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Quantitative Structure–Activity Relationships and Mixture Toxicity of Substituted Benzaldehydes to *Photobacterium phosphoreum*

B. Wang · G. Yu · H. Hu · L. Wang

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Substituted benzaldehydes, widely used as intermediates to synthesize pesticides and medicines, are being introduced into the environment (Dai et al., 2001). Aldehydes are known to be bioreactive electrophiles that may cause higher toxicity than narcotic chemicals (Dimitrov et al., 2004). Dai et al. (2001) have conducted some research on the toxicity of benzaldehydes to *Daphnia magna*. Toxicity testing has usually focused on the effects of single chemicals. However, organisms in the real environment are usually exposed to mixtures of various chemicals rather than single substances, so more attention should be paid to the combined effects caused by mixtures of substituted benzaldehydes.

Quantitative structure–activity relationships (QSAR) have been a useful tool for the prediction of the toxicity of single chemicals. Recently, QSARs have also been extended to study the toxicity of chemical mixtures (Nirmalakhandan et al., 1994; Xu and Nirmalakhandan 1998). Now some physiochemical descriptors of mixtures based on experiment or calculation have been used to predict mixture toxicities (Huang et al., 2003; Lin et al., 2002, 2003a, b, 2005), although these predictions have usually focused on narcotic chemicals. The prediction of the toxicity of mixture of reactive chemicals by QSAR based on mixture physiochemical descriptors is still unresolved. An alternative method is to predict mixture toxicities by a combination of QSAR models of single chemicals and sound assumptions of the mechanism of mixture toxicity, such as concentration addition (Altenburger et al., 2000) or independent action (Backhaus et al., 2000a). Concentration addition is based on the idea that mixture components act in a similar manner. The concept of concentration addition has been widely used to assess the combined effects of similarly acting chemicals (Altenburger et al., 2000; Faust et al., 2001; Backhaus et al., 2000b).

The purpose of this work was to determine experimentally the single and mixture toxicities of 22 substituted benzaldehydes to *Photobacterium phosphoreum*, and analyze, model and predict the mixture toxicities of substituted benzaldehydes based on QSAR models and the concept of concentration addition.

B. Wang · G. Yu (✉) · H. Hu
Department of Environmental Sciences and Engineering,
POPs Research Centre, Tsinghua University, Beijing 100084,
P. R. China
e-mail: yg-den@tsinghua.edu.cn

L. Wang
State Key Laboratory of Pollution Control and Resource Reuse,
School of Environment, Nanjing University,
Nanjing 210093, P.R. China

Materials and Methods

The tested substituted benzaldehydes, listed in Table 1, were synthesized by the College of Chemistry and Chemical Engineering of Nanjing University. The purities of all the tested substituted benzaldehydes were greater than 99%.

Photobacterium phosphoreum (T3 mutation) was supplied in the form of freeze-dried powder by the Institute of Soil Science, Chinese Academy of Sciences, Nanjing, P. R. China. It was reconstituted and maintained on agar slants at 4°C. Bioluminescence assays were performed using diluted bacteria that had been cultured at 20°C in yeast/tryptone salts/glycerol broth for 12 h.

The MICROTOX test instrument (toxicity analyzer model DXY-2), made by the Institute of Soil Science,

Table 1 Acute toxicities (15 min EC_{50}) of 22 substituted benzaldehydes to *Photobacterium phosphoreum*

No.	Chemicals	CAS no.	Log ($1/EC_{50}$) (mol/L)[1]	
			Obs. (95% CI)	Cal.
1	3-chlorobenzaldehyde	587-04-2	3.753 (3.652~3.855)	3.661
2	4-chlorobenzaldehyde	104-88-1	3.671 (3.597~3.745)	3.713
3	3,4-dichlorobenzaldehyde	6287-38-3	4.155 (4.096~4.212)	4.193
4	4-bromobenzaldehyde	1122-91-4	3.881 (3.807~3.954)	3.982
5	2,5-dibromobenzaldehyde	74553-29-0	4.442 (4.302~4.580)	4.315
6	5-bromo-2-hydroxybenzaldehyde	1761-61-1	4.529 (4.472~4.587)	4.534
7	3-bromo-4-hydroxybenzaldehyde	2973-78-6	4.584 (4.485~4.683)	4.691
8	5-bromo-2-methoxybenzaldehyde	25016-01-7	4.445 (4.408~4.482)	4.450
9	2,5-dihydroxybenzaldehyde	1194-98-5	3.401 (3.307~3.502)	3.315
10	3,4-dihydroxybenzaldehyde	139-85-5	3.740 (3.596~3.881)	3.552
11	4-hydroxy-3-methoxybenzaldehyde	121-33-5	3.375 (3.215~3.532)	3.597
12	4-hydroxy-3-ethoxybenzaldehyde	121-32-4	3.215 (3.154~3.277)	3.214
13	4-methoxybenzaldehyde	123-11-5	3.682 (3.619~3.743)	3.699
14	4-ethoxybenzaldehyde	10031-82-0	4.070 (3.924~4.209)	3.805
15	2,5-dimethoxybenzaldehyde	93-02-7	3.327 (3.212~3.445)	3.466
16	3,4-dimethoxybenzaldehyde	120-14-9	3.344 (3.162~3.523)	3.605
17	3-methoxy-4-ethoxybenzaldehyde	120-25-2	4.010 (3.897~4.116)	3.772
18	3,4,5-trimethoxybenzaldehyde	86-81-7	3.037 (2.949~3.120)	3.109
19	4-isopropoxybenzaldehyde	18962-05-5	3.509 (3.438~3.576)	3.512
20	3-phenoxybenzaldehyde	39515-51-0	3.986 (3.911~4.056)	4.011
21	isopropyl, 4-formylphenoxy acetate	3-42-0	3.802 (3.727~3.875)	3.750
22	4-dimethylaminobenzaldehyde	100-10-7	4.566 (4.497~4.634)	4.582

[1] Obs. = Observed values, 95% CI = 95% confidence interval; Cal. = Calculated by Eq. (3)

Chinese Academy of Sciences, Nanjing, P. R. China, was used. Toxicity was measured with the DXY-2 by quantifying the decrease in light emission from the bacteria as a result of exposure to the tested chemicals in 3% NaCl solution for 15 min. The decrease in light emission was measured at eight different concentrations, each tested in triplicate. Based on the decrease in light emission, the half effective concentration (EC_{50}) was calculated using the probit method. The toxicities of 22 single chemicals were measured. The toxicities of mixtures composed of different chemicals at certain toxic unit ratios were also tested in a similar manner to the single chemical tests.

The logarithm of the 1-octanol-water partition coefficients (log K_{ow}) was estimated using the KOWWIN v. 1.67 software. Quantum chemistry descriptors were calculated using the AM1 method (Dewar et al. 1985) in the MOPAC 2000 software. A total of 16 MOPAC descriptors reflecting the overall character of the substituted benzaldehydes were calculated in this study: molecular weight (MW), molecular surface (S in Å^2), the molecular volume (V_m in Å^3), the average molecular polarizability (α in au), the dipole moment (μ in D), the final heat of formation (HOF in kJ/mol), the ionization potential (IP in eV), the energy of the highest occupied molecular orbital (E_{HOMO} in eV), the energy of the lowest unoccupied molecular orbital (E_{LUMO} in eV), the total energy (TE in eV), the electronic energy (EE in eV), the core–core repulsion energy (CCR in eV), dielectric energy (DE in eV), the most positive net atomic charge on a hydrogen atom (qH^+ in acu), the most negative net atomic charge on an atom (q^- in acu), the most positive net atomic charge on an atom (q^+ in acu). Only the parameters that are selected into QSAR models are listed in Table 2.

If the toxicity mechanism of the mixture components is similar, the concept of concentration addition can be used to predict their mixture toxicity. Consequently, the half effective concentration of mixtures (EC_{50mix}) can be predicted by the following equation using the concept of concentration addition.

$$EC_{50mix} = \left[\sum_{i=1}^{n} \frac{p_i}{EC_{50i}}\right]^{-1} \quad (1)$$

Table 2 The parameters that are selected in the QSAR models

No.	log K_{ow}	MW	HOF	q^-	CCR
1	2.260	140.570	–116.555	–0.475	–418.479
2	2.100	140.570	–116.906	–0.476	–418.000
3	3.000	175.020	–139.706	–0.470	–536.811
4	2.600	185.020	–68.200	–0.472	–406.340
5	3.350	263.920	–29.285	–0.454	–505.520
6	2.900	201.020	–276.765	–0.482	–481.781
7	1.830	201.020	–270.608	–0.485	–483.116
8	2.680	215.050	–239.108	–0.478	–448.877
9	1.530	138.120	–495.900	–0.477	–452.955
10	1.090	138.120	–496.758	–0.482	–461.899
11	1.210	152.150	–461.562	–0.484	–393.400
12	1.580	166.180	–467.635	–0.473	–396.826
13	1.760	136.150	–266.244	–0.487	–351.674
14	2.280	150.180	–290.057	–0.487	–347.138
15	1.910	166.180	–423.076	–0.478	–390.901
16	1.220	166.180	–429.296	–0.480	–400.649
17	1.630	180.210	–450.662	–0.484	–376.473
18	1.390	196.200	–576.905	–0.468	–401.516
19	2.700	164.210	–301.163	–0.484	–282.550
20	3.380	198.220	–99.915	–0.473	–374.536
21	1.880	222.240	–684.442	–0.483	–362.480
22	1.810	149.190	–71.930	–0.504	–264.620

where, EC_{50mix} is the total concentration of the mixture provoking a 50% effect, EC_{50i} denotes the half effective concentration of the single chemical i and p_i denotes the molar fraction of component i in the mixture.

A stepwise linear regression analysis was performed with SPSS v. 13.0. The linear least-squares method was used to give the best fit of the predicted log $(1/EC_{50})$ values to the observed data. Model adequacy was measured by the squared correlation coefficient adjusted for degrees of freedom (r^2_{adj}), the standard error (SE), the Fisher criterion (F) and the significance level (p).

Results and Discussion

The observed toxicity data of 22 single substituted benzaldehydes to *Photobacterium phosphoreum* are listed in Table 1. 95% confidence intervals of observed log $(1/EC_{50})$ are also presented. log K_{ow} was used to model toxicity. The following equation was obtained:

$$\log\,(1/EC_{50}) = 0.377\,\log K_{ow} + 3.052 \qquad (2)$$

$n = 22$, $r^2_{adj} = 0.270$, SE = 0.401, $F = 8.774$, $p = 0.008$

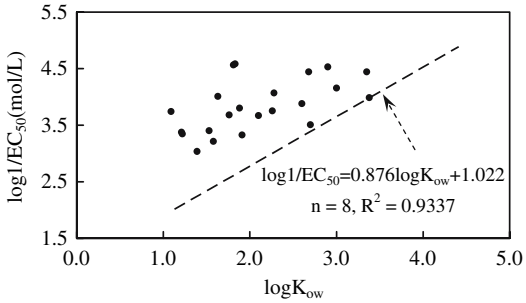

Fig. 1 Scatter plot of log $(1/EC_{50})$ versus log K_{ow} of substituted benzaldehydes. The dashed line represents the log K_{ow}-dependent QSAR model of some narcotic halogenated benzenes, presented for comparison. (Data from Lin et al. 2002)

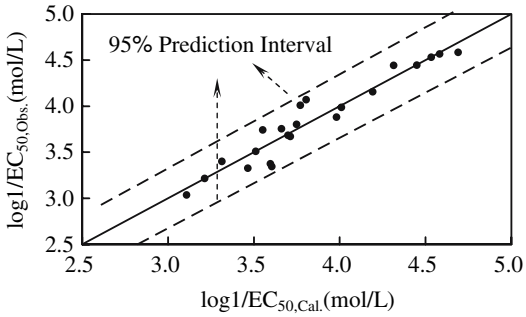

Fig. 2 Plot of observed log $(1/EC_{50})$ versus log $(1/EC_{50})$ calculated by Eq. (3)

Eq. (2) shows a very poor quality of log K_{ow}-dependent model, which indicates that liquid–biomembrane partition is not the main toxicity mechanism of substituted benzaldehydes. Figure 1 shows that their toxicities are higher than the baseline toxicities predicted from a log K_{ow}-dependent QSAR model of narcotic chemicals, which proves substituted benzaldehydes to be reactive chemicals.

Stepwise linear regression was performed between log $(1/EC_{50})$ and the 16 quantum chemistry descriptors mentioned above, leading to the following equation:

$$\begin{aligned}\log\,(1/EC_{50}) = {} & 1.535\times10^{-3}HOF \\ & + 9.343\times10^{-3}MW - 45.534q^- \\ & - 3.71\times10^{-3}CCR - 20.634\end{aligned} \qquad (3)$$

$n = 22$, $r^2_{adj} = 0.903$, SE = 0.146, $F = 49.610$, $p < 0.001$

The quality of Eq. (3) is very good. Figure 2 shows that all observed log $(1/EC_{50})$ are in the 95% prediction interval of Eq. (3). The toxicity data calculated using Eq. (3) coincide well with observed values. Leave-one-out cross-validation was conducted. The correlation coefficient of cross-validation r^2_{loo} was 0.881, which demonstrates the excellent predictive power of Eq. (3). The values of the t-test (Table 3) indicate that the most negative net atomic

Table 3 Fitting results of Eq. (3) for log ($1/EC_{50}$)

Independent variable	Coefficient	SE	*t*-value	Sig. level
constant	–20.634	2.470	–8.354	<0.001
HOF	1.535×10^{-3}	<0.001	8.830	<0.001
MW	9.343×10^{-3}	0.001	8.324	<0.001
q^-	–45.534	4.697	–9.694	<0.001
CCR	-3.17×10^{-3}	0.001	–6.012	<0.001

charge on an atom (q^-) plays a dominant role in the toxicities of substituted benzaldehydes. The most negative net charge (q^-) appears on the oxygen atom of the aldehyde group of the substituted benzaldehydes.

Aldehydes have the ability to produce a toxic effect as electrophiles via covalent bond rearrangement, forming Schiff bases with amino groups in biological macromolecules (Dimitrov et al., 2004). Such a specific mechanism implies the reactivity of aldehydes. As q^- becomes more negative, i.e., the oxygen atom of the carbonyl group becomes more negative, the electrophilic nature of the carbonyl group of benzaldehydes increases, and it is easier for benzaldehydes to form Schiff bases with the amino groups of the enzymes of *Photobacterium phosphoreum*, increasing their toxicity. The final heat of formation (HOF), molecular weight (MW) and core–core repulsion energy (CCR) are also important to the toxicity of substituted benzaldehydes. HOF and CCR reflect the stability of a molecule (Bello-Ramírez et al., 2002). The less stable the molecule is, the more easily the chemical reacts with organisms, and the higher the toxicity of the chemical. The sign of MW shows that toxicity increases with the molecular size of benzaldehydes.

In this study, chemicals 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 were chosen to conduct mixture toxicity experiments. The compositions and observed toxicities of mixtures are given in Table 4. Here, two methods were used to calculate the mixture toxicities of benzaldehydes. The first method calculates the half effective concentrations of mixtures with Eq. (1) using the observed single chemical toxicity values. The second method also uses Eq. (1) but based on the single chemical toxicity values calculated by Eq. (3). The calculated values are listed in Table 4.

The relationship between the observed log ($1/EC_{50\text{mix}}$) and log ($1/EC_{50\text{mix}}$) values calculated by method 1 is given in Fig. 3 and Eq. (4).

$$\log\left(1/EC_{50\text{mix,Obs.}}\right) = 0.973\,\log\left(1/EC_{50\text{mix,Cal. 1}}\right) + 0.100 \quad (4)$$

$n = 60$, $r^2_{\text{adj}} = 0.943$, SE = 0.060, $F = 979.544$, $p < 0.001$

From the high quality of Eq. (4) and Fig. 3, it can be seen that the calculated values coincided with the observed values very well. Figure 3 shows that the 95% prediction interval of Eq. (4) is narrow and all observed values fall in this interval. The concept of concentration addition can be successfully used to predict the mixture toxicities of substituted benzaldehydes that have a similar mode of action. Our previous studies (Wang et al. 2004) and some other studies (Chen et al., 1996; Nirmalakhandan et al., 1997) have shown that the mixture toxicities of narcotic chemicals can be predicted by concentration addition. This study shows that this is also true for mixtures of reactive chemicals with a similar mode of action. Backhaus et al. (2000b) also reached a similar conclusion in their study on mixture toxicities of quinolones. Whether it is a binary mixture or a multicomponent mixture, the mixture toxicity mechanism of substituted benzaldehydes is concentration addition. In a mixture composed of a large number of acting chemicals at a certain toxic unit ratio, the concentrations of the individual components is so low that their specific toxic effects may not be apparent if applied singly. However, their fractional toxicities will remain in the mixture, and the concentration addition effect of the individual components will cause the total mixture toxicity. However, in this study, we focused on the acute joint toxicities of mixtures. Whether this also holds true for chronic joint toxicities should be investigated in future research.

The relationship between th eobserved log ($1/EC_{50\text{mix}}$) and log ($1/EC_{50\text{mix}}$) values calculated by method 2 is given by Fig. 4 and Eq. (5).

$$\log\left(1/EC_{50\text{mix,Obs.}}\right) = 0.919\,\log\left(1/EC_{50\text{mix,Cal.2}}\right) + 0.274 \quad (5)$$

$n = 60$, $r^2_{\text{adj}} = 0.893$, SE = 0.082, $F = 494.275$, $p < 0.001$

From Eq. (5) and Fig. 4, it can be seen that the calculated values coincide well with the observed values. With the combination of the QSAR method and the concept of concentration addition, the mixture toxicity of substituted benzaldehydes with similar toxicity mechanisms can be successfully predicted.

Thus, for the vast majority of environmental pollutants whose toxicity data and knowledge on mechanisms of action are lacking, QSAR can be used to predict the toxicities of single chemicals and classify chemicals into groups of similarly acting ones. Then mixture toxicity can be predicted with the sound assumption that the joint toxicity mechanism applies. The quality of Eq. (5) is determined by the quality of Eqs. (3) and (4). This means that a good QSAR model of single chemical toxicities and a sound assumption of joint toxicity mechanism are necessary to predict the joint toxicity of chemical mixtures. We may be able to predict joint toxicities of chemical mixtures better if we obtain a better QSAR model that can predict the toxicities of single chemicals more accurately.

Table 4 The observed and calculated half effective concentrations of mixtures composed of substituted benzaldehydes

No.	Mixture components	Toxic unit ratio	Log ($1/EC_{50mix}$) (mol/L)[1]		
			Obs. (95% CI)	Cal. 1	Cal. 2
1	2:4	2:1	3.675 (3.541–3.808)	3.730	3.793
2		1:1	3.701 (3.575–3.825)	3.763	3.836
3		1:2	3.877 (3.788–3.964)	3.799	3.881
4	6:8	2:1	4.424 (4.328–4.517)	4.499	4.504
5		1:1	4.441 (4.296–4.583)	4.485	4.490
6		1:2	4.539 (4.470–4.606)	4.472	4.476
7	10:12	2:1	3.428 (3.342–3.512)	3.489	3.372
8		1:1	3.450 (3.315–3.584)	3.402	3.318
9		1:2	3.380 (3.255–3.503)	3.331	3.276
10	14:16	2:1	3.609 (3.431–3.785)	3.683	3.669
11		1:1	3.521 (3.382–3.659)	3.570	3.643
12		1:2	3.522 (3.423–3.618)	3.481	3.626
13	18:20	2:1	3.236 (3.166–3.306)	3.189	3.246
14		1:1	3.241 (3.090–3.392)	3.291	3.341
15		1:2	3.351 (3.190–3.511)	3.426	3.467
16	2:6:10	2:1:1	3.716 (3.547–3.885)	3.797	3.782
17		1:1:1	3.927 (3.809–4.043)	3.849	3.813
18		1:1:2	3.877 (3.761–3.994)	3.819	3.750
19	10:14:18	2:1:1	3.518 (3.337–3.701)	3.466	3.344
20		1:1:1	3.299 (3.136–3.459)	3.403	3.301
21		1:1:2	3.348 (3.220–3.473)	3.279	3.227
22	4:8:12	2:1:1	3.574 (3.406–3.742)	3.644	3.698
23		1:1:1	3.649 (3.513–3.783)	3.587	3.624
24		1:1:2	3.425 (3.339–3.507)	3.460	3.488
25	12:16:20	2:1:1	3.423 (3.262–3.580)	3.353	3.439
26		1:1:1	3.453 (3.337–3.566)	3.411	3.522
27		1:1:2	3.465 (3.372–3.558)	3.499	3.590
28	2:8:10:16	1:2:1:1	3.786 (3.708–3.864)	3.735	3.784
29		1:1:1:1	3.690 (3.611–3.768)	3.655	3.715
30		1:1:2:1	3.572 (3.485–3.657)	3.671	3.691
31	4:6:12:14	1:2:1:1	3.707 (3.655–3.754)	3.752	3.736
32		1:1:1:1	3.643 (3.591–3.692)	3.670	3.649
33		1:1:2:1	3.589 (3.495–3.681)	3.533	3.516
34	2:6:14:18	1:2:1:1	3.630 (3.562–3.693)	3.593	3.580
35		1:1:1:1	3.609 (3.552–3.665)	3.506	3.488
36		1:1:2:1	3.609 (3.487–3.728)	3.574	3.517
37	4:8:16:20	1:2:1:1	3.774 (3.694–3.851)	3.818	3.910
38		1:1:1:1	3.761(3.678–3.842)	3.743	3.853
39		1:1:2:1	3.572 (3.455–3.687)	3.628	3.773
40	2:4:10:12:18	1:2:1:1:1	3.458 (3.402–3.512)	3.438	3.470
41		1:1:1:1:1	3.430 (3.338–3.515)	3.386	3.402
42		1:1:1:2:1	3.412 (3.318–3.501)	3.352	3.366
43	6:8:14:18:20	1:2:1:1:1	3.798 (3.730–3.864)	3.696	3.682
44		1:1:1:1:1	3.572 (3.455–3.689)	3.630	3.612
45		1:1:1:2:1	3.404 (3.331–3.473)	3.458	3.457

Table 4 continued

No.	Mixture components	Toxic unit ratio	Log ($1/EC_{50mix}$) (mol/L)[1]		
			Obs. (95% CI)	Cal. 1	Cal. 2
46	2:4:6:10:16:20	1:2:1:1:1:1	3.811 (3.722–3.895)	3.750	3.817
47		1:1:1:1:1:1	3.777 (3.696–3.853)	3.732	3.793
48		1:1:1:1:2:1	3.725(3.611~3.837)	3.650	3.746
49	2:6:8:12:14:16:18	1:2:1:1:1:1:1	3.591(3.523~3.658)	3.527	3.563
50		1:1:1:1:1:1:1	3.421(3.352~3.486)	3.475	3.515
51		1:1:1:1:1:2:1	3.507(3.417~3.581)	3.456	3.531
52	4:6:8:10:12:14:16:18	1:1:2:1:1:1:1:1	3.501 (3.428~3.572)	3.561	3.583
53		1:1:1:1:1:1:1:1	3.541 (3.419~3.603)	3.515	3.540
54		1:1:1:1:1:2:1:1	3.501 (3.447~3.554)	3.551	3.552
55	4:6:8:10:12:14:16: 18:20	1:1:2:1:1:1:1:1:1	3.546 (3.462~3.627)	3.588	3.611
56		1:1:1:1:1:1:1:1:1	3.596 (3.533~3.655)	3.548	3.573
57		1:1:1:1:1:1:2:1:1	3.459 (3.365~3.548)	3.523	3.578
58	2:4:6:8:10 :12:14: 16:18:20	1:1:2:1:1:1:1:1:1:1	3.648 (3.588~3.706)	3.595	3.620
59		1:1:1:1:1:1:1:1:1:1	3.591 (3.503~3.671)	3.559	3.586
60		1:1:1:1:1:1:1:2:1:1	3.458 (3.341~3.562)	3.534	3.588

[1] Obs. = Observed values, 95% CI = 95% confidence interval; Cal. 1 = Calculated by method 1, Cal. 2 = Calculated by method 2

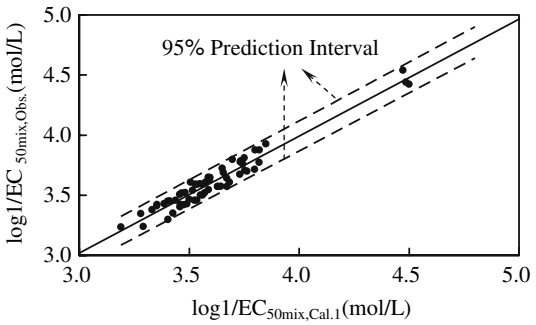

Fig. 3 Plot of observed log ($1/EC_{50mix}$) versus log ($1/EC_{50mix}$) calculated by method 1

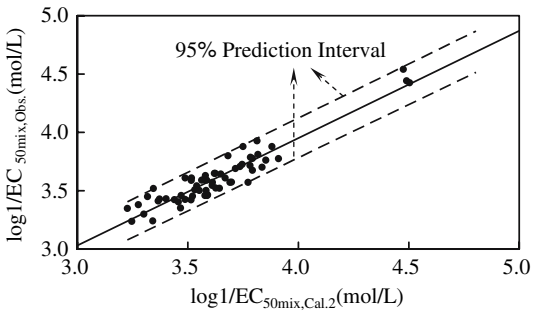

Fig. 4 Plot of observed log ($1/EC_{50mix}$) versus log ($1/EC_{50mix}$) calculated by method 2

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