Comparative Three-Dimensional Quantitative Structure−Activity Relationship Study of Safeners and Herbicides

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The competitive antagonist hypothesis for safeners and herbicides was investigated by studying the 3D similarity between 28 safener and 20 herbicide molecules in their putative biologically active, low-energy conformations using comparative molecular field analysis (CoMFA). In addition, CoMFA provided information about the structural requirements for the interactions of safeners and herbicides with a proteinaceous component (SafBP) isolated from etiolated corn seedlings. Statistically significant CoMFA models have been developed for the united and separate safener and herbicide molecule sets using retrospective binding affinity data of the ligands measured at the SafBP receptor. The predictive power of the models was characterized by squared cross-validated correlation coefficients (q^2) of 0.708, 0.564, and 0.4000 for the united safener plus herbicide set, the safener set, and the herbicide set, respectively. The CoMFA results support the competitive antagonist hypothesis between certain types of safeners and herbicides. The findings suggest that structural similarity between these two classes of agrochemicals is a useful guide in the design of new safeners.

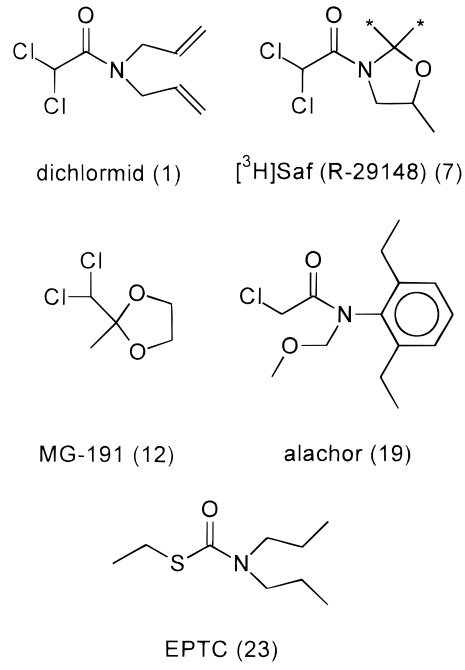
Keywords: *Safener; herbicide; QSAR; comparative molecular field analysis; CoMFA*

INTRODUCTION

Herbicide safeners are used to protect crop plants from the applied herbicide, thus allowing the control of closely related weed species or hard-to-control weed species without crop injury (Hatzios and Hoagland, 1989). Dichloroacetamide type safeners, for example, dichlormid (R-25788), are particularly effective at protecting maize (*Zea mays* L.) and sorghum against injury from thiolcarbamate- and chloroacetanilide-type herbicides (e.g., EPTC and alachlor, respectively). Chart 1 shows the structures of [^{3}H]Saf and selected compounds discussed in the text.

The exact mechanism by which safeners protect crops against herbicides is not known. Four general mechanisms of action have been proposed for herbicide safeners (Hatzios, 1983): (i) the safener may interfere with herbicide uptake and/or translocation; (ii) the safener may compete with the herbicide at a common site of action within the protected plant (competitive antagonism); (iii) the safener may stimulate herbicide degradation within the plant (enhanced degradation); (iv) the safener may act through a combination of the above processes. The potential involvement of gene activation, which regulates the expression of mRNAs encoding polypeptides involved in herbicide detoxication (Hatzios, 1989; Jepson et al., 1998), in the molecular action of herbicide safeners has also been proposed. The competitive antagonism theory and the enhanced degradation theory imply that the herbicide and safener molecules may share common molecular characteristics. In some cases, the structural similarity of herbicide and safener molecules is apparent. In an earlier study Stephenson et al. (1979) demonstrated that amides that are closely similar in structure to various thiolcarbamate herbicides are often effective antidotes to these herbicides in corn. In this study chemical similarity was assessed by visual inspection. Kömíves and Hatzios (1991) gave a systematic review of the chemical characteristics and structure−activity relationships (SAR) of herbicide safeners also indicating a close similarity in many instances between the structural features of herbicides and safeners. Discovery of the potent non-acetamide type safener,

Chart 1



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MG-191 (12), was based on structural similarity between herbicides and safeners (Dutka and Kömíves, 1987).

Molecular comparisons of compounds showing biological activity can be made by the use of quantitative structure−activity relationships (QSAR) analysis employing classical Hansch analysis (Hansch, 1971) or Free−Wilson analysis (Free and Wilson, 1964). Such approaches provide information about the identity, location, and relevant properties of functional groups on a general molecular skeleton required for biological activity. To date, however, no QSAR model has been developed for the protective effects of safeners.

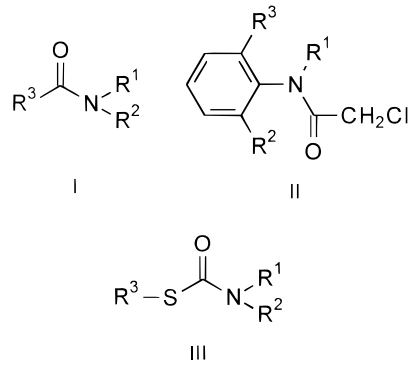
Yenne and Hatzios (1990) have published a comparative molecular modeling study of selected herbicides and their respective safeners to obtain evidence for or against the hypothesis that safeners may act as competitive antagonists of herbicides at a common target site. Three-dimensional structural comparisons included size, shape, principal moments, molecular volume, and connectivity indices, as well as visual evaluations of the superimposed molecular structures. The particular herbicide/safener combinations that were compared included EPTC/dichlormid, pretilachlor/fenchlorim, alachlor/flurazole, metolachlor/oxime ether safeners (cyometrinil, oxabetrinil, and CGA-133205), and metolachlor plus the safeners naphthalic anhydride and CGA-154281. Structural comparisons of the herbicides with their safener counterpart revealed that in terms of the investigated features the most successful safener/herbicide combinations are quite similar at the molecular level. The study was conducted using the molecular modeling program XICAMM running on personal computers. Due to software limitations, however, the study failed to provide a quantitative measure of the structural similarity between the safener/herbicide pairs.

During the past decade significant advances have been made in the field of molecular modeling, allowing the study of the spatial properties of molecules and the use of the derived knowledge in QSAR studies (Kubinyi, 1997). Among these so-called 3D QSAR methods, comparative molecular field analysis (CoMFA) (Cramer et al., 1988) is recognized as a powerful tool for the design and development of new bioactive molecules in the absence of the knowledge of the receptor structure. The structure of an active ligand in its biologically active conformation bound to the receptor may serve as a template for alignment of the rest of the molecules, greatly enhancing the performance of CoMFA. Such information may be obtained by X-ray crystallographic or NMR spectroscopic studies of the receptor−ligand complex. To date, however, no receptor has been identified or proposed for the herbicide safeners.

There are methodologies from which may be inferred biologically active conformations of a congeneric set of bioactive ligands in the absence of the receptor, for example, the active analogue approach proposed by Marshall et al. 1979). This method, however, requires good quality biological activity data, for example, binding affinity data of the ligands measured at the receptor.

Recently, Walton and Casida (1995) observed the high-affinity binding of safeners of type I as well as herbicides of types II and III (see Chart 2) to a proteinaceous component (safener binding protein, SafBP) in extracts of etiolated corn seedlings. Clear qualitative correlation was observed between safener potency and specific binding. Scott-Craig et al. (1998) purified SafBP and isolated its encoding gene. SafBP was identified as a type of *O*-methyltransferase, which may not be the primary site of action of the dichloroacetamide safeners and/or herbicides. Walton and Casida (1995) suggested that SafBP might be important in the pharmacokinetics of safener and/or herbicide action because of its abundance in the coleoptile.

Chart 2



Computer-generated pseudoreceptor models and pharmacophores with suitably placed amino acid residues or other interacting molecular fragments (Vedani et al., 1995) are often used to represent 3D SAR requirements in a concise manner, to rationalize available experimental and calculated data of the compounds, and to predict activities of newly designed molecules. In the present study, the SafBP receptor was taken as a nature-given receptor model for the safeners and herbicides investigated. Good qualitative correlation between the specific binding affinity of the safeners at SafBP and their in vivo safening potency rendered the receptor site of SafBP a suitable model. In this study, the competitive antagonist hypothesis between safeners and herbicides was further explored using the well-established 3D QSAR analysis tool, CoMFA, and the IC_{50} values measured at SafBP. General structures of safeners of type I and of acetanilide and thiolcarbamate herbicides of types II and III, respectively, are shown in Chart 2.

The objectives of this work were (i) to study the 3D similarity between safeners and herbicides in their putative biologically active, low-energy conformations on the basis of their steric and electrostatic fields to obtain arguments for or against the safener−herbicide antagonist hypothesis and (ii) to investigate structural requirements of the receptor−ligand interactions between the SafBP receptor and the safener and herbicide molecules by means of CoMFA for predictive purposes.

DATASETS SELECTED FOR THE ANALYSIS

The safeners (set 1) and herbicides (sets 2 and 3) and their specific binding (IC_{50}) values were taken from the publication by Walton and Casida (1995). Specific binding of 28 safeners and 20 herbicides at the SafBP receptor has been measured using tritium-labeled R-29148 ([^{3}H]Saf) as substrate. The structures of the selected safeners and herbicides are listed in Table 1.

COMPUTATIONAL METHODS

All calculations were performed using the Sybyl version 6.4 molecular modeling program package (Tripos, St. Louis, MO) running on a Silicon Graphics Octane workstation. The radioligand (Saf) used in the enzyme assay was selected as the starting structure to build the structures of the other molecules. Saf was built manually in Sybyl followed by

Table 1. Structures of Safeners and Herbicides

no.	compound	R^1	R^2	R^3
		Safeners of Type I (Set 1)		
1	dichlormid	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Cl_2CH
2		C_3H_7	C_3H_7	Cl_2CH
3		$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Cl_3C
4		$CH_2CH{=}CH_2$	C_3H_7	Cl_2CH
5		$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$(CH_3)_2CH$
6[a]		$C(CH_3)_2C{\equiv}CH$	H	Br_3C
7	Saf (R-29148)	$-C(CH_3)_2OCH(CH_3)CH_2-$	Cl_2CH	
8	R-25725	$-C(CH_3)_2OCH_2CH_2-$	Cl_2CH	
9		$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$ClCH_2$
10	benoxacor[b]			
11		$C(CH_3)_3$	H	Cl_2CH
12	MG-191[b]			
13	AD-67[b]	$-C(<(CH_2)_5)O(CH_2)_2-$		Cl_2CH
14		$CH_2CH{=}CH_2$	H	Cl_2CH
15		$2\text{-}C_2H_5{-}C_6H_5$	H	Cl_2CH
16[a]	furilazole	$-C(CH_3)_2OCH(2\text{-furyl})CH_2-$		Cl_2CH
17[a]		$C(CH_3)_2C{\equiv}CH$	H	$(CH_3)_2CH$
		Herbicides (Chloroacetanilides) of Type II (Set 2)		
18	metolachlor	$CH_3OCH_2CH(CH_3)$	C_2H_5	CH_3
19	alachlor	CH_3OCH_2	C_2H_5	C_2H_5
20	acetochlor	$C_2H_5)CH_2$	C_2H_5	CH_3
21	propachlor	$(CH_3)_2CH_2$	H	H
		Herbicides (Thiolcarbamates) of Type III (Set 3)		
22		C_3H_7	C_3H_7	CH_3
23	EPTC	C_3H_7	C_3H_7	C_2H_5
24	vernolate	C_3H_7	C_3H_7	C_3H_7
25		C_2H_5	C_2H_5	CH_3
26	pebulate	C_4H_9	C_2H_5	C_3H_7
27	molinate	$-(CH_2)_6-$		C_2H_5
28	EPTC sulfoxide	C_3H_7	C_3H_7	C_2H_5
29	butilate	$(CH_3)_2CH_2$	$(CH_3)_2CH_2$	C_2H_5
30	triallate	$(CH_3)_2CH_2$	$(CH_3)_2CH_2$	$Cl_2C{=}CCl{-}CH_2$
31	cycloate	c-hexyl	C_2H_5	C_2H_5
32	thiobencarb	C_2H_5	C_2H_5	$4\text{-}Cl{-}C_6H_4CH_2$
33[a]		C_3H_7	H	C_2H_5

[a] Outliers omitted from CoMFA. [b] Chemical names: (benoxacor), (*R*,*S*)-4-dichloroacetyl-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine; 12 (MG-191), 2-dichloromethyl-2-methyldioxolane; 13 (AD-67), *N*-dichloroacetyl-1-oxa-4-aza-spiro-4,5-decane.

molecular mechanics geometry optimization using the Tripos force field (with Pullman charges, the Powell minimization method, and a gradient of 0.05 kcal·mol^{-1}·Å^{-1} as termination criterion). In the next step Saf was optimized employing the MOPAC AM1 semiempirical method (Dewar et al., 1985) implemented in Sybyl. The energetically most favorable orientation of the R^3 substituent of Saf was determined by a systematic conformational search using the AM1 method and torsion angle increments of 30° in the range of 0−360°.

The structures of the other molecules were built step by step from the optimized Saf structure. The orientations of the R^3 substituents of general type CHX_2 and CH_2X, where X is halogen or methyl, were determined by using similar systematic searches as described above for Saf. The R^1 and R^2 substituents as well as the other R^3 substituents were not considered in these conformational searches because their orientations were mainly determined by the corresponding atoms in Saf, and the rest of the substituents were built in all-trans conformation. Finally, all structures were fully optimized using the AM1 method. All MOPAC AM1 calculations were carried out with the following keywords: AM1, PRECISE, MMOK, and GEO-OK.

CoMFA (implemented in the QSAR module of Sybyl) of the united set of safeners and herbicides (set 1 + set 2 + set 3), and the separate subsets of the safeners (set 1) and herbicides (sets 2 and 3) was performed. All molecules were aligned on the conformationally constrained safener structure, Saf (R-29148), as a template utilizing the amide substructure (>N−C(=O)−) present in each molecule except for MG-191. MG-191 was superimposed onto Saf such that its chlorine atoms corresponded to those in Saf and its dioxolane oxygen atoms to the carbonyl oxygen and the amide nitrogen in the template molecule.

CoMFA was used to correlate the pIC_{50} values of safeners and herbicides with their 3D structure represented by a steric (Lennard-Jones) and an electrostatic (Columbic) molecular field sampled at the intersections of a 3D lattice. The applied grid spacing was 2 Å, and the dimension of the box (in multiples of grid spacing) was 12 × 9 × 9. Atomic charges were calculated using the MOPAC AM1 method. The probe atom was an sp3 hybridized carbon atom with a charge of +1, the dielectric function was $1/r$, and the dielectric constant was $\epsilon = 1$.

As part of the CoMFA computations partial least-squares (PLS) analysis (projections to latent structures) was carried out to obtain a linear QSAR expression. Cross-validation was performed using the leave-one-out cross-validation technique. Column filtering with a minimum σ value of 1.5 kcal/mol was selected. The number of accepted PLS components was based on the first local maximum of q^2.

The r^2 value for the CoMFA model indicates how much of the training set's variation is accounted for by the model, whereas the cross-validated r^2 (q^2; Cramer et al., 1988) indicates how well binding affinity is predicted for each compound by the other analogues in the data set. In a summary of recommendations for a well-conducted CoMFA study, Martin et al. (1996) proposed that q^2 should be >0.3 such that the possibility of chance correlation is <5%.

RESULTS

Three significant CoMFA models were calculated using the data in Table 1. Model 1 was developed for the united set of safeners and herbicides (set 1 + set 2 + set 3), model 2 for the set of safeners (set 1), and model 3 for the two sets of herbicides (set 2 + set 3).

Table 2. Summary Statistics for the ComFA Models

model	n^a	N^b	$q^{2\,c}$	$r^{2\,d}$	s^e	F^f	steric^g	electrostatic^h
1	30	4	0.708	0.955	0.211	132.1	0.702	0.298
2	14	3	0.564	0.968	0.237	99.4	0.598	0.402
3	15	4	0.400	0.988	0.068	212.8	0.657	0.343

[a] Number of compounds. [b] Optimal number of PLS components. [c] Cross-validated r^2. [d] Variation accounted for by the model. [e] Standard error of estimate. [f] Fisher value as a measure for the statistical significance. [g] Contribution of steric field (percent). [h] Contribution of electrostatic field (percent).

Table 3. Observed and Predicted pIC_{50} Values as well as the Residuals for the Safeners (Set 1) and Herbicides (Sets 2 and 3) Calculated Using the Three CoMFA Models (Models 1−3)

		model 1		model 2		model 3	
no.	obs[a]	calcd[b]	residual	calcd[b]	residual	calcd[b]	residual
			Safeners (Set 1)				
1	2.00	1.740	0.260	1.706	0.294		
2	1.89	1.747	0.139	1.871	0.015		
3	1.85	1.792	0.062	1.866	−0.012		
4	1.85	1.790	0.063	1.786	0.068		
5	1.80	1.781	0.015	1.843	−0.047		
6	1.05	omitted		omitted			
7	0.92	0.848	0.073	0.975	−0.054		
8	0.80	0.668	0.128	0.588	0.208		
9	0.51	1.023	−0.515	0.683	−0.175		
10	0.13	0.560	−0.429	0.607	−0.476		
11	−0.36	−0.401	0.040	−0.505	0.143		
12	−0.64	−0.412	−0.232	−0.943	0.300		
13	−0.78	−0.496	−0.282	−0.558	−0.220		
14	−0.85	−0.742	−0.103	−0.778	−0.067		
15	−0.90	−0.976	0.073	−0.927	0.024		
16	−0.97	omitted		omitted			
17	−0.97	omitted		omitted			
			Herbicides (Chloroacetanilides) (Set 2)				
18	1.40	1.498	−0.100			1.440	−0.043
19	1.16	0.977	0.178			1.032	0.123
20	0.75	0.874	−0.129			0.828	−0.084
21	0.32	0.328	−0.009			0.355	−0.036
			Herbicides (Thiolcarbamates) (Set 3)				
22	1.22	1.324	−0.110			1.176	0.039
23	0.96	0.986	−0.027			0.939	0.019
24	0.92	0.915	0.006			0.927	−0.006
25	0.80	0.434	0.362			0.803	−0.007
26	0.64	0.587	0.051			0.637	0.002
27	0.42	0.143	0.277			0.409	0.011
28	0.28	0.342	−0.067			0.263	0.013
29	0.27	0.425	−0.158			0.361	−0.093
30	−0.08	−0.100	0.021			−0.102	0.022
31	−0.20	−0.359	0.154			−0.288	0.084
32	−0.36	−0.380	0.018			−0.316	−0.045
33	−1.28	−1.518	0.240			omitted	

[a] Observed binding affinity value (pIC_{50}, μM) (Walton and Casida, 1995). [b] Calculated pIC_{50} values.

The qualities of the three models were statistically similar. Table 2 shows the summary statistics for the three CoMFA models.

Table 3 shows the observed and predicted pIC_{50} values and residuals for the safeners and herbicides (1−32) calculated using the three CoMFA models (models 1−3).

Figures 1−3 show the plots of measured versus calculated pIC_{50} values for models 1−3, respectively.

The CoMFA contour maps of models 1−3 are shown in Figure 4−6, respectively.

DISCUSSION

Highly significant CoMFA models were calculated for the binding affinities of safeners (set 1) and herbicides

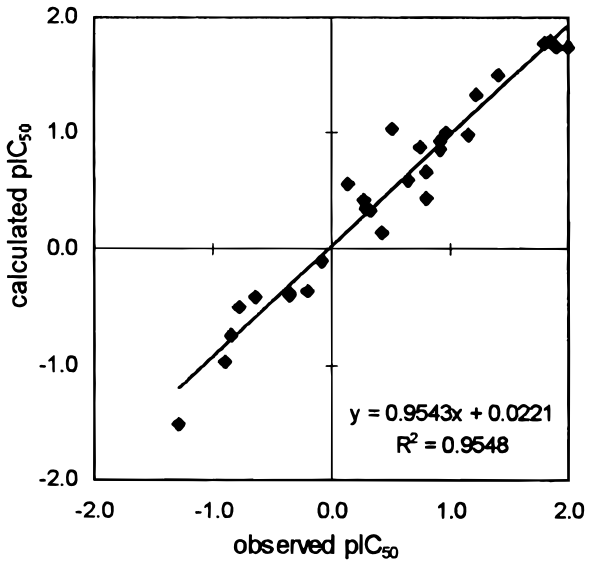


Figure 1. Plot of measured versus calculated pIC_{50} values for model 1.

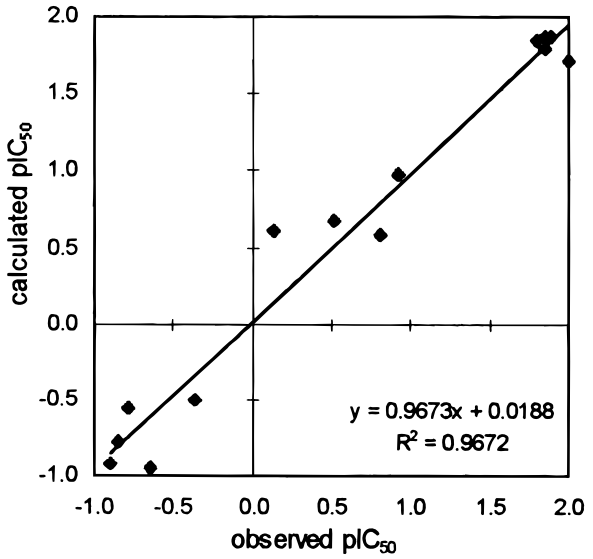


Figure 2. Plot of measured versus calculated pIC_{50} values for model 2.

(sets 2 and 3) at the SafBP receptor site indicating common 3D steric and electrostatic features of the two ligand sets that are relevant for binding. The same structural alignments were used for the three models, models 1−3, employing the sterically constrained safener, Saf (R-29148), as a template. The qualities of the three models were statistically similar. The statistical significance of model 1 indicates that the safener and herbicide molecules, in their aligned low-energy conformation, may interact with the same receptor site. This finding supports the competitive antagonist hypothesis.

The CoMFA contour maps shown in Figures 4−6 demonstrate that specific binding of the safener and herbicide molecules of general types I, II, and III is influenced by the substituents on both the amide nitrogen (R^1 and R^2) and the carbonyl carbon atom (R^3).

The CoMFA contour map for the entire set of safeners and herbicides (Figure 4) reveals a steric hindrance at the end of longer R^3 substituents and some steric hindrance at the outer region of the R^1 and R^2 substituents (yellow), a favorable steric field around the R^2

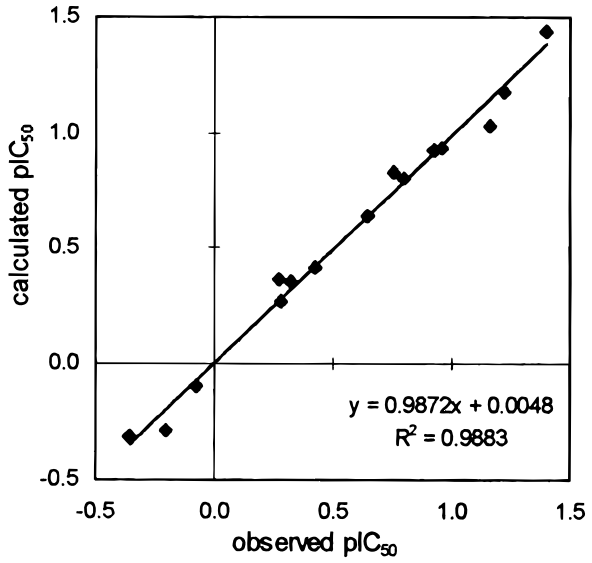


Figure 3. Plot of measured versus calculated pIC_{50} values for model 3.

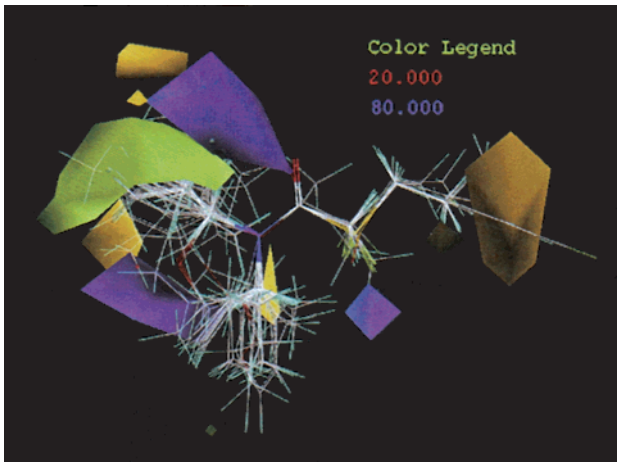


Figure 4. CoMFA contour map for model 1.

substituent (green), and a favorable electron deficiency around the R^2 substituent (blue).

The CoMFA contour map for the safeners (Figure 5) reveals a very strong steric hindrance around the R^1 and R^2 substituents (yellow), a favorable steric field around the R^2 substituent (green), favorable electron density near the R^2 substituent (red), and a favorable electron deficiency at the R^1 substituent (blue). No significant molecular fields could be observed near the R^3 substituent.

The CoMFA contour map for the herbicides (Figure 6) shows some steric hindrance at the end of longer R^3 substituents (yellow), a favorable steric field around the R^1 and R^2 substituents (green), a favorable electron density near the R^2 substituent (red), and a favorable electron deficiency between the R^1 and R^3 substituents (blue).

The CoMFA contour maps of model 2 for the safeners and of model 3 for the herbicides showed some differences from that of model 1 for the united safener plus herbicide set (set 1 + set 2 + set 3), indicating that the SafBP receptor may accommodate ligands of different size and offers slightly different binding alternatives for the safener and herbicide molecules.

Prediction of the pIC_{50} values of a potent experimental safener, *N*-allyl-*N*-methoxyethoxymethyldichloroacetamide, using models 1 and 2, gave $IC_{50} = 0.049$ and 0.082 μM, respectively. These values are in good agreement with the high safening potential of this safener candidate, developed in our laboratory, the second best after dichlormid in corn against thiolcarbamate and acetanilide herbicides. For comparison, the observed and calculated IC_{50} values for dichlormid, Saf, MG-191, and AD67 were 0.01 (0.018), 0.12 (0.142), 4.4 (2.582), 6.0 (3.133) μM, respectively (calculated values by model 1 are in parentheses), in good agreement with their in vitro safening potential.

Figure 5. CoMFA contour map for model 2.

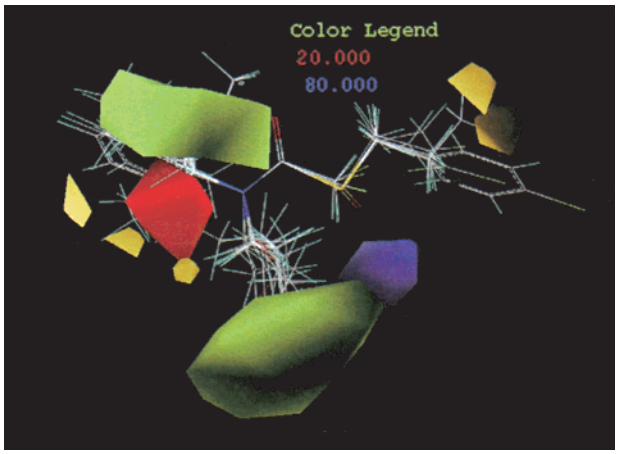


Figure 6. CoMFA contour map for model 3.

Clear correlation between the experimental pIC_{50} values and the observed safening potency of the safeners, as well as the statistical significance of the three developed CoMFA models, strengthens the safener–herbicide antagonist hypothesis and supports the long held, but quantitatively never substantiated, observation that structural similarity between a designed safener and the herbicide is an important factor that might contribute to the potency of a safener molecule. For the first time, models 1 and 2 quantitatively modeled this insight, and these models might be useful for designing novel and potent acetamide type safeners.

ABBREVIATIONS USED

SafBP, safener binding protein; SAR, structure–activity relationships; QSAR, quantitative structure–activity relationships; CoMFA, comparative molecular field analysis; 3D, three-dimensional.

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