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Predicting the Biological Activities of 2-Methoxyphenol Antioxidants: Effects of Dimers

SEIICHIRO FUJISAWA[1], MARIKO ISHIHARA[1], YUKIO MURAKAMI[1], TOSHIKO ATSUMI[1], YOSHINORI KADOMA[2] and ICHIRO YOKOE[3]

[1]*Meikai University School of Dentistry, 1-1 Keyakidai, Sakado, Saitama 350-0283;*
[2]*Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10, Kanda-Surugadai,Chiyoda-Ku, Tokyo 1010062;*
[3]*Faculty of Pharmaceutical Science, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan*

Abstract. *Selective cyclooxygenase (COX)-2 inhibitors have attracted much attention in relation to the design of non-steroidal anti-inflammatory agents (NSAIDs). The relationship between experimentally derived data on the antioxidant capacity, cytotoxicity and COX-2 inhibition for a range of 2-methoxyphenols and their calculated descriptors was investigated. Materials and Methods: Quantitative structure-activity relationship (QSAR) studies were performed on a series of 2-methoxyphenols that act as COX-2 inhibitors using electronic descriptors, such as the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), ionization potential (IP), chemical hardness (η), and electronegativity (χ), which were calculated by the CONFLEX/PM3 method. The antioxidant capacity of a range of 2-methoxyphenols was evaluated by 2,2'-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity, and the anti-peroxy radical activity (stoichiometric factor, n) was determined by the induction period method in the polymerization of methyl methacrylate (MMA) initiated by thermal decomposition of benzoyl peroxide (BPO). The 50% cytotoxic concentration (CC_{50}) against human submandibular gland tumor cell line (HSG) was determined by the MTT method. Results: Cytotoxicity declined in the order of curcumin > dehydrodiisoeugenol > isoeugenol >bis-MMP > eugenol > ferulic acid > 2-methoxy-4-methylphenol (MMP) > bis-eugenol > bis-ferulic acid. The inhibitory effects on LPS-induced COX-2 gene expression in RAW 264.7 cells were determined by Northern blot assay. The majority of 2-methoxyphenols studied were COX-2 inhibitors. In particular, dehydrodiisoeugenol was a potent inhibitor, followed by bis-ferulic acid and curcumin. A linear relationship between anti-DPPH radical activity (log $1/IC_{50}$) and IP for 2-methoxyphenols except for dehydrodiisoeugenol was observed (r^2=0.768.) The n for methoxyphenols was less than 2 in most cases. A linear relationship (r^2=0.713) between the log ($1/CC_{50}$) and the η-term except for ferulic acid was observed. COX-2 inhibition, except for hesperetin, was related to the χ-term (r^2=0.685). Conclusion: It may be possible to predict the mechanism responsible for the biological activities of 2-methoxyphenols.*

Correspondence to: Dr. S. Fujisawa, Meikai University School of Dentistry, 1-1 Keyakidai, Sakado, Saitama 350-0283, Japan. Tel/Fax: +81-492 85 5511. e-mail: fujisawa@dent.meikai.ac.jp / fujisawa 33@nifty.com

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The radical scavenging activity and cytotoxicity of 2-methoxyphenols and related compounds, and their effect on lipopolysaccharide (LPS)-induced cyclooxygenase-2 (COX-2) expression, in RAW 264.7 murine macrophages have previously been investigated, and the results have suggested that these compounds possess antioxidant and anti-inflammatory activity (1-15).

Computational chemistry is one of the most rapidly expanding and exciting areas of scientific endeavor in the medical and dental material sciences (16). Information available from computational methods may be useful for interpreting the molecular mechanism of interactions of 2-methoxyphenol antioxidants. Hansch *et al.* developed the concept of a quantitative structure-activity relationships (QSAR) for various phenolic compounds and the results have suggested that the QSAR can predict the conditions under which a phenol will exert toxic effects, such as carcinogenicity, and the quantity of phytophenols that an individual can consume before a toxic reaction occurs (17). Previous QSAR studies have focused on the classical descriptors, such as hydrophobicity (log P, 1-octanol-water partition coefficient), bond dissociation energy (BDE), and sigma and steric terms (18-20). In contrast, parameters related to global and local electrophilicity, such as electronegativity (χ) and chemical hardness (η) derived

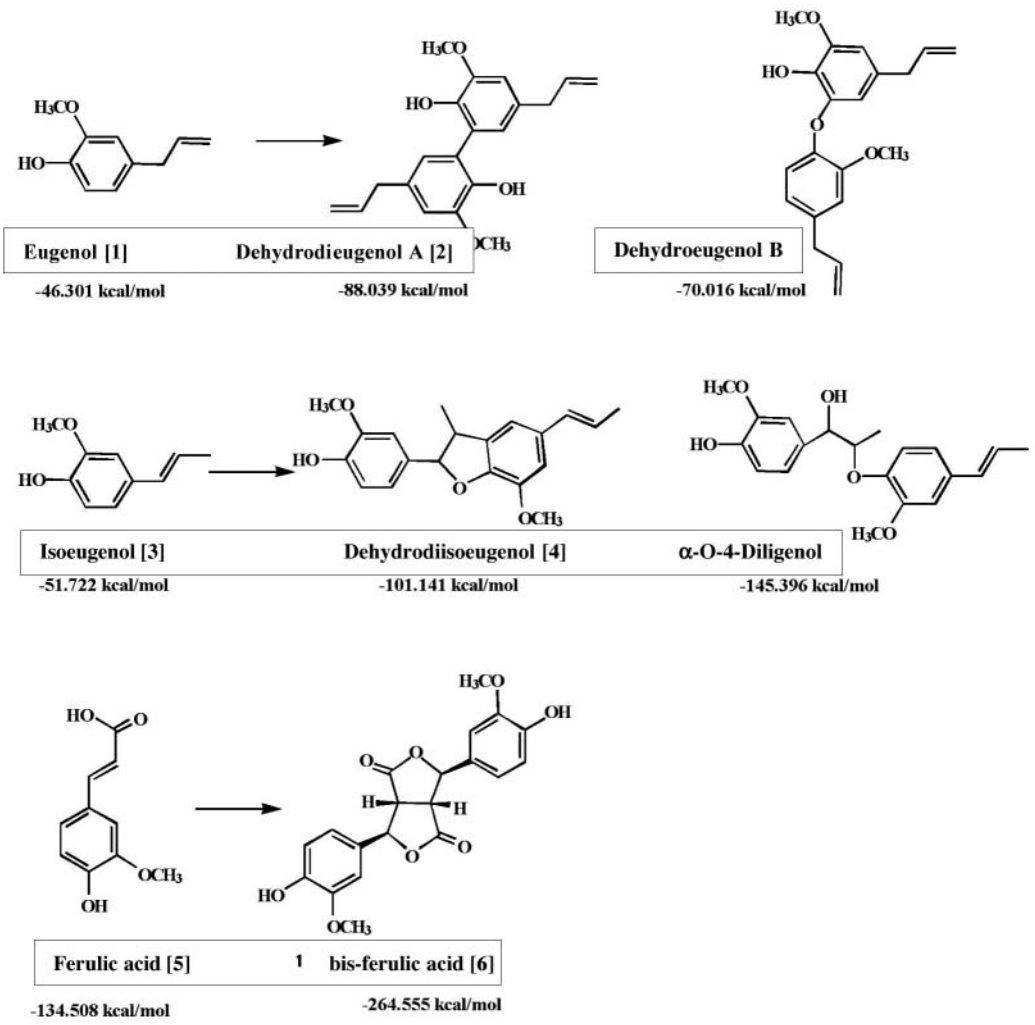

Figure 1. *The chemical structure for bis-eugenol (**2**), dehydrodiisoeugenol (**4**) and bis-ferulic acid (**6**) from corresponding monomers eugenol (**1**), isoeugenol (**3**) and ferulic acid (**5**) and their heat of formation.*

using Koopman's theorem, have been reported to explain the toxicity mechanisms of bioactive chemicals (21). QSAR studies of bioactive chemicals, such as environmental hormones have also been carried out with the help of quantum mechanical descriptors, such as χ and η (22, 23).

The aim of the present study was to investigate the relationship between experimentally derived data on antioxidant activity, cytotoxicity and COX-2 inhibition for 2-methoxyphenols and their calculated descriptors, such as the BDE, ionization potential (IP), highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), dipole moment, η, and χ. In this report, the results of our experiments are shown and the radical-scavenging activity and biological activities of 2-methoxyphenols using the chemical hardness concept with the QSAR equation are discussed.

Materials and Methods

Materials. The 2-methoxyphenol monomers and dimers studied here are shown in Figure 1 and Table I, respectively; compounds **1**, **3**, **5**, and **14** are widely used in the cosmetics and food industries. Phenolic monomers were purchased from commercial products.

Synthesis of dimers. Based on the heats of formation (Figure 1), the main products of the dimers were suggested to be as follows: 3,3'-dimethoxy-5, 5'-di-2-propenyl-1, 1'-biphenyl-2, 2'-diol (**2**) from **1**, 2-(3-methoxy-4-hydroxyphenyl)-3-methyl-5- (1-propenyl)-7-methoxy-2, 3-dihydrobenzofuran (**4**) from **3**; 4-cis, 8-cis-bis (4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo- [3.3.0] octane-2, 6-dione (**6**) from **5**; and 3,3'-dimethoxy-5, 5'-dimethyl-1, 1'-biphenyl-2, 2'-diol (**8**) from 2-methoxy-4-methyphenol (**7**). Compounds **2, 4, 6** and **8** were virtually synthesized and the yield of each corresponding compound was about 80%, 20%, 18%, and 80%, respectively (24, 25). The synthesis for compounds **2** and **8** was performed using

Table I. *Heats of formation, log P, ionization potential (IP), HOMO energy, LUMO energy, chemical hardness ($\eta=(\varepsilon_{LUMO}-\varepsilon_{HOMO})/2$), electronegativity ($\chi=-(\varepsilon_{LUMO}+\varepsilon_{HOMO})/2$) and ω for 2-methoxyphenols.*

Comp.	Heat of formation (kcal/mol)	log P	IP (eV)	HOMO (eV)	LUMO (eV)	η (eV)	χ (eV)	$\omega=\chi^2/2\eta$ (eV)
1	–46.301	2.554	8.773	–8.773	0.315	4.544	4.229	1.968
2	–87.761	4.746	8.900	–8.900	0.199	4.549	4.350	2.080
3	–51.722	2.509	8.565	–8.565	–0.000	4.282	4.283	2.142
4	–101.141	4.060	8.533	–8.533	–0.159	4.187	4.187	2.093
5	–134.508	1.616	8.932	–8.932	–0.836	4.048	4.884	2.947
6	–267.721	1.958	9.429	–9.429	–0.275	4.577	4.852	2.572
7	–66.851	1.977	8.707	–8.707	0.345	4.526	4.181	1.931
8	–127.195	3.591	8.555	–8.555	0.390	4.472	4.083	1.864
9	–57.634	1.510	8.859	–8.859	0.311	4.585	4.274	1.992
10	–131.996	1.616	9.093	–9.093	–0.636	4.229	4.864	2.797
11	–134.381	1.616	8.968	–8.968	–0.823	4.073	4.895	2.941
12	–196.404	1.735	9.079	–9.079	–0.580	4.249	4.830	2.746
13	–92.310	1.185	9.152	–9.152	–0.464	4.344	4.808	2.660
14	–154.015	2.517	8.613	–8.613	–1.033	3.790	4.823	3.068

1: eugenol; **2**: *bis*-eugenol; **3**: isoeugenol; **4**: dehydrodiisoeugenol; **5**: ferulic acid; **6**: *bis*-ferulic acid, **7**: *ortho*-methoxy-4-methyphenol (MMP); **8**: *bis*-MMP; **9**: *ortho*-methoxyphenol; **10**: *ortho*-ferulic acid; **11**: iso-ferulic acid; **12**: hesperetin; **13**: *ortho*-vanillin; **14**: curcumin.

CuCl(OH)/tetramethylenediamine as a catalyst, whereas that for **4** and **6** was performed using $FeCl_3/6H_2O$. Dehydrodieugenol B and α-O-4-dilignol could not be synthesized from the corresponding monomers. The heat of formation suggested the production of four kinds of dimers from **5**, and bis-ferulic acid (**6**) was the most preferable, having the lowest heat of formation.

Cell culture. Human submandibular gland carcinoma cells (HSG) and raw 264.7 cells were used for evaluating the cytotoxic activity using the MTT method) (8) and COX-2 inhibition using the northern blot assay (2), respectively.

Geometry. A procedure based on the density function theory has been used for the calculation of BDE and ionization potential of phenolic molecules. In general, the semiempirical PM3 method has been reported to be unable to yield details of the fine geometry and unpaired electron distribution of a molecule (26). By contrast, the density function theory (DFT) has proven to be reliable for studying the energetic and geometrical properties of proton transfer and other ion-molecule reactions (26). To obtain details of the fine geometry in the present study, calculations using the PM3 method, as implemented in the MOPAC 2000 program on a Tektronix CAChe workstation (Fujitsu Ltd., Japan) were carried out after geometry optimization for the investigated compounds, performed initially using CONFLEX5 (Conflex, Tokyo, Japan) (data not shown).

Results and Discussion

Computational data for descriptors. The IP, HOMO energy, LUMO energy, η, χ and electrophilicity index (ω) calculated using the CONFLEX/PM3 method are shown in Table I. The η, χ, and ω value were calculated from Equations, **1**, **2** and **3**, respectively:

$$\eta=1/2\ (\varepsilon_{LUMO}-\varepsilon_{HOMO}) \quad \textbf{[1]}$$

$$\chi=-1/2\ (\varepsilon_{LUMO}+\varepsilon_{HOMO}) \quad \textbf{[2]}$$

$$\omega=\chi^2/2\eta \quad \textbf{[3]}$$

The electronic energy derived by the single-point calculation of DFT for some 2-methoxyphenols using DFT B3LYP, set at the 6-31G*level has been reported previously (1). The BDE value of compounds **1**, **3**, **4**, **5**, **6**, **9**, **10** and **11** derived using the CONFLEX/PM3 method was compared with the corresponding value derived using the B3LYP. The BDE values calculated using the B3LYP, PM3 and AM1 methods were not identical to each other (Table II). The BDE value of the 2-methoxyphenols calculated by the AM1 method was higher than that calculated using the CONFLEX/PM3. Interestingly, the value of BDE (BDE calculated by the AM1 plus BDE calculated by the CONFLEX/PM3) x1/2 was close to that calculated by the B3LYP. To save computational time, this convenient method may be preferable as it shows the BDE value at the DFT level. On the other hand, we previously reported that the value of the HOMO energy of 2-methoxyphenols calculated at the DFT/6-31G* level could be adopted as an approximate IP value according to Koopman's theory (1). The relationship between the Koopman IP value and the IP value calculated by the CONFLEX/PM3 was found to be linear for compounds **1**, **3**, **4**, **5**, **6**, **9**, **10** and **11** ($r^2=0.874$) (data not shown).

NMR-chemical shifts. The ^{1}H-NMR chemical shifts of the OH group for the indicated 2-methoxyphenols were obtained on a JEOL JNM-Alpha 500 spectrometer at room

Table II. *Bond dissociation enthalpy (BDE), dipole moment, electron affinity and ionization potential (IP) for 2-methoxyphenols.*

Comp.	BDE[a] (kcal/mol) B3LYP[a]	BDE (kcal/mol) PM3	BDE (kcal/mol) AM1	BDE (kca/mol) (PM3+AM1)/2	dipole moment D PM3	electron affinity (eV) PM3	$IP_{koopman}$[a] (eV) 6-31G*
1	84.00	82.865	86.875	84.870	2.027	–0.315	7.91
2		78.080	85.980	82.030	1.594	–0.199	
3	82.96	80.635	86.467	83.551	2.27	0.000	7.49
4	85.90	82.786	87.102	84.944	1.132	0.159	7.60
5	84.70	82.765	88.061	85.413	1.999	0.836	8.03
6	85.76	80.172	87.923	84.047	2.592	0.275	8.36
7		82.68	85.816	84.248	2.213	–0.345	
8		80.765	85.529	83.147	0.032	–0.390	
9	87.16	83.583	87.500	85.541	2.093	–0.311	
10	84.49	83.286	87.681	85.483	4.438	0.636	8.30
11	86.18	83.316	88.553	85.934	3.751	0.823	8.09
12		84.417	88.075	86.246	3.182	0.58	
13		84.406	88.618	86.512	1.244	0.464	
14		83.792	88.218	86.005	1.379	1.033	

[a]Reference (1). For numbering of compounds see Table I.

Table III. *Radical scavenging activities (IC_{50}, n), cytotoxicity (CC_{50}) and COX-2 inhibition for 2-methoxyphenols.*

Comp.	DPPH method[a] IC_{50} (mM)	Induction period method[b], *n*	NMR chemical-shift[c] δ (ppm)	Cytotoxicity[d] CC_{50} (mM)	COX-2 inhibition[e] μM
1	0.080	1.44	8.66	0.195	none
2	0.030	2.33	8.08	0.689	300
3	0.050	1.89	8.91	0.029	non
4	1.312	1.00	5.80	0.005	0.1 ~ 10
5	0.237	2.20	9.25	0.3	none
6	3.160		9.55	>1	10
7	0.091	1.37		0.396	100 ~ 500
8	0.024	2.39		0.047	250 ~ 500
9	0.510	1.22	8.76		250 ~ 500*
10					none*
11	40.200				100 ~ 250
12	0.658	0.90			250 ~ 500
13	27.410	0.14			250 ~ 500*
14	0.043	3.87	9.66	0.003	10
Phenol			9.29		

[a]The concentration (mole/l) of inhibitor necessary to decrease the initial DPPH radical concentration by 50% (0.1 mM DPPH, results were, in part, drawn from reference 15); [b]*n*, stoichiometric factor; [c]proton-NMR chemical shift of the O-H groups of phenols in DMSO-d_6; [d]HSG cells; [e]RAW 264.7 cells (from references 1-5 and *present study). For numbering of compounds see Table I.

temperature, and chemical shifts were expressed as the δ value relative to an external TMS (tetramethylsilane) standard in DMSO-d_6. The results are shown in Table III.

It is well known that Hammett substituent constants are well correlated with various physical properties and spectral parameters of substituted benzene derivatives. The chemical shift of 2-methoxyphenols in DMSO is independent of concentration due to almost exclusive intermolecular hydrogen bonding between the –OH group and DMSO (27). Electron-withdrawing substituents shielded the hydrogen-bond OH-DMSO moiety, and the downfield chemical shift relative to phenol is designated as a positive Δδ value. Conversely, electron-donating substituents cause an upfield shift, designated as a negative Δδ value. The correlation between Hammett σ and NMR δ values is well known (28). The δ (ppm) for phenol, **6**, **5**, **9**, **1**, **3**, **2** and **4** was 9.29, 9.55, 9.25, 8.76, 8.66, 8.67, 8.08 and 5.80, respectively. The $\Delta\delta(\delta_{investigated\text{-}compoud} - \delta_{phenol})$ possibly exhibits the Hammett's value. Compound **4** had the greatest Δδ value. On the other hand, the ^{1}H-NMR chemical shift due to the

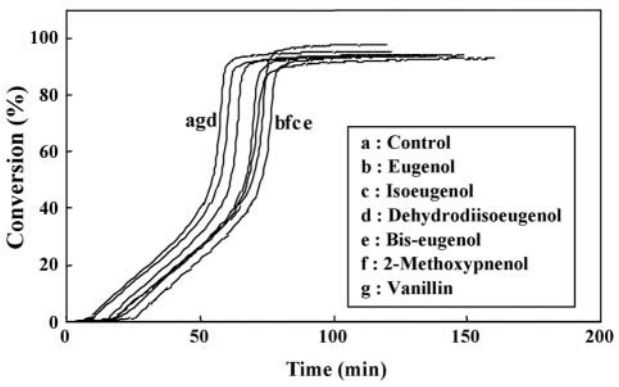

Figure 2. *Time-conversion curves for 2-methoxyphenols. MMA 9.4 mol/l, BPO 0.1 mol, 2-methoxyphenol 0.001 mol/l, 70˚C.*

phenolic –OH for compounds **1**, **2** and **6** in $CDCl_3$ was 5.53 ppm, 5.98 ppm and 5.95 ppm, respectively. This suggested a great difference in the electron milieu between monomer **1** and dimer **2** in $CDCl_3$ as well as in DMSO-d_6. Also, the δ for **6** in CDCl3 was shifted by 0.3 ppm to a higher field than that for **2**, indicating that the –OH group in **6** has a much greater shielding effect than that for **2**.

Anti-DPPH radical activity. The antiradical efficiency of the DPPH radicals for the 2-methoxyphenols investigated is shown in Table III as IC_{50} values (the concentration causing 50% reduction of DPPH) (25). Radical-scavenging activities were determined using DPPH as a free radical. For each inhibitor, various concentrations were tested in ethanol. The decrease in absorbance was determined at 517 nm for 10 min at room temperature. Antiradical activity was calculated as the concentration (mole/l) of inhibitor necessary to decrease the initial DPPH radical concentration by 50% (IC_{50}) (25).

The anti-DPPH radical activities declined in the order **11>13>6>4>12>9>5>7>1>3>14>2>8**. A linear relationship between the log $1/IC_{50}$ and IP for compounds **1-3**, **5-9**, **12** and **14** was observed as expressed in Equation **4**.

$$\log (1/IC_{50}) = -4.158\ (\pm 1.044)\ IP + 37.239\ (n=10,\ r^2=0.768,\ p<0.01) \quad \textbf{[4]}$$

The anti-DPPH radical activity for 2-methoxyphenols except for compounds **4**, **11** and **13**, appeared to be clearly controlled by the IP value. Compound **4** was great outlier of the equation.

Anti-peroxyradical activity. The radical scavenging activity of 2-methoxyphenols was also determined using the induction period method (25, 28) and the results are shown in Figure 2 and Table III, respectively. The induction period was determined using the method reported elsewhere (28). The number of moles of peroxy radicals trapped by moles of the relevant phenol, the *n* value, was calculated per unit of the phenolic moiety. Relative *n* values in Equation **5** can be calculated from the induction period in the presence of 2-methoxyphenols as an inhibitor:

$$n = R_i\,\tau/[IH] \quad \textbf{[5]}$$

where τ is the induction period and R_i is the rate of initiation. [IH] represents the concentration of inhibitor. In the case of [MMA]=9.4 mol/l and benzoyl peroxide [BPO]=0.1 mol/l, R_i was 2.28×10^{-6} mol/l x s at 70˚C.

In general, the stoichiometric factor (*n*) for fully oxidized monophenols is 2. Compounds **1**, **3**, **4**, **5**, **7**, **9** and **14**, which are less hindered phenols, are predicted to have an *n* value lower than 2 because of the strong internal hydrogen bond between the methoxy group and the phenolic hydroxy group. The *n* value for these compounds was less than 2 in most cases. In general, when the *n* value for monophenolics is less than 2, dimerization occurs due to the radical-radical coupling reaction (25). Compounds **2**, **4**, and **6** were derived from the corresponding less hindered phenolic monomers **1**, **3** and **5** by dimerization reactions, as shown in Figure 1. Dimers **2** and **8**, hindered phenols, showed an *n* value slightly but significantly greater than 2, suggesting further oxidation of their oxidized products. Curcumin showed an *n* value of 4, and in this case there were two stages to the inhibition, the first break occurring with an *n* factor of about 1.0 (data not shown), suggesting that it may undergo dimerization, and the resulting dimers could undergo further oxidation due to instability of the peroxidic dimer products at 70˚C. Curcumin acted as a polyphenol antioxidant.

Cytotoxicities. The cytotoxicity of 2-methoxyphenols against HSG cells is shown in Table III. The cytotoxicity of **3** was 10-fold greater than that of **1**. The cytotoxicity for both **14** and **4** was about 100-fold greater than that of **1**, and 10-fold greater than that of **3**. When the cytotoxicity of the monomers was compared with that of corresponding dimers, the cytotoxicity of **2** was less than that of **1**, whereas conversely, the cytotoxicity of **4** and **8** was greater than that of **3** and **7**, respectively. In contrast, the cytotoxicities of **5** and **6** were similar, and these compounds were less cytotoxic.

The cytotoxicity of phenolic compounds can be described as a linear or parabolic expression with parameters of log P, Hammet σ value, BDE and steric factors (17). The cytotoxicity of phenolic compounds was reported to be affected by the value of both log P, a hydrophobic term, and σ^+ in the phenol reaction, mostly because such reactions are correlated with a σ value derived from the ionization of phenols (18). In toxicodynamic processes, generally, phenolic toxicity is a two-step process: initial radical formation X-PhOH + R·X-PhO· + RH, and then reaction with a

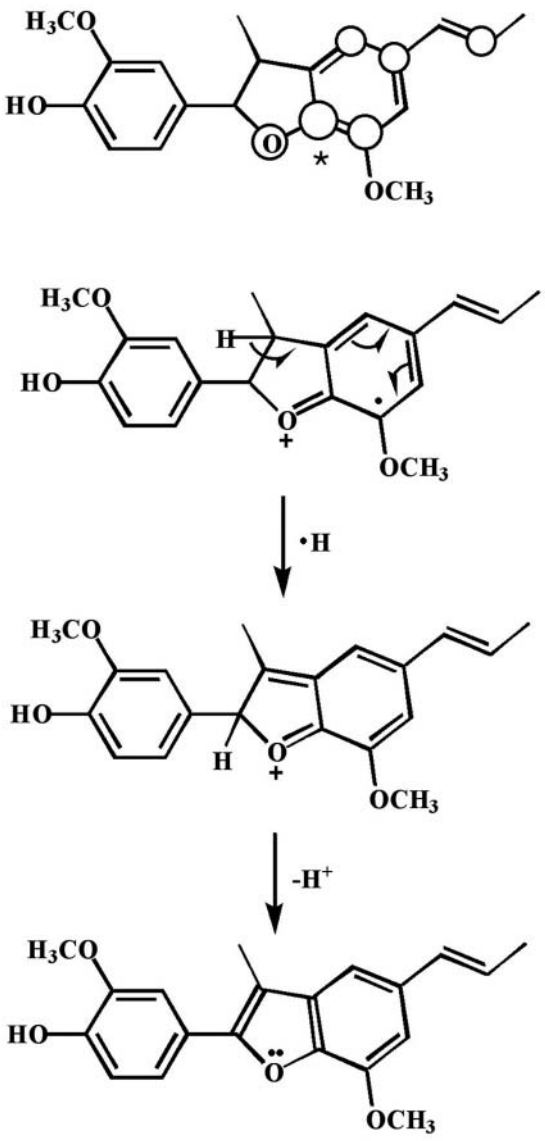

Figure 3. *The density distribution of the HOMO for dehydrodiisoeugenol* ***4*** *and possible radical oxidation pathway. *highest density (0.208) for the HOMO. The highest density (0.212) for the LUMO also exists at this carbon site.*

receptor. The hydrophobic term would seem to be involved in the second step. Reaction with DNA would account for the toxic and carcinogenic effects of phenols (18). However, in the present study, the cytotoxicity was not significantly correlated with the log P, BDE or IP (data not shown). This may be attributable to the possible dependency of 2-methoxyphenol cytotoxicity on a combination of phenol radicals, metabolism of phenol to quinone methides, and the cytotoxic contribution of quinone (29). A linear relationship between the cytotoxicity and the η value of 2-methoxyphenols except for **5** was observed as expressed in Equation **6**:

$$\log (1/CC_{50}) = 1.362\ (\pm 0.506)\ \eta\ \pm 6.840 \quad (n=8,\ r^2=0.713,\ p<0.05) \qquad \textbf{[6]}$$

The potency of cytotoxicity is clearly controlled by the η value, but not the χ or ω value. When the HOMO-LUMO gap was smaller, the cytotoxicity was greater. The energy difference between HOMO and LUMO for some bioactive compounds shows a good linear correlation with the potency of toxicity and biological activity, and compounds with lower values are more toxic (22). In the present study, compound **5** was an outlier of the equation, possibly due to its lower hydrophobicity. Compound **14**, with a low η value, was most cytotoxic, followed by compound **4**.

Dehydrodiisoeugenol **4** showed the greatest Δδ value, was a great outlier of the equation **4**, and had an *n* value of 1. To clarify why this compound showed such physicochemical properties, we examined its density distribution for HOMO and LUMO. The HOMO density distribution of **4** is shown in Figure 3. The PM3 calculation suggested that the reaction site with radicals exists in the benzofuran, and not the phenol ring (Figure 3). This suggests that radical oxidation of **4** depends on the C-H bond dissociation enthalpy, and not on the O-H bond counterpart.

Curcumin was the most highly cytotoxic of the compounds examined (Table III). We previously reported a possible mechanism for the effect of the curcumin dimer using PM3, which was radical-radical termination at the 2-position (9). The curcumin radical could react with itself or with other radicals to yield stable polymeric products such as vanillin, ferulic acid and curcumin dimers (30). Also, curcumin could be converted to cytotoxic quinone intermediates that would be expected to combine rapidly with cellular nucleophiles, especially sulfur nucleophiles. The formation of curcumin radicals may induce cytotoxicity.

Compound **3** showed a higher cytotoxicity than that of **1**, possibly due to the formation of benzyl radicals derived from **3**. Phenolic toxicity was likely to be responsible for the η-term.

COX-2 inhibition. Selective COX-2 inhibitors have attracted much attention in the design of NSAIDs. NSAID-like compounds interact with enzymes producing prostaglandin in the human body. We previously investigated the inhibitory effects of 2-methoxyphenols on LPS-induced COX-2 gene expression in RAW 264.7 cells using northern blot assay (1-5). Using similar method to that previously reported (1-5), we also investigated the inhibition of COX-2 by 2-methoxyphenols **10** and **13** (data not shown). Together with these findings, a QSAR study for various methoxyphenols was done using the BDE, IP, η, χ, and ω values as descriptors. There were significantly exponential relationships between COX-2 inhibitory activity (y, μM) and the χ-term (0, eV) except for compound **12**. The equation is expressed as follows:

$y=3.124\ 10^{0.328\chi}$ (n=9, r^2=0.685) **[7]**

The fact that hesperetin was an outlier of the equation may be a result of to its molecular structure (a flavanone), although this compound does have a methoxy group.

In contrast, there were no relationships between COX-2 inhibition and the BDE, IP, dipole moment, η or ω terms. We previously reported the theoretical prediction of the relationship between phenol function and COX-2/AP-1 inhibition for ferulic acid-related compounds, indicating that bis-ferulic acid and isoferulic acid, but not ferulic acid, showed COX-2 inhibition (1). These findings predicted that *o*-ferulic acid may not exert COX-2 inhibition because its BDE is less than that of ferulic acid. As expected, this compound did not show COX-2 inhibition. In the present study, COX-2 inhibiting activity for the indicated COX-2 inhibitors was related to the χ-term. In contrast, the cytotoxicity of these compounds was related to the η-term. These findings predicted a difference between the mechanisms responsible for cytotoxicity and COX-2 inhibition; cytotoxicity is related to chemical hardness (η)-controlled enzymes, whereas COX-2 inhibition is related to electronegativity (χ)-controlled enzymes. QSAR studies using electronic descriptors may be useful for the discovery of new anticancer agents (31).

Conclusion

The cytotoxicity of 2-methoxyphenols may be related to the η-tem and COX-2 inhibition may be related to the χ-tem. The use of descriptors obtained by the CONFLEX/PM3 method followed the QSAR equation better than corresponding descriptors calculated at the semiempirical PM3 level alone.

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