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Original article

Quantitative structure–activity relationships of antimutagenic benzalacetones and 1,1,1-trifluoro-4-phenyl-3-buten-2-ones

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Abstract

The antimutagenic activities (IC_{50}) of benzalacetones (BZ) and 1,1,1-trifluo-4-phenyl-3-buten-2-ones (TF) against UV-induced mutagenesis in *Escherichia coli* WP2s(*uvrA trpE*) were quantitatively analyzed in terms of physicochemical parameters by regression analyses. Structural requirements for maximal potency were derived from the results of quantitative structure–activity relationship (QSAR) analyses: (1) ring substituents should be electron-withdrawing; (2) 2-OH substituents incapable of intramolecular hydrogen-bonding notably increase the potency; and (3) replacement of CH_3 group by CF_3 in the side chain enhances the activity. Contrary to our expectations, the best correlation lacked hydrophobic effects. Antimutagenic activities against γ-induced mutagenesis in *Salmonella typhimurium* TA2638 were also studied for some derivatives in the BZ series, where, in addition to electronic and hydrogen-bonding factors, a hydrophobic term was also significant. Physicochemical meanings of the derived correlations are discussed. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: QSAR; antimutagenic activity; benzalacetones; 1,1,1-trifluo-4-phenyl-3-buten-2-ones; electronic substituent effect; hydrogen-bonding

1. Introduction

Curcumin is known to have bactericidal, antioxidative, anti-inflammatory and antitumor-promoting activities [1,2]. In the course of our studies of antimutagenic activity for curcumin and its structurally related compounds, we found that benzalacetone exerted potent antimutagenic activity against UV- and γ-induced mutations, but dehydrozingerone, which is regarded as 'half-curcumin', was almost inactive [3] (Fig. 1). Since dehydrozingerone is the 4-hydroxy-3-methoxy derivative of benzalacetone, this finding suggests that the substitution pattern on the benzene ring largely affects the antimutagenic potency. We therefore, investigated, in previous studies [3,4], the antimutagenic activity of a range of monosubstituted benzalacetones by post-treatment for UV-induced mutagenesis in *Escherichia coli* WP2s(*uvrA trpE*) and γ-induced mutagenesis in *Salmonella typhimurium* TA2638. Pre-analyses of the values for IC_{50}, the dose required to inhibit mutagenicity by 50%, showed that the activity was mainly related to the electronic properties (σ) of substituents for UV-induced mutation; introduction of an electron-withdrawing functional group increased the inhibitory potency, whereas the hydrophobicity ($\log P$) was a major factor governing the antimutagenic activity

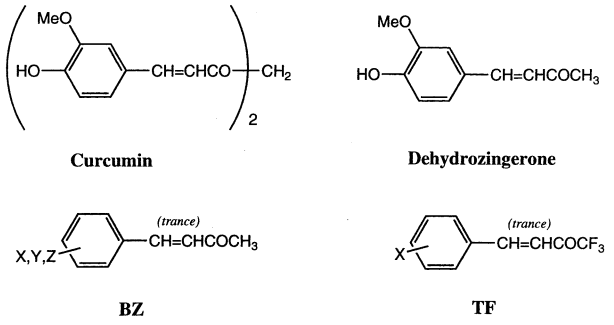

Fig. 1. Structures of curcumin and related compounds.

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for γ-induced mutation [4]. In addition, it seemed quite likely that, in certain cases, the presence of a phenolic OH group considerably enhanced the potency [4].

Many investigators [5–7] have studied quantitative structure–activity relationships (QSAR) for mutagenic or carcinogenic compounds with the intention of developing prediction models for toxicity of chemicals present in foods and in the environment. However, there have appeared in the literature only a few examples [8] of QSAR studies of antimutagenic compounds in spite of the fact that a large number of synthetic and natural products found to inhibit mutagenicity have had their potencies evaluated numerically [9,10]. We were interested in analyzing quantitatively the structure–activity relationships for our benzalacetone series by adding data for compounds which could provide useful information to solve two of the disputable problems raised in the previous study: (i) to examine how the hydrogen-bonding effect of phenolic OH affects the potency, several benzalacetones containing OH substituent(s) were examined; and (ii) to explore the effect of electron-withdrawing functional groups, which usually enhance the activity, 1,1,1-trifluoro-4-phenyl-3-buten-2-one and its ring-substituted derivatives (TF) were studied. In this work, we performed QSAR analyses of antimutagenic activity for UV-induced mutagenesis, with the combined data set (BZ and TF) and examined the structural requirements that provided increased activity. Further, the data for activity for γ-induced mutagenesis was subjected to a more extensive, quantitative analysis, and the results were compared with those for UV-induced mutagenesis.

2. Methods

2.1. Compounds

The compounds studied for UV-induced mutagenesis are listed in Table 1 (BZ) and Table 2 (TF). Those for γ-induced mutagenesis are given in Table 3.

2.2. Antimutagenic activity

Antimutagenic activity was evaluated by the inhibitory effect of these compounds on UV-induced mutagenesis in *E. coli* WP2s(*uvrA trpE*) and γ-induced mutagenesis in *S. typhimurium* TA2638. Briefly, the bacterial cells were cultured in nutrient broth (Oxoid nutrient broth No. 2) for WP2s; and in the same broth supplemented with 25 μg mL^{-1} ampicillin for TA2638. The reverse mutations were assayed using a semi-enriched minimal agar medium containing various concentrations of the test compound. The detail of these experiments has already been described in a previous paper [3].

Most of the IC_{50} (μmol mL^{-1}) values, representing the concentration of compounds required to reduce the mutation frequency to 50% of the control, were taken from our previous work [4] or calculated analogously by using our earlier data [3], and others were taken from our unpublished results [11] (Tables 1 and 2).

2.3. Chemical descriptors

2.3.1. Hydrophobicity parameter

log *P*—Experimentally determined partition coefficients, *P*, for the octanol–water system were used. Most of the log *P* values were taken from our previous work [12] and those not already reported were measured in this study by the shake-flask method according to the procedure described in our earlier paper [12].

2.3.2. Electronic parameters

σ°—Various electronic substituent constants such as, σ, σ° and σ^+ were tested. The set of values that worked most effectively in the present analyses (σ°) are given in Tables 1–3. This parameter was originally derived from the ionization constants of phenylacetic acids [13], and is supposed to be applicable to systems where substituent and reaction centre are insulated, preventing through resonance interaction. The values for *ortho* substituents, σ°_o, were replaced by those for *para* substituents; $\sigma^\circ_o = \sigma^\circ_p$ [14]. For benzalacetones with more than two substituents on the benzene ring, the sum of σ° values for all substituents, $\Sigma\,\sigma^\circ$, was used.

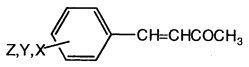
2.3.3. Indicator variables

HB_{2OH}, I_{TF}—For 2-OH-derivatives incapable of intramolecular hydrogen-bonding with the 3-substituent, a binary-type hydrogen-bonding parameter HB_{2OH} was defined as shown in Table 1. To combine BZ and TF series, an indictor variable I_{TF} was used.

2.4. Correlation analyses

Relationships between antimutagenic activity, expressed as $\log(1/IC_{50})$ from IC_{50} values (mmol mL^{-1}), and physicochemical parameters (X_i), were analyzed statistically by fitting the data to correlation equations consisting of various combinations of parameter terms: $\log(1/IC_{50}) = \Sigma\, a_i X_i + \text{constant}$. The intercept and regression coefficient, a_i, for each term were determined by the least-squares method. The levels of significance for all the correlations described below were better than 99.9%. The level of significance of each term was judged by the *t*-test.

Table 1
Inhibitory potency toward UV-induced mutagenesis in *E. coli* WP2s and physicochemical parameters for benzalacetones (BZ)



BZ

Number	Substituent(s)	IC_{50} [a]	log $1/IC_{50}$ [b]	$\Sigma\sigma^{\circ}$ [c]	HB_{2OH}
1	H	0.50	3.30	0.00	0
2	3-Me	1.50 [d]	2.82	−0.07	0
3	4-Me	1.60 [d]	2.80	−0.12	0
4	4-Et	1.20 [e]	2.92	−0.13	0
5	2-F	0.34 [e]	3.47	0.17	0
6	3-F	0.26	3.59	0.35	0
7	4-F	0.63	3.20	0.17	0
8	2-Cl	0.52 [e]	3.28	0.27	0
9	3-Cl	0.43	3.37	0.37	0
10	4-Cl	0.32	3.49	0.27	0
11	2-Br	0.40 [e]	3.40	0.26	0
12	3-Br	0.41	3.39	0.38	0
13	4-Br	0.52	3.28	0.26	0
14	3-CF_3	0.22	3.66	0.47	0
15	4-CF_3	0.11	3.96	0.53	0
16	3-OMe	0.71 [d]	3.15	0.06	0
17	4-OMe	1.60 [d]	2.80	−0.16	0
18	3-CN	0.28	3.55	0.62	0
19	4-CN	0.17	3.77	0.69	0
20	2-OH	0.23 [d]	3.64	−0.13	1
21	4-OH	1.20 [d]	2.92	−0.13	0
22	3-NO_2	0.15	3.82	0.70	0
23	4-NO_2	0.083	4.08	0.82	0
24	2-OH-3-Me	0.24 [e]	3.62	−0.20	1
25	2-OH-3-OMe	0.68 [e]	3.17	−0.07	0
26	2-OH-3-OEt	1.20 [e]	2.92	−0.09	0
27	3,4-diOH	0.98 [e]	3.01	−0.09	0
28	3,5-diMe-4-OH	1.10 [e]	2.96	−0.27	0

[a] μmol mL^{-1}, the data were taken from Ref. [4] unless otherwise described.
[b] mmol mL^{-1}.
[c] σ° values were taken from Ref. [20].
[d] Calculated using the data in Ref. [3] by non-linear regression from the plot of observed % inhibition against the concentration of test compound.
[e] Ref. [11].

3. Results and discussion

3.1. UV-induced mutagenesis in E. coli WP2s

According to the results of preliminary analyses [4], electronic parameters were examined first for 23 mono-substituted BZ (**1**–**23**). Only the 2-OH derivative **20** was an outlier, presenting a large positive deviation from the expected value. Excluding this compound, the use of σ° yielded a very good correlation Eq. (1)

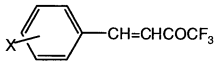
$$-\log IC_{50} = 1.165\ (\pm 0.212)\,\sigma^{\circ} + 3.059\ (\pm 0.083)$$

$$n = 22,\quad r = 0.932,\quad s = 0.137,\quad F = 132 \qquad (1)$$

In Eq. (1) and throughout this paper, n is the number of compounds used for calculations, r is the correlation coefficient and s is the standard deviation. F is the value of the F ratio between the variances of the observed and calculated values. The figures in parentheses are the 95% confidence intervals of the regression coefficients and the intercept. Among various kinds of electronic substituent constants tested, σ° was found to work most effectively in this (σ; $r = 0.919$, σ^{+}; $r = 0.868$) and the following correlations. Addition of a $\log P$ term in linear or parabolic form to Eq. (1) made no improvement to the correlation.

Analyses for a combined data set of mono and polysubstituted BZ (**1**–**28**) were performed by replacing σ° with $\Sigma\sigma^{\circ}$ in the polysubstituted derivatives. Again, a 2-OH-derivative, **24**, presented a large positive deviation. Omitting two 2-OH compounds, **20** and **24**, from the analysis yielded Eq. (2), which was almost equivalent to Eq. (1).

Table 2
Inhibitory potency toward UV-induced mutagenesis in *E. coli* WP2s and physicochemical parameters for 1,1,1-trifluoro-4-phenyl-3-buten-2-ones



TF

Number	Substituent(s)	IC_{50} [a]	log $1/IC_{50}$ [b]	σ° [c]
29	H	0.030 [d]	4.52	0.00
30	2-Cl	0.028	4.55	0.27
31	3-Cl	0.024	4.62	0.37
32	4-Cl	0.016	4.80	0.27
33	3-CN	0.017	4.77	0.62
34	4-CN	0.025	4.60	0.69
35	3-NO_2	0.017	4.77	0.70
36	4-OMe	0.074	4.13	−0.16

[a] μmol mL^{-1}, taken from Ref. [11] unless otherwise described.
[b] IC_{50}: mmol mL^{-1}.
[c] For the reference see the footnote in Table 1.
[d] Ref. [4].

$$-\log IC_{50} = 1.097\ (\pm 0.183) \sum \sigma^{\circ} + 3.089\ (\pm 0.066)$$

$$n = 26, \quad r = 0.930, \quad s = 0.137, \quad F = 154 \qquad (2)$$

As the residuals for **20** and **24** are numerically similar (0.694 and 0.751 for **20** and **24**, respectively), we introduced an indicator variable HB_{2OH} for these compounds, yielding Eq. (3) and showing excellent correlation.

$$-\log IC_{50} = 1.096\ (\pm 0.179) \sum \sigma^{\circ} + 0.722\ (\pm 0.213)\ HB_{2OH} + 3.089\ (\pm 0.065)$$

$$n = 28, \quad r = 0.934, \quad s = 0.134, \quad F = 85.0 \qquad (3)$$

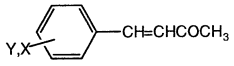
All the terms in Eqs. (1)–(3) were justified at the 99.9% level by the *t*-test. The additional correction term in Eq. (3) is required only for two (**20**, **24**) of the four 2-OH compounds examined. The other 2-OH compounds tested (**25**, **26**) conform to Eq. (2). It appears that intramolecular hydrogen-bonding with the adjacent alkoxy group in **25** and **26** may well occur, impeding intermolecular hydrogen-bonding to the bio-phase that may be the cause of the higher potency shown for **20** and **24**.

It is of interest to notice that the fit of Eqs. (1)–(3) remains unaffected even by inclusion in the data set of *ortho* substituted derivatives. Frequently, in considering the effects of *ortho*-substituents we need to take into account their inductive (field) and steric effects. Accordingly, Fujita and co-workers developed a procedure for correlating reactivity data of a set of *ortho*-substituted derivatives including the unsubstituted parent compound [14],

$$\log k = \rho\sigma_{\mathrm{ortho}} + \delta E_{\mathrm{s}}^{\mathrm{ortho}} + fF_{\mathrm{ortho}} + \mathrm{constant},$$

where, k is the rate or equilibrium constant, E_s and F are the Taft–Kutter–Hansch steric and Swain–Lupton

Table 3
Inhibitory potency toward γ-induced mutagenesis in *S. typhimurium* TA2638 and physicochemical parameters for benzalacetones (BZ)



BZ

Number	Substituent(s)	IC_{50} [a]	log $1/IC_{50}$ [b]	log P [c]	Σ σ° [d]	HB
1	H	0.42	3.38	2.18	0.00	0
2	3-Me	0.18	3.74	2.68	−0.07	0
3	4-Me	0.24	3.62	2.65	−0.12	0
4	4-Et	0.11	3.96	3.26	−0.13	0
10	4-Cl	0.094	4.03	2.80	0.27	0
13	4-Br	0.086	4.07	3.03	0.26	0
16	3-OMe	0.29	3.54	2.27	0.06	0
17	4-OMe	0.38	3.42	2.25	−0.16	0
20	2-OH	0.19	3.72	2.19	−0.13	1
21	4-OH	0.24	3.62	1.86	−0.13	1
37	2-OMe	0.22	3.66	2.42	−0.16	0
38	4-NMe_2	0.27	3.57	2.66	−0.44	0
39	3-OMe-4-OH	0.47	3.33	1.64 [e]	−0.07	0

[a] μmol mL^{-1}, the data were taken from Ref. [4].
[b] mmol mL^{-1}.
[c] Taken from Ref. [12] unless otherwise described.
[d] For the reference see the footnote in Table 1.
[e] Ref. [3].

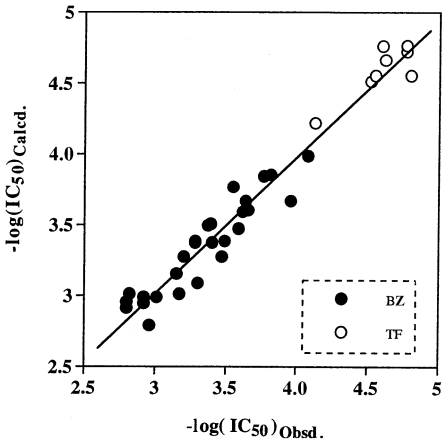


Fig. 2. Relationship between the observed $\log(1/IC_{50})$ and those predicted by Eq. (4). IC_{50}, the concentration of BZ and TF required for the 50% inhibition of UV-induced mutagenis in *E. coli* WP2s.

field effect constants [15,16], respectively and $\sigma_{ortho} = \sigma_{para}$. Subsequently, Charton's inductive substituent constant σ_I [17] has been substituted for *F*. For the compounds under examination in our work, addition of terms in E_s and/or F (σ_I) to Eq. (3), however, made no improvement, suggesting that the polar and steric effects are of minor importance.

Finding a positive coefficient for the electronic term (sigma) suggests that introduction of electron-withdrawing functional groups should enhance potency. A similar effect is evident when the terminal methyl group in the fixed side chain is replaced by the strongly electron-withdrawing trifluoromethyl group. The potency of the TF series was found to be much higher than that for the corresponding BZ series-compound (Table 2). Analyses on the combined data set (BZ and TF series) were performed by including an additional electronic term for TF, $\rho_{TF}\,\sigma^{\circ}_{TF}$, and an indicator variable I_{TF}, as in Eq. (4), leading to an excellent correlation for all the compounds (**1**–**36**).

$$-\log IC_{50} = 1.096\ (\pm 0.183) \sum \sigma^{\circ} + 0.722\ (\pm 0.217)\ HB_{2OH} + 0.511\ (\pm 0.335)\ \sigma^{\circ}_{TF} + 1.330\ (\pm 0.166)\ I_{TF} + 3.089\ (\pm 0.066)$$

$$n = 36, \quad r = 0.978, \quad s = 0.138, \quad F = 172 \qquad (4)$$

Here, I_{TF} takes the value of 1 for the TF series (**29**–**36**) and 0 for the BZ series (**1**–**28**), and the $\Sigma\,\sigma^{\circ}$ and σ°_{TF} terms apply separately to the BZ and TF series, respectively. In Eq. (4), each term was justified at the 99.9% level except for the σ°_{TF} term, which was justified at the 99.6% level. The predictive power of Eq. (4) is shown in Fig. 2.

The QSAR results should provide useful information about the mode of action. First, it is important to note that, in Eq. (4), both of the electronic terms have positive coefficients indicating that the more electron-deficient the reaction centre is, the more easily the reaction proceeds. In previous studies we have demonstrated that an α, β-unsaturated carbonyl system in the side chain is essential for antimutagenicity [3,4]. The antimutagenic activity is also found in a number of naturally occurring and synthetic compounds having an α, β-unsaturated carbonyl group, such as flavonoids, coumarins and dihydrofuranones [9,10,18,19]. It can therefore, be presumed that a nucleophilic attack of bio-component at the electron-deficient site in the α, β-unsaturated carbonyl system is involved in the rate determining or critical step. This reasoning is consistent with the hypothesis proposed by Kakinuma and co-workers who revealed from structure–activity relationship studies of 2(5H)- or 3(2H)-furanones against the UV-induced mutation of *E. coli* that an α, β-unsaturated carbonyl group would react with enzyme SH-groups by a Michael-type reaction [19]. The I_{TF} term introduced to combine the two series (BZ and TF) into one correlation is also likely to express mostly the electronic effect of the terminal CF_3 group. A large positive value of 1.3 as the coefficient seems to reflect a considerable reduction in electron density on the reaction centre due to the strong electron-withdrawing property of CF_3. Eq. (4) indicates a propensity for the electronic effect of the ring substituents in the BZ series to be more significant than for the TF series as is indicated by a larger coefficient of the σ term for BZ(1.1) than for TF (0.5). A possible reasoning would be that, for the TF series, electron density on the reaction centre is sufficiently low in the unsubstituted parent compound **29** to render further electronic assistance from the ring-substituent less important. The positive contribution of the HB_{2OH} term may suggest that hydrogen-bonding formation between 2-OH group and bio-phase might accelerate the critical reaction by holding the test compound in a preferable orientation for the nucleophilic attack.

Prior to analyses, we had expected that the log *P* parameter would be a dominant factor in inhibiting mutagenicity because drugs must penetrate through the membrane to the cell to demonstrate activity. However, the term for log *P* was found to be insignificant in all the correlations. This is in sharp contrast to the results with γ-irradiation as described below. The fact that the log *P* term is statistically insignificant probably suggests that the rate of permeation is not the rate determinant for the reaction of the conjugated carbonyl group with a nucleophile, or that some concomitant hydrophobic interactions may cancel the hydrophobic contribution related to the permeability.

3.2. γ-Induced mutagenesis in S. typhimurium TA2638

Analyses for inhibitory potency against γ-induced mutagenesis in *S. typhimurium* TA2638 were performed on the compounds listed in Table 3 where the parameters used for analyses are also given. It should be noted that compounds which exhibited no or very low activity in UV-induced mutagenesis, **37**–**39**, have inhibitory effect toward γ-induced mutagenesis. Since the assay using TA2638 strain is more troublesome than that using WP2*uvrA* strain due to high sensitivity of TA2638 toward oxidative agents, the assay with TA2638 was carried out on fewer compounds by selecting those that showed poor effects in the WP2*uvrA* assay. From preliminary analyses [4], log *P* is shown as the most effective descriptor ($r = 0.79$) among various candidates tested. Hydrogen-bonding was also found to play an important role and an attempt to add an indicator variable *HB* as a hydrogen-bonding parameter defined as shown in Table 3 provided an improved correlation ($r = 0.88$). Examination of the residuals showed electron-donating substituents tended to overestimate the activity, suggesting the presence of the electronic effects. Thus, Eq. (5) with addition of a σ° term improved the correlation and provided the best statistical fit (Fig. 3).

$$-\log \mathrm{IC50} = 0.471\ (\pm 0.132) \log P + 0.498\ (\pm 0.297)\ \sigma^\circ + 0.282\ (\pm 0.158)\ HB + 2.500\ (\pm 0.341)$$
$$n = 13, \quad r = 0.954, \quad s = 0.082, \quad F = 30.2 \qquad (5)$$

Here, all the terms were justified at better than 99.5% level by the *t*-test. In Eq. (5), both 2- and 4-OH derivatives incapable of intramolecular hydrogen-bonding are classified as in the hydrogen-bonding group ($HB = 1$) on the basis of statistical considerations. It is presumed, therefore, that different types of hydrogen-bonding effects operate in the cases of UV- and γ-irradiation mutagenesis. It should be noted that the hydrophobic factor, expressed by log *P*, is effective in γ-induced mutagenesis but not in UV-induced mutagenesis. The cell membrane in TA2638 is easier for chemicals to permeate due to the *rfa* mutation. Since permeability is thought to be correlated with log *P*, finding a positive coefficient of log *P*, 0.47, in Eq. (5) suggests that more lipophilic compounds could have higher potency because they are more permeable than less lipophilic compounds.

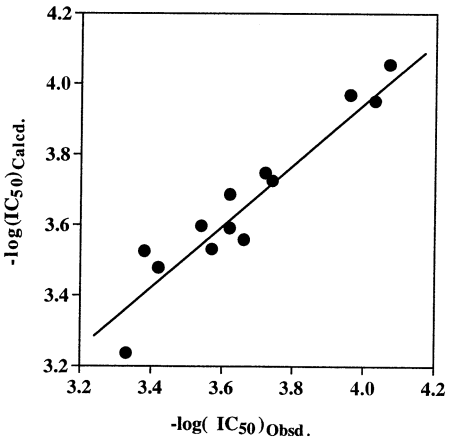


Fig. 3. Relationship between the observed $\log(1/\mathrm{IC}_{50})$ and those predicted by Eq. (5). IC_{50}, the concentration of BZ required for the 50% inhibition of γ-induced mutagenis in *S. typhimurium* TA2638.

In this study, the antimutagenic activities against UV- and γ-induced mutagenesis for BZ and TF were analyzed quantitatively in terms of physicochemical parameters. The derived results manifest the structural requirements for maximal potency. In both cases, electron-withdrawing substituents and phenolic hydroxyl substituents free from intramolecular hydrogen-bonding are preferred. Thus it may be deduced that in the critical process, a nucleophilic site in the bio-phase would react with the conjugated carbonyl system in the test compounds, which process would be facilitated by electron-withdrawing substituents. In γ-induced mutagenesis, more lipophilic substituents are also expected to increase the potency. The reason why the hydrophobic effects are not involved in the correlations for UV-irradiation is not explicit at present. Among numerous QSARs of mutagenic and carcinogenic chemicals so far reported, only a few examples lack hydrophobic term(s) [5–7]. Elucidation of this problem will be needed, not only for better understanding of the mode of action, but also for more accurate prediction of activity.

Acknowledgements

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