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Original article

A QSAR study for the cytotoxic activities of taxoids against macrophage (MΦ)-like cells

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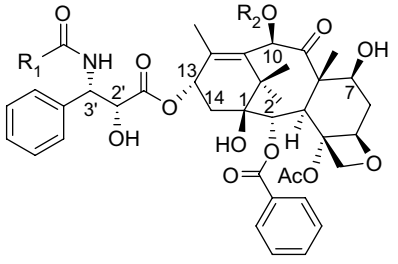
Abstract

A series of taxoids (modified at the C-3′N position) have been used for the development of two QSAR models for their cytotoxic activities against macrophage (MΦ)-like cells J774.1 and J7.DEF3. QSAR results suggest that hydrophobic and steric features influence the inhibitory activity in a linear model. The *C* log *P* values were not great enough to establish the upper limit of the inhibition. Internal [cross-validation, quality factor (*Q*), Fischer statistics (*F*), Y-randomization, and lack of overfitting tests] and external validation tests have validated both the QSAR models.

Keywords: Hydrophobicity; Macrophage (MΦ)-like cells; Molar refractivity; Quantitative structure–activity relationship (QSAR); Taxoids

1. Introduction

Taxoids such as paclitaxel (PTX, Taxol; **I**) and docetaxel (DTX, Taxotere; **II**) are the two most important anticancer drugs in clinical use today [1,2]. These two taxoid drugs were approved by the FDA for the treatment of various types of cancers, including breast, colon, lung, ovarian, and prostate cancer [3–5]. These drugs bind to the β-subunit of tubulin polymer in a stoichiometric ratio and promote tubulin polymerization. This phenomenon disrupts tubulin polymerization dynamics, leading to cell cycle arrest and ultimately, cell death by apoptosis [6–8]. It has been shown that PTX can mimic several biological activities of bacterial lipopolysaccharides (LPSs) [9,10]. Ding and co-workers [11] have suggested that like PTX, LPS is also capable of binding to the β-subunit of tubulin, as well as to microtubule-associated protein (MAP).



In this paper, we developed two QSAR (quantitative structure–activity relationship) models on one set of taxoids (modified at the C-3′N position) with respect to their cytotoxicities against macrophage (MΦ)-like cell lines J774.1 and J7.DEF3. In the past 44 years, the use of QSAR (one of the well developed areas in computational chemistry), since the advent of this methodology [12], has become increasingly helpful in understanding many aspects of chemical–biological interactions in drug and pesticide research, as well as in the areas of toxicology. This method is useful in elucidating the mechanisms of chemical–biological interaction in various biomolecules, particularly enzymes, membranes, organelles, and cells, as

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well as in humans [13–15]. It has also been utilized for the evaluation of absorption, distribution, metabolism, and excretion (ADME) phenomena in many organisms and in whole animal studies [16,17]. The QSAR approach employs extrathermodynamically derived and computational-based descriptors to correlate biological activity in isolated receptors, cellular systems, and in vivo. Four standard molecular descriptors routinely used in QSAR analysis are electronic, hydrophobic, steric, and topological indices. The quality of a QSAR model, however, depends mainly on the type and quality of the data, and is valid only for the compound structures analogs to those used to build the model. QSAR models can stand alone, augment other computational approaches, or be examined in tandem with equations of a similar mechanistic genre to establish their authenticity and reliability [18]. Potential use of QSAR models for screening of chemical databases or virtual libraries before their synthesis appears equally attractive to chemical manufacturers, pharmaceutical companies and government agencies.

2. Methods

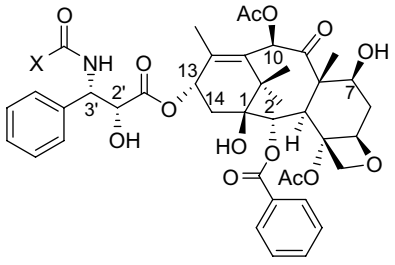
IC_{50} data of taxoids have been collected from Ref. [19] and converted into molar concentration. C is the molar concentration of a taxoid that inhibits 50% of growth of J774.1 cells and J7.DEF3 cells; log $1/C$ is the subsequent dependent variable that defines the biological parameter for QSAR development. Physicochemical descriptors are auto-loaded, and multi-regression analysis (MRA) is used to derive the QSAR by utilizing the C-QSAR program [20]. Selection of descriptors is made on the basis of permutation and correlation matrices among the descriptors in order to avoid collinearity problems. Details about the C-QSAR program, the search engine, the choice of parameters and their use in the development of QSAR models, have already been discussed [21,22]. The parameters used in this paper have already been discussed in detail along with their application [13]. Briefly, $C\log P$ is the calculated partition coefficient of a compound in n-octanol/water and is a measure of its hydrophobicity. CMR is the calculated molar refractivity for the whole molecule. Molar refractivity (MR) is calculated from the Lorentz–Lorenz equation and is described as follows: $[(n^2-1)/(n^2+2)](\mathrm{MW}/\delta)$, where n is the refractive index, MW is the molecular weight, and δ is the density of the substance. MR is dependent on volume and polarizability. It can be used for a substituent or for the whole molecule.

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 cross-validated r^2 (a measure of the quality of the QSAR model), and s is the standard deviation. The cross-validated $r^2(q^2)$ is obtained by using leave-one-out (LOO) procedure as described by Cramer et al. [23]. Q is the quality factor (quality ratio), where $Q = r/s$. Chance correlation, due to the excessive number of parameters (which increases the r and s values also), can, thus, be detected by the examination of the Q value. High values of Q indicate the high predictive power of the QSAR models and the lack of ''overfitting''. F is the Fischer statistics (Fischer ratio), $F = fr^2/[(1-r^2)m]$, where f is the number of degree of freedom, $f = n-(m+1)$, n is the number of data points, and m is the number of variables. The F-value is actually the ratio between explained and unexplained variance for a given number of degree of freedom. Thus, it indicates a true relationship, or the significance level for the MLR models. The modeling was taken to be optimal when Q reached a maximum together with F, even if slightly non-optimal F-values have normally been accepted. A significant decrease in F with the introduction of one additional variable (with increasing Q and decreasing s) could mean that the new descriptor is not as significant as expected, that is, its introduction has endangered the statistical quality of the combination. However, the statistical quality could be improved by the introduction of a more convincing descriptor [24–26]. Compounds were deemed to be outliers on the basis of their deviation between observed and calculated activities from the equation ($>2s$) [27–31]. Each regression equation includes 95% confidence limits for each term in parentheses.

3. Results and discussion

3.1. Inhibition of growth of J774.1 cells by taxoids **III**

Based on the data obtained from Ojima et al. [19] (Table 1).



III

$$\log 1/C = 0.51(\pm 0.25)C\log P - 0.50(\pm 0.15)\mathrm{MR}_X + 6.47(\pm 0.99); \quad n = 19,\ r^2 = 0.773,\ s = 0.215,\ q^2 = 0.662,\ Q = 4.088,\ F_{2,16} = 27.242 \qquad (1)$$

The most significant variable is MR_X (molar refractvity of X-substituents), which alone accounts for 50.9% of the variance in the data. Since MR_X is primarily a measure of the bulk and polarizability of X-substituent, the negative coefficient with this term suggests that (in the rough way) the smaller size of X promotes the inhibition with the corresponding derivatives. The positive $C\log P$ suggests that all the parts where substituents have been entered hydrophobic contacts have been made. The existence of a linear only correlation between log $1/C$ and $C\log P$ suggests that the $C\log P$ values were not great enough to establish the upper limit of the inhibition. Thus, the taxoids **III** should be more hydrophobic with

Table 1
Biological and physicochemical parameters used to derive QSAR Eqs. (1) and (2)

No.	X	log 1/*C* [Eq. (1)]			log 1/*C* [Eq. (2)]			*C* log *P*	MR_X	CMR
		Obsd.	Pred.	Δ	Obsd.	Pred.	Δ			
1	C_6H_5	7.48	7.62	−0.14	7.52	7.70	−0.18	4.73	2.50	22.13
2	$OC(CH_3)_3$	8.24	7.90	0.34	8.14	7.99	0.15	4.80	2.01	21.63
3	2-Thiophenyl	8.70	8.42	0.28	7.80	7.73	0.07	4.57	0.74	21.94
4[a]	2-Furyl	8.30	8.41	−0.11	6.70	7.78	−1.08	3.91	0.09	21.34
5	4-C_6H_5−C_6H_4	7.31	7.31	0.00	6.85	7.11	−0.26	6.62	5.01	24.64
6[a]	1-Naphthyl	7.17	7.33	−0.16	6.43	7.26	−0.83	5.90	4.26	23.82
7	2-Naphthyl	7.68	7.37	0.31	7.26	7.26	0.00	5.90	4.17	23.82
8	$CH_2C_6H_5$	7.11	7.45	−0.34	7.32	7.47	−0.15	4.79	2.89	22.59
9	$CH{=}CHC_6H_5$	7.52	7.66	−0.14	7.11	7.35	−0.24	5.48	3.17	23.34
10	4-CH_3−C_6H_4	7.77	7.64	0.13	7.82	7.65	0.17	5.23	2.96	22.59
11	4-Cl−C_6H_4	7.52	7.84	−0.32	7.59	7.80	−0.21	5.65	2.99	22.62
12	4-OCH_3−C_6H_4	7.23	7.41	−0.18	7.43	7.44	−0.01	4.93	3.12	22.75
13	3,4-$(OCH_3)_2$−C_6H_3	7.21	6.93	0.28	7.24	6.98	0.26	4.61	3.73	23.36
14	4-F−C_6H_4	7.68	7.78	−0.10	7.77	7.83	−0.06	5.08	2.52	22.14
15	4-C_2H_5−C_6H_4	7.82	7.67	0.15	7.85	7.61	0.24	5.76	3.43	23.06
16	4-$CH_2CH_2CH_3$−C_6H_4	7.74	7.71	0.03	7.77	7.58	0.19	6.29	3.89	23.52
17	4-$C(CH_3)_3$−C6H4	7.62	7.61	0.01	7.60	7.44	0.16	6.56	4.36	23.98
18	2,4-$(F)_2$−C6H3	7.59	7.68	−0.09	7.60	7.74	−0.14	4.88	2.53	22.16
19	2,4-$(OCH_3)_2$−C_6H_3	7.12	7.08	0.04	7.08	7.09	−0.01	4.89	3.73	23.36

[a] Not used in the derivation of QSAR Eq. (2).

less bulkier/polarizable *X*-substituent for the better cytotoxic activity against J774.1 cells. A comparison between observed and predicted log 1/*C* of taxoids **III** used in the development of QSAR Eq. (1) is shown in Fig. 1.

3.2. Inhibition of growth of J7.DEF3 cells by taxoids *III*

Based on the data obtained from Ojima et al. [19] (Table 1).

$$\log 1/C = 0.41(\pm 0.23)C\log P - 0.54(\pm 0.19)\mathrm{CMR} + 17.76(\pm 3.57);\quad n = 17,\ r^2 = 0.731,\ s = 0.186, q^2 = 0.536,\ Q = 4.597,\ F_{2,14} = 19.022;\quad \text{outliers}: X = 2-\text{furyl};\ 1-\text{naphthyl} \qquad (2)$$

QSAR (2) reveals that hydrophobic and steric features influence the inhibitory activity in a linear model. Positive *C* log *P* suggests that the inhibitory activity of the molecule increases with the increase of their hydrophobicity. On the contrary increases in the molar refractivity of the whole molecule (CMR), decreases the potency of the compounds (negative coefficient). Calculated molar refractivity of the whole molecule (CMR) is the most significant term, which alone accounts for 45.5% of the variance in the data. There is a high correlation between CMR and MR_X($r = 0.924$), where MR_X is the calculated molar refractivity of *X*-substituents. Thus, MR_X can replace CMR. By substituting MR_X for CMR in Eq. (2), we can develop Eq. (2a).

$$\log 1/C = 0.28(\pm 0.30)C\log P - 0.34(\pm 0.21)MR_X + 7.12(\pm 1.22);\quad n = 17,\ r^2 = 0.492,\ s = 0.256,\ q^2 = 0.103,\ Q = 2.738, F_{2,14} = 6.779;\ \text{outliers}: X = 2-\text{furyl};\ 1-\text{naphthyl} \qquad (2a)$$

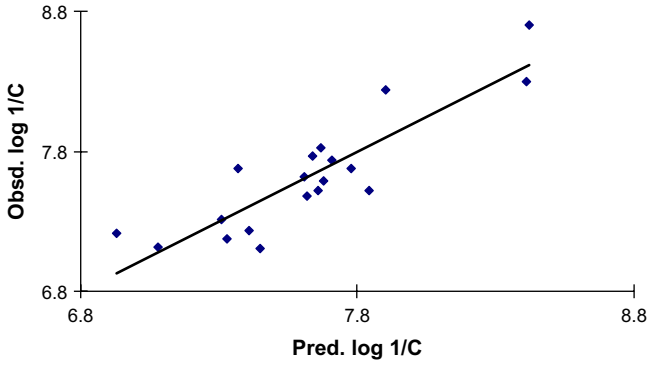


Fig. 1. Plot of observed versus predicted log 1/*C* [Eq. (1)].

Finally, we preferred Eq. (2) because Eq. (2a) is statistically not significant. Two compounds (X = 2-furyl; 1-naphthyl) were not used in the derivation of Eq. (2) due to their high deviation from the observed activity (Obsd. − Pred. $> 2 \times s$). When this correlation was developed without dropping any compounds, the statistics were not acceptable ($r^2 = 0.405$, $q^2 = 0.015$). By considering either one outlier (X = 2-furyl or 1-naphthyl), the statistics were $r^2 = 0.625$, $q^2 = 0.435$ and $r^2 = 0.442$, $q^2 = -0.023$, respectively, which were also unacceptable. Thus, the removal of these two compounds in the development of QSAR Eq. (2) is justified. A comparison between observed and predicted log 1/*C* of taxoids **III** used in the development of QSAR Eq. (2) is shown in Fig. 2.

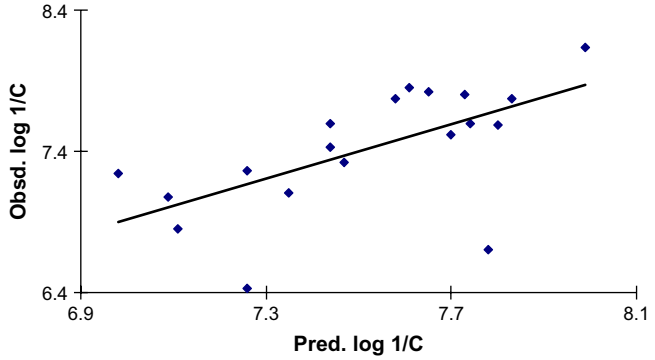


Fig. 2. Plot of observed versus predicted log 1/*C* [Eq. (2)].

4. Validation of QSAR models

QSAR model validation becomes an essential part in the development of a statistically valid and predictive model, because the real utility of a QSAR model is in its ability to predict accurately the modeled property for new compounds. The following approaches have been used for the validation of QSAR Eqs. (1) and (2).

4.1. Internal validation

- *Fraction of the Variance (r^2).* It is believed that the closer the value of r^2 to unity, the better the QSAR model. The values of r^2 for these QSAR models are 0.773 and 0.731, which suggest that these QSAR models explain 77.3% and 73.1% of the variance in the data, respectively. According to the literature, the predictive QSAR model must have $r^2 > 0.6$ [32,33].
- *Cross-validation test.* The values of q^2 for these QSAR models are 0.662 and 0.536. The high values of q^2 validate these QSAR models. According to the literature, the predictive QSAR model must have $q^2 > 0.5$ [32,33].
- *Standard deviation (s).* *s* is the standard deviation about the regression line. The smaller the value of *s* the better the QSAR model. The values of *s* for these QSAR models are 0.215 and 0.186.
- *Quality factor (Q).* Chance correlation, due to the excessive number of parameter is detected by the examination of *Q* value [24–26]. High values of *Q* (4.088 and 4.597) for these QSAR models suggest that their high predictive power.
- *Fischer statistics (F).* Fischer statistics (*F*) is the ratio between explained and unexplained variance for a given number of degree of freedom. The larger the value of *F* the greater the probability that the QSAR model is significant. The *F*-values for these QSAR models are 27.242 and 19.022, which are statistically significant at the 95% level.
- *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 5 runs have been listed in Table 2 [Eqs. (1) and (2)]. The poor values of r^2 and q^2 in the Y-randomization test ensure the robustness for these QSAR models [27,33–36].
- *Lack of overfitting.* A model overfits if it includes more descriptors than required. The lack of overfitting for these two QSAR models was confirmed by using the following conditions:
  (a) Number of data points/number of descriptors ≥ 4.
  (b) High values of *Q* for these QSAR models indicate the lack of overfitting.
  (c) Y-randomization test (Table 2) suggests that the high r^2 values of these two QSAR Eqs. (1) and (2) are not due to a chance correlation or overfitting [37].
  (d) Both QSARs were checked for their correlation with less number of descriptors than that of the original. None of them was found to be statistically significant (Table 3).

Table 2
Y-randomization data for QSAR Eqs. (1) and (2)

NOR	Eq. (1)		Eq. (2)	
	r^2	q^2	r^2	q^2
1	0.151	−0.519	0.457	0.223
2	0.297	0.014	0.187	−0.142
3	0.139	−0.290	0.186	−0.172
4	0.088	−0.207	0.179	−0.259
5	0.130	−0.227	0.473	0.288

NOR = number of Y-randomization.

4.2. External validation

- *Selection of the training and test sets.* The data set of QSAR Eq. (1) was divided into training [$n = 15(\sim 75\%)$] and test [$n = 4(\sim 25\%)$] sets in a random manner (five trials). The QSAR models for these five training sets were generated by using the same descriptors as

Table 3
QSAR obtained by the use of less number of descriptors than that of the original QSAR with their statistical parameters

Eq. no.	NSQ	QSAR with less number of descriptors than that of the original QSAR	*n*	r^2	q^2	*s*
(1)	1-a	$\log 1/C = -0.16\ (\pm 0.28)\ C \log P + 8.48\ (\pm 1.52)$	19	0.078	−0.159	0.420
	1-b	$\log 1/C = -0.25\ (\pm 0.13)\ \mathrm{MR}_X + 8.39\ (\pm 0.41)$	19	0.509	0.373	0.306
(2)	2-a	$\log 1/C = -0.09\ (\pm 0.27)\ C \log P + 8.02\ (\pm 1.43)$	17	0.036	−0.317	0.340
	2-b	$\log 1/C = -0.28\ (\pm 0.17)\ \mathrm{CMR} + 13.88\ (\pm 3.84)$	17	0.455	0.299	0.256

NSQ = number of QSAR models obtained by the use of less number of descriptors than that of the original QSAR. None of these QSARs were found to be statistically significant.

Table 4
A random selection pattern of the test sets, QSAR models of the training sets with their statistical parameters, and observed/predicted biological activities of the compounds in test sets

Eq. no.	NOS	QSAR for the training sets (rest of compounds after removing the test sets from the original set)	Random selection of the test sets			
			Compd. no.	log $1/IC_{50}$		
				Obsd.	Pred.	Δ
(1)	1A	$\log 1/C = 0.54\ (\pm 0.29)\ C\log P - 0.56\ (\pm 0.18)\ MR_X + 6.49\ (\pm 1.16)$; $n = 15$, $r^2 = 0.792$, $s = 0.217$, $q^2 = 0.651$, $Q = 4.101$, $F_{2,12} = 22.846$	**1**	7.48	7.67	−0.19
			4	8.30	8.56	−0.26
			11	7.52	7.89	−0.37
			16	7.74	7.74	0.00
	1B	$\log 1/C = 0.37\ (\pm 0.25)\ C\log P - 0.41\ (\pm 0.16)\ MR_X + 6.91\ (\pm 0.99)$; $n = 15$, $r^2 = 0.738$, $s = 0.191$, $q^2 = 0.639$, $Q = 4.497$, $F_{2,12} = 16.901$	**3**	8.70	8.31	0.39
			8	7.11	7.52	−0.41
			12	7.23	7.48	−0.25
			18	7.59	7.70	−0.11
	1C	$\log 1/C = 0.50\ (\pm 0.34)\ C\log P - 0.50\ (\pm 0.18)\ MR_X + 6.53\ (\pm 1.40)$; $n = 15$, $r^2 = 0.775$, $s = 0.241$, $q^2 = 0.632$, $Q = 3.653$, $F_{2,12} = 20.667$	**5**	7.31	7.30	0.01
			9	7.52	7.65	−0.13
			15	7.82	7.66	0.16
			17	7.62	7.60	0.02
	1D	$\log 1/C = 0.52\ (\pm 0.32)\ C\log P - 0.51\ (\pm 0.20)\ MR_X + 6.41\ (\pm 1.23)$; $n = 15$, $r^2 = 0.750$, $s = 0.239$, $q^2 = 0.553$, $Q = 3.623$, $F_{2,12} = 18.000$	**6**	7.17	7.34	−0.17
			10	7.77	7.64	0.13
			14	7.68	7.79	−0.11
			19	7.12	7.08	0.04
	1E	$\log 1/C = 0.49\ (\pm 0.29)\ C\log P - 0.50\ (\pm 0.17)\ MR_X + 6.60\ (\pm 1.15)$; $n = 15$, $r^2 = 0.788$, $s = 0.233$, $q^2 = 0.666$, $Q = 3.811$, $F_{2,12} = 22.302$	**9**	7.52	7.69	−0.17
			12	7.23	7.45	−0.22
			14	7.68	7.82	−0.14
			18	7.59	7.72	−0.13
(2)	2A	$\log 1/C = 0.37\ (\pm 0.27)\ C\log P - 0.54\ (\pm 0.22)\ CMR + 17.81\ (\pm 4.05)$; $n = 13$, $r^2 = 0.763$, $s = 0.199$, $q^2 = 0.552$, $Q = 4.387$, $F_{2,10} = 16.097$	**1**	7.52	7.73	−0.21
			8	7.32	7.50	−0.18
			10	7.82	7.67	0.15
			12	7.43	7.47	−0.04
	2B	$\log 1/C = 0.41\ (\pm 0.27)\ C\log P - 0.55\ (\pm 0.22)\ CMR + 17.95\ (\pm 4.01)$; $n = 13$, $r^2 = 0.772$, $s = 0.188$, $q^2 = 0.517$, $Q = 4.676$, $F_{2,10} = 16.930$	**3**	7.80	7.75	0.05
			8	7.32	7.48	−0.16
			11	7.59	7.81	−0.22
			15	7.85	7.62	0.23
	2C	$\log 1/C = 0.32\ (\pm 0.29)\ C\log P - 0.48\ (\pm 0.20)\ CMR + 16.87\ (\pm 3.92)$; $n = 13$, $r^2 = 0.748$, $s = 0.174$, $q^2 = 0.515$, $Q = 4.971$, $F_{2,10} = 14.841$	**5**	6.85	7.06	−0.21
			10	7.82	7.61	0.21
			16	7.77	7.49	0.28
			17	7.60	7.36	0.24
	2D	$\log 1/C = 0.33\ (\pm 0.26)\ C\log P - 0.52\ (\pm 0.20)\ CMR + 17.56\ (\pm 3.73)$; $n = 13$, $r^2 = 0.785$, $s = 0.181$, $q^2 = 0.576$, $Q = 4.895$, $F_{2,10} = 18.256$	**8**	7.32	7.52	−0.20
			9	7.11	7.37	−0.26
			16	7.77	7.55	0.22
			18	7.60	7.78	−0.18
	2E	$\log 1/C = 0.31\ (\pm 0.25)\ C\log P - 0.52\ (\pm 0.20)\ CMR + 17.64\ (\pm 3.62)$; $n = 13$, $r^2 = 0.800$, $s = 0.174$, $q^2 = 0.587$, $Q = 5.144$, $F_{2,10} = 20.000$	**10**	7.82	7.61	0.21
			15	7.85	7.53	0.32
			17	7.60	7.31	0.29
			18	7.60	7.72	−0.12

NOS = number of selection of the training and test sets.

those of Eq. (1) and validated on the basis of their statistics (acceptance criteria: $r^2 > 0.6$ and $q^2 > 0.5$). The resulting QSAR models of the training sets were used to predict the biological activities of the compounds present in their respective test sets. It was found that the predicted biological activities of the compounds in test sets are in very good agreement with their observed biological activities. These observations have validated the QSAR Eq. (1). A random selection pattern of the test sets, QSAR models of the training sets with their statistical parameters, and predicted biological activities of the compounds in test sets by using QSAR models (of the respective training sets) with their observed biological activities are given in Table 4. Similarly, the QSAR Eq. (2) was divided into training and test sets for the external validation. The details about the data used for the external validation of QSAR Eq. (2) are listed in the same Table 4.

5. Conclusion

Among novel chemotherapeutic agents, the taxoids such as paclitaxel and docetaxel are the two most important anticancer drugs in clinical use today. The antimitotic activities of these two drugs are due to their ability to bind to the β-subunit of

tubulin and cause tubulin polymerization. Our QSAR results for the cytotoxicities of a series of taxoids (modified at the C-3′N position) against macrophage (MΦ)-like cell lines J774.1 and J7.DEF3 suggest that hydrophobic and steric features influence the inhibitory activity in a linear model. The $C \log P$ values were not great enough to establish the upper limit of the inhibition.

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