

Quantitative Structure-Cytotoxicity Relationship Analysis of 3-Formylchromone Derivatives by a Semiempirical Molecular-orbital Method with the Concept of Absolute Hardness

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Abstract. A semiempirical molecular-orbital method (C_AC_he) was applied to delineate the relationship between the cytotoxicity (evaluated by 50% cytotoxic concentration, CC₅₀) of 11 3-formylchromone derivatives and 15 chemical parameters (descriptors). The most stable conformation of all these compounds was exhibited by the planar structure. Compounds [2], [3], [4] and [9] had additionally protruding branches from the coplanar. In HSG cells, the best correlation coefficient was observed between CC₅₀ and stability of hydration (ΔH), followed by electron affinity, lowest unoccupied molecular orbital energy (E_{LUMO}), highest occupied molecular orbital energy (E_{HOMO}), ionization potential, absolute electron negativity (χ) and reactivity index (ω). When the value for [1], which was off from the regression line, was omitted, higher correlation coefficients were obtained between CC₅₀ and electron affinity, E_{LUMO}, χ and ω . When CC₅₀ value was plotted vs. log P, a parabolic curve was produced, under the condition that the data for [5] were omitted. In HL-60 cells, moderate correlation was found between CC₅₀ and ΔH , electron affinity, E_{LUMO}, χ and ω . When the values for [1] and [6], which were off the regression line, were omitted, higher correlation coefficients were obtained between CC₅₀ and these five descriptors. In HSC-3 cells, there was moderate correlation between CC₅₀ and the dipole moment, but not with other descriptors. In HSC-2 and MT-4 cells, there was no clear-cut correlation between CC₅₀ and any of these descriptors. The present study indicates the applicability of HSG cells in searching for more active 3-formylchromone derivatives, using QSAR with the concept of absolute hardness.

The chromones (4H-1-benzopyran-4-ones) have been reported to exhibit antifungal, antiviral, antimicrobial, antiallergic, antitubulin and antitumor activities (1-4). In addition, many flavonoids are based on the chromone structure and have been found to possess therapeutically interesting biological activities (5). We recently reported some tumor-specific cytotoxic activity and anti-*Helicobacter pylori* activity of eleven 3-formylchromones (Figure 1) and four related compounds (6). Here, we investigated the quantitative structure-activity relationship (QSAR) of these 3-formylchromones, using conventional and recent techniques of computational chemistry, such as the concept of chemical hardness (7-9). The chemical hardness is a parameter that determines the softness and hardness of the test compound. In general, the softness means the higher reactivity whereas the hardness means the poorer reactivity. “Soft” molecule tends to affect profoundly on the biological system, whereas “hard” molecule is expected to have little or no biological activity.

Materials and Methods

Calculation. The most stable conformation of eleven 3-formylchromones was calculated by CONFLEX 5 (Confluex Co. Ltd., Tokyo). The optimization of the structure was achieved using a semiempirical molecular-orbital method (PM3), using a C_AC_he Worksystem 4.9 MOPAC (PM3) (Fujitsu Co. Ltd., Tokyo). The following descriptors were used: heat of formation (COSMO, non-COSMO; Kcal/mole), stability of hydration (=COSMO - nonCOSMO (ΔH); Kcal/mole), dipole moment (D), electron affinity (eV), ionization potential (eV), log P, highest occupied molecular orbital energy (E_{HOMO}; eV), lowest unoccupied molecular orbital energy (E_{LUMO}; eV), absolute hardness (η ; eV), absolute electron negativity (χ ; eV), reactivity index (ω ; eV), molecular weight (M.W.), length of molecule (Å), surface area (Å²) and volume range (Å³) (7) (Table I). The following equations were used to determine η , χ and ω :

$$\eta = (E_{LUMO} - E_{HOMO})/2$$

$$\chi = -(E_{LUMO} + E_{HOMO})/2$$

$$\omega = \chi^2/2\eta$$

The octanol-water distribution coefficients (log P) of [1-4, 6-11] were taken from a previous report (10). Log P of [5] was determined by ACD/log P DB6.0 (Fujitsu). QSAR between CC₅₀

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Key Words: 3-Formylchromone derivatives, QSAR, cytotoxicity, semiempirical molecular-orbital method, absolute hardness.

Table I. CC_{50} and chemical descriptors for the 3-formylchromone derivatives.

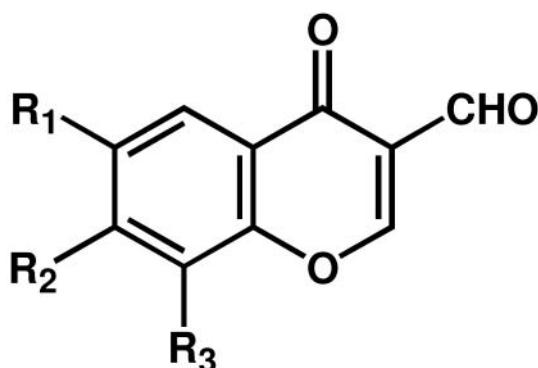
Compound	HSG cells CC_{50} (μM)	HL-60 cells CC_{50} (μM)	HSC-3 cells CC_{50} (μM)	HSC-2 cells CC_{50} (μM)	MT-4 cells CC_{50} (μM)	Heat of formation (Kcal/mole)	ΔH	Dipole moment (D)	Electron affinity (eV)	Ionization potential (eV)
[1]	332.0	59.0	225.0	89.0	177.0	-80.357	-16.644	6.801	0.847	9.727
[2]	128.0	13.0	184.0	47.0	211.0	-89.659	-16.538	6.925	0.849	9.542
[3]	95.0	20.0	172.0	42.0	49.0	-98.909	-16.379	6.881	0.850	9.612
[4]	166.0	30.0	99.0	80.0	474.0	-119.702	-18.311	5.461	0.896	9.365
[5]	546.0	78.0	262.0	84.0	162.0	-107.417	-36.827	7.883	1.315	10.047
[6]	91.0	8.0	165.0	22.0	88.5	-123.644	-17.66	6.27	0.943	9.715
[7]	92.0	17.0	73.0	46.0	85.8	-86.508	-16.84	6.327	0.923	9.510
[8]	169.0	41.0	81.0	64.0	111.0	-78.185	-17.948	6.259	0.940	9.770
[9]	115.0	30.0	102.0	42.0	86.2	-95.402	-16.667	6.753	0.943	9.489
[10]	215.0	52.0	117.0	56.0	361.0	-90.687	-16.631	5.334	1.042	9.443
[11]	216.0	40.0	131.0	75.0	278.0	-63.874	-18.767	5.244	1.068	9.823

Compound	$\log P$	E_{HOMO}	E_{LUMO}	η	χ	ω	M.W.	Length (\AA)	Surface area (\AA^2)	Volume range (\AA^3)
[1]	0.350	-9.727	-0.847	4.440	5.287	3.148	174.150	8.395	136.514	81.970
[2]	0.860	-9.542	-0.849	4.346	5.195	3.105	188.180	9.837	154.120	91.880
[3]	1.760	-9.612	-0.850	4.381	5.231	3.123	216.230	10.066	189.085	110.620
[4]	0.560	-9.365	-0.896	4.234	5.131	3.108	204.180	9.968	162.113	95.480
[5]	0.760	-10.047	-1.315	4.366	5.681	3.697	219.150	9.622	156.472	91.240
[6]	0.600	-9.715	-0.943	4.386	5.329	3.238	192.140	9.468	140.085	83.380
[7]	1.170	-9.510	-0.923	4.293	5.216	3.169	208.600	8.738	149.383	89.540
[8]	1.320	-9.770	-0.940	4.415	5.355	3.247	253.050	8.923	154.171	93.710
[9]	1.670	-9.489	-0.943	4.573	5.216	3.184	222.620	9.345	166.587	99.570
[10]	1.910	-9.443	-1.042	4.200	5.242	3.271	243.040	8.785	162.340	97.270
[11]	2.210	-9.823	-1.068	4.378	5.445	3.387	331.950	8.933	171.680	105.290

Table II. Correlation coefficients between CC_{50} against the indicated cell lines and each chemical descriptor.

Cell line	Heat of formation (Kcal/mole)	ΔH moment (D)	Dipole affinity (eV)	Electron potential (eV)	Ionization	$\log P$	E_{HOMO}	E_{LUMO}
HSG	0.001	0.719	0.184	0.565	0.470	C	0.470	0.566
HL-60	0.048	0.439	0.049	0.463	0.292	NC	0.292	0.463
HSC-3	0.038	0.345	0.449	0.118	0.382	C	0.382	0.118
HSC-2	0.090	0.189	0.000	0.121	0.115	C	0.115	0.121
MF-4	0.009	0.000	0.384	0.011	0.129	C	0.129	0.011
Cell line	η (eV)	χ (eV)	ω (eV)	M.W.	Length (\AA)	Surface area (\AA^2)	Volume range (\AA^3)	
HSG	0.711	0.616	0.636	0.001	0.001	0.037	0.059	
HL-60	0.433	0.486	0.486	0.032	0.002	0.007	0.013	
HSC-3	0.311	0.311	0.208	0.109	0.004	0.031	0.054	
HSC-2	0.134	0.141	0.141	0.037	0.009	0.007	0.007	
MF-4	0.035	0.035	0.000	0.037	0.028	0.003	0.003	

C: correlated, but r^2 values could be obtained due to the parabolic curve; NC: no parabolic curve was delineated.



Compd	R ₁	R ₂	R ₃
[1]	H	H	H
[2]	CH ₃	H	H
[3]	i-Pr	H	H
[4]	CH ₃ O	H	H
[5]	NO ₂	H	H
[6]	F	H	H
[7]	Cl	H	H
[8]	Br	H	H
[9]	Cl	CH ₃	H
[10]	Cl	H	Cl
[11]	Br	H	Br

Figure 1. The structure of the 3-formylchromone derivatives used.

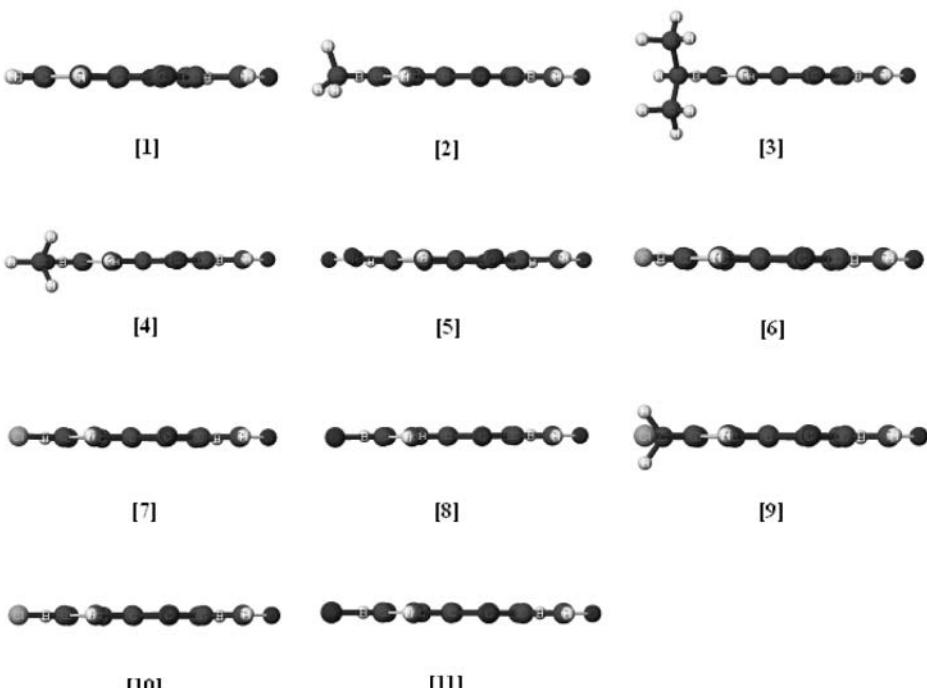


Figure 2. The most stable conformation of 3-formylchromone derivatives.

and each descriptor delineated from the molecular structure was investigated by a CAChE Worksystem 4.9 project reader. 3-Formylchromone derivatives were prepared as described elsewhere (6). Cytotoxicity assay and determination of 50% cytotoxicity (CC_{50}) against human submandibular gland carcinoma HSG, human oral squamous cell carcinoma HSC-2, HSC-3, human promyelocytic leukaemia HL-60 and human T-cell leukaemia MT-4 cell lines were performed as described elsewhere (6).

Results and Discussion

By determining the most stable conformation of eleven 3-formylchromone derivatives, their structure was approximated to the molecular form present *in vivo* (biomimetic). The most stable structure was next determined by a CAChE Worksystem 4.9 MOPAC (PM3) (Figure 2). The most stable conformation of all these compounds was found in the planar structure. Compounds [2], [3], [4] and [9] had additionally protruding branches from the coplanar surface (Figure 2). The CC_{50} value (determined by experiments) of 3-formylchromone derivatives against HSG, HL-60, HSC-3, HSC-2, MT-4 cells, and their respective chemical descriptors as determined by calculation are given in Table I. Using these values, whether there are any correlations between the CC_{50} and any of the descriptors was investigated (Table II) and the regression lines were drawn (Figure 3).

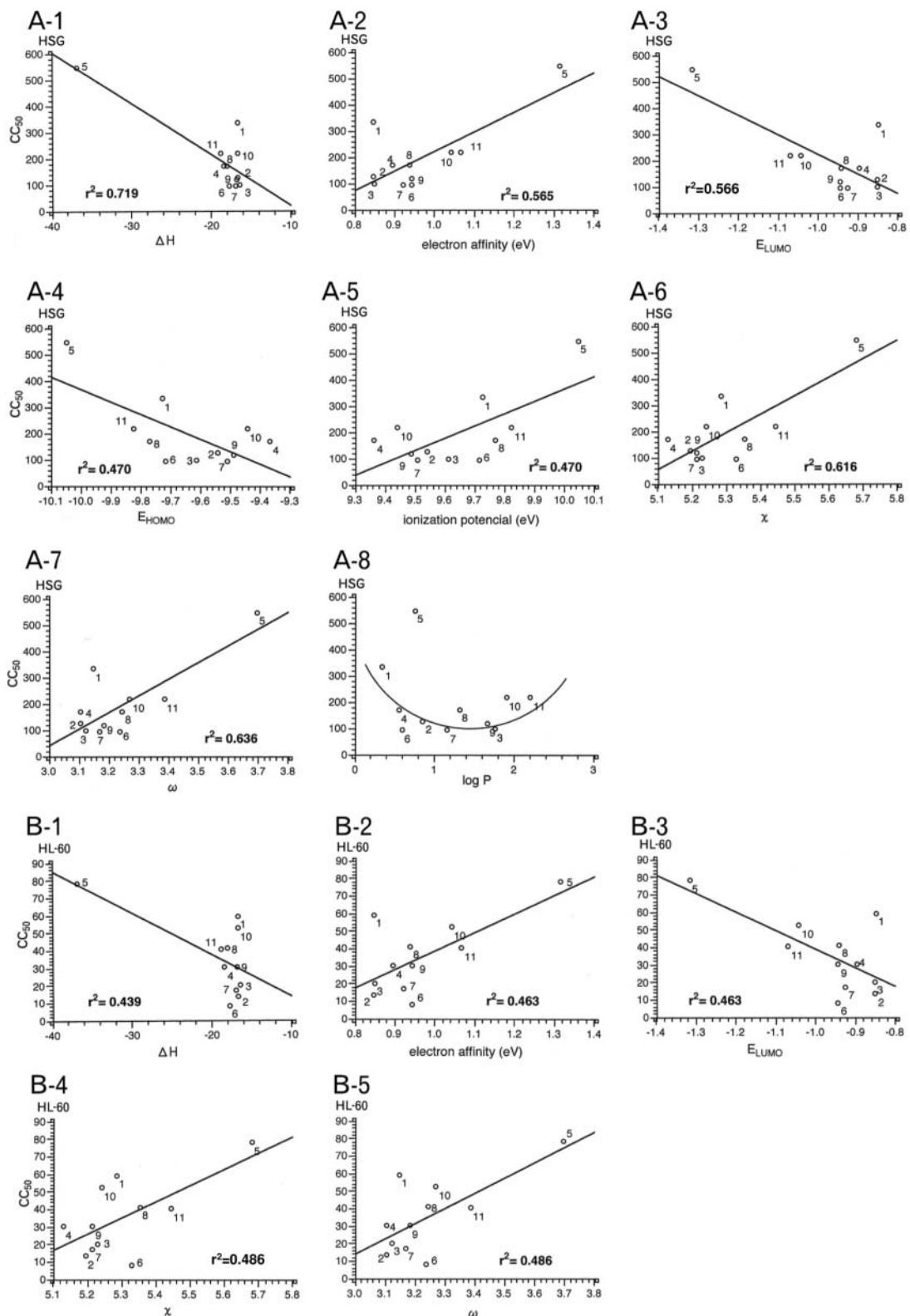


Figure 3. Correlation between CC_{50} values and each chemical descriptor of 3-formylchromone derivatives against HSG (A-1 to A-8) and HL-60 (B-1 to B-5) cells.

In HSG cells, the best correlation coefficient was observed between the CC_{50} and ΔH ($r^2=0.719$; A-1; Figure 3), followed by that with electron affinity ($r^2=0.565$; A-2), E_{LUMO} ($r^2=0.566$; A-3), E_{HOMO} ($r^2=0.470$; A-4), ionization potential ($r^2=0.470$; A-5), χ ($r^2=0.616$; A-6) and ω ($r^2=0.636$; A-7) (Table II). When the value for [1] for ΔH , which was an outlier from the regression line, was omitted, higher correlation coefficients were produced ($r^2=0.906$) (data not shown). The omission of [1] also elevated the correlation coefficient for electron affinity, E_{LUMO} , χ and ω to 0.872, 0.872, 0.711 and 0.835, respectively (data not shown). When CC_{50} values were plotted vs. $\log P$, a parabolic curve was produced, under the condition that the data for [5] were omitted (Figure 3, A-8).

In HL-60 cells, moderate correlation was found between the CC_{50} and five descriptors: ΔH ($r^2=0.439$; B-1), electron affinity ($r^2=0.463$; B-2), E_{LUMO} ($r^2=0.463$; B-3), χ ($r^2=0.433$; B-4) and ω ($r^2=0.486$; B-5) (Table II). When the values for [1] and [6], which were outliers, were omitted, the correlation coefficient for ΔH , electron affinity, E_{LUMO} , χ and ω were elevated up to 0.595, 0.777, 0.777, 0.520 and 0.700, respectively (data not shown).

In HSC-3 cells, there was moderate correlation between the CC_{50} and dipole moment ($r^2=0.449$), but not with other descriptors (Table II).

In HSC-2 and MT-4 cells, there was no clear-cut correlation between the CC_{50} and any descriptors (Table II).

In conclusion, the best correlation was found between the CC_{50} and descriptors in HSG cells. This cell line may provide the opportunity to seek more active 3-formylchromone derivatives, using QSAR with the concept of absolute hardness.

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