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Review

A QSAR review on melanoma toxicity

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Abstract—Melanoma is one of the most aggressive forms of skin cancer and is currently attracting our attention particularly in the area of quantitative structure–activity relationships (QSAR). In the present review, an attempt has been made to collect the data for different sets of compounds and to discuss their toxicities toward melanoma cells by the formulation of a total number of 36 QSAR.

Contents

Keywords: QSAR; Melanoma cells; Hydrophobicity; Molar refractivity; Sterimol parameters.
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1. Introduction

Melanoma is one of the most aggressive forms of skin cancer that continues to increase in most Western countries. If it is immediately removed, serious results can be avoided. However, once it has spread beyond the skin and into lymph nodes, it is very difficult to cure by the available chemotherapeutic agents. Epidemiological and experimental studies have suggested that intense exposures during early childhood to UV radiation may lead to melanoma in adults, but molecular and genetic studies have revealed few autosomal abnormalities, infrequent spectra, and very little epistatic and epigenetic mechanisms.[1] The occurrence of melanoma has been rapidly rising, especially in older men. Older men are also more likely to have thick melanomas, which confer high mortality and morbidity. The reasons for the rate of increase are not known; increasing sun and UV exposure, however, is the major hypothesized explanation. A new measure of sun exposure, based on individual residential history, confers substantially increased risk of melanoma. It is associated with two genes: CDKN2A and CDK4. Recently, a pigmentation-associated predisposition to cancer has also been indicated by the melanoma association of melanocortin-1 receptor (MCIR).[2,3]

Melanoma is notoriously resistant to all the current modalities of cancer therapy. A large set of genetic, functional, and biochemical studies suggest that melanoma cells become bullet proof against a variety of chemotherapeutic drugs by exploiting their intrinsic resistance to apoptosis and by reprogramming their proliferation and survival pathways during melanoma progression.[4] Recently, the US FDA approved high-dose interferon-α-2b for the postsurgical adjuvant therapy of high-risk melanoma. Unfortunately, the results of subsequent trials involving high-dose interferon-α-2b have not been clear, and its role in the adjuvant treatment of melanoma remains controversial.[5]

In recent years, the identification of molecules involved in the regulation and execution of apoptosis, and their alteration in melanoma, have provided new insights into the molecular basis for melanoma chemo resistance. Better understanding of apoptosis has enabled identification of diverse routes by which melanoma can manage to escape.[4,6,7] Despite aggressive investigations into vaccine therapy, no vaccine has yet received FDA approval. Recent evidence suggests that a cell vaccine may generate a class I-restricted immune response to melanoma antigen peptides and may have utility in the adjuvant therapy of

intermediate- and high-risk melanoma. It also describes some of the most promising of the multitude of new peptide vaccine approaches available to patients with resected and metastatic melanoma today.[8] Studies on melanoma have been extensively reviewed.[9–15]

Over the years, in the building of our database of 12,750 quantitative structure–activity relationships (QSAR) on all sorts of systems from DNA to humans, we have managed to collect some interesting examples of chemical toxicity to melanoma cells, which have been reported in the present review. For comparison we have 1004 QSAR for all sorts of cells of which 513 have a $\log P$ term and 371 of these have positive $\log P$ terms.

2. Materials and methods

All data have been collected from the literature (see individual QSAR for respective references). Physicochemical descriptors are autoloaded, and multiregression analyses (MRA) used to derive the QSAR were executed with the C-QSAR program.[16] The parameters used in this review have already been discussed in detail along with their application.[17] Briefly, $C\log P$ is the calculated partition coefficient in octanol/water and is a measure of hydrophobicity, and $C\pi$ is the calculated hydrophobic parameter for substituents. σ and σ^- are Hammett electronic parameters that apply to substituent effects on aromatic systems. The normal σ for substituents on aromatic systems in which strong resonance between substituent and reaction center does not occur is defined as $\sigma = \log K_X - \log K_H$, where K_H is the ionization constant for benzoic acid (normally in water or in 50% ethanol) and K_X is that for substituted benzoic acid. σ^- is employed when there is a strong resonance interaction between the substituent and reaction center. It is defined using the ionization constants from phenols or anilines similar to σ; $\sigma^- = \log K_X - \log K_H$, where K refers to the ionization of anilines or phenols. Whereas σ and σ^- are defined via equilibrium constant, σ^+ is defined by the rate of solvolysis of cumene chlorides in 90% acetone/10% water. σ_I is a measure of the inductive effect of aliphatic substituents. $B1$, $B5$, and L are Verloop's sterimol parameters for substituents. $B1$ is a measure of the width of the first atom of a substituent, $B5$ is an attempt to define the width of the whole substituent, and L is the substituent length.

CMR is the calculated molar refractivity for the whole molecule. MR is calculated as we describe: $(n^2 - 1/n^2 + 2)(\mathrm{MW}/\delta)$, where n is the refractive index, MW is the molecular weight, and δ is the density of a molecule. MR is dependent on volume and polarizability. MR can be used for a substituent or for the whole molecule. 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.

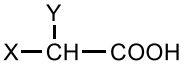
In QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction, and s is the standard deviation.

All the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced. In Tables 1–28 we have collected several experimental data from various types of molecules that we could find for sets large enough for a meaningful analysis for the chemical toxicity to melanoma cells.

3. Results and discussion

3.1. Acids

3.1.1. Inhibition of 1011 melanoma cells by acetic acid derivatives *I*. Data were obtained from Hudgins et al.[18] (Table 1)



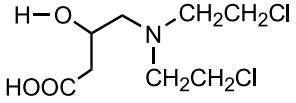
I

$$\log 1/C = 0.58(\pm 0.12)C\log P + 1.51(\pm 0.28) \quad (1)$$

$n = 15$, $r^2 = 0.887$, $s = 0.150$, $q^2 = 0.850$.

Linear $C\log P$ is the most significant model and suggests that the highly hydrophobic molecules will be more active.

3.1.2. Inhibition of A375 melanoma cells by II. Data were obtained from Faissat et al.[19] (Table 2)



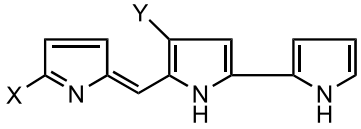
II

$$\log 1/C = 0.08(\pm 0.04)\mathrm{CMR} + 2.64(\pm 0.37) \quad (2)$$

$n = 5$, $r^2 = 0.938$, $s = 0.072$, $q^2 = 0.789$.

3.2. Bipyrroles

3.2.1. Inhibition of murine B16 melanoma cells by III. Data were obtained from D'Alessio et al.[20] (Table 3)



$$\log 1/C = 1.69(\pm 0.54)C\log P - 0.13(\pm 0.04) \times C\log P^2 + 1.60(\pm 1.44) \quad (3)$$

$n = 12$, $r^2 = 0.867$, $s = 0.183$, $q^2 = 0.745$; outliers: $X = C_7H_{15}$, $Y = OCH_3$; $X = C_{15}H_{31}$, $Y = OCH_3$; $X = CH_2CH_2C_6H_5$, $Y = OCH_3$; $X = C_{11}H_{23}$, $Y = H$; optimum $C\log P = 6.39$ (6.14–6.59).

Some of these derivatives have been shown to possess interesting immunosuppressive properties. They cause phosphorylation and activation of acytoplasmic tyrosine

Table 1. QSAR 1

Compound	X	Y	log 1/*C* (Eq. 1)			*C*log *P*
			Observed	Predicted	Δ	
1	H	Ph	2.31	2.33	−0.02	1.41
2	OCH_3	Ph	2.19	2.30	−0.11	1.36
3	CH_3	Ph	2.43	2.51	−0.08	1.72
4	C_2H_5	Ph	2.66	2.82	−0.16	2.25
5	H	CH_2CH_2Ph	3.05	2.83	0.22	2.28
6	H	CH_2CH_2Ph(4-Cl)	3.09	3.25	−0.16	3.00
7	H	CH_2CH_2Ph(4-I)	3.66	3.48	0.18	3.41
8	H	Ph(4-OH)	1.95	1.94	0.01	0.75
9	H	Ph(4-F)	2.57	2.41	0.16	1.56
10	H	Ph(4-Cl)	2.96	2.74	0.22	2.13
11	H	Ph(3-Cl)	2.84	2.74	0.10	2.13
12	H	Ph(2-Cl)	2.59	2.74	−0.15	2.13
13	H	Ph(2,6-Cl_2)	2.97	3.16	−0.19	2.84
14	H	Ph(4-I)	2.92	2.98	−0.06	2.54
15	H	1-Naphthyl	3.06	3.01	0.05	2.59

Table 2. QSAR 2

Compound	X	log 1/*C* (Eq. 2)			CMR
		Observed	Predicted	Δ	
1	H	3.06	3.11	−0.05	5.58
2	$COCH_2CH_3$	3.24	3.23	0.01	7.01
3	COC_7H_{15}	3.39	3.42	−0.03	9.33
4	$COCH_2C_6H_5$	3.51	3.40	0.11	9.06
5	$CO(CH_2)_3C_6H_4$-4-$N(CH_2CH_2Cl)_2$	3.71	3.75	−0.04	13.19

Table 3. QSAR 3

Compound	X	Y	log 1/*C* (Eq. 3)			*C*log *P*
			Observed	Predicted	Δ	
1	Pentyl	OCH_3	6.59	6.49	0.10	4.77
2[a]	Heptyl	OCH_3	6.32	6.80	−0.48	5.83
3	Decyl	OCH_3	6.39	6.70	−0.31	7.42
4	Undecyl	OCH_3	6.57	6.51	0.06	7.95
5	Tridecyl	OCH_3	6.17	5.93	0.24	9.00
6[a]	Pentadecyl	OCH_3	5.56	5.05	0.51	10.06
7[a]	Phenethyl	OCH_3	6.06	6.48	−0.42	4.75
8	6-Fluorohexyl	OCH_3	6.30	6.40	−0.10	4.57
9	7-Cyanoheptyl	OCH_3	6.19	6.21	−0.02	4.21
10	6-Hydroxyhexyl	OCH_3	5.63	5.58	0.05	3.31
11[a]	Undecyl	H	5.48	6.54	−1.06	7.88
12	Undecyl	OC_2H_5	6.32	6.26	0.06	8.47
13	Undecyl	OC_3H_7	6.12	5.93	0.19	9.00
14	Undecyl	$OCH(CH_3)_2$	6.17	6.08	0.09	8.78
15	Undecyl	OC_4H_9	5.46	5.53	−0.07	9.53
16	Undecyl	$OCH_2C_6H_5$	5.10	5.38	−0.28	9.71

[a] Data points not included in the derivation of Eq. 3.

kinase. QSAR 3 is a parabolic correlation in hydrophobic term. This suggests that the activity of compound III increases with an increase in hydrophobicity to an optimum *C*log *P* of 6.39 and then decreases.

3.3. Bis-benzimidazoles

3.3.1. Inhibition of LOX IMVI melanoma cell line by bis-benzimidazoles. Data were obtained from Singh and Lown[21] (Table 4)

$$\log 1/C = -1.06(\pm 0.45)C\log P + 0.18(\pm 0.10) \times C\log P^2 + 6.10(\pm 0.45) \quad (4)$$

$n = 8$, $r^2 = 0.936$, $s = 0.097$, $q^2 = 0.806$; inversion point: 2.88 (2.54–3.89); outliers: compounds **3**, **7**, and **8** (Table 4).

QSAR 4 is of particular interest because we find an inverted parabolic relationship. That is, as *C*log *P* increases in value, activity decreases. However, quadratic term takes over and activity begins to increase. This may be due to a change in receptor structure termed allosteric reaction. Over the years we have found many such examples[22–24] (and many not yet published). Understanding allosteric reactions via QSAR can be helpful in drug design.

Table 4. QSAR 4

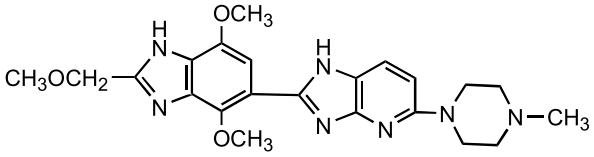
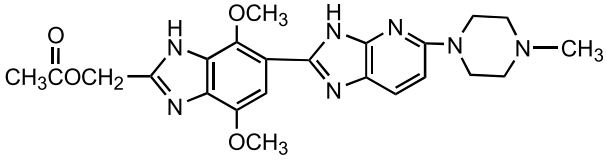
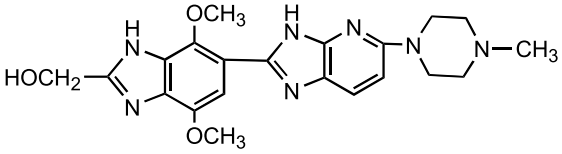
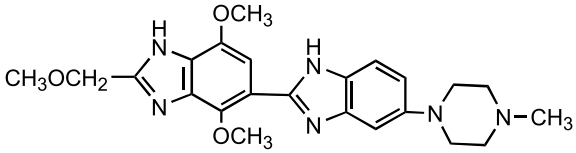
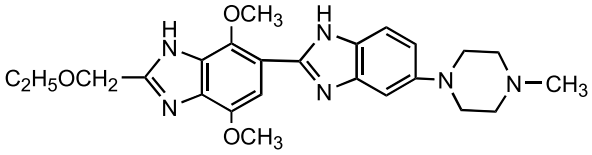
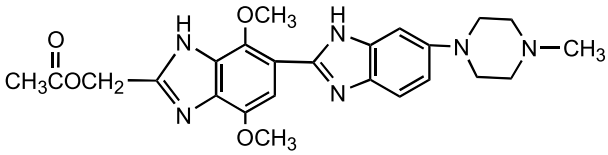
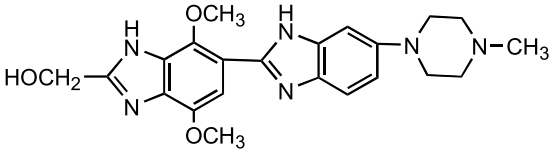
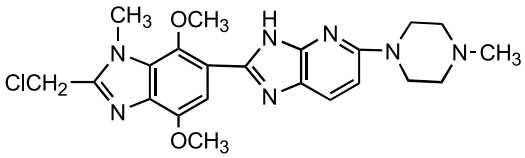
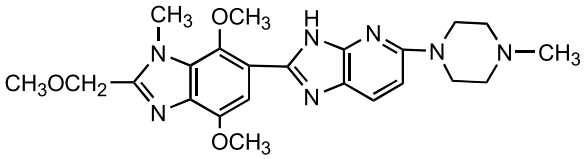
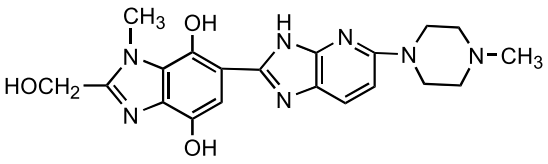
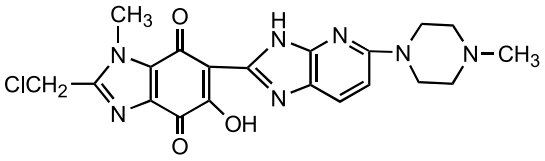
	Compound	log 1/*C* (Eq. 4)			*C*log *P*
		Observed	Predicted	*Δ*	
1		4.51	4.59	−0.08	2.65
2		4.59	4.59	0.00	2.67
3[a]		4.07	4.79	−0.72	1.81
4		4.73	4.61	0.12	3.27
5		4.68	4.69	−0.02	3.66
6		4.51	4.61	−0.10	3.29
7[a]		4.05	4.62	−0.56	2.43
8[a]		4.97	4.61	0.36	3.31
9		4.72	4.60	0.12	2.55
10		4.77	4.82	−0.05	1.74

Table 4 (*continued*)

	Compound	log 1/*C* (Eq. 4)			*C*log *P*
		Observed	Predicted	*Δ*	
11		5.51	5.50	0.01	0.64

[a] Data points not included in the derivation of Eq. 4.

Table 5. QSAR 5

Compound	X	Y	log 1/*C* (Eq. 5)			CMR
			Observed	Predicted	*Δ*	
1	OC_2H_5	*N*-(4-CH_3)-piperazine	5.80	5.92	−0.13	13.48
2[a]	OCH_3	$(CH_2)_3N(CH_3)_2$	5.00	5.51	−0.51	12.83
3	OCH_3	$(CH_2)_2N(CH_3)_2$	5.07	5.22	−0.15	12.36
4	OCH_3	$CH_2N(CH_3)_2$	5.00	4.92	0.08	11.90
5	OCH_3	$N(CH_3)_2$	4.59	4.63	−0.05	11.44
6[a]	OCH_3	NH_2	5.21	4.04	1.16	10.51
7	OCH_3	*N*-(4-CH_3)piperazine	5.96	5.63	0.33	13.02
8	OCH_3	*O*-(4-*N*-CH_3)piperidine	5.70	5.79	−0.09	13.27

[a] Data points not included in the derivation of Eq. 5.

Table 6. QSAR 6

Compound	X	Y	log 1/*C* (Eq. 6)			*C*log *P*
			Observed	Predicted	*Δ*	
1	$COOCH_3$	CH_3	4.75	4.79	−0.04	4.96
2	COOH	CH_3	4.23	4.26	−0.04	4.58
3	CH_2OH	CH_3	4.35	4.33	0.02	4.63
4[a]	CH_3	CH_3	4.70	7.14	−2.44	6.62
5	CH_3	COOH	4.67	4.60	0.06	4.82

[a] Data point not included in the derivation of Eq. 6.

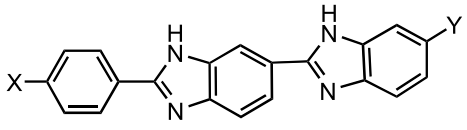
Table 7. QSAR 7

Compound	X	log 1/*C* (Eq. 7)			*C*log *P*
		Observed	Predicted	*Δ*	
1	4-CH_3	8.36	8.34	0.03	2.84
2	4-Cl	8.18	8.15	0.03	3.06
3	4-OCH_3	8.94	8.85	0.10	2.26
4	3,4$(OCH_3)_2$	8.89	9.07	−0.18	2.00
5	3,4,5$(OCH_3)_3$	9.51	9.39	0.12	1.64
6[a]	2,3,4$(OCH_3)_3$	8.55	9.39	−0.84	1.64
7	H	8.69	8.77	−0.09	2.34

[a] Data point not included in the derivation of Eq. 7.

3.3.2. Inhibition of SK-MEL melanoma cells by IV.

Data were obtained from Sun et al.[25] (Table 5)



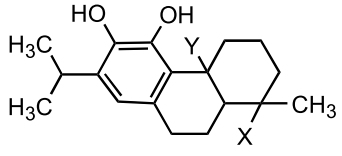
$$\log 1/C = 0.63(\pm 0.31)\mathrm{CMR} - 2.60(\pm 3.87) \quad (5)$$

$n = 6$, $r^2 = 0.891$, $s = 0.201$, $q^2 = 0.798$; outliers: X = OCH_3, Y = $(CH_2)_3N(CH_3)_2$; X = OCH_3, Y = NH_2.

3.4. Catechol derivatives

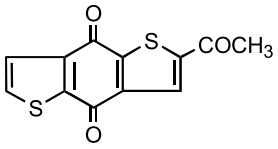
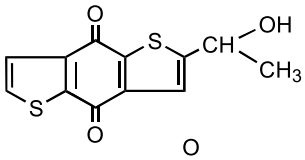
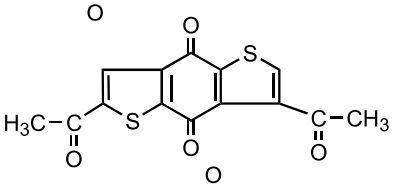
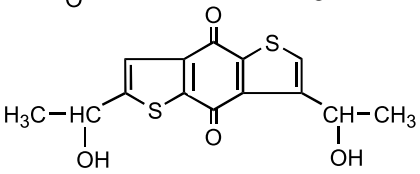
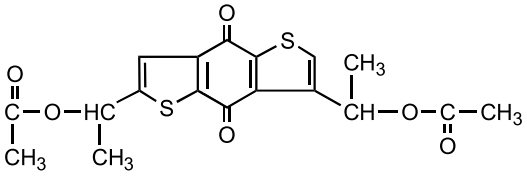
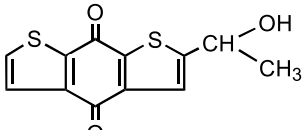
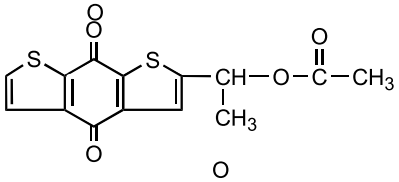
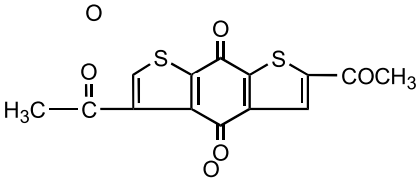
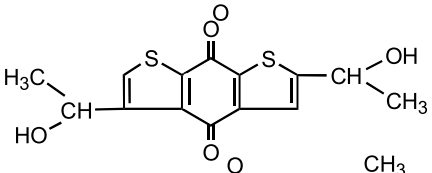
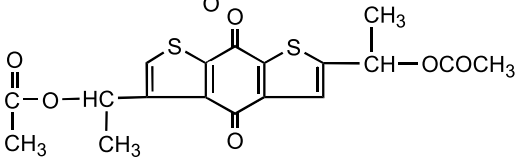
3.4.1. Inhibition of human UACC-62 melanoma cells by V.

Data were obtained from Gigante et al.[26] (Table 6)



V

Table 8. QSAR 8

	Compound	log 1/*C* (Eq. 8)			*C*log *P*
		Observed	Predicted	*Δ*	
1		7.60	7.64	−0.04	2.33
2		8.00	7.80	0.20	2.07
3[a]		5.96	7.74	−1.78	1.81
4		7.26	7.07	0.19	1.34
5		5.80	6.01	−0.21	3.06
6		7.62	7.80	−0.18	2.07
7		6.68	6.42	0.26	2.93
8		7.66	7.74	−0.08	1.81
9		6.92	7.07	−0.15	1.34
10[a]		6.92	6.01	0.91	3.06

[a] Data points not included in the derivation of Eq. 8.

$$\log\ 1/C = 1.41(\pm 0.87)C\log P - 2.22(\pm 4.15) \qquad (6)$$

$n = 4$, $r^2 = 0.960$, $s = 0.061$, $q^2 = 0.779$; outlier: X = Y = CH_3.

Catechols are important antioxidants that can react with free radicals. These compounds were found to be toxic to melanoma cells as well as other cancer cells. Although the statistics of QSAR 6 are good, the data set is too small yet to be very helpful.

Table 9. QSAR 9–13

Compd	X	log 1/*C* (Eq. 9)			log 1/*C* (Eq. 10)			log 1/*C* (Eq. 11)			log 1/*C* (Eq. 12)			log 1/*C* (Eq. 13)			*B*5-X_2	L-X_2
		Observed	Predicted	Δ	Observed	Predicted	Δ	Observed	Predicted	Δ	Observed	Predicted	Δ	Observed	Predicted	Δ		
1	2-Me	6.82	6.94	−0.12	6.74	6.78	−0.04	6.80	6.67	0.13	6.72	6.39	0.33	6.44	6.39	0.05	2.04	2.87
2[a,b]	2-COOH	5.77	7.31	−1.54	5.70	7.35	−1.65	—	—	—	5.76	7.05	−1.29	5.68	7.16	−1.48	2.66	3.91
3	2-CHO	7.00	7.13	−0.13	6.78	7.07	−0.29	6.79	6.98	−0.19	6.75	6.81	−0.06	6.74	6.88	−0.14	2.36	3.53
4	2-CH_2OH	—	—	—	7.64	7.38	0.26	7.48	7.31	0.17	7.26	7.09	0.17	7.50	7.21	0.29	2.70	3.97
5[b]	2-CH_2Cl	7.92	7.80	0.12	6.74	8.07	−1.33	7.98	8.05	−0.07	6.76	7.04	−0.28	6.93	7.15	−0.22	3.46	3.89
6[c]	3-Me	6.24	6.31	−0.07	5.83	5.83	0.00	6.55	5.65	0.90	5.79	5.87	−0.08	5.76	5.79	−0.03	1.00	2.06
7	3-CH_2OH	6.50	6.31	0.19	5.91	5.83	0.08	5.61	5.65	−0.04	5.79	5.87	−0.08	5.83	5.79	0.04	1.00	2.06

[a] Data point not included in the derivation of Eqs. 9, 12, and 13.
[b] Data point not included in the derivation of Eq. 10.

Table 10. QSAR 14

Compd	X	Y	log 1/*C* (Eq. 14)			CMR
			Observed	Predicted	Δ	
1	H	H	6.90	6.85	0.05	8.71
2	CH_3	H	6.20	6.25	−0.05	9.17
3	H	5-OMe	6.00	6.05	−0.05	9.32
4	H	5-OMe, 6-Me	5.50	5.45	0.05	9.79
5[a]	C_6H_5	H	5.50	3.60	1.90	11.22

Table 11. QSAR 15

Compd	X	Y	log 1/*C* (Eq. 15)			L-X
			Observed	Predicted	Δ	
1	Me	OMe	5.87	5.81	0.06	2.87
2	OMe	Me	6.05	6.06	−0.01	3.98
3	OMe	OMe	6.06	6.06	−0.01	3.98
4	H	H	5.59	5.62	−0.03	2.06
5	Me	Me	5.79	5.81	−0.02	2.87

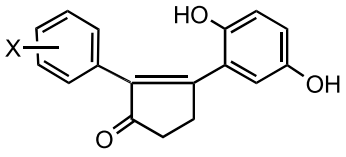
Table 12. QSAR16

Compd	X	Y	log 1/*C* (Eq. 16)			*C*log *P*	L-X_6
			Observed	Predicted	Δ		
1	6-Me	H	5.43	5.38	0.05	4.35	2.87
2	6-Me	2-Me	5.47	5.47	0.00	4.55	2.87
3	6-Me	4-Me	5.62	5.60	0.02	4.85	2.87
4	6-Me	4-Cl	5.62	5.70	−0.08	5.08	2.87
5	5-NMe_2	H	5.15	5.09	0.06	4.43	2.06
6	5-NMe_2	2-Me	5.03	5.18	−0.15	4.63	2.06
7[a]	5-NMe_2	3-Me	5.71	5.31	0.40	4.93	2.06
8	5-NMe_2	4-Cl	5.37	5.41	−0.04	5.16	2.06
9	5-NMe_2	4-Br	5.67	5.47	0.20	5.31	2.06
10[a]	5-NMe_2	4-OMe	5.40	5.02	0.38	4.28	2.06
11	H	H	4.93	4.84	0.09	3.85	2.06
12	H	4-OMe	4.79	4.78	0.01	3.70	2.06
13	H	4-Cl	5.03	5.16	−0.13	4.58	2.06
14	H	3-Me	5.00	5.06	−0.06	4.35	2.06

[a] Data points not included in the derivation of Eq. 16.

3.5. Cyclopenteneones

3.5.1. Inhibition of murine B16F10 melanoma cells by VI. Data were obtained from Nam et al.[27] (Table 7)



VI

$$\log 1/C = -0.87(\pm 0.31)C\log P + 10.82(\pm 0.74) \quad (7)$$

$n = 6$, $r^2 = 0.940$, $s = 0.130$, $q^2 = 0.843$; outlier: X = 2,3,4-tri-OCH_3.

This report discussed the authors' efforts to find antitumor agents for a variety of cancer cells. The authors concluded from their studies that by making more hydrophobic derivatives, they would get higher activity. QSAR shows the opposite to be true.

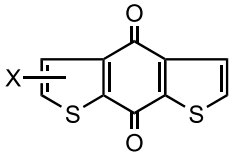
3.6. Dihydrobenzodithiophenediones

3.6.1. Inhibition of LOX IMVI melanoma cells by miscellaneous dihydrobenzodithiophenediones. Data were obtained from Chao et al.[28] (Table 8)

$$\log 1/C = 6.62(\pm 2.77)C\log P - 1.65(\pm 0.63) \times C\log P^2 + 1.15(\pm 2.88) \quad (8)$$

$n = 8$, $r^2 = 0.929$, $s = 0.224$, $q^2 = 0.762$; optimum $C\log P = 2.01$ (1.84–2.12); outliers: compounds **3** and **10** (Table 8).

3.6.2. Inhibition of human SK-MEL-5 melanoma cells by VII. Data were obtained from Chao et al.[29] (Table 9)



VII

$$\log 1/C = 0.61(\pm 0.26)B5\text{-}X_2 + 5.70(\pm 0.57) \quad (9)$$

$n = 5$, $r^2 = 0.947$, $s = 0.171$, $q^2 = 0.779$; outlier: 2-COOH.

The sterimol parameter (*B*5)[17] is a calculated parameter designed to estimate the maximum width of the substituent.

3.6.3. Action of the same compounds VII on human UACC-257 melanoma cells. Data were obtained from Chao et al.[29] (Table 9)

$$\log 1/C = 0.91(\pm 0.47)B5\text{-}X_2 + 4.92(\pm 0.91) \quad (10)$$

$n = 5$, $r^2 = 0.928$, $s = 0.231$, $q^2 = 0.777$; outliers: 2-COOH, 2-CH_2Cl.

Table 13. QSAR 17

Compound	Substituent	log 1/*C* (Eq. 17)			*C*log *P*	*I*	$B5_4$
		Observed	Predicted	Δ			
1	4-Me	6.75	6.84	−0.09	4.47	0	2.04
2	4-Cl	6.48	6.62	−0.15	4.76	0	1.80
3	4-OH	5.12	5.49	−0.37	3.85	1	1.93
4	4-OMe	6.74	6.84	−0.10	4.19	0	3.07
5	$4\text{-NH(CH}_2)_2\text{NMe}_2$	6.41	6.23	0.18	4.23	0	5.21
6	8-Cl	7.11	6.89	0.22	4.70	0	1.00
7	8-OH	6.57	6.13	0.44	3.44	1	1.00
8	8-OMe	7.28	7.61	−0.32	3.97	0	1.00
9	9-Cl	7.05	6.89	0.15	4.70	0	1.00
10[a]	9-OH	8.40	6.13	2.27	3.44	1	1.00
11[a]	9-OMe	6.79	7.61	−0.82	3.97	0	1.00
12	10-Me	7.09	7.12	−0.03	4.47	0	1.00
13	$10\text{-C}_6\text{H}_5$	5.73	5.77	−0.04	5.86	0	1.00
14	10-CN	8.00	8.11	−0.11	3.45	0	1.00
15	10-F	7.80	7.45	0.35	4.13	0	1.00
16	10-Cl	7.19	6.89	0.30	4.70	0	1.00
17	10-I	6.20	6.50	−0.29	5.11	0	1.00
18	10-OH	5.92	6.13	−0.21	3.44	1	1.00
19	10-OMe	7.28	7.46	−0.18	4.12	0	1.00
20	$10\text{-OC}_2\text{H}_5$	7.11	6.95	0.16	4.65	0	1.00
21	10-NO_2	7.74	7.81	−0.07	3.76	0	1.00
22[a]	11-Cl	5.69	6.89	−1.21	4.70	0	1.00
23	11-OH	6.27	6.13	0.14	3.44	1	1.00

[a] Data points not included in the derivation of Eq. 17.

Table 14. QSAR 18

Compound	X	Y	log 1/*C* (Eq. 18)			CMR	L-4,Y	B1–4,Y
			Observed	Predicted	Δ			
1	Cl	H	5.74	5.48	0.25	7.42	2.06	1.00
2[a]	Cl	4-OCF_3	5.49	6.56	−1.07	8.08	4.57	1.35
3[a]	Cl	4-OMe	7.20	6.29	0.91	8.04	3.98	1.35
4	Cl	$4\text{-OC}_2\text{H}_5$	6.91	6.89	0.03	8.50	4.80	1.35
5[a]	Cl	4-Me	6.24	5.56	0.68	7.88	2.87	1.52
6	Cl	$4\text{-C}_2\text{H}_5$	6.65	6.34	0.31	8.35	4.11	1.52
7	Cl	$4\text{-CH}_2\text{CH}_2\text{OH}$	6.61	6.72	−0.10	8.50	4.79	1.52
8[a]	Cl	4-F	6.53	5.39	1.13	7.44	2.65	1.35
9	Cl	4-Cl	5.42	5.58	−0.16	7.91	3.52	1.80
10	Cl	4-Br	5.74	5.71	0.03	8.20	3.82	1.95
11	Cl	4-I	6.25	5.98	0.27	8.73	4.23	2.15
12	Cl	4-CHMe_2	6.31	6.22	0.09	8.81	4.11	1.90
13	Cl	4-COMe	6.05	6.26	−0.21	8.38	4.06	1.60
14	Cl	3-COMe	5.85	6.01	−0.16	8.38	2.06	1.00
15	Cl	3,4-Di-OH	5.72	5.59	0.13	7.73	2.74	1.35
16	Cl	2,3,4-Tri-F	5.50	5.41	0.09	7.47	2.65	1.35
17	Cl	2,4-Di-F	5.35	5.40	−0.05	7.45	2.65	1.35
18[a]	Cl	3,4-Di-Me	5.31	5.82	−0.51	8.35	2.87	1.52
19	Cl	3-Br, 4-CF_3	5.89	5.73	0.15	8.71	3.30	1.99
20	Cl	3-NO_2, 4-Br	5.80	6.05	−0.25	8.81	3.82	1.95
21	Cl	3,4-Di-Cl	5.58	5.85	−0.27	8.40	3.52	1.80
22	H	H	5.26	5.21	0.04	6.93	2.06	1.00
23	H	4-F	5.07	5.12	−0.06	6.94	2.65	1.35
24	H	4-Cl	5.35	5.31	0.05	7.42	3.52	1.80
25	H	3,4-Di-F	4.94	5.13	−0.19	6.96	2.65	1.35

[a] Data points not included in the derivation of Eq. 18.

3.6.4. Action of compounds VII on human MAL-3M melanoma cells. Data were obtained from Chao et al.[29] (Table 9)

$$\log 1/C = 0.97(\pm 0.30)B5\text{-}X_2 + 4.68(\pm 0.74) \qquad (11)$$

$n = 5$, $r^2 = 0.972$, $s = 0.172$, $q^2 = 0.939$; outlier: 3-Me.

3.6.5. Action of compounds VII on human UACC-62 melanoma cells. Data were obtained from Chao et al.[29] (Table 9)

Table 15. QSAR 19

Compound	X	Y	Z	R	log 1/*C* (Eq. 19)			*C*log *P*	I-Z	MR-R
					Observed	Predicted	*Δ*			
1	2,5-Di-OH	CH=CH	H	$NHCH_2CH_2C_6H_5$	5.70	5.65	0.04	4.94	1	3.37
2	2,5-Di-OH	CH=CH	H	$NHCH_2CH_2(4\text{-F-}C_6H_4)$	5.68	5.59	0.08	5.08	1	3.39
3[a]	2,5-Di-OH	CH_2CH_2	H	$NHCH_2CH_2C_6H_5$	4.96	5.79	−0.83	4.64	1	3.37
4	2,5-Di-OH	CH_2CH_2	H	$NHCH_2CH_2(4\text{-F-}C_6H_4)$	5.55	5.73	−0.18	4.79	1	3.39
5	2,5-Di-OH	CH_2CH_2	H	$NH(CH_2)_5CH_3$	5.48	5.48	0.00	5.19	1	3.15
6	2,5-Di-OMe	CH=CH	Me	$NHCH_2CH_2C_6H_5$ (CIS)	4.79	4.82	−0.04	5.79	0	3.37
7[a]	2,5-Di-OMe	CH=CH	Me	$NHCH_2CH_2(4\text{-F-}C_6H_4)$ (CIS)	5.46	4.76	0.70	5.93	0	3.39
8	2,5-Di-OMe	CH=CH	Me	$NH(CH_2)_5CH_3$ (CIS)	4.60	4.51	0.09	6.34	0	3.15
9	2,5-Di-OH	CH=CH	H	$NHCH_2CH_2C_6H_5$ (CIS)	5.68	5.65	0.02	4.94	1	3.37
10	2,5-Di-OH	CH=CH	H	$NHCH_2CH_2(4\text{-F-}C_6H_4)$ (CIS)	5.64	5.59	0.04	5.08	1	3.39
11	2,5-Di-OH	CH=CH	H	$NH(CH_2)_5CH_3$ (CIS)	5.24	5.34	−0.10	5.49	1	3.15
12	2,5-Di-OMe	C≡C	Me	$NHCH_2CH_2C_6H_5$	4.61	4.84	−0.23	5.74	0	3.37
13	2,5-Di-OMe	C≡C	Me	$NHCH_2CH_2(4\text{-F-}C_6H_4)$	5.22	4.78	0.44	5.88	0	3.39
14	2,5-Di-OMe	C≡C	Me	$NH(CH_2)_5CH_3$	4.25	4.53	−0.29	6.28	0	3.15
15	2,5-Di-OH	C≡C	H	$NHCH_2CH_2C_6H_5$	5.72	5.68	0.04	4.88	1	3.37
16	2,5-Di-OMe	C≡C	Me	OMe	4.53	4.54	−0.01	4.69	0	0.62
17	2,5-Di-OMe	$CH_2C(O)$	H	$NHCH_2CH_2(4\text{-F-}C_6H_4)$	5.40	5.45	−0.05	5.39	1	3.39
18	2,5-Di-OMe	CH_2CH_2	H	$NHCH_2CH_2(4\text{-F-}C_6H_4)$	5.18	5.09	0.09	6.18	1	3.39
19	2,5-Di-OMe	C≡C	Me	OH	4.65	4.62	0.03	4.24	0	0.15

[a] Data points not included in the derivation of Eq. 19.

Table 16. QSAR 20

Compound	Substituent	log 1/*C* (Eq. 20)			*C*log *P*	MR-4′	*C*π-1
		Observed	Predicted	*Δ*			
1	1-Me	4.70	4.91	−0.21	2.74	0.00	0.00
2	3-Me	4.40	4.80	−0.41	2.62	0.00	0.00
3	4-Me	5.40	5.34	0.06	3.24	0.00	0.00
4	6-Me	5.10	5.34	−0.24	3.24	0.00	0.00
5[a]	7-Me	7.22	5.34	1.89	3.24	0.00	0.00
6	3′-Me	5.70	5.34	0.36	3.24	0.00	0.00
7	4-Me	7.00	6.46	0.54	3.24	0.46	0.00
8	5′-Me	5.00	5.34	−0.34	3.24	0.00	0.00
9	$1\text{-}CH_2CH_2NHCBZ$	4.70	4.75	−0.05	4.22	0.00	2.29
10	$1\text{-}CH_2CH_2NH_2$	4.52	4.21	0.32	1.93	0.00	0.00
11	$1\text{-}(CH_2)_4NH_2$	4.52	4.29	0.23	2.39	0.00	0.49
12	$4'\text{-}CH_2CO_2Me$	7.40	7.11	0.29	2.42	1.58	0.00
13	$4'\text{-}CH_2CO_2C_2H_5$	7.70	7.57	0.13	2.95	2.04	0.00
14	$4'\text{-}CH_2CO_2CMe_3$	7.16	7.21	−0.06	3.66	2.97	0.00
15	$4'\text{-}CH_2CO_2H$	5.70	6.43	−0.73	2.02	1.12	0.00
16[a]	$4'\text{-}CH_2CN$	7.70	6.34	1.36	2.17	0.94	0.00
17	$4'\text{-}CH_2NHCOCMe_3$	6.30	6.29	0.01	3.45	3.34	0.00
18	$4'\text{-}CH_2NH_2$	5.70	5.78	−0.08	1.70	0.83	0.00
19	$4'\text{-}CH_2OH$	5.74	5.43	0.31	1.71	0.62	0.00
20	$4'\text{-}COCF_3$	6.85	7.00	−0.14	2.82	1.01	0.00

[a] Data points not included in the derivation of Eq. 20.

Table 17. QSAR 21

Compound	X	Y	log 1/*C* (Eq. 21)			L-Y	*I*
			Observed	Predicted	*Δ*		
1	α-H, β-OH	CH_3	5.00	5.16	−0.15	2.87	0
2	=O	CH_3	6.46	6.44	0.02	2.87	1
3	α-H, $\beta\text{-}OCOCH_3$	CH_3	5.12	5.16	−0.03	2.87	0
4	α-H, β-OH	CH_2OH	5.32	5.35	−0.03	3.97	0
5	=O	CH_2OH	6.72	6.64	0.09	3.97	1
6	α-H, $\beta\text{-}OCOCH_3$	CH_2OCOCH_3	5.47	5.62	−0.15	5.46	0
7	α-H, β-OH	CHO	5.48	5.27	0.21	3.53	0
8	=O	CHO	6.46	6.56	−0.10	3.53	1
9	α-H, β-OH	COOH	5.39	5.34	0.05	3.91	0
10	α-H, β-OH	$COOCH_3$	5.60	5.49	0.11	4.73	0
11[a]	α-H, $\beta\text{-}OCOCH_3$	$COOCH_3$	6.89	5.49	1.40	4.73	0

[a] Data point not included in the derivation of Eq. 21.

Table 18. QSAR 22

	Compound	log 1/*C* (Eq. 22)			*C*log *P*
		Observed	Predicted	*Δ*	
1	3-Ethoxy-A	4.32	4.52	−0.20	3.94
2	2,3-Methylenedioxy-A	4.79	5.13	−0.34	3.73
3	2,3-Di-methyl-A	4.11	4.26	−0.14	4.02
4	3-Methoxyphenylamino-B	5.66	4.94	0.72	3.80
5[a]	6-(4-Ethoxyphenylamino)-B	5.67	3.07	2.59	4.33
6	2-Methoxy-C	6.17	6.15	0.01	2.01
7	3-Methoxy-C	6.21	6.15	0.06	2.01
8	3-Ethoxy-C	6.19	6.61	−0.42	2.54
9	3-Isopropoxy-C	6.68	6.56	0.12	2.85
10	2,3-Methoylenedioxy-C	6.59	6.48	0.10	2.30
11	3,4-Di-methyl-C	6.70	6.61	0.09	2.72

A = 6,11-Dihydro-benzo[2,3b]phenazine-6,11-dione; B = 7-Cl-5,8-quinolinedinone; C = 6,11-dihydro-pyrido[2,3b]phenazine-6,11-dione.
[a] Data point not included in the derivation of Eq. 22.

Table 19. QSAR 23

Compound	X	log 1/*C* (Eq. 23)			*C*log *P*	σ^+
		Observed	Predicted	*Δ*		
1	H	8.03	8.02	0.01	3.45	0.00
2	2-F	8.16	8.03	0.13	3.60	−0.07
3	2-Cl	8.31	8.23	0.08	4.17	0.11
4	3-Cl	8.30	8.32	−0.02	4.17	0.37
5	4-Cl	8.10	8.23	−0.13	4.17	0.11
6	4-Br	8.24	8.28	−0.04	4.32	0.15
7	4-NO_2	8.16	8.22	−0.06	3.20	0.79
8	2,3,4,5,6-$(F)_5$	8.19	8.30	−0.11	3.96	0.47
9	2,5-$(F)_2$	8.14	8.18	−0.04	3.74	0.27
10	2-Br, 5-OMe	8.50	8.34	0.16	4.37	0.27
11[a]	2-OMe, 5-Br	8.54	8.12	0.42	4.37	−0.39
12	2-Br, 5-OH	8.25	8.23	0.02	3.95	0.27
13	4-OMe	7.88	7.75	0.13	3.37	−0.78
14	4-$N(CH_3)_2$	7.40	7.51	−0.11	3.62	−1.70
15[a]	2,3-$(OH)_2$	8.44	7.45	0.99	2.19	−0.80
16[a]	3,4-$(OH)_2$	7.97	7.45	0.52	2.19	−0.80
17	2,5-$(OH)_2$	7.43	7.43	0.00	2.12	−0.80
18[a]	2,3,4-$(OMe)_3$	7.94	7.38	0.56	2.75	−1.44
19[a]	3,4,5-$(OMe)_3$	7.93	7.67	0.26	2.75	−0.54
20	4-Ph	8.42	8.43	−0.01	5.34	−0.18

[a] Data points not included in the derivation of Eq. 23.

Table 20. QSAR 24–26

Compd	X	Y	log 1/*C* (Eq. 24)			log 1/*C* (Eq. 25)			log 1/*C* (Eq. 26)			*C*log *P*
			Observed	Predicted	*Δ*	Observed	Predicted	*Δ*	Observed	Predicted	*Δ*	
1	C_6H_4(4-Me)	Me	4.77	4.77	0.00	4.73	4.72	0.01	4.71	4.81	−0.10	4.00
2[a,b]	C_6H_4(4-OMe)	Me	4.30	4.67	−0.38	4.28	4.64	−0.36	4.44	4.62	−0.18	3.18
3[a,b]	C_6H_4(4-Cl)	C_6H_4(4-Me)	5.38	5.03	0.35	4.73	4.92	−0.19	5.38	5.33	0.05	6.15
4	C_6H_4(4-Cl)	C_6H_4(4-Cl)	5.08	5.06	0.02	4.95	4.94	0.01	5.37	5.38	−0.01	6.39
5	2-Pyridyl(4-Me)	C_6H_4(4-OMe)	4.84	4.82	0.02	4.80	4.75	0.05	4.77	4.90	−0.13	4.37
6[c]	2-Pyridyl(4-Me)	C_6H_4(4-Cl)	4.86	4.90	−0.04	4.81	4.82	−0.01	4.73	5.08	−0.35	5.12
7	$CH_2C_6H_5$	Me	4.71	4.65	0.06	4.62	4.62	0.00	4.62	4.57	0.05	2.97
8[a]	$CH_2C_6H_5$	C_6H_3(3,4-Cl_2)	5.50	4.98	0.53	4.86	4.88	−0.02	5.33	5.22	0.11	5.71
9	$CH_2CH_2CH_3$	Me	4.55	4.60	−0.05	4.52	4.58	−0.06	4.61	4.47	0.13	2.58
10	$CH(Me)_2$	Me	4.59	4.57	0.02	4.62	4.56	0.06	4.49	4.42	0.07	2.36
11	$CH(Me)_2$	C_6H_5	4.71	4.73	−0.02	4.64	4.69	−0.04	4.76	4.74	0.02	3.70
12[c]	C_6H_4(4-Cl)	C_6H_4(4-OMe)	—	—	—	—	—	—	4.64	5.19	−0.55	5.59
13[b,c]	$CH_2C_6H_5$	C_6H_4(4-Me)	—	—	—	5.24	4.80	0.44	5.44	5.02	0.42	4.87
14[b,c]	$CH_2C_6H_5$	C_6H_4(4-Cl)	—	—	—	5.77	4.82	0.95	5.75	5.08	0.67	5.11

[a] Data points not included in the derivation of Eq. 24.
[b] Data points not included in the derivation of Eq. 25.
[c] Data points not included in the derivation of Eq. 26.

Table 21. QSAR 27

Compound	R	R_1	R_2	R_3	log 1/*C* (Eq. 27)			*C*log *P*	*I*
					Observed	Predicted	*Δ*		
1	CN	CH_3	C_6H_5	C_6H_5	5.38	5.44	−0.06	5.28	1
2	CN	CH_3	C_6H_5	C_6H_4-4-OCH_3	5.51	5.43	0.08	5.20	1
3[a]	CN	CH_3	C_6H_5	C_6H_4-4-Cl	7.05	5.52	1.53	5.99	1
4	CN	CH_3	C_6H_5	C_6H_4-3-Cl	5.90	5.52	0.38	5.99	1
5	CN	CH_3	C_6H_5	C_6H_4-4-NO_2	5.02	5.42	−0.40	5.02	1
6	CN	C_6H_5	CH_3	C_6H_4-4-OCH_3	4.55	4.52	0.03	4.85	0
7	CN	C_6H_5	CH_3	C_6H_4-4-Cl	4.57	4.60	−0.03	5.64	0
8	CN	C_6H_5	CH_3	C_6H_4-3-Cl	4.56	4.60	−0.04	5.64	0
9[a]	CN	C_6H_5	CH_3	C_6H_4-4-NO_2	5.05	4.50	0.55	4.67	0
10	CN	C_6H_5	CH_3	C-Hexyl	4.50	4.51	−0.01	4.74	0
11[a]	$COOC_2H_5$	CH_3	C_6H_5	C_6H_5	4.84	5.54	−0.70	6.20	1
12	Mitozolomide				4.00	4.00	0.00	−0.22	0
13	Temozolomide				4.00	3.94	0.06	−0.81	0

[a] Data points not included in the derivation of Eq. 27.

Table 22. QSAR 28

Compound	R	R_1	R_2	R_3	log 1/*C* (Eq. 28)			*Cπ*-R_3	*I*
					Observed	Predicted	*Δ*		
1	CN	CH_3	C_6H_5	C_6H_5	5.39	5.57	−0.18	3.65	1
2	CN	CH_3	C_6H_5	C_6H_4-4-OCH_3	5.48	5.41	0.07	3.57	1
3	CN	CH_3	C_6H_5	C_6H_4-4-Cl	7.26	7.00	0.26	4.36	1
4[a]	CN	CH_3	C_6H_5	C_6H_4-3-Cl	5.12	7.00	−1.88	4.36	1
5	CN	CH_3	C_6H_5	C_6H_4-4-NO_2	4.99	5.06	−0.07	3.39	1
6	CN	C_6H_5	CH_3	C_6H_4-4-OCH_3	4.47	4.71	−0.24	3.57	0
7	CN	C_6H_5	CH_3	C_6H_4-4-Cl	6.15	6.31	−0.16	4.36	0
8[a]	CN	C_6H_5	CH_3	C_6H_4-3-Cl	4.06	6.31	−2.25	4.36	0
9	CN	C_6H_5	CH_3	C_6H_4-4-NO_2	4.76	4.36	0.40	3.39	0
10	$COOC_2H_5$	CH_3	C_6H_5	C_6H_5	5.49	5.57	−0.08	3.65	1

[a] Data points not included in the derivation of Eq. 28.

Table 23. QSAR 29

Compound	X	log 1/*C* (Eq. 29)			*B*5-X
		Observed	Predicted	*Δ*	
1[a]	$OCMe_3$	−0.64	0.25	−0.89	4.35
2	OC_4H_9	−0.22	−0.10	−0.12	4.79
3	$OCH_2C_6H_5$	0.60	0.92	−0.32	3.50
4	C_5H_{11}	−0.29	−0.22	−0.08	4.94
5	CMe_3	1.34	1.19	0.16	3.17
6	CH_2CHMe_2	0.43	0.17	0.26	4.45
7	CH_2CMe_3	0.49	0.39	0.11	4.18

[a] Data point not included in the derivation of Eq. 29.

Table 24. QSAR 30

Compound	X	log 1/*C* (Eq. 30)			*B*5-X
		Observed	Predicted	*Δ*	
1	C_6H_5	7.53	7.30	0.23	3.11
2	4-Me-C_6H_4	7.54	7.30	0.24	3.11
3	Me	5.85	5.84	0.01	2.04
4	CMe_3	7.37	7.38	−0.01	3.17
5	CH_2CMe_3	8.17	8.75	−0.58	4.18
6[a]	NH-CMe_3	8.26	9.04	−0.78	4.39
7	*O*-CMe_3	9.32	8.99	0.34	4.35
8	*O*-Tert-amyl	9.45	9.08	0.37	4.42
9	*O*-$CHMe_2$	8.57	8.65	−0.07	4.10
10[a]	*O*-Neopentyl	8.06	9.08	−1.02	4.42
11[a]	*O*-CH_2CHMe_2	8.08	9.08	−1.00	4.42
12	OC_2H_5	7.65	7.64	0.01	3.36
13	*O*-$CH_2C_6H_5$	7.30	7.83	−0.53	3.50

[a] Data points not included in the derivation of Eq. 30.

Table 25. QSAR 31

Compound	X	Y	Z	log 1/*C* (Eq. 31)			σ_I-X
				Observed	Predicted	Δ	
1	H	CH_2CH_2Cl	H	5.30	5.30	0.00	0.00
2[a]	H	CH_2CH_2Br	H	5.74	5.30	0.45	0.00
3	H	CH_2CH_2Cl	CH_2CH_2Cl	5.29	5.30	−0.01	0.00
4	Br	CH_2CH_2Br	H	6.36	6.23	0.12	0.44
5[a]	NMe_2	CH_2CH_2Br	H	4.28	5.43	−1.14	0.06
6	CN	CH_2CH_2Br	H	6.35	6.43	−0.08	0.53
7	$CONH_2$	CH_2CH_2Br	H	5.85	5.89	−0.04	0.28

[a] Data points not included in the derivation of Eq. 31.

Table 26. QSAR 32

Compound	Substituent	log 1/*C* (Eq. 32)			*C*log *P*	*I*	I_1
		Observed	Predicted	Δ			
1[a]	1-OH	3.84	5.06	−1.21	3.61	0	0
2	3-OH	3.93	3.93	−0.01	2.71	0	0
3	4-OH	4.18	3.93	0.25	2.71	0	0
4	1-OCH_3	4.11	4.12	−0.01	3.08	0	0
5	2-OCH_3	4.23	4.12	0.11	3.08	0	0
6	3-OCH_3	4.13	4.12	0.01	3.08	0	0
7[a]	1,2-Di-OH	4.85	4.36	0.49	3.06	1	0
8	1,7-Di-OH	4.29	4.36	−0.07	3.06	1	0
9	2,3-Di-OH	4.50	4.55	−0.05	2.23	1	0
10	3,4-Di-OH	4.67	4.55	0.12	2.23	1	0
11[a]	3,5-Di-OH	4.11	4.65	−0.54	2.16	1	0
12	1,2-Di-OCH_3	3.86	3.94	−0.07	2.77	0	0
13	2,3-Di-OCH_3	3.90	3.94	−0.04	2.77	0	0
14	3,4-Di-OCH_3	3.79	3.94	−0.15	2.77	0	0
15	1-OCH_3, 2-OH	4.41	4.47	−0.06	2.49	0	1
16	3-OH, 5-OCH_3	4.43	4.40	0.04	2.70	0	1
17[a]	3-OCH_3, 4-OH	4.11	4.47	−0.36	2.49	0	1
18	3-OCH_3, 5-OH	4.42	4.40	0.03	2.70	0	1
19	2-CH_3-1,3-di-OH	4.70	4.71	−0.01	3.46	0	0
20	2,3-Di-OH-4-OCH_3	4.70	4.69	0.02	2.00	0	0
21	1-CHO, 4-OH, 3-OCH_3	4.18	4.27	−0.09	2.24	0	0

[a] Data points not included in the derivation of Eq. 32.

Table 27. QSAR 33 and 34

	Compound	log 1/*C* (Eq. 33)			log 1/*C* (Eq. 34)			*C*log *P*
		Observed	Predicted	Δ	Observed	Predicted	Δ	
1	Meridianin-D	4.60	4.64	−0.04	4.61	4.60	0.01	2.86
2[a]	Bis(*N*-tosylindolyl) pyrimidine	6.32	7.21	−0.89	6.44	7.56	−1.11	8.15
3	2,4-Bis(3′-indolyl) pyrimidine	5.55	5.31	0.24	5.70	5.38	0.32	4.25
4	5-CH_3-2,4-bis(3′-indolyl) pyrimidine	5.44	5.41	0.03	5.36	5.49	−0.13	4.45
5	5-OCH_3-2,4-bis(3′-indolyl) pyrimidine	5.32	5.31	0.01	5.39	5.37	0.01	4.24
6	2-NH_2-3-(*N*-tosyl-3′-indolyl)-5-bromopyrazine	5.58	5.59	−0.01	5.75	5.70	0.06	4.82
7	2-NH_2-3-OCH_3-5-(3′-indolyl) pyrazine	4.60	4.66	−0.06	4.52	4.63	−0.11	2.91
8	2-(*N*,*N*-Dimethyl) amino-3,5-bis(3′-indolyl) pyrazine	5.60	5.75	−0.15	5.72	5.89	−0.16	5.16

[a] Data point not included in the derivation of Eqs. 33 and 34.

Table 28. QSAR 35 and 36

Compound	X	Y	log 1/*C* (Eq. 35)			log 1/*C* (Eq. 36)			σ'-X
			Observed	Predicted	Δ	Observed	Predicted	Δ	
1[a]	NH_2	Me	7.55	6.36	1.19	6.92	6.25	0.67	0.62
2	$NHCOC_6H_5$	H	9.72	9.84	−0.11	8.51	8.79	−0.28	1.68
3	NHCOMe	H	9.46	8.92	0.54	8.29	8.12	0.18	1.40
4[a,b]	H	H	8.60	5.93	2.67	7.74	5.93	1.81	0.49
5	OH	H	8.42	8.82	−0.40	8.26	8.05	0.21	1.37
6	NH_2	H	6.40	6.36	0.04	5.89	6.25	−0.36	0.62
7	NH_2	Me	6.29	6.36	−0.07	5.82	6.25	−0.42	0.62

[a] Data points not included in the derivation of Eq. 35.
[b] Data point not included in the derivation of Eq. 36.

$$\log 1/C = 0.64(\pm 0.35)L\text{-}X_2 + 4.56(\pm 1.09) \quad (12)$$

$n = 6$, $r^2 = 0.868$, $s = 0.242$, $q^2 = 0.734$; outlier: 2-COOH.

3.6.6. Action of compounds VII on human SK-MEL-2 melanoma cells. Data were obtained from Chao et al.[29] (Table 9)

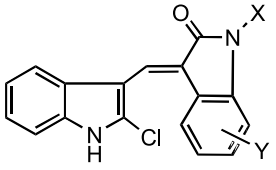
$$\log 1/C = 0.74(\pm 0.28)L\text{-}X_2 + 4.26(\pm 0.90) \quad (13)$$

$n = 6$, $r^2 = 0.929$, $s = 0.199$, $q^2 = 0.829$; outlier: 2-COOH.

Although the same compounds VII have been used in the formulation of five QSAR (Eqs. 9–13), we get two different types of equations. Eqs. 9–11 have linear correlations with $B5\text{-}X_2$ and are nearly identical. $L\text{-}X_2$ is the weaker parameter for these equations. On the other hand, Eqs. 12 and 13 have linear correlations with $L\text{-}X_2$ and are nearly identical. $B5\text{-}X_2$ is the bad parameter for these equations. The results of QSAR 9–13 suggest that the compounds VII may target a receptor of one kind in human SK-MEL-5, UACC-257, and MAL-3M melanoma cells and another kind in human UACC-62 and SK-MEL-2 melanoma cells. The COOH containing compound is badly fit as one might expect because it would be partially ionized.

3.7. Indole derivatives

3.7.1. Inhibition of melanoma cells by indole derivatives VIII. Data were obtained from Andreani et al.[30] (Table 10)



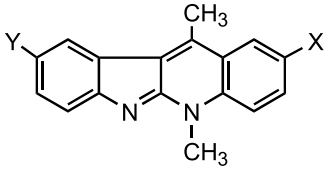
VIII

$$\log 1/C = -1.30(\pm 0.39)\text{CMR} + 18.13(\pm 3.65) \quad (14)$$

$n = 4$, $r^2 = 0.990$, $s = 0.071$, $q^2 = 0.918$; outlier: X = C_6H_5, Y = H.

3.8. Indoloquinoline derivatives

3.8.1. Inhibition of melanoma cells by indoloquinoline derivatives IX. Data were obtained from Kaczmarek et al.[31] (Table 11)



IX

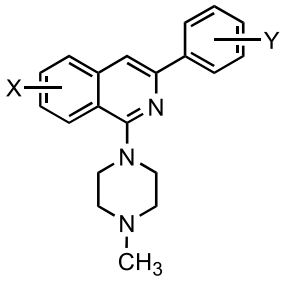
$$\log 1/C = 0.23(\pm 0.08)L\text{-X} + 5.15(\pm 0.26) \quad (15)$$

$n = 5$, $r^2 = 0.965$, $s = 0.042$, $q^2 = 0.907$.

Activity is strongly correlated with the length of X, and is independent of Y. The authors were interested in making some novel DNA topoisomerase II inhibitors and studied six different cell lines including melanoma. All cell lines yielded good QSAR.

3.9. Isoquinolines

3.9.1. Inhibition of human melanoma cells by isoquinolines X. Data were obtained from Cho et al.[32] (Table 12)



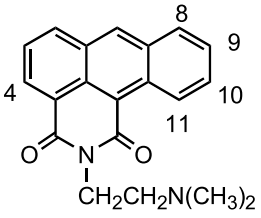
X

$$\log 1/C = 0.43(\pm 0.15)C\log P + 0.40(\pm 0.19)L\text{-}X_6 + 2.35(\pm 0.74) \quad (16)$$

$n = 12$, $r^2 = 0.901$, $s = 0.107$, $q^2 = 0.805$; outliers: X = 5-NMe_2, Y = 3-Me; X = 5-NMe_2, Y = 4-OMe.

3.10. Isoquinolinediones

3.10.1. Inhibition of UACC 375 melanoma cells by XI. Data were obtained from Sami et al.[33] (Table 13)

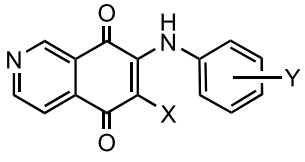


XI

$$\log 1/C = -0.97(\pm 0.24)C\log P - 1.99(\pm 0.37)I - 0.27(\pm 0.12)B5\text{-}4 + 11.72(\pm 1.12) \quad (17)$$

$n = 20$, $r^2 = 0.898$, $s = 0.252$, $q^2 = 0.803$; outliers: 9-OH, 9-OMe, 11-Cl.

3.10.2. Inhibition of human SK-MEL-2 melanoma cells by XII. Data were obtained from Ryu et al.[34] (Table 14)



XII

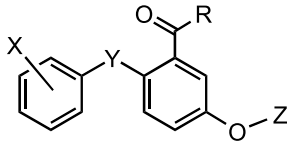
$$\log 1/C = 0.55(\pm 0.21)\text{CMR} + 0.42(\pm 0.16)L\text{-4, Y} - 0.99(\pm 0.36)B1\text{-4, Y} + 1.53(\pm 1.30) \quad (18)$$

$n = 20$, $r^2 = 0.893$, $s = 0.190$, $q^2 = 0.828$; outliers: X = Cl, Y = 4-OCF_3; X = Cl, Y = 4-OMe; X = Cl, Y = 4-Me; X = Cl, Y = 4-F; X = Cl, Y = 3,4-di-Me.

These compounds are quite effective in cleaving the DNA of tumor cells.

3.11. Lavendustin-A derivatives

3.11.1. Inhibition of UACC melanoma cells by XIII. Data were obtained from Mu et al.[35] (Table 15)



XIII

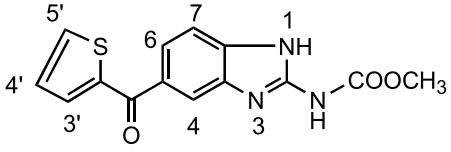
$$\log 1/C = -0.46(\pm 0.26)C\log P + 0.44(\pm 0.30)I\text{-Z} + 0.28(\pm 0.17)\text{MR-R} + 6.52(\pm 1.17) \quad (19)$$

$n = 17$, $r^2 = 0.897$, $s = 0.177$, $q^2 = 0.821$; outliers: X = 2,5-di-OH, Y = CH_2CH_2, Z = H, R = $NHCH_2CH_2C_6H_5$; X = 2,5-di-OMe, Y = CH=CH, Z = Me, R = $NH(CH_2)_2CH_2$(4-F-C_6H_4) (Cis).

This is an extremely complex set of substitutents that gives a good correlation. *I*-Z is an indicator variable that takes the value of 1 when Z = H. MR-R is a measure of the volume and polarizability of R according to the Lorentz–Lorenz equation.[17]

3.12. Oncodazoles

3.12.1. Inhibition of monolayer B16 melanoma cells by XIV. Data were obtained from Kruse et al.[36] (Table 16)



XIV

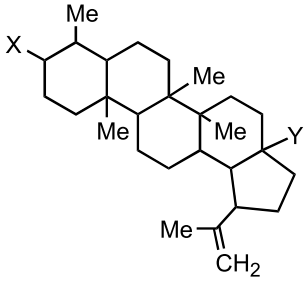
$$\log 1/C = 0.86(\pm 0.38)C\log P + 2.77(\pm 0.65)\text{MR-4}' - 0.76(\pm 0.23)\text{MR-4}'^2 - 0.63(\pm 0.42)C\pi\text{-1} + 2.54(\pm 1.09) \quad (20)$$

$n = 18$, $r^2 = 0.913$, $s = 0.364$, $q^2 = 0.767$; outliers: 7-Me; 4′-CH_2CN; optimum MR-4′ = 1.82 (1.67–2.06).

$C\pi$-1 is the calculated π value of the substituents at position-1. MR-4′ is the calculated molar refractivity of the substituents at position-4′.

3.13. Pentacyclic triterpenes

3.13.1. Inhibition of mouse B16 2F2 melanoma cells by XV. Data were obtained from Hata et al.[37] (Table 17)



XV

$$\log 1/C = 0.18(\pm 0.13)L\text{-Y} + 1.28(\pm 0.22)I + 4.65(\pm 0.52) \quad (21)$$

$n = 10$, $r^2 = 0.963$, $s = 0.133$, $q^2 = 0.913$; outlier: X = α-H, β-$OCOCH_3$, Y = $COCH_3$.

A very good correlation depending on the length of Y. Indicator variable $I = 1$ for X = (=O).

3.14. Phenazinedione derivatives

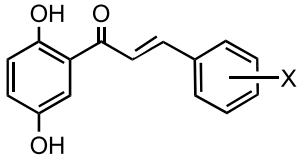
3.14.1. Inhibition of human SK-MEL-2 melanoma cells by phenazine-6 11-dione derivatives. Data were obtained from Kim et al.[38] (Table 18)

$$\log 1/C = 6.45(\pm 4.59)C\log P - 1.23(\pm 0.75) \times C\log P^2 - 6.59(\pm 1.86) \quad (22)$$

$n = 10$, $r^2 = 0.895$, $s = 0.361$, $q^2 = 0.825$; outlier: compound **5** (Table 18); optimum $C\log P = 2.63$ (1.94–2.82).

3.15. Phenols

3.15.1. Inhibition of murine B16 melanoma cells by XVI. Data were obtained from Nam et al.[39] (Table 19)



XVI

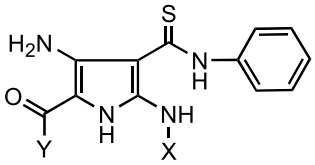
$$\log 1/C = 0.25(\pm 0.09)C\log P + 0.33(\pm 0.10)\sigma^+ + 7.17(\pm 0.33) \quad (23)$$

$n = 15$, $r^2 = 0.917$, $s = 0.098$, $q^2 = 0.853$; outliers: X = 2-OMe, 5-Br; 2,3-di-OH; 3,4-di-OH; 2,3,4-tri-OMe; 3,4,5-tri-OMe.

The authors were interested in the antiangiogenesis properties of anticancer compounds.

3.16. Pyrrolecarbothioamides

3.16.1. Toxicity to MALME-3M melanoma cells by various pyrrolecarbothioamides XVII. Data were obtained from Cocco et al.[40] (Table 20)



XVII

$$\log 1/C = 0.12(\pm 0.03)C\log P + 4.29(\pm 0.11) \quad (24)$$

$n = 8$, $r^2 = 0.953$, $s = 0.039$, $q^2 = 0.910$; outliers: compounds **2**, **3**, and **8** in Table 20.

3.16.2. Inhibition of melanoma UACC-257 cells by various pyrrolecarbothioamides XVII. Data were obtained from Cocco et al.[40] (Table 20)

$$\log 1/C = 0.094(\pm 0.025)C\log P + 4.34(\pm 0.11) \quad (25)$$

$n = 9$, $r^2 = 0.920$, $s = 0.042$, $q^2 = 0.862$; outliers: compounds **2**, **3**, **13**, and **14** in Table 20.

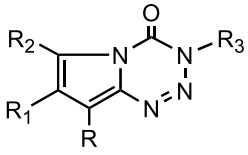
3.16.3. Inhibition of SK-MEL-28 melanoma cells by pyrrolecarbothioamides XVII. Data were obtained from Cocco et al.[40] (Table 20)

$$\log 1/C = 0.24(\pm 0.06)C\log P + 3.86(\pm 0.25) \quad (26)$$

$n = 10$, $r^2 = 0.919$, $s = 0.112$, $q^2 = 0.881$; outliers: compounds **6**, **12**, **13**, and **14** in Table 20.

3.17. Pyrrolotetrazine derivatives

3.17.1. Inhibition of SK-MEL-2 melanoma cells by XVIII. Data were obtained from Diana et al.[41] (Table 21)

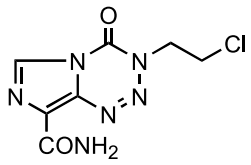


XVIII

$$\log 1/C = 0.10(\pm 0.08)C\log P + 0.88(\pm 0.36)I + 4.03(\pm 0.32) \quad (27)$$

$n = 10$, $r^2 = 0.912$, $s = 0.214$, $q^2 = 0.838$; outliers: R = CN, R_1 = Me, $R_2 = C_6H_5$, $R_3 = C_6H_4$-4-Cl; R = CN, $R_1 = C_6H_5$, R_2 = Me, $R_3 = C_6H_4$-4-NO_2; R = $COOC_2H_5$, R_1 = Me, $R_2 = C_6H_5$, $R_3 = C_6H_5$.

The indicator variable takes the value of 1 for $R_2 = C_6H_5$. Mitozolomide (figure XIX) was an effective antitumor agent, but it is too toxic to be used in humans. The study by Diana et al.[41] was an attempt to find similar less toxic compounds.



XIX

3.17.2. Inhibition of LOX IMVI melanoma cells by XVIII. Data were obtained from Diana et al.[41] (Table 22)

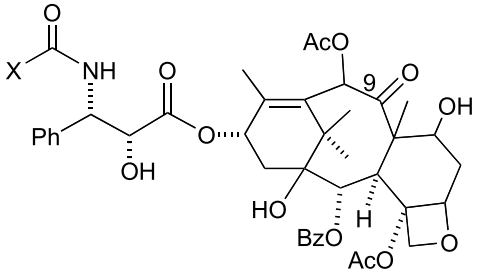
$$\log 1/C = 2.01(\pm 0.66)C\pi\text{-}R_3 + 0.70(\pm 0.50)I - 2.45(\pm 2.52) \quad (28)$$

$n = 8$, $r^2 = 0.934$, $s = 0.268$, $q^2 = 0.748$; outliers: R = CN, $R_1 = CH_3$, $R_2 = C_6H_5$, $R_3 = C_6H_4$-3-Cl; R = CN, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = C_6H_4$-3-Cl.

The indicator variable takes the value of 1 for $R_2 = C_6H_5$. $C\pi$-R_3 is the calculated π value for R_3 substituents.

3.18. Taxol derivatives

3.18.1. Cytotoxicity of taxol derivatives XX to B16 melanoma cells. Data were obtained from Georg et al.[42] (Table 23)

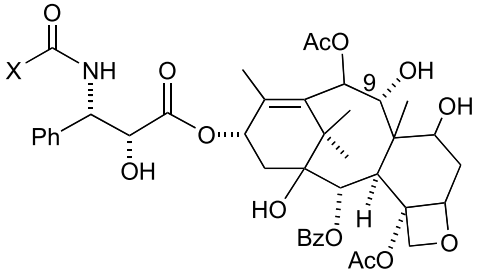


XX

$$\log \mathrm{RBA} = -0.93(\pm 0.42)B5\text{-X} + 3.70(\pm 1.77) \quad (29)$$

$n = 6$, $r^2 = 0.874$, $s = 0.239$, $q^2 = 0.700$; outlier: $OC(CH_3)_3$; RBA = relative biological activity.

3.18.2. Inhibition of mouse B16F10 melanoma by XXI. Data were obtained from Maring et al.[43] (Table 24)



XXI

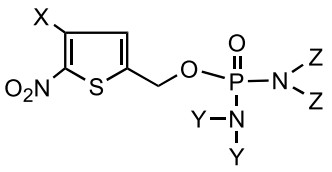
$$\log 1/C = 1.36(\pm 0.36)B5\text{-X} + 3.07(\pm 1.31) \quad (30)$$

$n = 10$, $r^2 = 0.903$, $s = 0.351$, $q^2 = 0.857$; outliers: $NH(CH_3)_3$, *o*-neopentyl, $OCH_2CH(CH_3)_2$.

Compounds XX (Eq. 29) and XXI (Eq. 30) have similar structures, were tested in two different types of melanoma cell lines, yet their QSAR appear with same parameters *B*5-X (*B*5 of X-substituents) with opposite sign. This may be due to the variation in X-groups and the difference at C-9 position, because both compounds XX and XXI differ from each other due to the variation of X-groups and the substitution at C-9 position.

3.19. Thiophene derivatives

3.19.1. Inhibition of murine B16 melanoma cells by XXII. Data were obtained from Borch et al.[44] (Table 25)



XXII

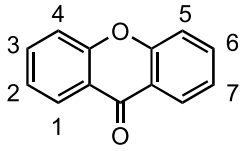
$$\log 1/C = 2.13(\pm 0.57)\sigma_I\text{-X} + 5.30(\pm 0.19) \qquad (31)$$

$n = 5$, $r^2 = 0.980$, $s = 0.087$, $q^2 = 0.941$; outliers: X = H, Y = CH_2CH_2Br, Z = H; X = $N(CH_3)_2$, Y = CH_2CH_2Br, Z = H.

QSAR 31 suggests that the electron withdrawing X-groups will increase cytotoxicities of compounds XXII under aerobic conditions.

3.20. Xanthone derivatives

3.20.1. Inhibition of UACC-62 melanoma cells by XXIII. Data were obtained from Pedro et al.[45] (Table 26)



XXIII

$$\log 1/C = -7.79(\pm 1.95)C\log P + 1.43(\pm 0.36) \times C\log P^2 + 0.27(\pm 0.16)I + 0.46(\pm 0.16)I_1 + 14.54(\pm 2.60) \qquad (32)$$

$n = 17$, $r^2 = 0.899$, $s = 0.107$, $q^2 = 0.827$; inversion point: 2.72 (2.70–2.78); outliers: 1-OH; 1,2-di-OH; 3,5-di-OH; 3-OCH_3, 4-OH.

$I = 1$ for the presence of dihydroxy and $I_1 = 1$ for the presence of one hydroxy and one methoxy groups.

Eq. 32, like Eq. 4 may correspond to an allosteric reaction. Despite the different types of compounds, the inversion points are similar. This suggests that the two receptors are much the same.

3.21. Miscellaneous

3.21.1. Inhibition of LOX IMVI melanoma cells by pyrimidine and pyrazines. Data were obtained from Jiang et al.[46] (Table 27)

$$\log 1/C = 0.49(\pm 0.16)C\log P + 3.24(\pm 0.65) \qquad (33)$$

$n = 7$, $r^2 = 0.929$, $s = 0.132$, $q^2 = 0.869$; outlier: bis(*N*-tosylindolyl) pyrimidine.

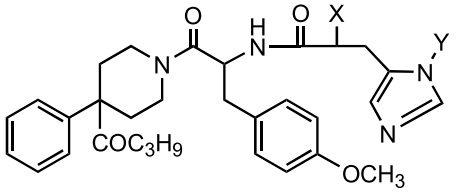
3.21.2. Inhibition of M14 melanoma cells by pyrimidines and pyrazines. Data were obtained from Jiang et al.[46] (Table 27)

$$\log 1/C = 0.56(\pm 0.21)C\log P + 3.00(\pm 0.89) \qquad (34)$$

$n = 7$, $r^2 = 0.902$, $s = 0.180$, $q^2 = 0.830$; outlier: bis(*N*-tosylindolyl) pyrimidine.

Eqs. 33 and 34 describe the ability of the same compounds to inhibit LOX IMVI and M14 melanoma cells, respectively. The equations represent parallel linear relationships between activity and hydrophobicity, which suggests that these compounds target the same kind of receptor in each cell line.

3.21.3. Inhibition of MC-1R receptor in HBL melanoma cells by XXIV. Data were obtained from Herpin et al.[47] (Table 28)



XXIV

$$\log 1/C = 3.28(\pm 1.29)\sigma'\text{-X} + 4.32(\pm 1.57) \qquad (35)$$

$n = 5$, $r^2 = 0.956$, $s = 0.395$, $q^2 = 0.915$; outliers: X = NH_2, Y = Me; X = Y = H.

It is surprising that only the inductive effect of X has a detectable effect on activity. The authors were interested in the anti-inflammatory actives of these rather complicated molecules. In a study with the same compounds as used for QSAR 35 the same authors measured the binding affinity to HBL melanoma cells.

3.21.4. Binding affinity of compounds XXIV to HBL melanoma cells measured using [125I]-NDPA-MSH stimulating hormone. Data were obtained from Herpin et al.[47] (Table 28)

$$\log 1/C = 2.40(\pm 1.23)\sigma'\text{-X} + 4.76(\pm 1.40) \qquad (36)$$

$n = 6$, $r^2 = 0.881$, $s = 0.479$, $q^2 = 0.723$; outlier: X = Y = H.

4. Overview

An analysis of our QSAR 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 36 QSAR, 20 contain a correlation between activity and hydrophobicity. A positive linear correlation is found in 12 Eqs.: 1, 6, 16, 20, 23–28, 33, and 34. The coefficient with the hydrophobic parameter varies considerably, from a low value of 0.09 (Eq. 25) to a high value of 2.01 (Eq. 28). These data suggest that although activity might be improved by increasing compound hydrophobicity, this will produce considerably different results for different compounds. A negative linear correlation is found in four Eqs., 7, 17, 19, 20, and the coefficients range from −0.46 (Eq. 19) to −0.97 (Eq. 17). Less hydrophobic congeners in these compound families might display enhanced activity (note: Eq. 20 contains a positive correlation with $\log P$ and a negative correlation with π-1, so one should preserve a hydrophilic group at N1 while boosting the molecule's overall hydrophobicity). Parabolic correlations with hydrophobicity are found in five Eqs.: 3, 4, 8, 22, and 32. Two of these (4 and 32) reflect situations where activity declines with increasing hydrophobicity and then changes direction and increases. These may correspond to allosteric reactions. The other three (3, 8 and 32) situations show that activity is optimal for a particular value, or range of values, of $\log P$. The optimal $\log P$ are 6.39 (Eq. 3, bipyrroles), 2.01 (Eq. 8, dihydrobenzodithiophenediones), and 2.63 (Eq. 22, phenazinediones). The wide variation in optimal $\log P$ suggests that these compounds act by very different mechanisms and/or at very different receptors. Other parameters, steric and electronic, also appear in several QSAR. 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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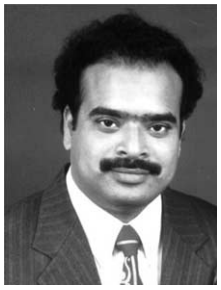
Biographical sketches



Rajeshwar P. Verma was born in 1966 in Barh (India). He received his M.Sc. (1988) and Ph.D. (1992) degrees in chemistry from Magadh University, Bodh-Gaya. He spent a year at the same university as a postdoctoral fellow with Professor K. S. Sinha. He joined Roorkee University (now IIT Roorkee) as a research associate and worked with Professor S. M. Sondhi (1993–1997). He also worked as a Lecturer of Chemistry at Gurukula Kangri University, Hardwar (1994–1995). He won a Research Associateship Award in December 1994 from the Council of Scientific & Industrial Research, New Delhi (India). In 1997, he moved to Pomona College to join the renowned QSAR research group of Professor Corwin Hansch and Cynthia Selassie, working as a postdoctoral research associate. Dr. Verma's research interests include the following: isolation, characterization, and synthesis of natural products derived from medicinal plants; chemistry of isothiocyanates; synthesis of biologically important heterocycles and phenolic/active hydrogen compounds; application of principles of quantitative structure–activity relationships (QSAR) to the study of antifolates, multidrug resistance, free-radical-mediated toxicity of phenolic/active hydrogen compounds and computer-assisted drug design.

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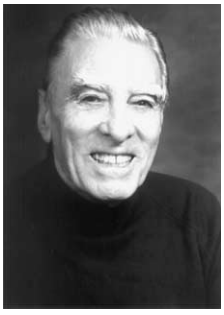

Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in organic chemistry from New York University in 1944. After working with the Du Pont Co., first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich, Switzerland, with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. He is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.