Three-Dimensional Quantitative Structure Activity Relationship Studies on the Flavone Cytotoxicity and Binding to Tubulin

Ja Hong Kim*, Sung Ho Sohn and Sun Wan Hong[1]

Department of Chemistry Education, Chonbuk National University, Chonju 561-756, Korea

[1]Department of Chemistry, Woosuk University, Wanju 565-701, Korea

Three-Dimensional Quantitative Structure-Activity Relationship(QSAR) has been investigated over 67 flavonoids to correlate and predict GI_{50} values. The partial least-squares(PLS) model was performed to calculate the activity of each derivatives, and this was compared with the actual value. The results of the cross-validated(γ^2=0.997) values show that cytotoxic activities play an important role which is in good agreement with the observed GI_{50} values.

key words: 3D-QSAR, CoMFA, flavone cytotoxicity

INTRODUCTION

Flavonoids are ubiquitous in nature and have been reported to be weak cytotoxins in a variety of systems [1-5]. Flavones related to centaureidin (3,6,4'-trimethoxy-5,7,3'-trihydroxyflavone) were tested *in vitro* human tumor cell screen for cytotoxicity, and the resulting dose-response curves were analyzed for the differential cytotoxicity pattern and further demonstrated inhibitory effects on tubulin polymerization [6]. The structure of flavone derivatives is given below.

Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR)[7,8] is a powerful method for the design of bioactive compounds and the prediction of corresponding activity with GI_{50} values. The purpose of this research was to design 3D-QSAR models by analysis of training set containing 67 molecules.

From the theoretical and experimental results, a reasonable flavone model for promising activity is proposed.

COMPUTATION

A series of 67 flavone derivatives were used in this work.

The computational calculations were performed using the molecular modeling software, Sybyl 6.5.3 version on a Silicon Graphics with the standard bond lengths and angles [9]. The probe used to compute the Comparative Molecular Field Analysis(CoMFA) steric and electrostatic fields was the default sp^3 carbon with a +1 charge. The initial structures were optimized using a molecular mechanics method with Tripos force field and atomic charges were calculated by Gasteiger

Hückel method [10,11].

RESULTS AND DISCUSSION

The results of 3D-QSAR calculations are summarized in Table 2. The geometry optimization of 67 flavone derivatives was performed to obtain fixed core structure using the minimizing interparameter correlations by ab initio calculation with 6-31G basis set of Gaussian 98 program [12].

In Table 2, the best 3D-QSAR model [13] can be used as a molecular design of the various structure of flavone derivatives in tubulin polymerization.

The optimum value is the observed significance probability of obtaining a greater F value by chance alone if a 3D-QSAR model fits no better than the overall response mean. The flavone derivatives produced good cross-validated results and conventional value (γ^2=0.921, standard error of estimate= 0.6555) with the optimum components by CoMFA analysis.

Table 2 compares measured GI_{50} with calculated GI_{50} by CoMFA methods for flavone derivatives, and it illustrates this correlation graphically.

Low energy conformation was investigated using a systematic and grid conformational search. All the structures generated were aligned in a 3D lattice by fitting them with flavone derivatives.

In the case of the molecules 39, 40, 43, they express good correlations with measured GI_{50}. This correlation patterns represent that these descriptors can describe biological activities effectively.

The partial least-square(PLS) model was performed to calculate the activity of each derivative and this was compared with the actual value in Table 2.

Table 2 shows that the CoMFA indicates satisfactory agreement between observed and calculated GI_{50} values.

Table 1. The structure of flavone derivatives in the training sets

Compound	C-3	C-5	C-6	C-7	C-8	C-3'	C-4'	C-5'
FLA 23	-OH	-OH	-OCH₃	-OCH3	-H	-OH	-OCH₃	-H
FLA 24	-OH	-OH	-OCH₃	-OH	-H	-H	-OCH₃	-H
FLA 25	-OH	-H	-H	-OCH₃	-H	-H	-OCH₃	-H
FLA 26	-OH	-H	-H	-OCH₃	-H	-OCH₃	-OCH₃	-H
FLA 27	-OH	-H	-H	-H	-H	-2', 4', 6' - tri - MeO		
FLA 28	-OH	-OCH₃	-H	-OCH₃	-H	-OCH₃	-OCH₃	-H
FLA 29	-OH	-OH	-H	-OCH₃	-H	-OH	-OH	-H
FLA 30	-OH	-OCH₃	-OCH₃	-OCH₃	-H	-OH	-OCH₃	-H
FLA 31	-OH	-H	-H	-OH	-H	-OH	-OH	-H
FLA 32	-OH	-H	-H	-H	-H	-OCH₃	-OCH₃	-H
FLA 33	-OH	-OH	-H	-OH	-H	-OH	-OH	-OH
FLA 34	-OH	-OH	-H	-OCH₃	-H	-OH	-OCH₃	-H
FLA 35	-OH	-OH	-H	-OH	-H	-OH	-OH	-H
FLA 36	-OH	-H	-H	-H	-H	-H	-OCH₃	-H
FLA 37	-H	-OH	-OCH₃	-OCH₃	-OCH₃	-OH	-OH	-H
FLA 38	-H	-OH	-OCH₃	-OH	-H	-OH	-OCH₃	-H
FLA 39	-H	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-H	i-Pr-O	-H
FLA 40	-H	-OH	-OCH₃	-OH	-H	-OCH₃	-OCH₃	-H
FLA 41	-H	-OH	-OCH₃	-OCH₃	-OCH₃	-H	-OCH₃	-OCH₃
FLA 42	-H	-H	-H	-H	-H	-OCH₃	-OCH₃	-OCH₃
FLA 43	-H	-OH	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-OCH₃
FLA 44	-H	-OH	-OCH₃	-OCH₃	-OCH₃	-OCH³	-OH	-H
FLA 45	-H	-OCH3	-OCH3	-OCH3	-OCH3	-2', 5' - di - MeO		
FLA 00	-H	-H	-H	-H	-H	-H	-H	-H
FLA 01	-OCH₃	-OH	-OCH₃	-OH	-H	-OH	-OCH₃	-H
FLA 02	-OCH₃	-OH	-OCH₃	-OCH₃	-OCH₃	-OH	-OCH₃	-H
FLA 03	-OCH₃	-OH	-H	-OH	-H	-OH	-OCH₃	-H
FLA 04	-OCH₃	-OH	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-H
FLA 05	-OCH₃	-OH	-OCH₃	-OCH₃	-OCH₃	-OCH₃	-OH	-H
FLA 06	-OCH₃	-OH	-H	-OH	-H	-OBn	-OCH₃	-H
FLA 07	-OCH₃	-OH	-H	-OCH₃	-OCH₃	-OCH₃	-OH	-H
FLA 08	-OCH₃	-OH	-H	-OEt	-H	-OH	-OCH₃	-H
FLA 09	-OCH₃	-CH₃	-CH₃	-OH	-H	-OH	-OCH₃	-H
FLA 10	-OCH₃	-AcO	-H	-OAc	-H	-H	-OCH₃	-H
FLA 11	-OCH₃	-OH	-OCH₃	-H	-OCH₃	-OCH₃	-OCH₃	-OCH₃
FLA 12	-OCH₃	-H	-OCH₃	-OH	-H	-OH	-OCH₃	-H
FLA 13	-OCH₃	-OH	-OCH₃	-OH	-OCH₃	-OH	-OH	-H
FLA 14	-OCH₃	-OH	-H	-OH	-H	-H	-OCH₃	-H
FLA 15	-OCH₃	-OH	-OCH₃	-OH	-OCH₃	-OCH₃	-OH	-H
FLA 16	-OCH₃	-OH	-H	-OCH₃	-H	-OH	-OCH₃	-H
FLA 17	-OCH₃	-OH	-OCH₃	-OH	-OCH₃	-OH	-OCH₃	-OCH₃
FLA 18	-OCH₃	-CH₃	-CH₃	-OCH₃	-H	-OH	-OCH₃	-H
FLA 19	-OCH₃	-OH	-OCH₃	-OH	-OCH₃	-OCH₃	-OCH₃	-OCH₃
FLA 20	-OCH₃	-OH	-H	-OCH₃	-H	-H	-OCH₃	-H
FLA 21	-OCH₃	-OCH₃	-OH	-OCH₃	-H	-OH	-OCH₃	-H
FLA 22	-OCH₃	-OH	-H	-OCH₃	-H	-OCH₃	-OCH₃	-H

It suggests that the CoMFA sampling 12, 13 of the steric and electrostatic interactions of flavone derivatives may be able to provide useful information about cytotoxicity and binding to tubulin.

In Table 2, sterically favored areas (contribution level 60%) are shown as green polyhedra; sterically disfavored area (contribution level 40%) are shown as yellow polyhedra. The value of the CoMFA γ^2 indicates satisfactory agreement between observed and calculated GI_{50}.

In conclusion, the results of CoMFA derived models were

Table 2. The cross-validated r^2 values from CoMFA methods

	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7
Training sets	-	40	39, 40, 43	-	43	4,43	4, 40, 43
PLS	GI_{50}-CoMFA3	GI_{50}-CoMFA3	GI_{50}-CoMFA3	$LogGI_{50}$-CoMFA3	$LogGI_{50}$-CoMFA3	$LogGI_{50}$-CoMFA3	$LogGI_{50}$-CoMFA3
Optimum Value	0.550	0.640	0.782	0.464	0.521	0.559	0.593
Number of Component	5	5	6	4	4	4	4
Standard Error of Estimation	1.011	0.972	0.655	0.279	0.262	0.244	0.235
R square	0.890	0.843	0.921	0.746	0.776	0.807	0.827
F values	55.074	64.673	110.110	45.420	52.783	62.672	67.225

available for the flavone derivatives to predict their biological activity. Further analysis of this data indicated that CoMFA calculation might predict the cytotoxicity and binding to tubulin.

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