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Research Article

Synthesis, Herbicidal Evaluation, and Structure-Activity Relationship of Benzophenone Oxime Ether Derivatives

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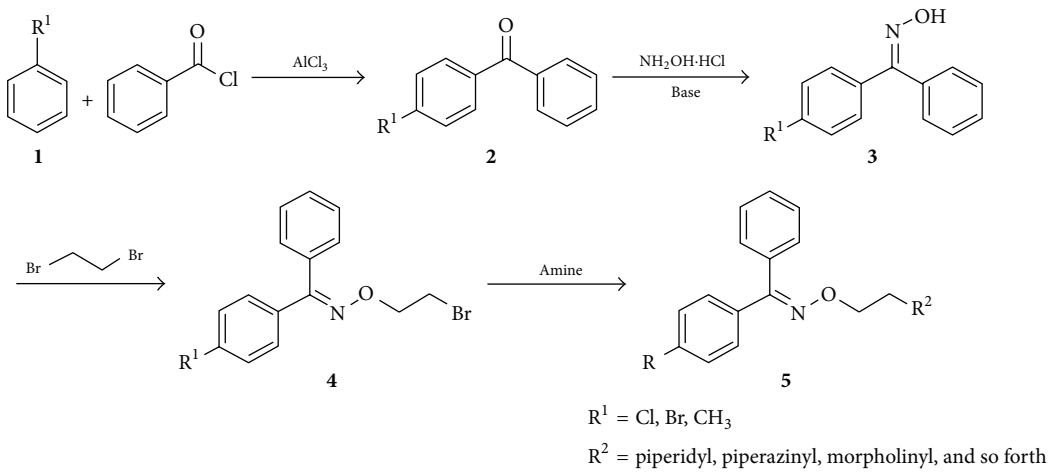
A novel series of benzophenone oxime ether derivatives with tertiary amine groups were synthesized and their herbicidal activities of 24 compounds against *Oryza sativa, Sorghum sudanense, Brassica chinensis*, and *Amaranthus mangostanus* L. were also evaluated. Most of these compounds exhibited significant inhibitory effect on root growth at 20 ppm. Based on the herbicidal activity data, computational Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR) analysis and molecular docking were undertaken. CoMFA contour maps were generated for the design of benzophenone oxime ether analogues with enhancing activity.

1. Introduction

Pesticides are extensively used in agriculture and undoubtedly play a pivotal role in retaining high production and quality of crop [1]. Nevertheless, with the escalating demand of environment protection and food safety, the economic, health, and environmental costs of pesticides have to be considered [2]. This requires that pesticides must be selective, effective, of less residue, and safe. On the other hand, most pesticides could lose efficacy due to resistance after long-term usage. Thus, continuous effort has been made to develop new pesticides with broad spectrum, low dosage and cost, long efficacy duration, less environmental pollution, and safety to humans [3, 4].

In recent years, oxime ether derivatives exhibit high potential to be developed as pesticides. For example, flucycloxuron is an insect growth regulator and trifloxystrobin has been used as a fungicide. Moreover, various novel oxime ethers have been reported to possess remarkable antibacterial, insecticidal, and fungicidal activities [5–9]. A series of *O*-benzyl oxime ethers containing β-methoxyacrylate moiety was synthesized by Liu et al. and was found to possess both fungicidal and insecticidal activities [5, 10, 11]. Kabilan group revealed that oxime ethers derived from 1-allyl substituted 2,6-diphenylpiperidin-4-ones displayed excellent antibacterial and antifungal activity [12]. Zhang et al. demonstrated that 4-methoxybenzaldehyde *O*-(4-bromobenzyl) oxime exerted good larvicidal activity against *Myzus persicae* and its analogues exhibited excellent fungicidal activity against *Rhizoctonia solani* [13]. Sun et al. reported that some benzoylphenylureas containing an oxime ether group showed excellent larvicidal activities against mosquito and oriental armyworm [6]. Besides, some 2,4-diphenyl-1,3-oxazolines containing oxime ether moiety exhibited higher acaricidal activity than etoxazole [2]. A few pyrazole oxime ether derivatives exhibited both good acaricidal and insecticidal activities [14–16]. More recently, a series of benzofuran-substituted oxime ethers were identified to possess good to excellent fungicidal activities by Xie et al. [17, 18].

However, very few results on the herbicidal activities of oxime ether compound were reported [19]. In this paper, a series of aryl oxime ether compounds with tertiary amino groups which are conducive to enhancing environmental compatibility [17, 20] were designed and synthesized. The herbicidal activities of these compounds on *Oryza sativa*, *Sorghum sudanense*, *Brassica chinensis*, and *Amaranthus mangostanus* L. were investigated. Computational Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR) analysis and molecular docking were also undertaken.



Scheme 1: The synthetic route to target compounds.

2. Materials and Methods

2.1. General. All reagents and solvents (Analytical Reagent grade) were commercially available and used without further purification. Melting points were measured on an RY-2 apparatus. IR spectra were recorded on a Thermo Nicolet FT-IR Avatar 330 instrument with KBr. ^{1}H NMR spectra were collected at room temperature on 400 MHz Bruker AM, 600 MHz Bruker DRX spectrometers. The residual solvent signals were taken as the reference (7.26 ppm in $CDCl_3$ and 2.50 ppm in d_6-DMSO). Chemical shift (δ) is reported in ppm; coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, and m = multiplet or unresolved. MS (ESI) spectra were recorded on Agilent 6100 Single Quad spectrometer.

2.2. Chemical Synthesis. Aryl ketone was prepared from substituted benzene and arylcarboxylic chloride through Friedel-Crafts reaction. Reaction of ketone with hydroxylamine hydrochloride in the presence of base would result in corresponding oxime, which converted to substituted benzophenone-*O*-(2-bromoethyl) oxime. Finally, the target products could be obtained by substitution (Scheme 1).

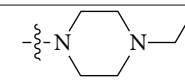
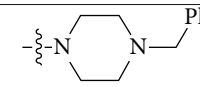
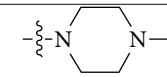
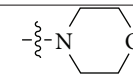
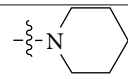
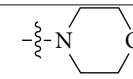
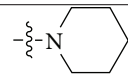
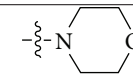
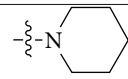
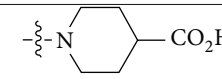
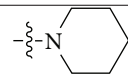
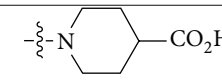
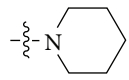
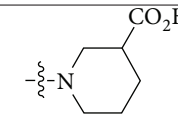
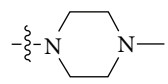
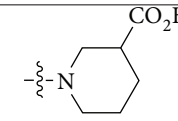
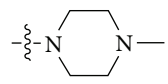
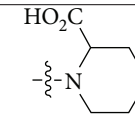
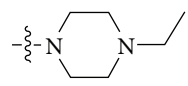
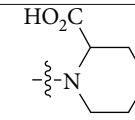
2.2.1. General Procedure for the Synthesis of Substituted Benzophenones. Benzoyl chloride (0.12 mol) was added dropwise to a mixture of substituted benzene (0.1 mol) and $AlCl_3$ (0.12 mol) at room temperature. After complete addition, the mixture was refluxed for another 6 h. Then, the reaction was quenched with ice-water and extracted with chloroform (3 × 30 mL). The combined organic phase was washed with water, Na_2CO_3 solution, and brine successively, dried over $MgSO_4$, filtered, and evaporated. The crude product was used directly for next step without any further purification.

2.2.2. General Procedure for the Synthesis of Substituted Benzophenone Oximes. Aqueous NaOH solution (10 mL, 20 M) was added to a mixture of substituted benzophenone (0.05 mol) and hydroxylamine hydrochloride (0.1 mol) in ethanol (50 mL) at room temperature. Then, the reaction was heated to 75°C and stirred until the starting material was completely consumed as indicated by TLC. The mixture was cooled to room temperature and filtered. The filtrate was evaporated and dissolved in chloroform, washed with water. The crude compound was recrystallized by ethanol to give a white solid [21].

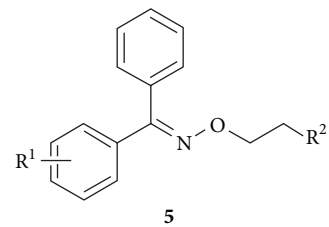
2.2.3. General Procedure for the Synthesis of Substituted Benzophenone-O-(2-bromoethyl) Oxime. Aqueous NaOH solution (10 mL, 25 M) was added to a mixture of substituted benzophenone oxime (0.025 mol), 1,2-dibromoethane (0.03 mol), and *tert*-butylammonium bromide (0.2 g) in toluene (20 mL). The mixture was stirred at room temperature and monitored by TLC. After the reaction was completed, the resulting solution was separated. The organic phase was washed with water until neutral, dried over $MgSO_4$, and filtered. The filtrate was evaporated and purified by column chromatography on silica gel to give substituted benzophenone-*O*-(2-bromoethyl) oxime [22].

2.2.4. General Procedure for the Synthesis of Target Compounds. A mixture of substituted benzophenone-*O*-(2-bromoethyl) oxime (0.01 mol), amine (0.012 mol), and Na_2CO_3 (0.01 mol) in acetone (20 mL) was stirred at room temperature. The reaction was monitored by TLC. After the reaction was completed, the resulting suspension was filtered. The filtrate was evaporated to remove acetone and the residue was dissolved in EtOAc (20 mL), washed with water, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel [23]. The unreacted substituted benzophenone-*O*-(2-bromoethyl) oxime was removed by Et_2O/petroleum ether = 1 : 10. The final products (Table 1) were obtained by eluting with the indicated solvent. The characterization of compounds **5a**–**5x** was included in the Supporting Information in Supplementary Material available online at http://dx.doi.org/10.1155/2015/435219.

Table 1: Chemical structure of the target compounds **5a**–**5x**.

Compound	R^1	R^2	Compound	R^1	R^2
5a	*p*-Cl	$-N(CH_2CH_2CH_3)_2$	**5m**	*p*-Me	
5b	*p*-Cl	$-N(CH_2CH_2CH_2CH_3)_2$	**5n**	*p*-Cl	
5c	*p*-Me	$-N(CH_2CH_2CH_3)_2$	**5o**	*p*-Me	
5d	*p*-Me	$-N(CH_2CH_2CH_2CH_3)_2$	**5p**	*p*-Cl	
5e	*p*-Me		**5q**	*p*-Br	
5f	*p*-Cl		**5r**	*p*-Me	
5g	*p*-Br		**5s**	*p*-Cl	
5h	*o*-Cl		**5t**	*p*-Br	
5i	*p*-NO_2		**5u**	*p*-Cl	
5j	*p*-Cl		**5v**	*p*-Br	
5k	*p*-Br		**5w**	*p*-Cl	
5l	*p*-Cl		**5x**	*p*-Br	

See Scheme 2.



5

Scheme 2

2.3. Biological Testing. The *in vivo* herbicidal activities of compounds **5a**–**5x** against monocotyledon (*Oryza sativa*, *Sorghum sudanense*) and dicotyledon (*Brassica chinensis, Amaranthus mangostanus* L.) were examined according to the plating method in agricultural industry standard of China pesticide indoor bioassay test criteria (herbicide) (NY/T 1155.1, 2006).

The weeds were soaked in 25°C water for 12 h and then transferred to moist gauze, which was put in manual climatic box at 28°C to germinate. 0.12 g of the target compounds

was diluted with 3 mL DMF. 0.5 mL of the diluted solution was diluted to 100 mL with 0.1% aqueous Tween-80 solution to prepare a mother solution (200 g/L). The test solutions were then prepared by diluting suitable mother solution to 100 mL with 0.1% aqueous Tween-80 solution. 10 germinating seeds were selected and put in the Petri dish matted with a filtered paper, to which 9 mL of testing solution was added. 0.1% aqueous Tween-80 solution was used as blank control. The Petri dishes were put in manual climatic box setting temperature as 25°C and humidity as 98% in dark condition. The root length was measured after 5 days and the inhibitory rate was calculated with the following equation. All the samples were repeated for 3 times. The abnormal data was got rid of by SPSS19.0. Consider

$$R = \frac{L_0 - L_1}{L_0} \times 100. \quad (1)$$

R is growth inhibitory rate (%); L_0 is the root length of control; L_1 is the root length of testing sample.

A coordinate plot was built with concentration as X axial and inhibitory rate as Y axial. Linear fitting was processed for each compound to give the univariate linear regression equation (the correlation data was attached in the supporting information). IC_{90} was calculated by the linear equation. pIC_{90} was the value of log IC_{90}.

2.4. Molecular Modeling. The analysis is based on SYBYL 7.3 (Tripos Inc., USA). A training set of 19 compounds was used to construct the 3D-QSAR models. Considering the distribution of the structural diversity, 5 compounds were randomly selected as prediction test set to evaluate the obtained 3D-QSAR model.

Since the acceptor is unknown, the low energy conformation was chosen as the active conformation [24, 25]. Molecules are minimized by Tripos force field and the Powell conjugate gradient algorithm with a convergence criterion of 0.05 kcal/(mol Å) to give the low energy conformation, and then all compounds were aligned by Database Alignment method. Compound **5k** was selected as template molecule [26]. Other molecules are overlapped to reduce the root-mean-square derivation. The common skeleton was shown in Figure 1.

The composite data and pIC_{90} data were imported to calculate the CoMFA field parameters by Tripos Standard force field (the steric and electrostatic field). Default parameters such as dielectric constant were used to obtain the molecular force parameters [27, 28]. Partial Least-Square (PLS) methodology was employed to construct the relationships between the target compound and biological activity. The leave-one-out (LOO) cross-validation was performed to obtain the cross-validation correlation coefficient (q^2) and the optimum number of components (n). A non-cross-validated (NV) analysis was carried out to obtain the non-cross-validated correlation coefficient (r^2) and F test values and standard error of estimate (SEE).

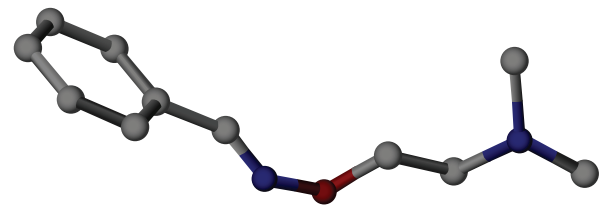


Figure 1: Common skeleton of target compounds.

3. Results and Discussion

3.1. Herbicidal Activity Evaluation. After a preliminary study, the concentration of testing compounds was set as 1, 2.5, 5, 10, 20, and 40 mg/L in the herbicidal activity investigation. The root growth was observed and the collected data was analyzed by SPSS to calculate the inhibitory rate. The results showed that the inhibitory effect became stronger as the concentration was increased and most of these compounds' inhibitory rates were up to 80% above at 20 mg/L (see Supporting Information). It indicated that these oxime ether compounds with tertiary amines significantly inhibited the crop root growth, which is another example to support the point that nitrogen functional groups are significant for the biological activity in most agrochemicals [29]. IC_{90}, the concentration inhibiting 90% of activity, was calculated according to the correlation analysis between the inhibitory rate on root growth and the concentration of the testing solution (see Supporting Information). Compound **5f** exhibited the best herbicidal activity against *Oryza sativa* with an IC_{90} of 13.70 mg/L. Compound **5o** effectively inhibited the root growth of *Sorghum sudanense* with an IC_{90} of 11.27 mg/L. Compounds **5k** and **5i** showed the highest herbicidal activity against *Brassica chinensis* and *Amaranthus mangostanus* L. with an IC_{90} of 16.83 and 11.22 mg/L, respectively. The herbicidal activities of these compounds are comparable to those of tribenuron, which is a commonly used commercial herbicide [30] (Table 2).

It was noteworthy that the benzophenone oxime ethers containing piperidine or piperazine moiety (**5e**–**5o**) showed significant inhibitory activities. Increase of the concentration of these kinds of compounds to 20 mg/L caused plants' fatality. The compounds containing oxygen atom on amino moiety (**5p**–**5r**) show less inhibitory effect than that of those without oxygen (**5a**–**5o**). In particular, incremental carboxylic acid group on piperidine ring (**5s**–**5x**) strongly reduced the herbicidal activities. The inhibitory effects of the testing compound on *Oryza sativa* were generally stronger than those of *Sorghum sudanense* in terms of monocotyledon, while the inhibitory effects on *Amaranthus mangostanus* L. were better than those of *Brassica chinensis* as for dicotyledon.

3.2. Comparative Molecular Field Analysis (CoMFA). The CoMFA analysis results for *Oryza sativa* and *Amaranthus mangostanus* L. were listed in Table 3. The activities data of *Sorghum sudanense* and *Brassica chinensis* did not show satisfactory regularity and CoMFA model was not analyzed.

Table 2: Calculated IC_{90} of compounds **5a**–**5x**.

Compound	IC_{90}			
	Oryza sativa	*Sorghum sudanense*	*Brassica chinensis*	*Amaranthus mangostanus* L.
Tribenuron	12.28	13.70	11.89	11.06
5a	21.11	33.55	25.28	12.71
5b	21.09	26.55	43.81	22.14
5c	42.04	17.81	35.72	17.96
5d	44.92	34.27	68.52	31.56
5e	14.85	60.06	33.92	18.38
5f	13.70	48.10	32.73	34.01
5g	34.19	55.20	32.17	17.32
5h	52.88	36.42	52.34	25.51
5i	24.79	17.23	28.02	11.22
5j	20.13	25.54	22.84	16.83
5k	18.11	20.65	16.83	11.72
5l	20.55	35.74	17.21	15.70
5m	21.28	36.87	48.70	17.69
5n	17.47	21.52	87.47	19.22
5o	20.44	11.27	23.67	14.67
5p	56.79	55.64	97.02	46.68
5q	102.32	52.96	146.21	50.55
5r	72.32	244.24	439.01	53.68
5s	107.40	39.85	68.15	43.25
5t	106.86	387.23	134.91	139.05
5u	67.62	194.54	108.17	203.32
5v	90.00	733.00	140.28	115.99
5w	89.43	121.02	130.27	216.57
5x	121.02	133.36	147.23	379.80

Table 3: Summary of CoMFA results.

Fields	LOO		NV			Steric	Electrostatic
	q^2	n	r^2	SEE	F		
Oryza sativa	0.567	2	0.997	0.020	751.322	0.446	0.554
Amaranthus mangostanus L.	0.621	3	0.879	0.185	53.325	0.481	0.519

The CoMFA model for *Oryza sativa* has a q^2 value of 0.567 and r^2 value of 0.997. It has an F value of 751.322 and an SEE value of 0.020. The CoMFA model for *Amaranthus mangostanus* L. has a q^2 value of 0.621 and r^2 value of 0.879. It has an F value of 53.325 and an SEE value of 0.185. According to the literature [31], the q^2 ($q^2 > 0.5$) and r^2 ($r^2 > 0.6$) values illustrated that the resulted models have good robustness and internal prediction ability. Both models revealed that the electrostatic field (55.4%, 51.9%) has a little bit more contribution than that of steric fields (44.6%, 48.1%). This indicated that the electronic effect of testing compounds structure has more influence on the inhibitory activities against the plants' roots.

The 3D-QSAR models established with the training set were further validated with the test set. The CoMFA model gave reasonable predictions of both training and test set compounds. The experimental activity and predicted activity of the compounds and their residuals are listed in Tables 4 and 5. In both models, most of the predicted pIC_{90} values are pretty close to the corresponding experimental values. All the deviations are smaller than 1 log unit and the maximum deviation is only 0.321.

3.3. Contour Map Analysis. The 3D contour maps were generated as scalar products of coefficients and standard deviation associated with each CoMFA. The active compound **5k** was superimposed with the CoMFA contour maps for *Oryza sativa* and *Amaranthus mangostanus* L.

In Figure 2, yellow region near benzene ring shows that substituents at this position have unfavorable steric interaction. This is verified by the observation that compound **5h** with *o*-Cl on benzene exhibited less inhibition than that of **5f** with *p*-Cl. Blue region below the chain especially around the amino groups indicates that electronegative groups are unfavored in this region. This is rightly explained by the fact that compounds **5s**–**5x** with extra carboxylic acid group

Table 4: Observed and predicted activities for training and test set of *Oryza sativa* CoMFA model.

Compound	pIC_{90}		
	Observed	Predicted	Residual
5a	1.32	1.345	−0.025
5b	1.32	1.311	0.009
5c	1.62	1.600	0.020
5d*	1.65	1.591	0.059
5e	1.17	1.207	−0.037
5f	1.14	1.158	−0.018
5g*	1.53	1.558	−0.028
5h	1.72	1.716	0.004
5i	1.39	1.361	0.029
5j	1.30	1.326	−0.026
5k	1.26	1.248	0.012
5l	1.31	1.274	0.036
5m*	1.33	1.352	−0.022
5n	1.24	1.259	0.019
5o	1.31	1.511	−0.201
5p*	1.75	1.746	0.004
5q	2.01	1.992	0.018
5r	1.86	2.156	−0.296
5s*	2.03	2.056	−0.026
5t	2.03	2.019	0.011
5u	1.83	1.807	0.023
5v	1.95	1.943	0.007
5w	1.95	1.921	0.029
5x	2.08	2.103	−0.023

The compound marked with ∗ was selected for test set.

Table 5: Observed and predicted activities for training and test set of *Amaranthus mangostanus* L. CoMFA model.

Compound	pIC_{90}		
	Observed	Predicted	Residual
5a	1.10	1.414	−0.314
5b	1.35	1.307	0.043
5c	1.25	1.110	0.140
5d*	1.50	1.456	0.044
5e	1.26	1.268	−0.008
5f*	1.53	1.539	−0.009
5g	1.24	1.261	−0.021
5h	1.41	1.313	0.097
5i	1.05	1.199	−0.149
5j*	1.23	1.059	0.171
5k	1.07	1.065	0.005
5l	1.20	1.004	−0.196
5m	1.25	0.971	−0.279
5n	1.28	1.083	0.197
5o*	1.17	1.075	0.095
5p	1.67	1.775	−0.105
5q	1.70	1.402	0.298
5r	1.73	1.409	0.321
5s	1.64	1.891	−0.251
5t	2.14	1.904	0.236
5u*	2.31	2.134	0.176
5v	2.06	2.165	−0.105
5w	2.34	2.461	−0.121
5x	2.58	2.480	0.10

The compound marked with ∗ was selected for test set.

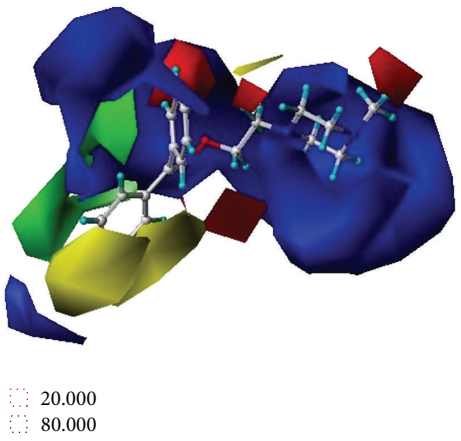


Figure 2: CoMFA contour map for *Oryza sativa*.

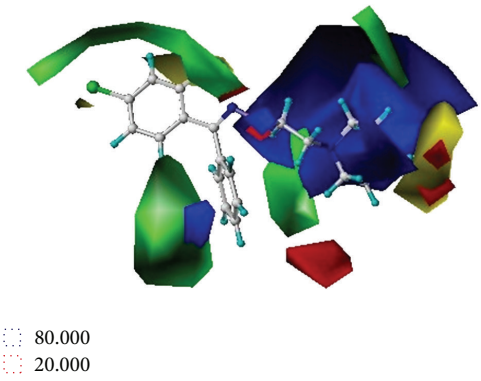


Figure 3: CoMFA contour map for *Amaranthus mangostanus* L.

showed worse inhibitory effect than those of **5f** and **5g**. The inhibitory activity on *Oryza sativa* may increase if electron-positive groups were introduced.

In Figure 3, green region near benzene ring and blue region near amino groups manifested that increasing the size of substituent on benzene ring and importing electron-positive group on tertiary amino part are beneficial for enhancing the inhibitory effect on *Amaranthus mangostanus* L. Actually, compounds **5a**–**5o** showed stronger inhibitory effect than that of **5p**–**5r** with morpholine tail and **5s**–**5x** with carboxylic acid on piperidine ring.

On the whole, the structural insights obtained from molecular docking and 3D-QSAR contour maps are consistent with the experimental data, indicating that the molecular docking and the developed 3D-QSAR models are reliable to some extent. The 3D-QSAR contour maps show that the

electronic effect contributes to the strong herbicidal activity. Introduction of electron-positive group to the amino group of the test compounds may facilitate improving the inhibitory effect on *Oryza sativa* and *Amaranthus mangostanus*.

4. Conclusions

A series of benzophenone oxime ether derivatives with tertiary amines were synthesized and characterized. These compounds exhibited good herbicidal activities to both monocotyledon and dicotyledon. Based on the experimental results, the combined 3D-QSAR modeling and molecular docking analysis was performed with the data of *Oryza sativa* and *Amaranthus mangostanus* L. Due to the insufficient compounds structure diversity and variable influence factor, the models were assumed to be predictive but not perfectly reliable. However, these results threw a light on the research and development on the oxime ethers with amino groups to be herbicides.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Jimei Ma and Mingwei Ma contributed equally to this paper.

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