J. Korean Soc. Appl. Biol. Chem. **53**(4), 440-445 (2010)

Article

Minimum Structural Requirements for Herbicidal Evaluation of 5-(R_1)-6-(R_2)-N-(R_3-Phenyl)-Pyrazine-2-Carboxamide Analogues as New Class Potent Herbicide

Jae-Heung Lee[1], Pyung-Keun Myung[2], Sang-Jin Kim[3], and Nack-Do Sung[4]*

[1]*Korea University of Technology and Education, Cheonan 330-708, Republic of Korea*
[2]*Department of Pharmacology, Chungnam National University, Daejeon 305-764, Republic of Korea*
[3]*Daejeon Health Sciences College, Daejeon 300-711, Republic of Korea*
[4]*Department of Applied Biology & Chemistry, Chungnam National University, Daejeon 305-764, Republic of Korea*

Received March 11, 2010; Accepted April 15, 2010

To search the minimum structural requirements for herbicidal evaluation of 5-(R_1)-6-(R_2)-*N*-(R_3-phenyl)-pyrazine-2-carboxamide analogues (1-19) as new class potent herbicide, 3D-QSARs models between the substituents (R_1-R_3) changes of the analogues and their herbicidal activity were derived and discussed quantitatively using comparative molecular field analysis (CoMFA) and comparative molecular similarity indice analysis (CoMSIA) method. The herbicidal activity of the optimized CoMFA model I was principally dependent on steric fields. Also, it was found that the optimized CoMFA model I with the sensitivity to the perturbation ($d_q^{2'}/dr^2_{yy'}$=0.959) and the prediction (q^2=0.414) produced by a progressive scrambling analyses were not dependent on chance correlation. Also, it was predicted that the herbicidal activity increases when large steric substituents were introduced to one part of *ortho*- and *meta*- position on *N*-phenyl ring as R_3-substituent and small steric substituents to the other part.

Key words: CoMFA, CoMSIA, 3D-QSARs, herbicidal activity, pyrazine-2-carboxamide analogues

Pyrazinamide family compound is used as a therapeutic agent of tuberculosis. To cure Verrucous Tuberculosis of skin and eyelid Tuberculosis [Cha *et al*., 2001], anti-fungal drugs like isoniazid and rifampicin are used merging with the compound [Bay and Roh, 2001]. Also, it is predicted that the compound will be used to cure a latency tuberculosis through merging remedy with RMP (rifampicin) [Choi *et al*., 2006]. 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuran-oside, which is one of a carboxamide family, made activation of MP-activated protein kinase in the undifferentiated thyroid cancer in order to prevent the growth of cancer cells and to stimulate natural death of the cells [Song, *et al*. 2006]. 1,2-benzothiazine-3-carboxamide (oxicam) species is known as a superior non steroidal anti-inflammatory drug [Suh, *et al*. 1987].

In case of *N*-phenyl-1,3,5-trimethylpyrazole-4-carboxamide, which has a pyrazole ring and is one of carboxamide analogues, it showed a high fungal activity against rice sheath blight disease [Kim *et al*., 1992]. Carboxamide, which was newly developed and is a carboxamide analogues, has an effect on divers plant diseases caused by Oomycetes [Ra *et al.,* 1995], which come from grapes, potatoes and vegetables etc., preventing the growth of mycelium after germination [Kim *et al*., 1999; Kim *et al*., 2004]. It has also an effect on the diseases which are resistant against fungal drugs of phenylamide family such as Metalaxyl.

Recently, the chloroplast obstruction drug like pyrazine-2-carboxamide analogues is eco-friendly and has no toxicity for human being [Hong *et al*., 2004]. It was found that the herbicidal activity was concerned with inhibition of oxygen evolution rate (OER) in photosynthesis by pyrazine-2-carboxamide analogues [Dolezal *et al*., 2006; 2008]. So far, to understand the physico-chemical properties

*Corresponding author
Phone: +82-42-821-6737; Fax.: +82-42-821-6731
E-mail: ndsung15@hanmail.net

doi:10.3839/jksabc.2010.068

and characteristics of substituents in the various molecular that contribute to the herbicidal activities, we have reported that the structure activity relationships on the herbicidal activity of 2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy-*N*-phenylpropionamides [Sung *et al.,* 2005], 5-benzofuryl-2-[1-(alkoxyimino)alkyl]-3-hydroxycyclohex-2-en-1-ones [Chung *et al.,* 2006], *O*,*O*-dialkyl-1-phenoxyacetoxy-1-methylphosphonates [Sung *et al.,* 2007; Soung *et al.,* 2010a], 2-*N*-phenylisoindolin-1-ones [Soung *et al.,* 2009], and thioureas [Soung *et al.,* 2010b] were evaluated and discussed quantitatively using 2 dimensional quantitative structure-activity relationships (2D-QSARs) [Hansh, 1976], holographic quantitative structure-activity relationships (HQSARs) [Lowis, 1997] and 3 dimensional quantitative structure-activity relationships (3D-QSARs) [Akamatsu, 2002] analyses.

To search the minimum structural requirements for herbicidal evaluation of 5-(R_1)-6-(R_2)-*N*-(R_3-phenyl)-pyrazine-2-carboxamide analogues (**1-19**) as new class potent herbicide, this study examines the correlation between the obstruction of OER according to the R_1-R_3 substituents changes of pyrazine-2-carboxamide analogues and herbicidal activity with comparative molecular field analysis (CoMFA) [Cramer *et al*., 1988b] and comparative molecular similarity indice analysis (CoMSIA) method [Klebe *et al*., 1994] based on 3D-QSARs.

Materials and Methods

Molecule modeling. Among R_1-R_3 substituted 5-(R_1)-6-(R_2)-*N*-(R_3-phenyl)-pyrazine-2-carboxamide (**1-19**) analogues as a substrate compound, we used literature values [Dolezal *et al*., 2008] for herbicidal activity of substituents (R_1-R_3) concerned with the chloroplast obstruction of spinach (*Spinacia oleracea* L.*)*. For 3D-QSARs analysis, Sybyl molecule modeling program (Ver. 8.1) [Tripos, 2001] is used. Through simulated annealing method [Kerr *et al.,* 1994], we searched the most stable form of optimized substrate molecules based on fundamental framework excluding substituents and alignmented the molecules (Fig. 1), by means of atom-based fit (AF) and field fit (FF) [Marshall *et al.,* 1979; Clark *et al.,* 1990] superimposing on the three dimensional space. 3D-QSARs models were derived from training set (n=14) among 19 data sets in total and we divided the herbicidal activity values (*Obs*.pI_{50}) by 3 groups of size. Then, we selected one or two from each group, established a test set (n=5) and finally examined the level of prediction of 3D-QSARs model.

PLS and scrambling analysis. To decide an optimized component number, final 3D-QSARs models were derived by partial least square (PLS) analysis [Cramer *et al.,* 1988a]. The results are shown as $r^2_{cv.}$ values (or q^2) through cross validation and it uses leave-one-out (LOO) method. 3D-QSARs model were finally derived by non-cross validation using obtained component number. The model is stable and predictable when correlativity is $r^2_{ncv.}$ ≥0.90 and predictability is q^2 (or $r^2_{cv.}$) ≥0.50. The contour maps on the three dimensional space are to analyze visually the structural characteristics of substrate molecules. And, we evaluated a chance correlation and a rate of dependency of CoMFA and CoMSIA model through progressive scrambling analysis [Clark and Fox, 2004].

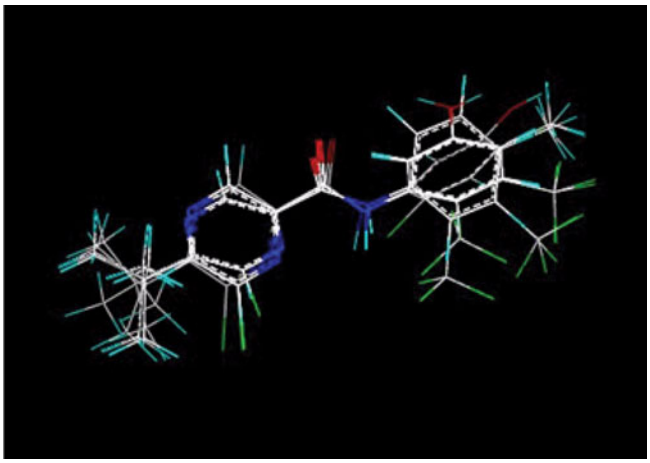
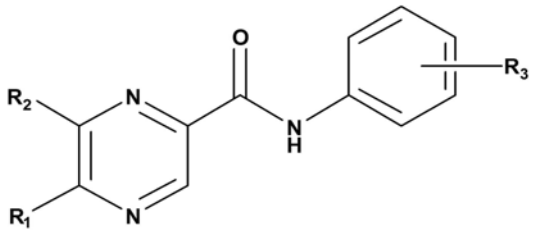


Fig. 1. Alignment of the potential energy minimized substrate structures according to a least-squares atom based fit.

Results and Discussion

Induction of 3D-QSAR models. In order to analyze informations about CoMFA and CoMSIA fields of derived model, we summarized observed herbicidal activity values (*Obs*.pI_{50}) of 5-(R_1)-6-(R_2)-*N*-(R_3-phenyl)-pyrazine-2-carboxamide (**1-19**) analogues and herbicidal activity values predicted by 3D-QSAR analysis (*Pred*.pI_{50}) and the differences (Dev.) between these two values on the Table 1. The herbicidal activity value of compound (**12**) was the biggest (pI_{50}=4.26) and the smallest (pI_{50}=2.82) one was compound number (**10**). Their difference was Δ*Obs*.pI_{50}=1.44. Table 2 indicates a grid (1.0~3.0Å) according to alignment methods (AF & FF) and statistic values of the models. The predictability of CoMFA 1 model ($r^2_{cv.}$ (q^2)=0.588, $r^2_{ncv.}$=0.978) which was derived from the condition of AF alignment combined with standard field, indicator field and hydrogen bonding field, is a little bit low but its correlativity was good. Component number was 5 and it was better than CoMSIA 1 model as an optimized model. Fig. 2 explains that statistic values of CoMFA 1 model are significant

Table 1. Observed herbicidal activity (*Obs.*pI_{50}) of R_1-R_3 substituted 5-(R_1)-6-(R_2)-N-(R_3-phenyl)pyrazine-2-carboxamide (1-19) analogues against spinach chloroplasts and predicted herbicidal activity (*Pred.*pI_{50}) by 3D-QSAR models



No.	Substituents (R)			Obs.pI_{50}	CoMFA I[a]		CoMSIA I	
	1	2	3		Pred.[b]	Δ[c]	Pred.[b]	Δ[c]
1	H	H	2-Cl, 5-OH	3.14	3.15	-0.01	3.21	-0.07
2	H	H	4-F	3.32	3.29	0.03	3.30	0.02
3	H	H	2-CF_3	3.42	3.47	-0.05	3.43	-0.01
4	H	H	3-CF_3	3.89	3.85	0.04	3.85	0.04
6	H	Cl	2-Cl, 5-OH	3.20	3.08	0.12	3.04	0.17
8	H	Cl	2-CF_3	3.25	3.26	-0.01	3.25	0.00
9	H	Cl	3-CF_3	3.64	3.63	0.01	3.66	-0.02
10	H	Cl	4-CH_3	2.82	2.94	-0.12	2.94	-0.12
11	$(CH_3)_3C$	H	4-F	3.28	3.23	0.05	3.24	0.04
12	$(CH_3)_3C$	H	2-CF_3	4.26	4.27	-0.01	4.31	-0.04
15	$(CH_3)_3C$	Cl	2-Cl, 5-OH	3.20	3.24	-0.04	3.23	-0.03
16	$(CH_3)_3C$	Cl	4-F	3.99	4.09	-0.10	4.06	-0.07
18	$(CH_3)_3C$	Cl	3-CF_3	3.76	3.73	0.03	3.77	-0.01
19	$(CH_3)_3C$	Cl	4-CH_3	4.14	4.08	0.06	4.00	0.14

[a]Optimized 3D-QSAR models (AF), [b]predicted activity by the 3D-QSAR models, [c]different between observed activity and predicted activity.

Table 2. Summary of the statistical results for 3D-QSAR models with two alignments

Models	Alignments	PLS Analyses						
		Grid (Å)	α	NC	$r^2_{cv.}$[a]	$r^2_{ncv.}$[b]	SE_{ncv}[c]	F
CoMFA I[d]	AF	3.0	-	5	0.588	0.978	0.081	70.234
CoMFA II	FF	2.5	-	4	0.593	0.942	0.123	36.738
CoMSIA I	AF	3.0	0.9	5	0.738	0.965	0.102	44.174
CoMSIA II	FF	1.5	0.3	5	0.369	0.713	0.292	3.974

Notes: α; Attenuation factor, NC; number of component, F; fraction of explained versus unexplained variance, [a]cross-validated r^2, [b]non-cross-validated r^2, [c]standard error estimate, [d]the optimized CoMFA model.

from relational equation (*Pred.*pI_{50}=0.981*Obs.*pI_{50}+0.066, n=14, s=0.068, F=478.014, r^2=0.978 & q^2=0.964) between observed values (*Obs.*pI_{50}) and values predicted by CoMFA 1model (*Pred.*pI_{50}).

Predictability of optimized model. Table 3 shows PRESS and average values of each model in training set (Table 1) and test set (Table 4) in order to verify the predictability and contribution ratio of characteristic fields of CoMFA & CoMSIA models which were derived from each alignment methods (AF & FF). The predictability of the optimized CoMFA 1 model is good because it has a small PRESS (0.53 & 0.20) and average values (Ave.= 0.11 & 0.15) in training set and test set. The contribution order of CoMFA 1 model is as follows: steric field (60.0%), electrostatic field (33.7%), hydrophobic field (6.3%). The contribution ratio of the steric field was two-fold higher than that of the electrostatic field and the hydrophobic field had the least influence. That is, steric field is the most contributive for the herbicidal activity of substrate compounds against spinach chloroplast. The herbicidal activity is concerned with inhibition of OER depend on hydrophobicity and on the electron withdrawing

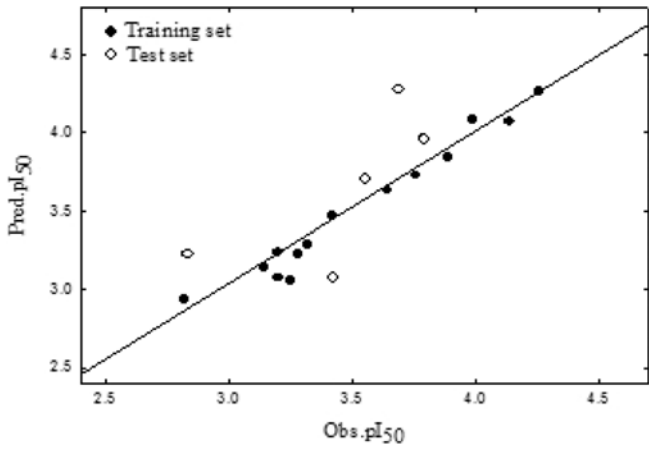


Fig. 2. Relationships between observed herbicidal activity (*Obs*.pI_{50}) and predicted the activity (*Pred*.pI_{50}) by the optimized CoMFA model I (For training set; *Pred*.pI_{50}= 0.981*Obs*.pI_{50}+0.066, n=14, s=0.068, F=478.014, r^2=0.978 & q^2=0.964).

force of substituents in pyrazine-2-carboxamide analogues [Dolezal *et al*., 2008].

Progressive scrambling. Progressive scrambling analysis is data which evaluate the ratios of dependency of values predicted by the optimized model [Juan and Cho, 2007]. Table 5 shows the slopes of the ratios of dependency of CoMFA 1 and CoMSIA 1 models ($d_q^{2'}/dr^2_{yy'}$), standard errors (CSDEP; Calculated standard error of prediction) and the predictability (q^2) of component number 5. As a result, the predictability of CoMFA 1 model (q^2=0.414 & CSDEP=0.418) was lower than that of CoMSIA 1 model (q^2=0.599 & CSDEP=0.338). However, when we take consideration into the fact that both of models ($d_q^{2'}/dr^2_{yy'}$ =0.8~1.2) satisfied the slope values of the optimized model without chance correlation (CoMFA 1 model; $d_q^{2'}/dr^2_{yy'}$=0.959, CoMSIA 1 model; $d_q^{2'}/dr^2_{yy'}$=1.040), we can say that the two models are very pertinent not being dependent on chance correlation [Clark and Fox, 2004].

Contour map analysis. To analyze the contribution ratios (%) of characteristic fields of the optimized CoMFA I model among substrate analogues, Fig. 3 and 4 indicate the CoMFA contour maps of compound **12** which has the highest activity. In the contour maps of steric and electrostatic fields (Fig. 3), herbicidal activity is expected to improve in two cases; the first is when large sterically favored groups (green) come into the one part of *ortho*- and meta-positions where trifluoromethyl group as electron withdrawing group on *N*-phenyl ring was located. The second is when small sterically favored groups (yellow) come into the other part of *ortho*- and *meta*-positions. Especially for the contour map of electrostatic field, the activity is expected to improve in two cases; one is when the positively charged groups (blue) are introduced to the part of N_1 atom on pyrazine

Table 3. Summary of field contribution ratio (%), PRESS and Ave. of training set and test set with 3D-QSAR models

Models	Field contribution (%)					Training set		Test set	
	S	H	E	HD	HA	PRESS	Ave.	PRESS	Ave.
CoMFA I[a)]	60.0	6.3	33.7	-	-	0.53	0.11	0.20	0.15
CoMFA II	82.2	17.8	-	-	-	0.57	0.13	0.17	0.12
CoMSIA I	-	-	72.0	-	28.0	0.52	0.13	0.52	0.22
CoMSIA II	-	-	-	54.4	45.6	0.62	0.14	0.80	0.33

Notes: S; steric field, H; hydrophobic field, E; electrostatic field, HD; hydrogen bond donor field, HA; hydrogen bond acceptor field, PRESS; predictive residual sum of squares, Ave.; average residual, [a)]optimized model.

Table 4. Observed herbicidal activity (*Obs*.pI_{50}) against spinach chloroplast and predicted activity (*Pred*.pI_{50}) by 3D-QSAR models for the test set compounds

No.	Substituents (R)			Obs.pI_{50}	CoMFA I[a)]		CoMSIA I	
	1	2	3		Pred.[b)]	Δ[c)]	Pred.[b)]	Δ[c)]
5	H	H	4-CH_3	2.83	3.23	-0.40	3.12	-0.29
7	H	Cl	4-F	3.42	3.08	0.34	3.12	0.30
13	$C(CH_3)_3$	H	3-CF_3	3.55	3.71	-0.16	4.20	-0.65
14	$C(CH_3)_3$	H	4-CH_3	3.79	3.96	-0.17	4.28	-0.49
17	$C(CH_3)_3$	Cl	2-CF_3	3.69	4.28	-0.59	4.03	-0.34

[a)]Optimized 3D-QSAR models (AF), [b)]predicted activity by the models., [c)]different between observed activity and predicted activity.

Table 5. Model stability test for 3D-QSAR models by progressive scrambling

Components	CoMFA I[a)]			CoMSIA I		
	q^{2}[b)]	cSDEP[c)]	$d_q^{2'}/dr^2_{yy'}$[d)]	q^{2}[b)]	cSDEP[c)]	$d_q^{2'}/dr^2_{yy'}$[d)]
2	0.250	0.399	1.783	0.527	0.314	1.572
3	0.356	0.390	1.331	0.457	0.351	2.277
4	0.355	0.411	1.118	0.566	0.330	1.664
5	0.414	0.418	0.959	0.599	0.338	1.040

[a)]Optimized model, [b)]q^2=1-(sSDEP)^2, predictivity of the models, [c)]calculated cross-validated standard error as function of correlation coefficient between the true values (y) of the dependent variables and the perturbed values (y') of the dependent variables, [d)]slope of q^2 (cross-validated correlation coefficient from Sybyl) with respect correlation of the original dependent variables versus the perturbed dependent variables.

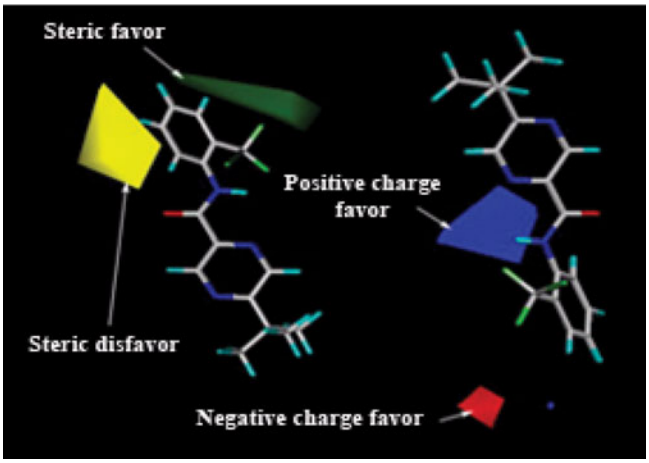


Fig. 3. The contour maps (stdev*coeff) for steric and electrostatic field with the optimized CoMFA I model. Left: the steric field & Right: electrostatic field. The highest active compound (12) is shown in capped sticks (favor: 80% & disfavor: 20%).

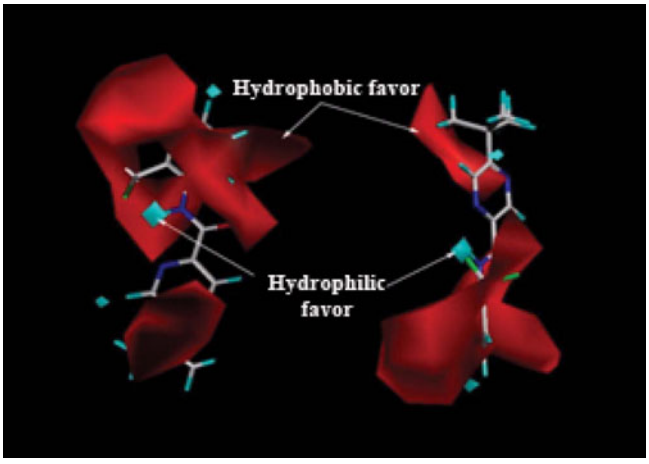


Fig. 4. CoMFA-HINT contour maps (stdev*coeff) for hydrophobic field. Left: front view & Right: side view. The most active compound (12) is shown in capped sticks (hydrophobic favor: 80%, hydrophilic favor: 20%).

ring and near amide group of carboxamide. The other is when their negatively charged groups (red) are introduced to the *ortho*- and *meta*-positions on *N*-phenyl ring.

In the Fig. 4 concerned with contour map of hydrophobic field (logP), the activity would increase when hydrophobic groups (red) are introduced to the *para*-position of *N*-phenyl ring and N_4 atom of pyrazine ring. None the more, it would do so when large hydrophilic groups (cyan) are introduced to the amide, its *para*-position and the *meta*-position of pyrazine ring. Generally speaking, the more hydrophobic groups (red) are introduced, the more herbicidal activity would increase. As you see in Fig. 3 and 4, the results of contour maps analysis are appeared on the structure of the most active compound **12**. Based on this, we want to design the structure of molecules for new herbicidal drugs.

Acknowledgments. This paper was supported by the Education and Research Promotion Program of KUT.

References

Akamatsu M (2002) Current state and perspectivies of 3D-QSAR. *Curr Topics Med Chem* **2**, 1381-1394.

Bay SW and Roh JH (2001) Primary lid tuberculosis occuring at preaponeurotic portion after upper lid blepharoplasty. *J Korean Ophthalmol Soc* **42**, 169-174.

Cha JH, Jang SH, Oh CK, and Kwon KS (2001) A case of tuberculosis verrucosa cutis. *Korean J Dermatol* **39**, 96-98.

Choi IS, Park IN, Hong SB, Oh YM, Lim CM, Lee SD, Koh YS, Kim WS, Kim DS, Kim WD, and Shim TS (2006) Hepatotoxicity of rifampicin and pyrazinamide treatment excluding isoniazid. *Tuber Respir Dis* **60**, 38-43.

Chung KS, Jang SC, Choi KS, and Sung ND (2006) Comparative molecular field analyses on the herbicidal activities of new 5-benzofuryl-2-[1-(alkoxyimino)alkyl]-3-hydroxycyclohex-2-en-1-one derivatives. *J Korean Soc Appl Biol Chem* **49**, 238-242.

Clark M, Cramer III RD, Jones DM, Patterson DE, and Simeroth PE (1990) Comparative molecular field analysis (CoMFA): 2. Toward its use with 3D-structural databases. *Tetrahedron Comput Methodol* **3**, 47-59.

Clark RD and Fox PC (2004) Statistical variation in progressive scrambling. *J Comput-Aided Mol Design* **18,** 2821-2826.

Cramer RD, Bunce JD, and Patterson DE (1988a) Cross-validation, bootstrapping and partial least squares compared with multiple regression in conventional QSAR studies. *Quant Struct Act Relat* **7**, 18-25.

Cramer RD, Patterson DE, and Bunce JD (1988b) Comparative molecular field analysis (CoMFA): 1. Effect of shape on the binding of steroid to carrier proteins. *J Am Chem Soc* **110**, 5959-5967.

Dolezal M, Cmedlova P, Palek, L, Vinsova J, Kunes J, Buchta V, Jampilek J, and Kralova K (2008) Synthesis and antimycobacterial evaluation of substituted pyrazincarboxamides. *Eur J Med Chem* **43**, 1105-1113.

Dolezal M, Palek L, Vinsova J, Buchta V, Jampilek J, and Kralova K (2006) Substituted pyrazincarboxamides: Synthesis and biological evalution. *Molecules* **11**, 242-256.

Hansh C (1976) The structure of medicinal chemistry. *J Med Chem* **19**, 1-6.

Hong KS, Hwang IT, Kim HR, Jeon DJ, Lee BH, Song JH, and Cho KY (2004) Inhibition of protoporphyrinogen oxidase activity and selectivity of new compound EK-5439. *Korean J Pestic Sci* **8**, 79-87.

Juan AAS and Cho SJ (2007) 3D-QSAR study of microsomal prostaglandin E synthase (mPGES-1) inhibitors. *J Mol Model* **13**, 601-610.

Kerr R (1994) Parallel helix bundles and ion channels: molecular modeling via simulated annealing and restrained molecular dynamics. *Biophys J* **67**, 1501-1515.

Kim DS, Chun SJ, Jeon JJ, Lee SW, and Joe GH (2004) Synthesis and fungicidal activity of ethaboxam against Oomycetes. *Pest Manag Sci* **60**, 1007-1012.

Kim DS, Park HC, Chun SJ, Yu SH, Choi KJ, Oh JH., Shin KH, Koh YJ, Kim BS, Hahm YI, and Chung BK (1999) Field performance of a new fungicide ethaboxam against cucumber downy mildew, potato late blight and pepper phytophthora blight in Korea. *Plant Phathol J* **15**, 48-52.

Kim YW, Jeon WB, and Park CK (1992) Synthesis and antifungal activity of N-substituted-5-chloro-1,3-dimethyl-pyrazole-4-carboxamide. *J Korean Agric Chem Soc* **32**, 87-91.

Klebe G, Abraham U, and Mietzner T (1994) Molecular similarity indices in a comp- arative analysis (CoMSIA) of drug molecules to correlate and predict their biological activity. *J Med Chem* **37**, 4130-4146.

Lowis DR (1997) HQSAR. A new highly prediction QSAR technique. Tripos Technical Notes, Vol. 1. No. 5.

Marshall GR, Barry CD, Bosshard HE, Dammkoehler RA, and Dunn DA (1979) The Con- formational parameter in drug design; active analog approach. In *Computer-assisted Drug Design,* Olsen EC and Christoffersen RE (eds), No. 112, pp. 205-226. American Chemical Society, Washington DC, U.S.A.

Ra CS, Rew YS, and Cho WB (1995) Synthesis and fungicidal activity of novel 2-aminothiazole carboxamide derivatives. *Korean J Med Chem* **5**, 72-75.

Song JY, Kim TY, Kim WB, Shong YK, Rhee YS, Suck JH, and Hong SJ (2006) Role of 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside in the growth regulation of anaplastic thyroid cancer cells lines. *J Korean Soc Endocrinol* **21**, 125-131.

Soung MG, Lee YJ, and Sung ND (2009) 3D-QSARs of herbicidal 2-N-phenylisoindolin-1-one analogues as a new class of potent inhibitors of protox. *Bull Korean Chem Soc* **30**, 613-617.

Soung MG, Park KY, and Sung ND (2010a) Synthesis and 3D-QSARs analyses of herbicidal *O,O*-dialkyl-1-phenoxy-acetoxy-1-methylphosphate analogues as a new class of potent inhibitors of pyruvate dehydrogenase. *Bull Korean Chem Soc* **31**, 1361-1367.

Soung MG, Park KY, and Sung ND (2010b) 3D-QSAR study on the influence of alrylamino (R) substituents on herbicidal activity of thiourea analogues. *Bull Korean Chem Soc* **31**, 1469-1473.

Suh JJ, Hong YH, and Kim BC (1987) Synthesis and anti-inflammatory activity of 4-substituted-1, 2-benzothiazine-3-carboxamide-1,1-dioxides. *J Kor Pharm Sci* **2**, 61-65.

Sung ND and Jung HS (2005) 3D-QSAR on the herbicidal activities of new 2-(4-(6-chloro-2-benzoxazolyloxy) phenoxy-*N*-phenylpropionamide derivatives. *J Korean Soc Appl Biol Chem* **48**, 252-257.

Sung ND, Jang SC, and Hwang TY (2007) 2D-QSAR and HQSAR analysis on the herbicidal activity of new *O,O*-dialkyl-1-phenoxyacetoxy-1-methylphosphonate analogues. *Korean J Pestic Sci* **11**, 72-81.

Tripos S (2001) In *Molecular Modeling and QSAR Software on CD-Rom (Ver. 7.3)*, Tripos Associates, Inc., St. Louis, MO, U.S.A.