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Quantitative structure-activity relationship (QSAR) analysis of the inhibitory effects of furanocoumarin derivatives on cytochrome P450 3A activities

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Furanocoumarin derivatives (FCs) present in grapefruit and other plants cause pharmacokinetic interactions such as increased absorption of various drugs because the constituents have inhibitory effects on drug metabolizing activities of cytochrome P450 (CYP) 3A that is expressed in intestinal mucosal cells. Though it has been 20 years since such an interaction was discovered, little is still known about the relationship between the molecular characters of FCs and their inhibitory effects. Therefore, the chemical and physicochemical characterizations of the biological activities of FCs were examined by quantitative structure-activity relationship (QSAR) analysis using 37 types of FCs. Common logarithmic IC_{50} values of human liver microsomal testosterone 6 β -hydroxylations were configured as objective variables. A variety of structural, physicochemical, and quantum chemical descriptors were calculated from 2D and optimized 3D structures in the 37 FCs as explanatory variables. Simple and multiple linear regression analyses were used to evaluate these parameters. Constructed regression models were validated with leave-one-out cross validation and applicable regression diagnostic methods. As a result, logP value, molecular volume, molecular weight, molecular surface area, polar surface area, minimal electrostatic potential, formation energy, and homo energy of each FC were significantly related with the $\log IC_{50}$ value. These relationships indicate that molecular characteristics including lipophilicity, molecular size, electrostatic stabilization, and electron-donating ability of FCs can control FC-CYP interactions. These findings could be useful to predict CYP inhibitory effects of other FCs in foods, drinks, and other natural products such as grapefruit juice and herbal drugs.

1. Introduction

Grapefruit juice is known to undergo pharmacokinetic interactions, cause increase in plasma drug concentrations, with a variety of medical drugs (Uesawa and Mohri 2008a). The mechanism for the interactions was suggested to be a specific inhibition of CYP3A (Lown et al. 1997; Schmiedlin-Ren et al. 1997) in intestinal mucosal epithelium by furanocoumarin derivatives (FCs) such as bergamottin (FC24), 6',7'-dihydroxybergamottin (FC26), and paradiscins (FC28, FC29, and FC32) (Schmiedlin-Ren et al. 1997; Guo et al. 2000a, b; Fukuda et al. 2000; Wangenstein et al. 2003) in grapefruit juice (Lown et al. 1997; Schmiedlin-Ren et al. 1997) (Fig. 1). This affects disconcertion of barrier dysfunction in the intestine. As a result, plasma concentrations of drugs that are substrates of CYP3A increased due to increased absorption. FCs exist in citrus fruits such as lime (Saita et al. 2004) and pomelo (Uesawa and Mohri 2005) and umbellifers (Fujioka et al. 1999) as well as grapefruit. Like grapefruit, foods, drinks, and medicines from these plants might affect drug absorption. In fact, it was reported that pomelo juice, which has 8 kinds of FCs (Uesawa and Mohri 2005), increased the bioavailability of cyclosporine A (Grenier et al. 2006), an immunomodulating agent and a substrate of CYP3A. In one study, IC_{50} values of a

variety of FCs on testosterone 6 β -hydroxylation were evaluated using human liver microsomes as the inhibitory effects (Guo et al. 2000b). However, there is no report on the structural characterization of FC molecules, and some points are still unclear regarding the relationship between the CYP-inhibitory effects and physicochemical profiles of FCs. Therefore, the quantitative structure-activity relationship (QSAR) study on the CYP3A inhibitory effects of FCs was designed such that the structural, physicochemical, and quantum chemical properties on FCs can be elucidated by of computational chemical predictions.

2. Investigation, results and discussion

IC_{50} values (Table 1) were taken from the literature and used as parameters that indicate the CYP3A inhibitory effect of the 37 kinds of FCs (Fig. 1) (Guo et al. 2000b). Common logarithms of the parameters ($\log IC_{50}$) were used as objective variables in the present regression analyses as it was confirmed by a Shapiro-Wilk test that the $\log IC_{50}$ values were within the normal range. Table shows the regression coefficients, intercepts, and determination coefficients of the explanatory variables in the simple regression analyses and the $\log IC_{50}$ values and p-values in the analyses of variances on the regression equations.

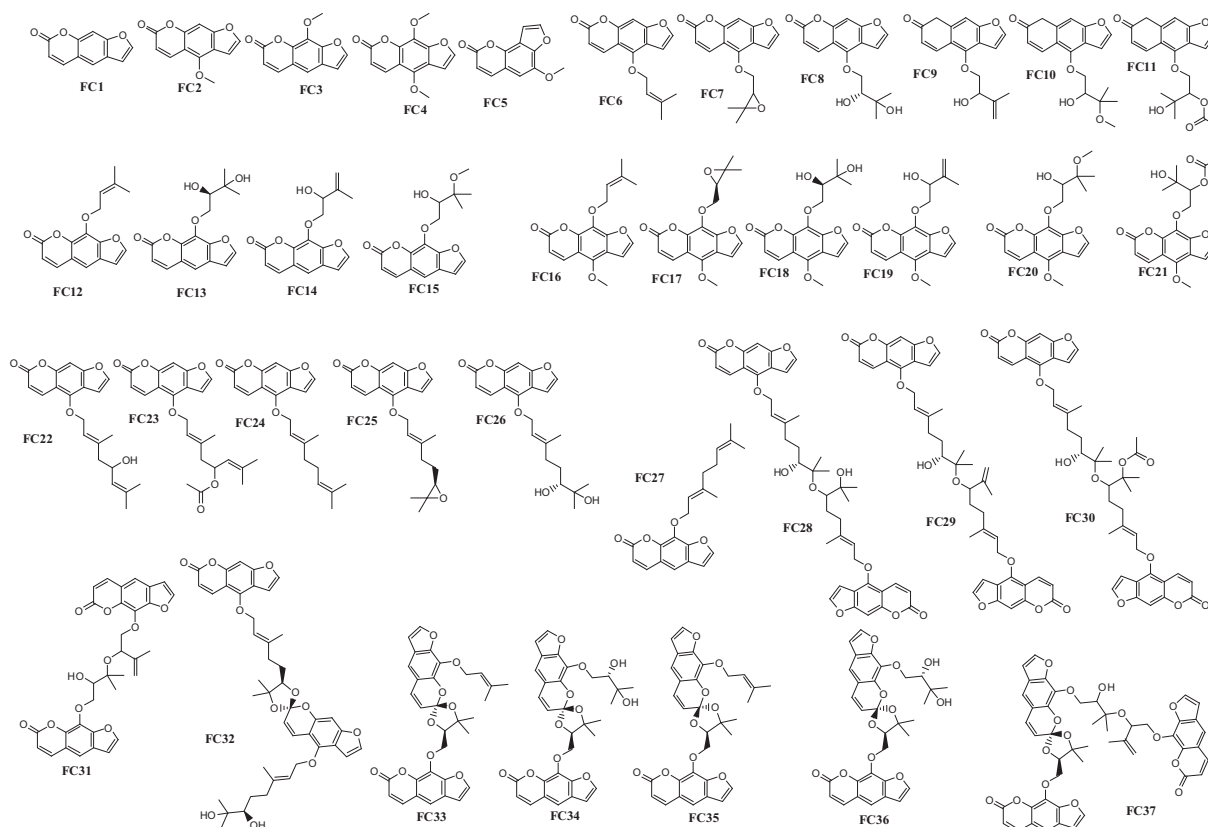


Fig. 1: Chemical structures of FCs

2.1. Effects of lipophilicity

A scatter plot of Ghose-Crippen-Viswanadhan octanol-water partition coefficient (AlogP) values (Ghose and Crippen 1986; Viswanadhan et al. 1993), a descriptor of lipophilicity (logP), and log IC₅₀ values is shown in Fig. 2A. However, FC24, bergamottin, was an outlier in the plotting. All FCs except FC24 were highly interrelated with log IC₅₀ values in the quadratic function ($r=0.901$) more than the linear function ($r=0.855$). Since Hansch and Fujita (1964), proposed a QSAR analytical method (Hansch and Fujita 1964), non-linear relationships have been found between log P values and physiological/biological activities including absorptions (Lien 1970), distributions (Laznick et al. 1985), metabolisms (Devinsky and Gorrod 1987), and excretions (Laznick et al. 1985) of compounds like medicines. In other words, lipophilicities of compounds have optimum values on multiple bioactivities. In the present study, the log P value of the maximal CYP3A-inhibition of FCs was estimated at 7.6. Log P value of FC30 indicating the highest activity of the inhibition was also 8.0. These findings suggest that lipophilicities of FCs contribute to the interactions with the CYP3A protein. We reported a relationship between log P values of 1,4-dihydropyridine derivatives and pharmacokinetic interaction strength of grapefruit juice in clinical research (Uesawa and Mohri 2008b). This finding is related to the CYP inhibition by FCs discussed in the present study, and suggests that lipophilicity contributes to the interaction between these compounds and the CYP3A protein as the pharmaceutical effect of grapefruit juice is due to inhibition of intestinal CYP3A by FCs present in grapefruit juice.

2.2. Effect of molecular size

Descriptors involved in molecular size such as molecular volume (MV), molecular surface area (MA), molecular weight (MW),

and heat of formation (E) indicated a good correlation with the log IC₅₀ values (Table 2). Fig. 2B shows a scatter plot of molecular volumes against log IC₅₀ values. These findings indicate that larger sizes of FCs have stronger inhibitory effects, and molecular size might be an important factor in the FCs-CYP3A interactions. It was assumed that a flexible binding pocket for FCs may be present on the enzyme. This assumption corresponds with the multiple substrate specificity of CYP3A (Schrag and Wieners 2001). All descriptors related with molecular size correlated with the log P values (Table 3). It was suggested that increase in size contributes to the hydrophobic interaction via lipophilicity of FCs.

2.3. Effect of electrostatic potential

Polar surface area (PSA) and minimal electrostatic potential (MEP) correlated with log IC₅₀ values significantly (Table 2). Fig. 2D and 2E show scatter plots of PSA against log IC₅₀, and MEP against log IC₅₀, respectively. PSA in this study indicates the total superficial area of hydroxyl and amino groups exposed from the molecule. FC with a larger PSA indicated more potent inhibition of CYP3A activities. This result suggests that hydrogen bonding and electrostatic binding contribute to the stabilization of interactions between the inhibitors and the enzyme. PSA correlated with the parameters involved in molecular size such as MV and MA (Table 3). This correlation could have resulted because PSA is a part of the total molecular surface area, MA. On the other hand, FCs with a smaller MEP tended to have more potent inhibitory effects on CYP3A activity. The electrostatic parameter should be independent of molecular size. In fact, MEP hardly correlated with the molecular size parameters and log P (Table 3). These relationships suggest that electrostatic interaction is an important factor in the FC-CYP interactions independent of hydrophobic binding.

Table 1: Calculated physicochemical properties and IC₅₀ values of FCs

FC no.	AlogP	MW (amu)	MV (Å ³)	MA (Å ²)	E (kJ/μmol)	PSA (Å ²)	MEP (kJ/mol)	E _{HOMO} (kJ/mol)	IC ₅₀ (μM)
FC 1	2.20	186	179	191	-1.70	29.4	-203	-597	5.1
FC 2	2.19	216	206	220	-2.00	36.7	-204	-592	3.1
FC 3	2.19	216	206	220	-2.00	34.6	-211	-562	2.9
FC 4	2.17	246	233	249	-2.30	41.8	-215	-550	1.9
FC 5	2.19	216	206	220	-2.00	35.0	-203	-555	25
FC 6	3.65	270	275	295	-2.41	36.3	-206	-584	2.9
FC 7	2.49	286	281	300	-2.61	47.8	-200	-595	1.8
FC 8	1.72	304	294	314	-2.81	72.1	-195	-600	3.8
FC 9	2.60	284	292	311	-2.52	48.9	-196	-581	1.5
FC 10	1.99	316	323	342	-2.82	54.2	-194	-585	18
FC 11	1.96	344	344	367	-3.12	67.0	-203	-579	8.4
FC 12	3.65	270	275	294	-2.41	34.2	-218	-556	1.1
FC 13	1.72	304	294	314	-2.81	70.1	-196	-583	30
FC 14	2.74	286	283	304	-2.61	53.9	-212	-565	4.8
FC 15	2.13	318	314	336	-2.91	61.6	-181	-601	35
FC 16	3.64	300	303	324	-2.71	41.4	-218	-544	1.0
FC 17	2.47	316	308	329	-2.91	53.5	-199	-565	3.2
FC 18	1.70	334	321	343	-3.11	77.4	-197	-571	5.8
FC 19	2.72	316	310	333	-2.91	61.2	-212	-555	2.6
FC 20	2.11	348	342	365	-3.21	68.9	-182	-591	19
FC 21	2.08	376	361	383	-3.51	76.1	-195	-588	4.3
FC 22	4.38	354	370	397	-3.12	55.8	-202	-587	0.44
FC 23	4.76	396	411	440	-3.52	56.5	-216	-576	0.42
FC 24	5.48	338	363	388	-2.93	36.3	-205	-583	22
FC 25	4.18	354	368	393	-3.12	47.7	-218	-570	0.67
FC 26	3.41	372	381	399	-3.32	70.6	-191	-578	1.9
FC 27	5.48	338	363	387	-2.93	36.5	-204	-573	0.59
FC 28	7.59	727	742	762	-6.45	111.5	-211	-573	0.086
FC 29	8.61	709	730	741	-6.25	92.8	-203	-543	0.15
FC 30	7.97	769	781	779	-6.85	109.8	-185	-590	0.052
FC 31	5.23	573	557	570	-5.22	93.0	-224	-571	0.16
FC 32	8.35	727	734	746	-6.45	99.7	-225	-525	0.62
FC 33	6.90	557	543	559	-5.02	72.9	-234	-527	0.23
FC 34	4.96	591	560	564	-5.42	97.9	-225	-552	0.32
FC 35	6.90	557	543	557	-5.02	71.7	-241	-526	0.21
FC 36	4.96	591	562	578	-5.42	106.2	-204	-557	0.42
FC 37	8.47	859	824	833	-7.83	127.5	-214	-515	0.19

MW, molecular weight; MV, molecular volume; MA, molecular surface area; E, heat of formation; PSA, polar surface area; MEP, minimal electrostatic potential; E_{HOMO}, HOMO energy

2.4. Quantum chemical parameter

FCs' HOMO energy, a quantum chemical parameter, was significantly related with log IC₅₀ value (Table 2 and Fig. 2F). FC with a large HOMO energy tended to have relatively potent inhibitory effect on the oxidation activity of CYP3A. This parameter is known to be involved in the electron-releasing properties of molecules. This finding indicates that charge transfer from FC molecules to the CYP protein contributes to the binding affinity in the interaction. It was reported that HOMO energy was an

important descriptor for dog liver microsomal oxidation of 1,4-dihydropyridine derivatives that constitute a category of CYP3A substrates (Bäårnhelm and Westerlund 1986). Our result is in excellent agreement with that.

2.5. Construction of a prediction model

We attempted to construct multiple regression equations using descriptors and their square values that were calculated in this

Table 2: Simple linear regression analysis for each explanatory variable

Explanatory variable	Regression coefficient	Intercepts	R ²	p-value
AlogP	0.272 ± 0.035	1.30 ± 0.16	0.630	<0.0001
MW (amu)	0.00315 ± 0.00049	1.47 ± 0.21	0.542	<0.0001
MV (Å ³)	0.00319 ± 0.00049	1.48 ± 0.21	0.551	<0.0001
MV (Å ²)	0.00324 ± 0.00050	1.56 ± 0.22	0.549	<0.0001
E (kJ/μmol)	0.349 ± 0.056	1.48 ± 0.22	0.530	<0.0001
PSA (Å ²)	0.0161 ± 0.0042	1.25 ± 0.29	0.300	0.0004
MEP (kJ/mol)	0.0289 ± 0.0082	6.18 ± 1.70	0.261	0.0012
E _{HOMO} (kJ/mol)	0.0157 ± 0.0051	-8.74 ± 2.88	0.217	0.0037

MW, molecular weight; MV, molecular volume; MA, molecular surface area; E, heat of formation; PSA, polar surface area; MEP, minimal electrostatic potential; E_{HOMO}, HOMO energy

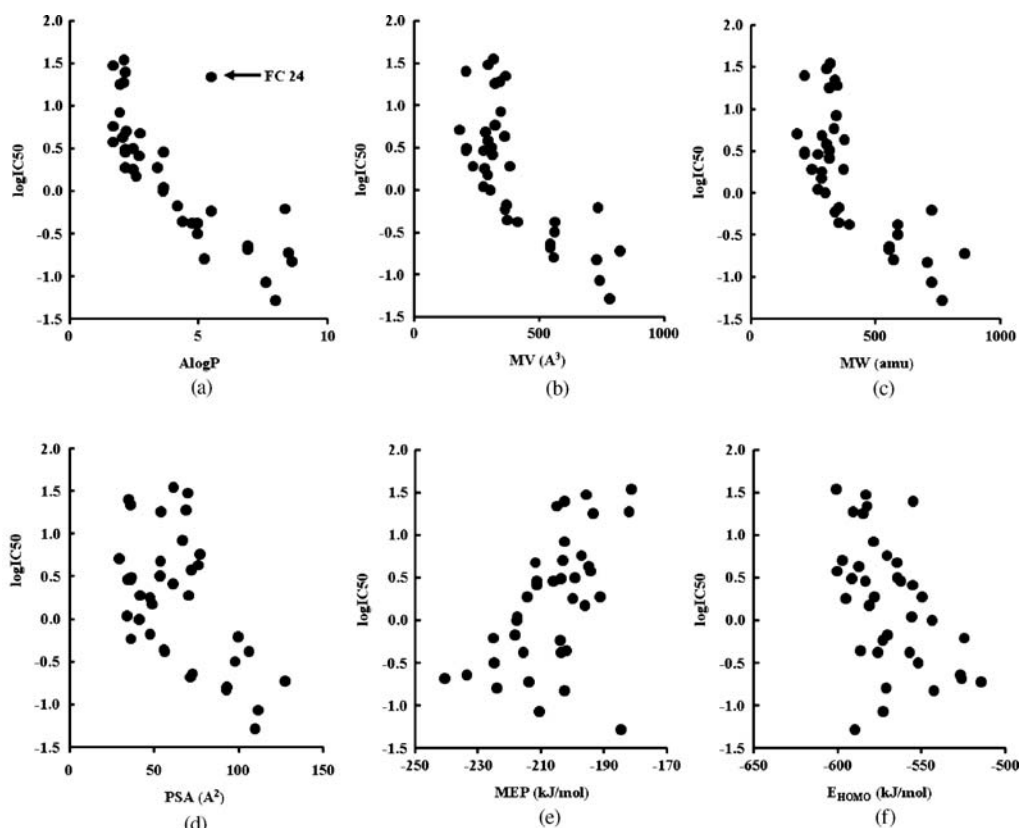


Fig. 2: Relationship between AlogP values of FCs and the corresponding logarithmic IC_{50} values of CYP3A activities

study. The regression models including not more than 7 descriptors were searched by the genetic algorithm approach (Leardi et al. 1992) with leave-one-out cross-validation (Cruciani et al. 1992) as the selection pressure. Furthermore, 100 constructed models were prioritized by bootstrap validation (Efron et al. 1987) and regression diagnostics. As a result, the best model was a quadratic function with $\log P$ and $\log P^2$ (Fig. 3). The final model is

$$\begin{aligned} \log IC_{50} &= 1.44(\pm 0.12) - 0.385A \log P(\pm 0.037) \\ &\quad + 0.0528(A \log P - 4.00)^2(\pm 0.0141) [n = 36, R^2 \\ &= 0.812, Q^2(\text{leave-one-out}) \\ &= 0.775, Q^2(\text{bootstrap}) \\ &= 0.775, F = 71.1, s = 0.11] \end{aligned}$$

Bootstrap-validated R^2 ($Q^2_{\text{bootstrap}}$) in the model was 77.5% and the regression diagnostics showed normal results. On the other hand, all models with Q^2_{boot} exceeding this value indi-

cated anomalous results in Variance-Inflation-Factors (VIF) and/or Lack-of-Fit (LOF) test. Variation of $\log IC_{50}$ values was interpretable in $\log P$ because the contribution ratio of the regression model constructed from $\log P$ was 81.2% for 36 FCs except FC24. In this model, only FC24 showed a large Mahalanobis distance (4.17). The presence of an outlier on FC24 suggests that unknown physicochemical properties might differentiate the inhibitory effects of FC24 from that of the other FCs. The structural characteristics of FC24 are difficult to distinguish from those of the other FCs such as FC25, FC26, and FC27 with $\log P$ values close to that of FC24.

On the other hand, we have reported that an effect of FC24 (bergamottin) on nifedipine oxidation activity with rat-liver microsomes was greater than those of FC26 (6',7'-dihydroxybergamottin), FC2 (bergapten), and bergaptol (Mohri and Uesawa 2001). Herein, $\log P$ values of 6',7'-dihydroxybergamottin, bergapten and bergaptol, 3.41, 2.19 and 1.94, respectively, were lower than bergamottin's (5.48). This order of inhibitory effects of the FCs also perfectly correlates with the order from the model equation. In the model, the IC_{50} value of bergamottin was estimated at 280 nM. In fact, it

Table 3: Coefficients of internal correlations of the explanatory variables

	AlogP	MW	MV	MA	E	PSA	MEP	E_{HOMO}
AlogP	1.000	0.887	0.907	0.907	-0.871	0.620	-0.451	0.579
MW	0.887	1.000	0.997	0.995	-0.999	0.905	-0.281	0.513
MV	0.907	0.997	1.000	1.000	-0.992	0.883	-0.267	0.492
MA	0.907	0.995	1.000	1.000	-0.990	0.882	-0.265	0.488
E	-0.871	-0.999	-0.992	-0.990	1.000	-0.917	0.281	-0.518
PSA	0.620	0.905	0.883	0.882	-0.917	1.000	-0.067	0.338
MEP	-0.451	-0.281	-0.267	-0.265	0.281	-0.067	1.000	-0.738
E_{HOMO}	0.579	0.513	0.492	0.488	-0.518	0.338	-0.738	1.000

MW, molecular weight; MV, molecular volume; MA, molecular surface area; E, heat of formation; PSA, polar surface area; MEP, minimal electrostatic potential; E_{HOMO} , HOMO energy

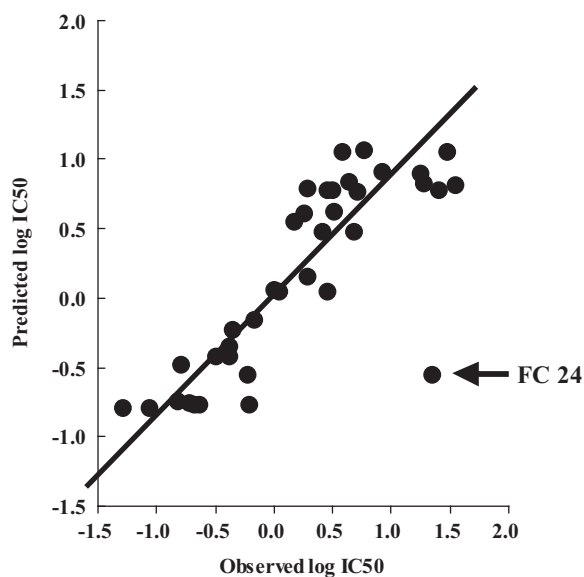


Fig. 3: Linear regression between predicted and observed values of IC_{50} in CYP3A activities of FCs obtained in the model with AlogP and AlogP²

became evident that bergamottin is one component involved in the grapefruit juice-drug interaction that results in inhibition of the CYP3A enzyme in the intestinal lumen *in vivo* (Goosen et al. 2004). Goosen et al. reported a significant increase in felodipine AUC when subjects concomitantly received bergamottin at the same concentration as in grapefruit juice. These findings and our estimation from the regression model suggest that bergamottin could be an important factor in the grapefruit juice-interactions.

2.6. Conclusion

Structural, physicochemical and quantum chemical features contributing to the inhibitory effects of FCs on CYP3A activities were extracted in a variety of FCs. As a result, it was shown that lipophilicity, molecular size, electrostatic feature, and homo energy of the compounds were significantly important factors. The quadratic equation with log P values as a descriptor was the most applicable model. These finding might be useful to determine the safety of pharmaceutical interactions with furanocoumarin-included foods, drinks, and other natural products such as grapefruit juice and herbal drugs. These results suggest that hydrophobic bonding, static attraction, and charge transfer interaction were involved in the interactions between FCs and CYP3A protein.

3. Experimental

3.1. Data set

IC_{50} values of testosterone 6 β -hydroxylation activities with human liver microsomes of 37 kinds of FCs usable for the QSAR study were taken from the literature (Guo et al. 2000b), and the logarithm of the values were used as the objective variables of this study. A list of the structures and their corresponding experimental activities are shown in Fig. 1 and Table 1.

3.2. Molecular descriptor

The minimal energy conformation of each FC was searched using Merck Molecular Force Field (MMFFaq), and then single point energy was refined by DFT calculation (B3LYP/6-311+G**) using Spartan'06 for Windows (Wavefunction, Inc., Irvine, CA, U.S.A.). The geometric, electronic, and physicochemical features of the FCs including MW, MV, MA, E, PSA, MEP, HOMO energies, LUMO energies, dipole moments, electronegativities, chemical hardness, reaction indices, and maximal electrostatic potentials were sought from the compounds. AlogP descriptors as estimation values of logP were calculated by Dragon software version 5.5 (Talet srl, Pisani, Milano, Italy) from 2D-structure information of FCs.

3.3. Multiple linear regression analysis

The relation between the objective variables and the descriptors was investigated using statistical techniques including multi-regression analysis with variable subset selection-genetic algorithm (VSS-GA) by MobyDigs software version 1.0 (Talet). To test the quality of the regression equation, the coefficient of determination in the cross-validation test using the "leave-one-out" method was also the statistical parameter. Furthermore, to verify the validity and stability of the model obtained, the bootstrap-validation test by MobyDigs and regression diagnostics using VIF, Mahalanobis distance, and LOF test by JMP version 8.0.1 (SAS Institute Inc., Cary, NC, U.S.A.) were performed.

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