

## Quantitative Structure–Fungitoxicity Relationships of Some Monohydric Alcohols

EUGENE SEBASTIAN J. NIDIRY<sup>†</sup>

Indian Institute of Horticultural Research, Hessaraghatta Lake P.O., Bangalore 560 089, India

The fungitoxicity data of some monohydric alcohols on the mycelial growth inhibition of *Colletotrichum gloeosporioides* were subjected to quantitative structure–activity relationship (QSAR) studies. The very large variation in the median effective concentrations ranging from >24000 mg/L [pEC<sub>50</sub> (mol/L) = 0.11] in the case of methanol to <100 mg/L [pEC<sub>50</sub> (mol/L) = 3.27] in the case of citronellol was found to depend mainly on changes in calculated partition coefficients (CLogP) of the compounds. The other three factors that affected the variation in fungitoxicity are the number of hydrogen atoms on the carbon bearing the hydroxyl group ( $N_H$ ), which determines the class of the alcohol to be primary, secondary, or tertiary, the number of double bonds ( $N_{=}$ ), and the branching of the alkyl moiety. Because many compounds in the set under study belonged to homologous series, there was a collinearity between CLogP values and Kier's molecular connectivity values ( $\chi$ ), which are usually used as branching indices. The problem of collinearity between CLogP values and branching indices was overcome by taking the relative molecular connectivity ( $\chi_{rel}$ ), which is defined as the ratio of molecular connectivity of the alcohol under consideration to the molecular connectivity of the corresponding straight-chain primary alcohol with the same number of carbon atoms. Apart from the excellent correlations obtained in the equations, the credibility of the QSAR model could also be demonstrated by its application to published data taken from the literature.

**KEYWORDS:** Monohydric alcohols; fungitoxicity; *Colletotrichum gloeosporioides*; quantitative structure–activity relationships; calculated partition coefficient; relative molecular connectivity; class of alcohol; double bonds

### INTRODUCTION

Monohydric alcohols are widespread in nature. They are produced by bacteria, fungi, plants, and animals. They exhibit varied biological activities. Many simple monohydric alcohols contribute to the pleasures of natural flavors and fragrances (1). Because many of them are found to exhibit antibacterial and antifungal properties, they must be contributing to the defense mechanisms of the organisms that produce them. Apart from methanol, which is used as a seed dressing agent, some chlorinated alcohols are used in plant disease management (2). Structure–fungitoxicity relationships of some C6 and C9 alcohols have been reported (3), and structure–fungitoxicity relationships of some monoterpene alcohols and mushroom alcohols have been reported from this institute (4–6).

A survey of the literature showed only a few studies on the quantitative structure–activity relationships (QSAR) of monohydric alcohols and their fungitoxicity. In the first study, the variation in fungitoxicity of five alcohols was correlated with changes in the partition coefficient (7). Subsequently, the variation in fungitoxicity of 25 alcohols was separately correlated with changes in molecular negentropy, partition coefficient, and molecular connectivity (8, 9), but there was

collinearity between all of these parameters. Thus, if we presume that change in the partition coefficient, the most extensively used and easily computable parameter, is an important factor for determining the variation in fungitoxicity of monohydric alcohols, it can be concluded that the effects of factors other than the partition coefficient have not been distinctly understood in a quantitative way. In the present study, the fungitoxicity data of a series of monohydric alcohols that inhibit the mycelial growth of *Colletotrichum gloeosporioides* on potato-dextrose–agar (PDA) medium were subjected to QSAR analysis. Attempts have been made to distinctly understand the effects of factors other than the calculated partition coefficient.

### MATERIALS AND METHODS

The percent mycelial growth inhibition of *C. gloeosporioides* exhibited by compounds at five different concentrations were determined by poisoned food technique, each treatment being replicated twice (10), and the median effective concentrations (EC<sub>50</sub>) were determined by probit analysis (11). The EC<sub>50</sub> (mg/L) values thus obtained were converted to molar concentrations, and the pEC<sub>50</sub> (mol/L) values equivalent to negative logarithms of EC<sub>50</sub> (mol/L) were taken for QSAR studies. The fungitoxicity of 14 compounds, namely, 1-butanol, 1-pentanol, 1-hexanol, 1-octanol, 2-methylpropanol, 3-methylbutanol, citronellol, geraniol, menthol, neomenthol, 1-octen-3-ol, linalool, benzyl alcohol, and phenyl ethyl alcohol, were reported in

<sup>†</sup> E-mail nidiry@yahoo.co.in.

**Table 1.** Fungitoxicity Data of Monohydric Alcohols on the Mycelial Growth Inhibition of *C. gloeosporioides*<sup>a</sup>

Ser ial No	Name of the compound	Structure	EC <sub>50</sub> (mg/L) (±S.E)	pEC <sub>50</sub> (moles/L) (±S.E)
(i)	(ii)	(iii)	(iv)	(v)
1.	Methanol		24687(±1063)	0.11(±0.02)
2.	Ethanol		17683(±769)	0.42(±0.02)
3.	1-Propanol		8979(±248)	0.83(±0.02)
4.	1-Butanol		3694(±205)	1.30(±0.02)
5.	1-Pentanol		2129(±90)	1.62(±0.02)
6.	1-Hexanol		1271(±43)	1.92(±0.01)
7.	1-Heptanol		546(±22)	2.33(±0.02)
8.	1-Octanol		298(±14)	2.64(±0.02)
9.	1-Decanol		112(±4)	3.15(±0.02)
10	Cetyl alcohol*		>1200	<2.28
11	Stearyl alcohol*		>225	<2.90
12	2-Methyl propanol		8205(±580)	0.96(±0.03)
13	3-Methyl butanol		3713(±237)	1.38(±0.02)
14	Geraniol		100(±10)	3.19(±0.04)
15	Citronellol		84(±7)	3.27(±0.04)
16	Benzyl alcohol		1181(±91)	1.96(±0.04)
17	Phenyl ethyl alcohol		1000(±58)	2.09(±0.03)
18.	2-Propanol		18175(±910)	0.52(±0.02)
19.	(-)-Menthol		452(±25)	2.54(±0.02)
(i)	(ii)	(iii)	(iv)	(v)
20.	(+)-Neomenthol		488(±29)	2.51(±0.02)
21.	1-Octen-3-ol		1286(±37)	2.00(±0.01)
22	Tertiary butyl alcohol		17106(±558)	0.64(±0.02)
23.	Linalool		1090(±74)	2.15(±0.03)

<sup>a</sup> EC<sub>50</sub> = median effective concentration (mg/L) for mycelial growth inhibition of *C. gloeosporioides*. S.E = standard error. pEC<sub>50</sub> (mol/L) = negative logarithm of median effective molar concentration. \*, EC<sub>50</sub> in the cases of cetyl alcohols and stearyl alcohol could not be calculated because of their poor solubility in acetone, which was used to dissolve the compounds before incorporation into the medium.

the earlier studies (4–6). Another 9 compounds were additionally included in the present study. In all cases, commercially available compounds were taken for the study. The data are presented in **Table 1**.

Although all compounds in **Table 1** are monohydric alcohols, they do differ structurally and can be grouped into different categories for an in-depth understanding of structure–activity relationships. Compounds **1** to **11** are aliphatic saturated straight-chain primary alcohols. Compounds **12** and **13** are aliphatic saturated branched primary alcohols. Thus, compounds **1–13** can be categorized as saturated primary alcohols. Compounds **14** and **15** are aliphatic unsaturated branched primary alcohols. Thus, compounds **1–15** can be categorized as aliphatic primary alcohols. Compounds **16** and **17** are aromatic primary alcohols. Thus, compounds **1–17** can be categorized as primary alcohols. In the set of 23 monohydric alcohols, compounds **18–21** are secondary alcohols and compounds **22** and **23** are tertiary alcohols.

Exclusion of compounds **14–17**, **21**, and **23** gives another category, which includes only aliphatic saturated alcohols.

**Calculated Partition Coefficients (CLogP).** Partition coefficients (log *P* values) of many compounds mentioned in the study have been experimentally determined by different workers, and there are slight variations in the reported values. However, if one gives importance to the predictive values of equations to be developed in QSAR studies, it is always better to take calculated values of partition coefficients. In view of this, calculated partition coefficients (CLogP) of all alcohols mentioned in the present study were computed by the fragment method of Rekker described by Hansch and Leo, taking the standard value of methanol as  $-0.77$  from the literature (12).

Thus, the following formulas were used in the calculation of partition coefficients for different types of alcohols:

for saturated alcohols

$$\text{CLogP}_{\text{saturated alcohol}} = \log P_{\text{methanol}} + (n_{\text{H}} - 4)f_{\text{H}} + (n_{\text{C}} - 1)f_{\text{C}} + (n_{\text{b}} - 1)f_{\text{b}} \quad (\text{i})$$

In eq i the numerical value of log *P*<sub>methanol</sub> is taken as  $-0.77$ , *n*<sub>H</sub> is the total number of hydrogen atoms in the molecule, *n*<sub>C</sub> is the total number of carbon atoms in the molecule, *f*<sub>H</sub> is the fragment constant for the hydrogen atom, the numerical value of which is 0.23, *f*<sub>C</sub> is the fragment constant for the carbon atom, the numerical value of which is 0.20, *n*<sub>b</sub> is the total number of C–C bonds in the molecule, and *f*<sub>b</sub> is the fragment constant for C–C bonds, the numerical value of which is  $-0.09$ .

In the case of saturated straight-chain alcohols, eq i reduces to eq ii

$$\text{CLogP}_{\text{saturated alcohol}} = \log P_{\text{methanol}} + n_{\text{CH}_2}f_{\text{CH}_2} + (n_{\text{b}} - 1)f_{\text{b}} \quad (\text{ii})$$

In eq ii *n*<sub>CH<sub>2</sub></sub> = the number of CH<sub>2</sub> groups in the alcohol and *f*<sub>CH<sub>2</sub></sub> = fragment constant of the CH<sub>2</sub> group, the numerical value of which is 0.66.

For unsaturated alcohols, CLogP was calculated from that of the corresponding saturated alcohols with the same number of carbon atoms using the following formula:

$$\text{CLogP}_{\text{unsaturated alcohol}} = \text{CLogP}_{\text{saturated alcohol}} + n_{=}f_{=} \quad (\text{iii})$$

In eq iii *n*<sub>=</sub> is the number of double bonds in the alcohol and *f*<sub>=</sub> is the fragment constant of the double bond, the numerical value of which is  $-0.55$ .

For benzyl alcohol, the following formula was used:

$$\text{CLogP}_{\text{benzyl alcohol}} = \log P_{\text{methanol}} + f_{\phi} - f_{\text{H}} \quad (\text{iv})$$

In eq iv *f*<sub>φ</sub> is the fragment constant for the aromatic ring, the numerical value of which is 1.90.

For phenyl ethyl alcohol, the following formula was used:

$$\text{CLogP}_{\text{phenyl ethyl alcohol}} = \text{CLogP}_{\text{benzyl alcohol}} + f_{\text{CH}_2} \quad (\text{v})$$

The CLogP values computed with these formulas for various alcohols are presented in **Table 3**. It is known that branching and the class of the alcohol affect the partition coefficient of the alcohol. Correction factors have been proposed for the branching effect on the partition coefficient (12), but these factors were ignored in the computation because they are considered separately.

**Branching Index.** Molecular connectivity is now defined as a method of molecular structure quantitation in which weighted counts of substructure fragments are incorporated into numerical indices (13). However, connectivity indices were initially developed by Kier mainly as indices of branching (14). The method of calculation of molecular connectivity has been described in his papers. However, relative molecular connectivity, which has been found to be more useful in the present study, is not often cited. Therefore, for the sake of clarity, the method of calculation of these values is explained by taking two examples, namely, 1-butanol and 2-methylpropanol.

At each carbon atom (or oxygen atom), the number of neighboring carbon (or oxygen) atoms bonded to it (hydrogen atoms are ignored) is recorded as  $\delta$  values. The skeleton formula is dissected at each point

**Table 2.** Calculated Partition Coefficients (CLogP) of Straight-Chain Alcohols along with Experimental and Calculated Fungitoxicity Data<sup>a</sup>

serial no.	compound	CLogP	pEC <sub>50</sub> exptl	pEC <sub>50</sub> (mol/L) calcd by eq 2	LOEC (mg/L) exptl	pLOEC (mol/L)	
						exptl	calcd by eq 4
1	methanol	-0.77	0.11	-0.56	7999	0.60	0.30
2	ethanol	-0.11	0.42	0.51	5492	0.93	0.96
3	1-propanol	0.43	0.83	0.89	4426	1.13	1.43
4	1-butanol	0.97	1.30	1.26	910	1.91	1.85
5	1-pentanol	1.51	1.62	1.61	712	2.09	2.21
6	1-hexanol	2.05	1.92	1.95	772	2.12	2.51
7	1-heptanol	2.59	2.33	2.28	182	2.80	2.77
8	1-octanol	3.13	2.64	2.60	87	3.17	2.96
9	1-decanol	4.21	3.15	3.19	52	3.48	3.19
10	cetyl alcohol <sup>b</sup>	7.65	<2.28	4.74	1200	2.31	2.43
11	stearyl alcohol <sup>b</sup>	8.73	<2.90	8.47	>225	<3.08	1.73

<sup>a</sup> LOEC = lowest observed effect concentration. <sup>b</sup> For cetyl and stearyl alcohols, the highest concentrations tried were 1200 and 225 mg/L, respectively, due to their poor solubility in acetone, which was used to dissolve the compounds before incorporation into the medium.

**Table 3.** Physicochemical Parameters of Compounds Considered for Detailed QSAR Study

serial no.	compound	CLogP	N <sub>H</sub>	χ	χ <sub>rel</sub>	N <sub>=</sub>
I	methanol	-0.77	2	1.00	1.00	0
II	ethanol	-0.11	2	1.41	1.00	0
III	1-propanol	0.43	2	1.91	1.00	0
IV	1-butanol	0.97	2	2.41	1.00	0
V	1-pentanol	1.51	2	2.91	1.00	0
VI	1-hexanol	2.05	2	3.41	1.00	0
VII	1-heptanol	2.59	2	3.91	1.00	0
VIII	1-octanol	3.13	2	4.41	1.00	0
IX	1-decanol	4.21	2	5.41	1.00	0
X	2-methylpropanol	0.97	2	2.27	0.94	0
XI	3-methylbutanol	1.51	2	2.77	0.95	0
XII	geraniol	3.11	2	5.16	0.95	2
XIII	citronellol	3.66	2	5.16	0.95	1
XIV	benzyl alcohol	0.90	2	3.93	1.01	3
XV	phenyl ethyl alcohol	1.64	2	4.43	1.00	3
XVI	2-propanol	0.43	1	1.73	0.91	0
XVII	1-octen-3-ol	2.58	1	4.31	0.97	1
XVIII	menthol	3.90	1	5.11	0.94	0
XIX	tertiary butyl alcohol	0.97	0	2.00	0.83	0
XX	linalool	3.11	0	4.98	0.92	2

<sup>a</sup> CLogP = partition coefficient calculated ignoring branching effect. N<sub>H</sub> = number of hydrogen atoms on the carbon bearing the hydroxyl group. χ = molecular connectivity. χ<sub>rel</sub> = relative molecular connectivity. N<sub>=</sub> = number of double bonds.

into constituent bonds retaining the δ values, and molecular connectivity (χ) is obtained with the formula

$$\chi = \sum(\delta_1 \delta_2)^{-1/2} \quad (\text{vi})$$

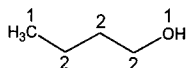
[More complicated connectivity indices developed by Kier (14) are not considered here for the sake of brevity.]

Relative molecular connectivity (χ<sub>rel</sub>) is calculated by using the formula

$$\chi_{\text{rel}} = \frac{\text{molecular connectivity of the alcohol under consideration}}{\text{molecular connectivity of the corresponding straight-chain primary alcohol}} \quad (\text{vii})$$

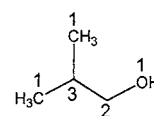
In the above formula, “corresponding” means that the number of carbon atoms remains the same.

Numbering for 1-butanol:



$$\text{Molecular connectivity } (\chi) \text{ on 1-butanol} = (1 \times 2)^{-1/2} + (2 \times 2)^{-1/2} + (2 \times 2)^{-1/2} + (2 \times 1)^{-1/2} = 2.41$$

Numbering for 2-methyl propanol:



$$\text{Molecular connectivity of 2-methyl propanol} = (1 \times 3)^{-1/2} + (1 \times 3)^{-1/2} + (2 \times 3)^{-1/2} + (1 \times 2)^{-1/2} = 2.27$$

Relative molecular connectivity (χ<sub>rel</sub>) of 2-methyl propanol

$$= \frac{\text{Molecular connectivity of 2-methyl propanol}}{\text{Molecular connectivity of 1-butanol}} = \frac{2.27}{2.41} = 0.94$$

**Class of the Alcohol.** The number of hydrogen atoms (N<sub>H</sub>) attached to the carbon bearing the hydroxyl group determines if the class of alcohol is primary, secondary, or tertiary.

**Multiple Regression.** This was done by the SPSS program (15).

## RESULTS AND DISCUSSION

In the study presented here, QSAR analyses have been done stage by stage. Initially a set of well-defined alcohols are taken and regression is done using parameters relevant to that set. Then other alcohols are also included, the set is redefined, parameters relevant to the new set are included in the regression analysis, and the results are compared with the earlier results.

When the first nine straight-chain saturated primary alcohols in **Table 1** were taken into consideration, the following regression equation was obtained when CLogP was taken as the independent variable.

$$\text{pEC}_{50} = 0.600 (\pm 0.080) + 0.637 (\pm 0.037) \text{CLogP} \quad (1)$$

$$n = 9, R = 0.997, R^2 = 0.994, s = 0.085, F = 1165.07$$

In this and the following equations, pEC<sub>50</sub> = negative logarithm of the median effective molar concentration for the mycelial growth inhibition, n = number of compounds, R = correlation coefficient, s = standard deviation, and F = significance index of the equation. The figures in parentheses are for 95% confidence interval.

Introduction of the squared term of CLogP did not significantly improve the correlation as is evident from eq 2.

$$\text{pEC}_{50} = 0.589 (\pm 0.065) + 0.711 (\pm 0.071) \text{CLogP} - 0.022 (\pm 0.020) (\text{CLogP})^2 \quad (2)$$

$$n = 9, R = 0.998, R^2 = 0.996, s = 0.067, F = 925.31$$

A parabolic relationship between fungitoxicity and partition coefficients was reported by Hansch and Lien (7), who had observed that the activity decreases with alcohols larger than C10 alcohols. It may be noted that eq 2 does not explain the very low activity of cetyl alcohol and stearyl alcohol (Table 2).

It is well recognized that median effective concentration ( $\text{EC}_{50}$ ) is the most statistically sound term for expressing fungitoxicity, but  $\text{EC}_{50}$  values of cetyl alcohol and stearyl alcohol could not be determined because of their poor solubility in acetone and their poor activity. (As per the procedure, each compound was dissolved in 0.25 mL of acetone and incorporated into 30 mL of PDA medium, the same amount of acetone being added in the control also.) However, cetyl alcohol exhibited 5% inhibition at a concentration of 1200 mg/L. This concentration was considered to be the lowest observed effect concentration (LOEC), and LOEC values were evaluated for all of the straight-chain compounds except stearyl alcohol.

The following regression equation was obtained for the first 10 compounds in Table 1 when pLOEC (negative logarithm of the lowest observed effect molar concentration) was taken as the dependent variable and CLogP was taken as the independent variable.

$$\text{pLOEC} = 1.482 (\pm 0.629) + 0.264 (\pm 0.198) \text{CLogP} \quad (3)$$

$$n = 10, R = 0.680, R^2 = 0.462, s = 0.742, F = 6.87$$

There was substantial improvement in the correlation when the squared term of CLogP was introduced, as is evident from eq 4.

$$\text{pLOEC} = 1.056 (\pm 0.253) + 0.906 (\pm 0.184) \text{CLogP} - 0.095 (\pm 0.026) (\text{CLogP})^2 \quad (4)$$

$$n = 10, R = 0.969, R^2 = 0.939, s = 0.267, F = 54.00$$

Although LOEC is not a statistically sound term like  $\text{EC}_{50}$ , the parabolic relationship between fungitoxicity and CLogP values is clearly demonstrated by eq 4. Equation 4 also explains the very low activity of stearyl alcohol, which was excluded from the regression analysis (Table 2).

For detailed QSAR studies,  $\text{pEC}_{50}$  was taken as the dependent variable. Therefore, cetyl alcohol and stearyl alcohol, the  $\text{EC}_{50}$  values of which could not be determined, were excluded from the regression analysis. Similarly, neomenthol, which had all of the physicochemical parameters (considered under the present study) exactly the same as those of menthol, was excluded. The remaining 20 compounds, numbered from I to XX, given in Table 3 were taken for the detailed study. The first 11 compounds in Table 3 are all saturated monohydric aliphatic alcohols, of which X and XI are branched alcohols.

The following equations were obtained when the CLogP and branching index (molecular connectivity),  $\chi$ , were successively

Table 4. Correlation Matrix for the Parameters in Table 3 ( $n = 20$ )

	CLogP	$\chi$	$\chi_{\text{rel}}$	$N_{=}$	$N_{\text{H}}$
CLogP	1.00	0.93	-0.06	-0.13	0.13
$\chi$		1.00	0.07	0.48	-0.06
$\chi_{\text{rel}}$			1.00	0.08	0.79
$N_{=}$				1.00	-0.06
$N_{\text{H}}$					1.00

introduced.

$$\text{pEC}_{50} = 0.550 (\pm 0.106) + 0.643 (\pm 0.051) \text{CLogP} \quad (5)$$

$$n = 11, R = 0.993, R^2 = 0.986, s = 0.121, F = 594.49$$

$$\text{pEC}_{50} = -0.743 (\pm 0.121) - 0.123 (\pm 0.663) \text{CLogP} + 0.844 (\pm 0.729)\chi \quad (6)$$

$$n = 11, R = 0.995, R^2 = 0.990, s = 0.099, F = 436.82$$

If we presume that CLogP is the most important parameter affecting fungitoxicity, as is evident from eqs 1 and 5, then the negative coefficient of CLogP in eq 6 shows that eq 6 is untenable. Compared to eq 5 there is a reduction in  $F$  value, too. The high collinearity between CLogP values and  $\chi$  ( $r = 0.998$ ) is the reason for this. It is very clear that molecular connectivity ( $\chi$ ) is not acting as a true branching index, where most of the compounds belong to homologous series.

When  $\chi$  was substituted by  $\chi_{\text{rel}}$  (relative molecular connectivity), eq 7 was obtained.

$$\text{pEC}_{50} = -3.425 (\pm 2.195) + 0.637 (\pm 0.035) \text{CLogP} + 4.024 (\pm 2.221)\chi_{\text{rel}} \quad (7)$$

$$n = 11, R = 0.997, R^2 = 0.994, s = 0.080, F = 686.96$$

Over and above the improved correlation, it may be noted that the coefficient of CLogP is now positive in eq 7. There is no intercorrelation between CLogP and  $\chi_{\text{rel}}$  ( $r = 0.096$ ) for the set of compounds under study. This shows that orthogonality could be achieved between changes in lipophilicity and branching effect. Calculated values by eq 7 are given in Table 5.

In the next stage of study, compounds XII and XIII, which are unsaturated alcohols, were also included in the analysis. Thus, compounds I–XIII are monohydric primary alkyl alcohols. The following equation was obtained when CLogP alone was introduced.

$$\text{pEC}_{50} = 0.699 (\pm 0.186) + 0.527 (\pm 0.080) \text{CLogP} \quad (8)$$

$$n = 13, R = 0.981, R^2 = 0.962, s = 0.215, F = 286.18$$

Equation 9 was obtained when  $N_{=}$  (depicting the number of double bonds) and  $\chi_{\text{rel}}$  were introduced in eq 8.

$$\text{pEC}_{50} = -3.024 (\pm 2.232) + 0.644 (\pm 0.035) \text{CLogP} + 0.413 (\pm 0.102)N_{=} + 3.614 (\pm 2.256)\chi_{\text{rel}} \quad (9)$$

$$n = 13, R = 0.998, R^2 = 0.996, s = 0.084, F = 649.54$$

Values calculated by eq 9 are given in Table 5.

The first 15 compounds in Table 3 are all primary alcohols. The following regression equations were obtained when CLogP



Table 5. Experimental and Calculated Fungitoxicity Values of Monohydric Alcohols<sup>a</sup>

serial no.	compound	pEC <sub>50</sub>					
		exptl	calcd by eq 7	calcd by eq 9	calcd by eq 11	calcd by eq 13	calcd by eq 15
I	methanol	0.11	0.11	0.09	0.03	0.16	0.10
II	ethanol	0.42	0.53	0.52	0.47	0.56	0.51
III	1-propanol	0.83	0.87	0.87	0.82	0.89	0.86
IV	1-butanol	1.30	1.22	1.21	1.17	1.22	1.20
V	1-pentanol	1.62	1.56	1.56	1.53	1.55	1.54
VI	1-hexanol	1.92	1.90	1.91	1.88	1.88	1.88
VII	1-heptanol	2.33	2.25	2.26	2.24	2.21	2.22
VIII	1-octanol	2.64	2.59	2.61	2.59	2.54	2.56
IX	1-decanol	3.15	3.28	3.30	3.30	3.19	3.24
X	2-methylpropanol	0.96	0.98	1.00	1.17	0.98	1.20
XI	3-methylbutanol	1.38	1.36	1.38	1.53	1.32	1.54
XII	geraniol	3.19	NC	3.24	3.09	NC	3.03
XIII	citronellol	3.27	NC	3.18	3.20	NC	3.14
XIV	benzyl alcohol	1.96	NC	NC	1.89	NC	1.88
XV	phenyl ethyl alcohol	2.09	NC	NC	2.38	NC	2.22
XVI	2-propanol	0.52	NC	NC	NC	0.54	0.46
XVII	1-octen-3-ol	2.00	NC	NC	NC	NC	2.08
XVIII	menthol	2.54	NC	NC	NC	2.77	2.67
XIX	tertiary butyl alcohol	0.64	NC	NC	NC	0.55	0.44
XX	linalool	2.15	NC	NC	NC	NC	2.28

<sup>a</sup> NC = not calculated.

and  $N_{=}$  were successively introduced.

$$pEC_{50} = 0.666 (\pm 0.259) + 0.671 (\pm 0.118) CLogP \quad (10)$$

$$n = 15, R = 0.951, R^2 = 0.904, s = 0.319, F = 123.94$$

$$pEC_{50} = 0.537 (\pm 0.104) + 0.657 (\pm 0.045) CLogP + 0.255 (\pm 0.057)N_{=} \quad (11)$$

$$n = 15, R = 0.993, R^2 = 0.986, s = 0.122, F = 455.61$$

The introduction of  $\chi_{rel}$  did not significantly improve the correlation, although there is no significant intercorrelation between  $N_{=}$  and  $\chi_{rel}$  ( $r = 0.015$ ). This is probably because of the high values of  $\chi_{rel}$  for benzyl alcohol and phenyl ethyl alcohol obtained due to their ring structure. [Connectivity values of cyclic and acyclic compounds are difficult to compare. For a fixed number of carbon atoms the cyclic compound will have one additional bond (higher connectivity and relative connectivity) compared to its acyclic counterpart, although we cannot consider the latter more branched than the former. The lower values of  $\chi$  and  $\chi_{rel}$  for menthol compared to those for 1-decanol are because of the branching outside the ring.] Values of pEC<sub>50</sub> calculated by using eq 11 are given in Table 5.

Exclusion of compounds XII–XV, XVII, and XX gives a set of 14 saturated alcohols. The following regression equations were obtained when log P and  $\chi_{rel}$  were successively introduced.

$$pEC_{50} = 0.484 (\pm 0.178) + 0.623 (\pm 0.084) CLogP \quad (12)$$

$$n = 14, R = 0.972, R^2 = 0.945, s = 0.230, F = 205.65$$

$$pEC_{50} = -3.286 (\pm 1.129) + 0.610 (\pm 0.041) CLogP + 3.912 (\pm 1.168)\chi_{rel} \quad (13)$$

$$n = 14, R = 0.994, R^2 = 0.988, s = 0.108, F = 485.44$$

Introduction of  $N_H$  did not significantly improve the correlation because of the intercorrelation between  $N_H$  and  $\chi_{rel}$  ( $r = 0.910$ ) for the set of compounds. Values of pEC<sub>50</sub> calculated by using eq 13 are given in Table 5.

When all 20 compounds were taken, the following regression equation (eq 14) was obtained when CLog P alone was taken as the independent variable.

$$pEC_{50} = 0.593 (\pm 0.276) + 0.633 (\pm 0.122) CLogP \quad (14)$$

$$n = 20, R = 0.924, R^2 = 0.853, s = 0.378, F = 104.45$$

There was substantial improvement in the correlation when  $N_H$  and  $N_{=}$  were introduced as given in eq 15

$$pEC_{50} = -0.175 (\pm 0.188) + 0.632 (\pm 0.043) CLogP + 0.379 (\pm 0.090)N_H + 0.242 (\pm 0.057)N_{=} \quad (15)$$

$$n = 20, R = 0.992, R^2 = 0.984, s = 0.133, F = 325.44$$

Introduction of  $\chi_{rel}$  did not significantly improve the correlation because of the intercorrelation between  $N_H$  and  $\chi_{rel}$  (Table 4). Values calculated by eq 15 are given in Table 5.

To test the reliability of the QSAR model given here, the antifungal activity data of 25 monohydric alcohols against Madison fungus taken from the literature (9) (Table 6) were subjected to the same analysis.

Exclusion of compounds 4, 7, 8, 10, 13, 14, 19, and 23 gives a set of primary alcohols. Equation 16 was obtained when CLogP and  $\chi$  were taken as independent variables.

$$pC = -0.050 (\pm 0.218) + 0.719 (\pm 0.116) CLogP + 0.107 (\pm 0.118)\chi \quad (16)$$

$$n = 17, R = 0.995, R^2 = 0.990, s = 0.114, F = 700.94$$

Substitution of  $\chi$  with  $\chi_{rel}$  resulted in eq 17

$$pC = -3.780 (\pm 2.530) + 0.809 (\pm 0.039) CLogP + 3.962 (\pm 2.564)\chi_{rel} \quad (17)$$

$$n = 17, R = 0.996, R^2 = 0.992, s = 0.099, F = 948.56$$

Apart from the improved correlation obtained in eq 17, it may be noted that the independent variables are orthogonal ( $r = 0.14$ ), whereas they are correlated in eq 16 ( $r = 0.93$ ). It is

**Table 6.** Physicochemical Parameters of Monohydric Alcohols along with Experimental and Calculated Activity against Madison 517 Fungus [Activity Data Taken from the Literature (9)]<sup>a</sup>

no.	compound	CLogP	$\chi$	$\chi_{rel}$	$N_H$	pC		
						exptl	calcd by eq 17	calcd by eq 19
1	methanol	-0.77	1.00	1.00	2	-0.24	-0.44	-0.49
2	ethanol	-0.11	1.41	1.00	2	-0.04	0.09	0.05
3	1-propanol	0.43	1.91	1.00	2	0.44	0.53	0.49
4	2-propanol	0.43	1.73	0.91	1	0.24	NC	0.25
5	butanol	0.97	2.41	1.00	2	0.87	0.97	0.94
6	isobutyl alcohol	0.97	2.27	0.94	2	0.77	0.73	0.78
7	secondary butanol	0.97	2.27	0.94	1	0.60	NC	0.78
8	tertiary butyl alcohol	0.97	2.00	0.83	0	0.46	NC	0.48
9	pentanol	1.51	2.91	1.00	2	1.38	1.40	1.38
10	secondary pentanol	1.51	2.77	0.95	1	1.08	NC	1.25
11	2-methylbutanol	1.51	2.81	0.97	2	1.19	1.28	1.30
12	3-methylbutanol	1.51	2.77	0.96	2	1.25	1.21	1.25
13	3-pentanol	1.51	2.81	0.95	1	1.01	NC	1.25
14	tertiary pentyl alcohol	1.51	2.56	0.88	0	1.44	NC	1.06
15	1-hexanol	2.05	3.41	1.00	2	1.83	1.84	1.82
16	2-ethylbutanol	2.05	3.35	0.98	2	1.73	1.76	1.77
17	1-heptanol	2.59	3.91	1.00	2	2.32	1.84	2.27
18	1-octanol	3.13	4.41	1.00	2	2.86	2.71	2.71
19	1-methylheptanol	3.13	4.27	0.97	1	2.49	NC	2.63
20	2-ethylhexanol	3.13	4.35	0.99	2	2.55	3.15	2.68
21	nonanol	3.67	4.91	1.00	2	3.18	2.88	3.15
22	decanol	4.21	5.41	1.00	2	3.57	3.59	3.60
23	diphenylmethanol	2.57	6.88	1.00	1	2.57	NC	2.25
24	phenylethanol	1.64	4.43	1.00	2	1.57	1.51	1.49
25	3-phenylpropanol	2.18	4.93	1.00	2	2.00	1.95	1.93

<sup>a</sup> NC = not calculated.**Table 7.** Correlation Matrix for the Parameters in Table 6 ( $n = 25$ )

	CLogP	$\chi$	$\chi_{rel}$	$N_H$
CLogP	1.00	0.86	0.27	0.12
$\chi$		1.00	0.41	0.14
$\chi_{rel}$			1.00	0.82
$N_H$				1.00

also noteworthy that the confidence interval of the  $\chi$  term in eq 16 is higher than the coefficient.

When all 25 compounds including the three aromatic alcohols were taken, eq 18 was obtained when CLogP and  $\chi$  were taken as independent variables.

$$pC = -0.214 (\pm 0.174) + 0.692 (\pm 0.106) \text{CLogP} + 0.153 (\pm 0.088)\chi \quad (18)$$

$$n = 25, R = 0.989, R^2 = 0.978, s = 0.159, F = 478.28$$

When  $\chi$  was substituted by  $\chi_{rel}$ , eq 19 was obtained.

$$pC = -2.522 (\pm 1.427) + 0.821 (\pm 0.055) \text{CLogP} + 2.663 (\pm 1.492)\chi_{rel} \quad (19)$$

$$n = 25, R = 0.989, R^2 = 0.978, s = 0.157, F = 490.10$$

In addition to the improved  $F$  value, it is noteworthy that there is orthogonality between the parameters in eq 19 vis-à-vis the collinearity between the parameters in eq 18. Introduction of  $N_H$  did not significantly improve the correlation because of the intercorrelation between  $N_H$  and  $\chi_{rel}$  (Table 7). Introduction of  $N_{=}$  (not given in Table 6) also did not significantly improve the correlation. Values calculated by eq 19 are given in Table 6.

The study shows that variation in fungitoxicity of monohydric alcohols depends mainly on changes in calculated partition

coefficients. The other factors that affect the fungitoxicity are the class of the alcohol (primary, secondary, or tertiary), unsaturation, and branching. Excellent correlations were obtained in all equations. It may be noted that the class of the alcohol is directly related to the vulnerability of the alcohol to dehydration and oxidation. The positive coefficient of  $N_H$  in eq 15 shows that this vulnerability favors fungitoxicity. The problem of collinearity between partition coefficient and Kier's molecular connectivity was overcome by taking relative molecular connectivity defined as the ratio of molecular connectivity of the alcohol under consideration to the molecular connectivity of the corresponding straight-chain primary alcohol with the same number of carbon atoms. In this way, effects of lipophilicity and branching could be orthogonalized. Because the class of the alcohol, as quantified by  $N_H$ , itself affects branching, these effects could not be orthogonalized. Nevertheless, relative molecular connectivity can be considered as a true branching index in the case of acyclic primary alcohols. Even when secondary and tertiary alcohols were included, relative molecular connectivity improved the correlation in one case (eq 13). Furthermore, when cyclic compounds are included, relative molecular connectivity can give better correlation than molecular connectivity (eq 19). It may be noted that the problem of collinearity between the size of the molecules and branching was overcome by Kier by taking difference molecular connectivity values (13). However, relative molecular connectivity proposed in this study appears to be simple in theory, interpretation, and application. In future QSAR studies on compounds with well-defined toxophores and a substantial number of homologous compounds, when changes in partition coefficient are found to affect the variation in biological activity, relative molecular connectivity may play the useful role of a branching index. In those cases, the general definition of relative molecular connectivity should be the ratio of the molecular connectivity of the compound under consideration to the molecular connectivity of the corresponding straight-chain compound with the same number of carbon atoms and with the same toxophore.

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#### LITERATURE CITED

- (1) Wilkinson, S. G. Alcohols In *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds, Vol. 1. Stereochemistry, Hydrocarbons, Halo Compounds, Oxygen Compounds*, Stoddart, J. F., Ed.; Pergamon Press: Oxford, U.K., 1979; p 579.
- (2) Kramer, W. Fungicides and Bactericides In *Chemistry of Pesticides*; Buchel, K. H., Ed.; Wiley: New York, 1983; p 291.
- (3) Anderson, R. A.; Hamilton, K.; Thomas, R.; Hildenbrand, D. F.; McCracken, C. T., Jr.; Collins, R. W.; Fleming, P. D. Antifungal activity relationships among volatile C6 and C9 aliphatic aldehydes, ketones and alcohols. *J. Agric. Food Chem.* **1994**, *42*, 1563–1568.
- (4) Chandravadana, M. V.; Nidiry, E. S. J. Antifungal activity of essential oil of *Pelargonium graveolens* and its constituents against *Colletotrichum gloeosporioides*. *Indian J. Exp. Biol.* **1994**, *32*, 908–909.
- (5) Nidiry, E. S. J. Structure–fungitoxicity relationships of the monoterpenoids of the essential oils of peppermint (*Mentha*

- piperita*) and scented geranium (*Pelargonium graveolens*). *J. Essent. Oil Res.* **1998**, *10*, 628–631.
- (6) Nidiry, E. S. J. Structure–fungitoxicity relationships of some volatile flavour constituents of the edible mushrooms *Agaricus bisporus* and *Pleurotus florida*. *Flavour Fragrance J.* **2001**, *16*, 245–248.
- (7) Hansch, C.; Lien, E. J. Structure–activity relationships in antifungal agents, a survey. *J. Med. Chem.* **1971**, *14*, 653–670.
- (8) Kier, L. B.; Murray W. J.; Hall, L. H. Molecular connectivity 4. Relation to biological activities. *J. Med. Chem.* **1975**, *18*, 1272–1274.
- (9) Gombar, V. K.; Wadhwa, L. Quantitative structure–activity relationships IV. Use of molecular negentropy as structural parameter. *Arzneim-Forsch./Drug Res.* **1982**, *32*, 715–718.
- (10) Nene, Y. L.; Thapliyal A. N. *Fungicides in Plant Disease Control*; Oxford and IBH Publishing: New Delhi, India, 1993; p 691.
- (11) Finney, D. J. *Probit Analysis*; Cambridge University Press: Cambridge, U.K., 1981; pp 283–287.
- (12) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979; pp 18–174.
- (13) Hall, L. H.; Kier, L. B. The Molecular Connectivity Chi Indexes and Kappa Shape Indexes in Structure–Property Relations. In *Reviews of Computational Chemistry*; Boyd, D., Lipkowitz, K., Eds.; VCH Publishers: Weinheim, Germany, 1991; Vol. 2, 9, pp 367–422.
- (14) Kier, L. B. Molecular connectivity as a descriptor of structure for SAR analyses In *Physical Chemical Properties of Drugs*; Yalkowski, S., Sinkula, A., Eds.; Dekker: New York, 1980; pp 277–319.
- (15) SPSS/PC Varian 2.0 Advanced Statistics, SPSS release 4.0, 1990.

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