[16] using the method of Abraham and McGowan.[20] Hammett σ, σ^-, and σ^+ constants are electronic parameters that apply to substituent effects on aromatic systems.[12] B1, B5, and *L* are Verloop's sterimol parameters for substituents.[21] B1 is a measure of the width of the first atom of a substituent, B5 is an attempt to define width of the whole substituent, and *L* is the substituent length. The indicator variable *I* is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used. Each regression equation includes 95% confidence limits for each term in parentheses.

In QSAR equations, *n* is the number of data points, *r* is the correlation coefficient between observed values of the dependent and the values calculated from the equation, r^2 is the square of the correlation coefficient and represents the goodness of fit, q^2 is the square of the cross-validated (leave-one-out) correlation coefficient and represents the goodness

Table 6. Biological and Physicochemical Parameters Used To Derive QSAR 7 for the Inhibition of OVCAR-3 Human Ovarian Cancer Cells by Isoquinoline Derivatives (**VI**)

		log1/*C* (eq 7)					
no.	X	obsd	pred	Δ	Clog *P*	*I*	$B5_{X-4}$
1	4-CH_3	6.91	6.84	0.07	4.47	0	2.04
2	4-Cl	6.74	6.75	−0.01	4.76	0	1.80
3	4-OH	5.26	5.22	0.04	3.85	1	1.93
4	4-OCH_3	6.29	6.67	−0.38	4.19	0	3.07
5	4-$NH(CH_2)_2N(CH_3)_2$	6.15	5.99	0.16	4.23	0	5.21
6	8-Cl	7.41	7.03	0.38	4.70	0	1.00
7	8-OH	6.67[a]	5.72	0.95	3.44	1	1.00
8	8-OCH_3	7.28	7.42	−0.14	3.97	0	1.00
9	9-Cl	6.64	7.03	−0.39	4.70	0	1.00
10	9-OH	7.66[a]	5.72	1.94	3.44	1	1.00
11	9-OCH_3	6.27[a]	7.42	−1.15	3.97	0	1.00
12	10-CH_3	7.17	7.15	0.02	4.47	0	1.00
13	10-C_6H_5	6.46	6.42	0.04	5.86	0	1.00
14	10-CN	7.92	7.70	0.22	3.45	0	1.00
15	10-F	8.17[a]	7.33	0.84	4.13	0	1.00
16	10-Cl	7.19	7.03	0.16	4.70	0	1.00
17	10-I	6.75	6.81	−0.06	5.11	0	1.00
18	10-OH	5.67	5.72	−0.05	3.44	1	1.00
19	10-OCH_3	7.11	7.34	−0.24	4.12	0	1.00
20	10-OC_2H_5	7.11	7.06	0.05	4.65	0	1.00
21	10-NO_2	7.64	7.54	0.10	3.76	0	1.00
22	11-Cl	5.05[a]	7.03	−1.98	4.70	0	1.00
23	11-OH	5.72	5.72	0.00	3.44	1	1.00

[a] Not included in the derivation of QSAR 7.

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Table 7. Biological and Physicochemical Parameters Used To Derive QSAR 8 for the Inhibition of OVCAR-3 Human Ovarian Cancer Cells by Lavendustin A Derivatives (**VII**)

					log1/*C* (eq 8)				
no.	X	Y	R	R_1	obsd	pred	Δ	Clog *P*	*I*
1	2,5-$(OH)_2$	CH=CH	H	$NH(CH_2)_2C_6H_5$	5.54	5.58	−0.04	4.94	1
2	2,5-$(OH)_2$	CH=CH	H	$NH(CH_2)_2$-(4-F-C_6H_4)	5.57	5.65	−0.08	5.08	1
3	2,5-$(OH)_2$	CH_2CH_2	H	$NH(CH_2)_2C_6H_5$	5.36	5.35	0.01	4.64	1
4	2,5-$(OH)_2$	CH_2CH_2	H	$NH(CH_2)_2$-(4-F-C_6H_4)	6.00[a]	5.47	0.53	4.79	1
5	2,5-$(OH)_2$	CH_2CH_2	H	$NH(CH_2)_5CH_3$	5.62	5.70	−0.08	5.19	1
6[b]	2,5-$(OCH_3)_2$	CH=CH	CH_3	$NH(CH_2)_2C_6H_5$	5.30	5.31	−0.01	5.79	0
7[b]	2,5-$(OCH_3)_2$	CH=CH	CH_3	$NH(CH_2)_2$-(4-F-C_6H_4)	5.38	5.25	0.12	5.93	0
8[b]	2,5-$(OCH_3)_2$	CH=CH	CH_3	$NH(CH_2)_5CH_3$	4.79	4.96	−0.17	6.34	0
9[b]	2,5-$(OH)_2$	CH=CH	H	$NH(CH_2)_2C_6H_5$	6.00[a]	5.58	0.42	4.94	1
10[b]	2,5-$(OH)_2$	CH=CH	H	$NH(CH_2)_2$-(4-F-C_6H_4)	5.68	5.65	0.02	5.08	1
11[b]	2,5-$(OH)_2$	CH=CH	H	$NH(CH_2)_5CH_3$	5.77	5.74	0.03	5.49	1
12	2,5-$(OCH_3)_2$	C≡C	CH_3	$NH(CH_2)_2C_6H_5$	5.17	5.33	−0.15	5.74	0
13	2,5-$(OCH_3)_2$	C≡C	CH_3	$NH(CH_2)_2$-(4-F-C_6H_4)	5.52	5.28	0.25	5.88	0
14	2,5-$(OH)_2$	C≡C	H	$NH(CH_2)_2C_6H_5$	5.55	5.54	0.01	4.88	1
15	2,5-$(OCH_3)_2$	C≡C	CH_3	OCH_3	4.87	5.01	−0.15	4.69	0
16	2,5-$(OCH_3)_2$	$CH_2C(O)$	H	$NH(CH_2)_2$-(4-F-C_6H_4)	5.85	5.74	0.11	5.39	1
17	2,5-$(OCH_3)_2$	CH_2CH_2	H	$NH(CH_2)_2$-(4-F-C_6H_4)	5.49	5.48	0.02	6.18	1
18	2,5-$(OCH_3)_2$	C≡C	CH_3	OH	4.61	4.50	0.11	4.24	0
19[c]	2,5-$(OCH_3)_2$	$CH_2C(O)$	H	$NH(CH_2)_4CH_3$		5.72		5.27	1
20[c]	2,5-$(OCH_3)_2$	$CH_2C(O)$	H	$NH(CH_2)_5CH_3$		5.69		5.80	1
21[c]	2,5-$(OH)_2$	$CH_2C(O)$	H	$NH(CH_2)_7CH_3$		5.74		5.47	1

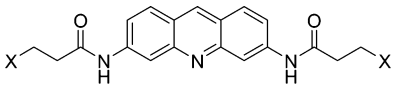
[a] Not included in the derivation of QSAR 8. [b] *Z* isomers. [c] Predicted compounds from eq 8, which may be the next synthetic target.

of prediction (a measure of the quality of the QSAR model, calculated as described by Cramer et al.[22]), and *s* is the standard deviation. Compounds were assigned to be outliers on the basis of their deviation between observed activity and calculated activity from the equation (>2*s*).[23] All the QSARs reported here were derived by us and were not given with the original data sets taken from the literature as referenced.

Results and Discussion

1. Acridines. 1.1. Inhibition of CH1 Human Ovarian Carcinoma Cells by 3,6-Disubstituted Acridines (I). Data were obtained from Harrison et al.[24] (Table 1).

Telomerase is an attractive target for the design of new anticancer drugs. Harrison et al.[24] synthesized a series of 3,6-disubstituted acridines (**I**) on the basis that inhibition of telomerase occurs by stabilizing G-quadruplex structures formed by the folding of telomeric DNA. We derived eq 1 from the data in Table 1, which showed a good correlation between the inhibition potencies and the hydrophobicity of the compounds.



I

$$\log 1/C = 0.19(\pm 0.05)\ \text{Clog}\ P + 4.33(\pm 0.31) \quad (1)$$

$$n = 15, \quad r^2 = 0.832, \quad q^2 = 0.765, \quad s = 0.183$$

Hydrophobicity is found to be the single important parameter for this data set, which shows that at all the parts where substituents have been entered, hydrophobic contacts have been made. The linear Clog *P* model suggests that the highly hydrophobic molecules will be more active. Equation 1 explains 83.2% of variance in log 1/*C*.

1.2. Inhibition of SKOV-3 Human Ovarian Carcinoma Cells by 3,6-Disubstituted Acridines (I). Data were obtained from Harrison et al.[24] (Table 1).

$$\log 1/C = 0.16(\pm 0.04)\ \text{Clog}\ P - 0.57(\pm 0.18)\ \text{MgVol} + 6.87(\pm 0.63) \quad (2)$$

$$n = 13, \quad r^2 = 0.893, \quad q^2 = 0.775, \quad s = 0.095$$

outliers: X = piperidinyl; morpholinyl

Two compounds in Table 1 were deemed to be outliers on the basis of their deviations (>2*s*). A positive hydrophobic parameter is present in QSAR 2, expressing that highly

(22) Cramer, R. D., III; Bunce, J. D.; Patterson, D. E.; Frank, I. E. Cross validation, Bootstrapping and partial least squares compared with multiple regression in conventional QSAR studies. *Quant. Struct.-Act. Relat.* **1988**, *7*, 18−25.

(23) Selassie, C. D.; Kapur, S.; Verma, R. P.; Rosario, M. Cellular apoptosis and cytotoxicity of phenolic compounds: a quantitative structure−activity relationship study. *J. Med. Chem.* **2005**, *48*, 7234−7242.

(24) Harrison, R. J.; Gowan, S. M.; Kelland, L. R.; Neidle, S. Human telomerase inhibition by substituted acridine derivatives. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2463−2468.

Table 8. Biological and Physicochemical Parameters Used To Derive QSAR 9 for the Inhibition of OVCAR-3 Human Ovarian Cancer Cells by Quinolones (**VIII**)

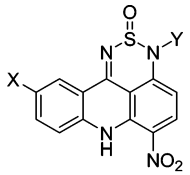
			log1/*C* (eq 9)				
no.	X	Y	obsd	pred	Δ	Clog *P*	$B1_X$
1	$NHCH_3$	6-OCH_2O-7	6.47[a]	5.26	1.21	0.56	1.35
2	F	6-OCH_2O-7	6.54	6.24	0.30	1.20	1.35
3	Cl	6-OCH_2O-7	6.74[a]	5.73	1.01	1.77	1.80
4	Br	6-OCH_2O-7	5.37	5.50	−0.13	1.92	1.95
5	CF_3	6-OCH_2O-7	5.93	5.41	0.52	1.94	1.99
6	OCF_3	6-OCH_2O-7	7.20	7.58	−0.38	2.08	1.35
7	OC_2H_5	6-OCH_2O-7	6.78	6.70	0.08	1.50	1.35
8	Cl	6-NH_2	5.54	5.31	0.23	1.49	1.80
9	CF_3	6-NH_2	4.58	5.00	−0.42	1.67	1.99
10	OCH_3	6-NH_2	5.56	5.48	0.08	0.70	1.35
11	OCH_3	6-$N(CH_3)_2$	7.82	7.53	0.29	2.05	1.35
12	F	6-$NHCOCH_3$	5.99	6.18	−0.19	1.16	1.35
13	Cl	6-$NHCOCH_3$	5.47	5.67	−0.20	1.73	1.80
14	OCH_3	6-$NHCOCH_3$	5.66	5.84	−0.18	0.93	1.35

[a] Not included in the derivation of QSAR 9.

hydrophobic acridines (**I**) would be favored. MgVol is the calculated molar volume according to Abraham and McGowan[20] and has sometimes been used lately instead of MR as an alternative theoretically assessable bulk factor. Thus, the negative MgVol brings out a steric problem. With respect to eq 2, there is no high mutual correlation between Clog *P* and MgVol ($r^2 = 0.444$, $q^2 = 0.297$). Although the same compounds (**I**) have been used in the formulation of QSARs (eqs 1 and 2), we get two different types of equations. The result of QSARs 1 and 2 suggests that the compounds (**I**) may target a receptor of one kind in human CH1, and another kind in human SKOV-3 ovarian carcinoma cells.

1.3. Inhibition of CH1 Human Ovarian Carcinoma Cells by Thiadiazinoacridines (II). Data were obtained from Antonini et al.[25] (Table 2).

For another set of acridine derivatives (**II**), eq 3 was derived.



II

$$\log 1/C = -1.05(\pm 0.37)\ \mathrm{CMR} + 0.69(\pm 0.40)\ C\pi_Y + 16.23(\pm 3.53) \quad (3)$$

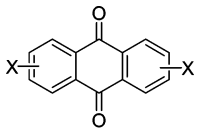
$$n = 10,\quad r^2 = 0.882,\quad q^2 = 0.729,\quad s = 0.140$$

outlier: X = H, Y = $(CH_2)_2$-piperidinyl

The major conclusion to be drawn from the above QSAR is that $C\pi_Y$ (calculated hydrophobicity of Y) promotes the inhibitory activity. CMR refers to the overall molar refractivity. Since MR is primarily a measure of bulk, a negative coefficient suggests steric hindrance.

2. Anthraquinones. 2.1. Inhibition of CH1 Human Ovarian Carcinoma Cells by 9,10-Anthraquinones (III). Data were obtained from Perry et al.[26] (Table 3).

Perry et al.[26] synthesized a series of 9,10-anthraquinones (**III**) on considering that the inhibition of telomerase occurs via stabilization of telomeric G-quadruplex structures. We derived eq 4 from their results in Table 3.



III

Clog *P* is the most significant term, followed by MgVol and

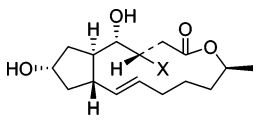
$$\log 1/C = 0.44(\pm 0.16)\ \mathrm{Clog}\ P - 2.77(\pm 0.72)\ \mathrm{MgVol} + 1.12(\pm 0.27)I + 14.58(\pm 2.39) \quad (4)$$

$$n = 18,\quad r^2 = 0.909,\quad q^2 = 0.836,\quad s = 0.225$$

outliers: X = 1,4-$NHCO(CH_2)_2$-pyrrolidinyl;
1,5-$NHCO(CH_2)_2$-piperidinyl;
1,5-$NHCO(CH_2)_2$-pyrrolidinyl;
1,5-$NHCO(CH_2)_2N(C_2H_5)_2$;
2,6-$NHCO(CH_2)_2$-pyrrolidinyl

an indicator variable. Positive Clog *P* suggests that highly hydrophobic anthraquinones (**III**) would be more active. The negative MgVol brings out a steric problem. The indicator variable *I* applies to those compounds which have X-substituents at the 1- and 4-positions. The positive coefficient with *I* means that derivatives with X-substituents at the 1- and 4-positions are correlated with higher activity.

3. Brefeldin A Derivatives. 3.1. Inhibition of OVCAR-3 Human Ovarian Carcinoma Cells by Antibiotic Brefeldin A Derivatives (IV). Data were obtained from Fox et al.[27] (Table 4).



IV

Equation 5 was derived from the data in Table 4.

$$\log 1/C = -3.99(\pm 0.99)\ \mathrm{MgVol} - 1.29(\pm 0.28)I + 19.42 (\pm 3.18) \quad (5)$$

$$n = 13,\quad r^2 = 0.961,\quad q^2 = 0.931,\quad s = 0.219$$

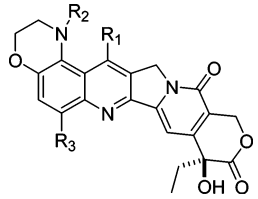
(25) Antonini, I.; Polucci, P.; Magnano, A.; Cacciamani, D.; Konieczny, M. T.; Paradziej-Łukowicz, J.; Martelli, S. Rational design, synthesis and biological evaluation of thiadiazinoacridines: a new class of antitumor agents. *Bioorg. Med. Chem.* **2003**, *11*, 399−405.

outliers: X = $SCH_2CH(OH)CH_3$;
$S(CH_2)_4OH$;
$SO(CH_2)_3OH$

The negative sign with molar volume suggests steric hindrance. The indicator variable *I* acquires a value of 1 for the presence of thio derivatives and 0 for the presence of sulfinyl derivatives. The negative coefficient with *I* suggests that sulfinyl derivatives of antibiotic brefeldin A will be more active than those of thio derivatives, and it can be easily seen in the data of Table 4.

4. Camptothecin Derivatives. 4.1. Inhibition of SKOV-3 Human Ovarian Cancer Cells by Camptothecin Derivatives (V). Data were obtained from Kim et al.[28] (Table 5).

From the data of Kim et al.[28] in Table 5, we derived a parabolic correlation 6 in terms of CMR. It suggests that the anticancer activities of camptothecin derivatives (**V**) against SKOV-3 cells first increases with an increase in molar refractivity up to an optimum CMR value of 10.50 and then decreases.



V

$$\log 1/C = 6.90(\pm 3.25)\,\mathrm{CMR} - 0.33(\pm 0.14)\,\mathrm{CMR}^2 - 28.31(\pm 18.62) \quad (6)$$

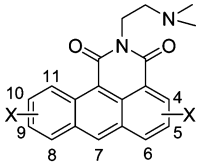
$$n = 10, \quad r^2 = 0.921, \quad q^2 = 0.723, \quad s = 0.278$$

optimum CMR = 10.50(9.65−10.90)

outliers: $R_1 = R_3 = H$, $R_2 = (CH_2)_2NH_2$;
$R_1 = R_2 = H$, $R_3 = CH_2N(CH_3)_2$

Clog *P* cannot replace CMR. Substituting log *P* for MR in eq 6 gives a very poor fit, indicating interaction in nonhydrophobic space (Clog *P* vs CMR = 0.036).

5. Isoquinoline Derivatives. 5.1. Inhibition of OVCAR-3 Human Ovarian Cancer Cells by (4,8,9,10, or 11)-X-2-[2′-(dimethylamino)ethyl]-1,2-dihydro-3*H*-dibenz[*de*,*h*]-isoquinoline-1,3-diones (VI). Data were obtained from Sami et al.[29] (Table 6).



VI

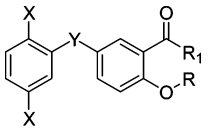
$$\log 1/C = -0.53(\pm 0.21)\,\mathrm{Clog}\,P - 1.98(\pm 0.35)I - 0.31(\pm 0.10)\,B5_{X-4} + 9.84(\pm 0.98) \quad (7)$$

$$n = 18, \quad r^2 = 0.926, \quad q^2 = 0.858, \quad s = 0.214$$

outliers: X = 8-OH;
9-OH;
9-OCH_3;
10-F;
11-Cl

I is an indicator variable, which acquired a value of 1 if X = OH and unfavorable for the inhibitory activity. $B5_{X-4}$ represents the sterimol parameter for the largest width of the groups at position 4, indicating unfavorable steric effect. The negative coefficient with Clog *P* suggests that highly hydrophobic molecules (**VI**) will be less active.

6. Lavendustin A Derivatives. 6.1. Inhibition of OVCAR-3 Human Ovarian Cancer Cells by Lavendustin A Derivatives (VII). Data were obtained from Mu et al.[30] (Table 7).



VII

$$\log 1/C = 6.09(\pm 2.41)\,\mathrm{Clog}\,P - 0.56(\pm 0.23)\,\mathrm{Clog}\,P^2 + 0.38(\pm 0.16)I - 11.33(\pm 6.29) \quad (8)$$

$$n = 16, \quad r^2 = 0.899, \quad q^2 = 0.745, \quad s = 0.126$$

optimum Clog *P* = 5.49(5.37−5.68)

outliers: X = 2,5-$(OH)_2$, Y = CH_2CH_2, R = H, R_1 = $NH(CH_2)_2$-(4-F-C_6H_4);
X = 2,5-$(OH)_2$, Y = CH═CH, R = H, R_1 = $NH(CH_2)_2C_6H_5$

It is a parabolic correlation in terms of Clog *P*, which suggests that the inhibitory activities of lavendustine A derivatives (**VII**) against OVCAR-3 cells first increase with

(26) Perry, P. J.; Reszka, A. P.; Wood, A. A.; Read, M. A.; Gowan, S. M.; Dosanjh, H. S.; Trent, J. O.; Jenkins, T. C.; Kellaand, L. R.; Neidle, S. Human telomerase inhibition by regioisomeric distributed amidoanthracene-9,10-diones. *J. Med. Chem.* **1998**, *41*, 4873−4884.

(27) Fox, B. M.; Vroman, J. A.; Fanwick, P. E.; Cushman, M. Preparation and evaluation of sulfide derivatives of the antibiotic Brefeldin A as potential prodrug candidate with enhanced aqueous solubilities. *J. Med. Chem.* **2001**, *44*, 3915−3924.

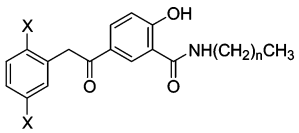
(28) Kim, D.-K.; Ryu, D. H.; Lee, J. Y.; Lee, N.; Kim, Y.-W.; Kim, J.-S.; Chang, K.; Im, G.-J.; Kim, T.-K.; Choi, W.-S. Synthesis and biological evaluation of novel A-ring modified hexacyclic camptothecin analogues. *J. Med. Chem.* **2001**, *44*, 1594−1602.

(29) Sami, S. M.; Dorr, R. T.; Alberts, D. S.; Sólyom, A. M.; Remers, W. A. (2-[2′-(Dimethylamino)ethyl]-1,2-dihydro-3*H*-dibenz[*de*,*h*]-isoquinoline-1,3-diones with substituents at positions 4, 8, 9, and 10. Synthesis, antitumor activity, and quantitative structure−activity relationships. *J. Med. Chem.* **1996**, *39*, 4978−4987.

Table 9. Biological and Physicochemical Parameters Used To Derive QSAR 10 for the Inhibition of OVCAR-5 Human Ovarian Carcinoma Cells by Miscellaneous Indolylpyrimidines and Indolylpyrazines

		log1/*C* (eq 10)			
no.	compound	obsd	pred	Δ	Clog *P*
1	meridianin D	4.76	4.61	0.15	2.86
2	bis(*N*-tosylindolyl)pyrimidine	6.42	6.45	−0.03	8.15
3	5-methyl-2,4-bis(3′-indolyl)pyrimidine	5.26	5.16	0.10	4.45
4	5-methoxy-2,4-bis(3′-indolyl)pyrimidine	5.09	5.09	0.00	4.24
5	2-amino-3-(*N*-tosyl-3′-indolyl)-5-bromopyrazine	5.38	5.29	0.09	4.82
6	2-amino-3-methoxy-5-(3′-indolyl)pyrazine	4.40	4.63	−0.23	2.91
7	2-(*N*,*N*-dimethylamino)-3,5-bis(3′-indolyl)pyrazine	5.33	5.41	−0.08	5.16

an increase in hydrophobicity up to an optimum Clog *P* of 5.49 and then decrease. *I* is an indicator variable, which acquired a value of 1 if R = H. The positive coefficient with *I* indicates that it is favorable for the activity. Equation 8 is an interesting example, and we believe that this equation may be the predictive model to narrow the synthetic challenges in order to yield very specific OVCAR-3 inhibitors. On the basis of this model, we can predict three compounds (compounds 19, 20, and 21 in Table 7) that may be the next synthetic target.

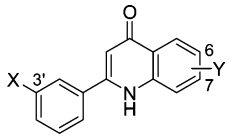


VII-19: X = OCH_3, n = 4; log 1/C = 5.72 (predicted from Eq. 8); Clog *P* = 5.27

VII-20: X = OCH_3, n = 5; log 1/C = 5.69 (predicted from Eq. 8); Clog *P* = 5.80

VII-21: X = OH, n = 7; log 1/C = 5.74 (predicted from Eq. 8); Clog *P* = 5.47

7. Quinolones. 7.1. Inhibition of OVCAR-3 Human Ovarian Cancer Cells by Quinolones (VIII). Data were obtained from Li et al.[31] (Table 8).



VIII

$$\log 1/C = 1.52(\pm 0.55)\ \text{Clog}\ P - 3.06(\pm 0.86)\ B1_X + 8.55 (\pm 1.25) \quad (9)$$

$$n = 12, \quad r^2 = 0.891, \quad q^2 = 0.780, \quad s = 0.328$$

outliers: X = $NHCH_3$, Y = 6-OCH_2O-7; X = Cl, Y = 6-OCH_2O-7

The major conclusions to be drawn from the above QSAR are that hydrophobicity promotes anticancer activity. $B1_X$, the sterimol parameter for the smallest width of the first atom of substituents X, has a negative sign indicating that steric interaction at the X-substituent of the phenyl ring is unfavorable.

Table 10. Biological and Physicochemical Parameters Used To Derive QSAR 11 for the Inhibition of SKOV-3 Human Ovarian Carcinoma Cells by Miscellaneous Compounds **IX**, **X**, **XI**, and Doxorubicin

			log1/*C* (eq 11)				
no.	R_1	R_2	obsd	pred	Δ	Clog *P*	I
IXa	H	H	8.85	8.73	0.13	2.78	0
IXb	CH_3	H	8.14	8.50	−0.37	3.28	0
IXc	OCH_3	H	8.14	8.68	−0.54	2.89	0
IXd	C_2H_5	H	8.11	8.27	−0.16	3.81	0
IXe	OC_2H_5	H	8.30	8.45	−0.15	3.42	0
IXf	*n*-C_3H_7	H	8.31	8.04	0.27	4.34	0
Xa	H	H	9.51	9.64	−0.13	0.71	0
Xb	CH_3	H	9.45	9.42	0.03	1.21	0
Xc	OCH_3	H	9.51	9.48	0.03	1.09	0
Xd	C_2H_5	H	9.45	9.19	0.27	1.74	0
Xe	OC_2H_5	H	9.37	9.24	0.13	1.62	0
Xf	*n*-C_3H_7	H	9.17	8.95	0.22	2.27	0
Xg	*n*-C_4H_9	H	9.27	8.72	0.55	2.80	0
XIa	H	H	10.57	10.61	−0.04	1.65	1
XIb	CH_3	H	10.54	10.34	0.20	2.27	1
XIc	H	CH_3	10.59	10.34	0.25	2.27	1
XId	H	C_2H_5	9.68	10.11	−0.43	2.80	1
XIe	H	Cl	10.63	10.24	0.38	2.49	1
XIf	H	Br	9.82	10.18	−0.36	2.64	1
XII	doxorubicin		9.53	9.82	−0.28	0.32	0

8. Miscellaneous. 8.1. Inhibition of OVCAR-5 Human Ovarian Cancer Cells by Miscellaneous Indolylpyrimidines and Indolylpyrazines. Data were obtained from Jiang et al.[32] (Table 9).

$$\log 1/C = 0.35(\pm 0.08)\ \text{Clog}\ P + 3.62(\pm 0.41) \quad (10)$$

$$n = 7, \quad r^2 = 0.959, \quad q^2 = 0.917, \quad s = 0.139$$

Hydrophobicity is the most important single parameter for this data set, showing that the highly hydrophobic molecules will be more active.

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Table 11. Comparison of the Statistics Obtained from the Multiregression Analysis (MRA) Process for QSARs 1−11

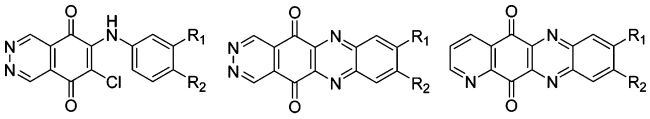
QSAR no.	compound type	human ovarian cancer cell lines	n	descriptor coefficient: hydrophobic	descriptor coefficient: steric/pol	descriptor coefficient: others	r^2	q^2	s	intercept
1	acridines	CH1	15	0.19 Clog *P*			0.832	0.765	0.183	4.33
2	acridines	SKOV-3	13	0.16 Clog *P*	−0.57 MgVol		0.893	0.775	0.095	6.87
3	acridines	CH1	10	0.69 Cπ_Y	−1.05 CMR		0.882	0.729	0.140	16.23
4	anthraquinones	CH1	18	0.44 Clog *P*	−2.77 MgVol	1.12*I*	0.909	0.836	0.225	14.58
5	brefeldin A derivatives	OVCAR-3	13		−3.99 MgVol	−1.29*I*	0.961	0.931	0.219	19.42
6	camptothecin derivatives	SKOV-3	10		6.90 CMR − 0.33 CMR^2		0.921	0.723	0.278	−28.31
7	isoquinolines	OVCAR-3	18	−0.53 Clog *P*	−0.31 B5$_{X-4}$	−1.98*I*	0.926	0.858	0.214	9.84
8	lavendustin A derivatives	OVCAR-3	16	6.09 Clog *P* − 0.56 Clog *P*^{2}		0.38*I*	0.899	0.745	0.126	−11.33
9	quinolones	OVCAR-3	12	1.52 Clog *P*	−3.06 B1$_X$		0.891	0.780	0.328	8.55
10	miscellaneous	OVCAR-5	7	0.35 Clog *P*			0.959	0.917	0.139	3.62
11	miscellaneous	SKOV-3	20	−0.44 Clog *P*		1.39*I*	0.875	0.830	0.314	9.96

Table 12. Y-Randomization Data for QSARs 1−11

QSAR no.	NOR-1[a] r^2	NOR-1[a] q^2	NOR-2 r^2	NOR-2 q^2	NOR-3 r^2	NOR-3 q^2	NOR-4 r^2	NOR-4 q^2	NOR-5 r^2	NOR-5 q^2
1	0.035	−0.213	0.295	0.120	0.306	0.105	0.000	−0.315	0.066	−0.313
2	0.140	−0.524	0.186	−0.443	0.305	−0.280	0.022	−0.813	0.078	−0.587
3	0.008	−0.746	0.151	−0.992	0.112	−0.671	0.160	−0.757	0.016	−2.055
4	0.299	−0.096	0.408	−0.001	0.430	0.070	0.302	−0.071	0.230	−0.211
5	0.468	0.018	0.254	−0.245	0.024	−1.014	0.182	−0.433	0.107	−0.511
6	0.379	−2.438	0.073	−1.306	0.103	−0.537	0.106	−0.686	0.488	−2.904
7	0.057	−1.902	0.174	−1.137	0.024	−0.574	0.178	−0.976	0.063	−2.267
8	0.071	−0.756	0.047	−0.747	0.074	−0.565	0.144	−0.567	0.137	−1.045
9	0.353	−0.110	0.025	−0.855	0.021	−0.973	0.322	−0.278	0.024	−0.794
10	0.173	−0.165	0.188	−0.886	0.033	−1.884	0.152	−2.663	0.069	−0.881
11	0.204	−0.156	0.202	−0.204	0.083	−0.418	0.200	−0.199	0.334	0.016

[a] NOR = number of Y-randomization.

8.2. Inhibition of SKOV-3 Human Ovarian Cancer Cells by Miscellaneous Compounds IX, X, XI, and Doxorubicin. Data were obtained from Lee et al.[33] (Table 10).



IX **X** **XI**

Hydrophobicity should be taken under consideration as an

$$\log 1/C = -0.44(\pm 0.15)\text{Clog } P + 1.39(\pm 0.32)I + 9.96(\pm 0.38) \quad (11)$$

$$n = 20,\ r^2 = 0.875,\ q^2 = 0.830,\ s = 0.314$$

important variable for this data set. The negative Clog *P* term shows that hydrophilic molecules would present better inhibitory activity. The indicator variable *I* takes the value of 1 for the presence of pyrido derivatives (**XI**). The positive coefficient shows that the derivatives of **XI** will be more active as seen in Table 10.

A comparison of the statistics of QSARs 1−11 obtained from multiregression analyses (MRA) has been shown in Table 11. All the QSARs are found to be statistically significant, which also fulfill the conditions given by Golbraikh and Tropsha[34] as the acceptable models. These QSAR models also fulfill the condition of (number of data points)/(number of descriptors) ≥ 5.

Validation of QSAR

The real utility of a QSAR model is in its ability to accurately predict the modeled property for new compounds. Thus, the validation of QSAR models is absolutely essential for its successful application and interpretation. The following

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approaches have been used for the validation of QSARs 1−11:

(i) Statistics. It is important to note that a QSAR model must have a sufficiently high quality of statistics. The amount of dependent variable variance explained by an MRA model is expressed by r^2 (measure of the goodness of fit between model-predicted and experimental values). It is believed that the closer the value of r^2 to unity, the better the QSAR model. In this paper, the values of r^2 for QSAR models 1−11 are found to be 0.832−0.961 (Table 11). The high values of r^2 confirmed the validity of the models.

(ii) Cross-Validation Test. The cross-validated correlation coefficient (q^2) was obtained by using the leave-one-out procedure.[22] In this paper, the values of q^2 for QSAR models 1−11 are found to be 0.723−0.931 (Table 11). The high values of q^2 supported the validation of QSAR models. According to the literature, it must be greater than 0.5.[34]

(iii) Y-Randomization Test. In this test, the dependent-variable vector (Y-vector) is randomly shuffled and a new QSAR model is developed using the original independent variable matrix. The process is repeated several times. It is expected that the resulting QSAR models should have low r^2 and low q^2 values. This is a widely used technique to ensure the robustness of a QSAR model. The statistical data of r^2 and q^2 for five runs have been listed in Table 12. The poor values of r^2 and q^2 in the Y-randomization test (Table 12) ensure the robustness of the QSAR models 1−11.[23,35−37]

Conclusion

An analysis of our QSARs on the cytotoxicity of organic compounds against ovarian cancer cells reveals a number of interesting points. The most important of these is hydrophobicity, which is one of the most important determinants of activity. Out of 11 QSARs, 9 contain a correlation between activity and hydrophobicity. A positive linear correlation is found in 6 equations (eqs 1−4, 9, and 10). The coefficient with the hydrophobic parameter varies considerably, from a low value of 0.16 (eq 2) to a high value of 1.52 (eq 9). These data suggest that activity might be improved by increasing compound hydrophobicity. A negative linear correlation is found in 2 equations (eqs 7 and 11), and the coefficients range from −0.53 (eq 7) to −0.44 (eq 11). Less hydrophobic congeners in these compound families might display enhanced activity. Parabolic correlation with hydrophobicity is found in one equation (8). This may be an encouraging example, where the optimal hydrophobicity is well-defined that is log $P = 5.49$. We believe that this may be the predictive model to narrow the synthetic challenges in order to yield very specific OVCAR-3 inhibitors. On the basis of this model, we predict three compounds (**VII**-19, **VII**-20, and **VII**-21) that may be the next synthetic target.

Other parameters, that is, steric parameters and polarizability, also appear in several QSARs. In some cases, these parameters correlate all of the observed variation in activity, but they do not seem to play as important a role as hydrophobicity for the data sets that we have examined.

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