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Discovery of *ortho*-Alkoxy Substituted Novel Sulfonylurea Compounds That Display Strong Herbicidal Activity against Monocotyledon Grasses

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ABSTRACT: In the present study, we have designed and synthesized a series of 42 novel sulfonylurea compounds with *ortho*-alkoxy substitutions at the phenyl ring and evaluated their herbicidal activities. Some target compounds showed excellent herbicidal activity against monocotyledon weed species. When applied at 7.5 g ha^{-1}, **6−11** exhibited more potent herbicidal activity against barnyard grass (*Echinochloa crus-galli*) and crab grass (*Digitaria sanguinalis*) than commercial acetohydroxyacid synthase (AHAS; EC 2.2.1.6) inhibitors triasulfuron, penoxsulam, and nicosulfuron at both pre-emergence and postemergence conditions. **6−11** was safe for peanut for postemergence application at this ultralow dosage, suggesting that it could be considered a potential herbicide candidate for peanut fields. Although **6−11** and triasulfuron share similar chemical structures and have close K_i values for plant AHAS, a significant difference has been observed between their LUMO maps from DFT calculations, which might be a possible factor that leads to their different behaviors toward monocotyledon weed species.

KEYWORDS: *sulfonylurea, monocotyledon, herbicide, AHAS, peanut, LUMO*

INTRODUCTION

Sulfonylurea herbicides have been invented for nearly 40 years, and it is estimated that over 30 commercial products have been used globally for crop protection.[1,2] Although weed resistance to these families of herbicides due to overuse by farmers has become an inevitable concern,[3] new sulfonylurea herbicides are continuously produced by clever modification based on structure−activity relationships. For example, monosulfuron, recently developed in China, is a special herbicide used for millet fields, where traditional sulfonylurea herbicides are harmful to millet and no other effective herbicides are available for this agricultural crop.[4] The sulfonylureas control weeds by inhibiting acetohydroxyacid synthase (AHAS, EC 2.2.1.6, also referred to as acetolactate synthase, ALS), an essential enzyme playing an important role in the biosynthesis pathway of branched-chain amino acids (BCAAs), which is regarded to be a biologically safe target because it does not exist in mammal bodies.[5,6] The mode of action and the binding site of sulfonylurea herbicides have become clear at the molecular level since crystal structures of plant AHAS in complex with these inhibitors have been determined in the past containing only the AHAS catalytic subunit bound with sulfonylureas.[4,7−10] Lately, AHAS full structures composed of both catalytic and regulatory subunits, from plant and microbial sources, have been successfully elucidated using either cryo-EM or X-ray crystallography, and these advances have provided a more detailed understanding of the functional features and the inhibitory mechanism.[11,12]

Most sulfonylurea herbicides are effective against broadleaf weeds belonging to the dicotyledon species; however, not many are ideal toward gramineous weeds from the monocotyledon families. For example, barnyard grass (*Echinochloa crus-galli*) has been a pernicious weed in agricultural fields worldwide for the past few decades, and losses of yield in rice due to *E. crus-galli* competition are estimated to be about 35%.[13,14] Another case is crab grass (*Digitaria sanguinalis*), a troublesome annual weed that causes up to 90% losses of yield in soybean fields in some parts of the world.[15] There is an urgent need to develop novel herbicides to control these malignant grasses. It has been difficult to design and discover AHAS inhibitors with a totally new chemical skeleton. We had previously found that some isatin derivatives and nonsymmetrical aryl disulfides are novel AHAS inhibitor families; however, the in vivo herbicidal activities are much weaker than those of the commercial AHAS-inhibiting herbicides.[16,17] Yang and Xi et al. developed a conformational flexible inhibitor design strategy to combat plant AHAS Pro-197-Leu mutation via rational modification of the pyrimidinylbenzoate family, through which some excellent herbicidal compounds against dicot weeds flixweed (*Descurainia sophia*) and amaranth (*Ammannia arenaria*) were identified;[18−23] nevertheless, these studies did not especially aim at eliminating the monocotyledon grass.

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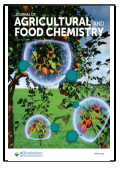

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AHAS inhibition contributes enormously to herbicidal activity; however, this is not the sole factor for the herbicidal behavior of these agrochemicals. As is known, commercial herbicidal imidazolinones and sulfonylureas are two typical families of AHAS inhibitors, the application rates of which are at very similar levels.[24] Surprisingly, the K_i values of imidazolinone herbicides are at the micromolar level, while the inhibition constants of the sulfonylurea herbicides are at nanomolar potency.[7] In addition, as a totally new class of AHAS inhibitors, nonsymmetrical disulfides have in vitro inhibition constants equal to those of imidazolinones, but the greenhouse herbicidal activity of the former is much weaker than that of the latter.[17] These are the cases for different types of AHAS inhibitors. If we compare only the sulfonylurea compounds themselves, such different herbicidal activities also exist. For example, K_i values of monosulfuron and tribenuron methyl against plant AHAS are 245 and 316 nM, respectively, while for chlorsulfuron it is only 14nM,[25] but their herbicidal activities from the rape root growth inhibition method are at the same level.[26] Obviously, other factors involved in the absorption, distribution, metabolism, and excretion (ADME) process also have significant contributions to the in vivo herbicidal activity. Therefore, it is hard to predict the in vivo herbicidal activity of an AHAS inhibitor even if the in vitro enzyme inhibition data is available.

In many cases, sulfonylurea herbicides have an ester group attached to the *ortho*-position for the phenyl ring or the five-member aromatic ring.[25,26] It is notable that some other sulfonylurea herbicides have an alkoxy substituent at this position, such as ethoxysulfuron and triasulfuron. Ethoxysulfuron is a selective herbicide used to control the dicot weed species in paddy fields,[27] while triasulfuron is a selective herbicide for the control of the dicot weeds in wheat fields.[28] Previously, ethoxysulfuron was also found to possess very strong antifungal activity against *Candida albicans*, indicating that the sulfonylurea compounds with an alkoxy substituent instead of the ester group might possess better efficiency in the ADME process,[29] based on which a series of novel ethoxysulfuron derivatives were synthesized and biologically evaluated.[30] For triasulfuron, the heterocycle ring connected to the urea part is triazine; yet, many sulfonylurea herbicides such as chlorimuron ethyl, monosulfuron, and ethoxysulfuron have a pyrimidine ring at this position instead. Although triazine and pyrimidine are bioisosteric groups, the replacement of one by the other might result in unexpected biological activity.[31−33] In the present context, a series of *ortho*-alkoxy substituted novel sulfonylurea compounds were designed and synthesized. The in vitro inhibitory data against plant AHAS were measured, and in vivo herbicidal activities were also determined by both the rape root growth inhibition method and the greenhouse pot assay. From the biological results, compounds **6-11** and **6-21** exhibited fairly exciting herbicidal activity against the monocotyledon weed species, much better than the commercial triasulfuron and nicosulfuron. **6-11** also displayed better herbicidal activity against crab grass than the commercial AHAS inhibitor penoxsulam. This study has hence provided meaningful guidance for the discovery of herbicides to effectively tackle some monocotyledon grasses for crop protection. The general structures of sulfonylureas, imidazolinones, isatin derivatives, nonsymmetrical aryl disulfides, and pyrimidinylbenzoates are shown in Figure 1. The structures of monosulfuron, tribenuron methyl, chlorsulfuron, ethoxysulfuron, triasulfuron, chlorimuron ethyl, penoxsulam, and nicosulfuron are shown in Figure 2.

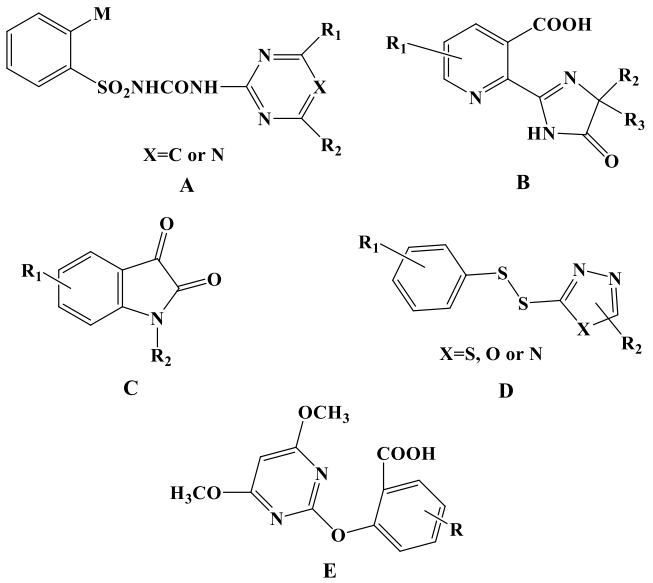

Figure 1. General structures of sulfonylureas (**A**), imidazolinones (**B**), isatin derivatives (**C**), nonsymmetrical aryl disulfides (**D**), and pyrimidinylbenzoates (**E**).

MATERIALS AND METHODS

Instruments and Chemicals. Chemical materials and reagents were purchased from the following commercial suppliers: Ailai Chemical (Shanghai), Sanbang Chemical (ChangChun), J&K Chemical (Beijing), Aladdin Chemical (Shanghai), Fengyan Chemical (Beijing), Shaoyuan Chemical (Shanghai), Energy Chemical (Shanghai), Xiezun Chemical (Nanjing), PharmaCore (Kunshan), Guangfu-Chem (Tianjin), Heowns Chemical (Tianjin), Hedong Guangda Chemical (Tianjin), and Tianjin Chemical & Reagents. All solvents and liquid reagents were dried in advance using standard methods and distilled before use. Melting points were determined using an RT-2 melting apparatus (Shanghai PuZhe photoelectric Co., Shanghai, China) and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer (Bruker Corporation, Switzerland). The chemical shift values (d) for the NMR spectra were reported as parts per million (ppm) using deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO-d_6), or acetone-d_6 as the solvent and tetramethylsilane (TMS) as an internal reference standard. High-resolution mass spectra were recorded on an FT-ICR mass spectrometer (Ionspec, 7.0 T). Single-crystal X-ray diffraction analyses were performed on a Bruker Smart 1000 CCD diffractometer (Bruker Corporation, Switzerland). In vitro AHAS inhibition was recorded on a BioTek ELx800 absorbance microplate reader (BioTek Instruments, Inc., USA). The chemical preparation procedures of the intermediates (**2**, **3**, **4**, and **5**) and target sulfonylurea compounds (**6-1** to **6-42**) are illustrated in Figure 3.

Synthesis of 2-1 and 2-2. The starting material 2-hydroxybenzenesulfonamide **1** was commercially available at PharmaCore. Potassium carbonate (34.5 g, 250 mmol) was added to a solution of **1** (8.65 g, 50 mmol) in 150 mL of dimethylformamide (DMF) and the reactants were stirred at room temperature for 30 min. Then, 1-fluoro-2-iodoethane or iodoethane (50 mmol) was added to the reacting mixture. Next, the reaction was heated and continued overnight under reflux. Subsequently, the mixture was cooled and filtered. Water (300 mL) was added to the filtrate, and the product was extracted with ethyl acetate (100 mL × 3). The organic phase was dried, and the final product **2-1** or **2-2** was further purified in medium yield using column chromatography.

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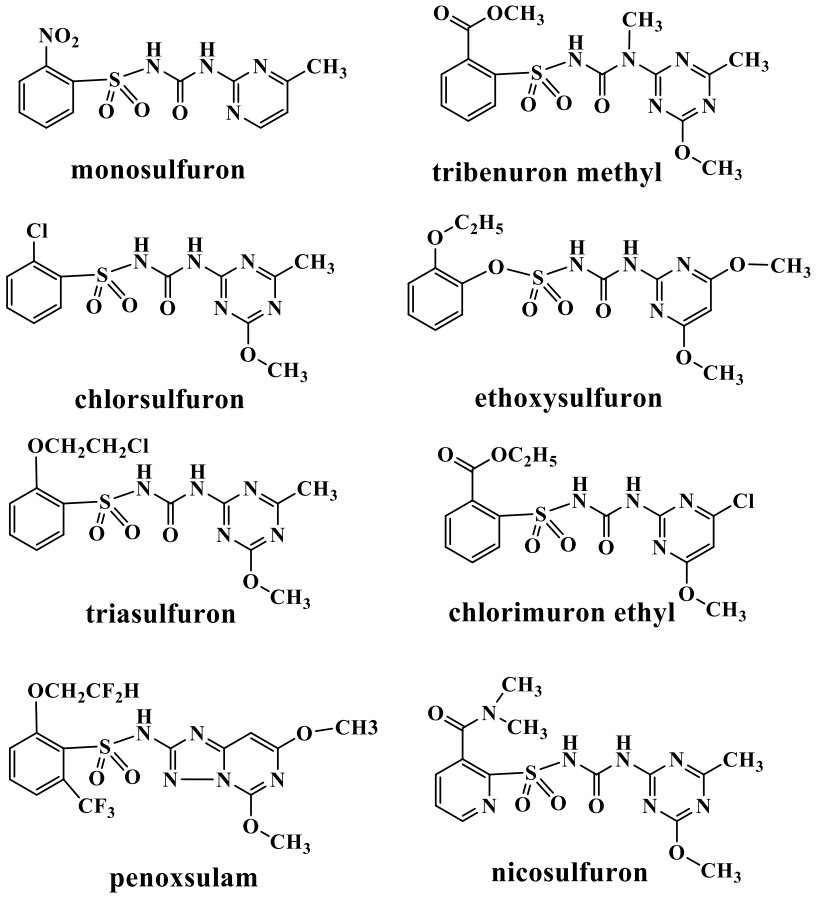

Figure 2. Structures of monosulfuron, tribenuron methyl, chlorsulfuron, ethxoysulfuron, triasulfuron, chlorimuron ethyl, penoxsulam, and nicosulfuron.

Synthesis of ***2-3****.* 2-Hydroxybenzenesulfonamide **1** (6.27 g, 36 mmol), 1,3-dioxolan-2-one (4.12 g, 47 mmol), and imidazole (83 mg, 1.2 mmol) were mixed together, and the reactants were then protected using a nitrogen atmosphere. Then, the temperature was increased to 90 °C until the mixture melted completely. The reaction continued at 160 °C for 4 h and the temperature was decreased to 90 °C again. Ethanol (15 mL) was added to dissolve the mixture in the next step. A suitable amount of silica gel was added and the solvent was removed by evacuation. The resulting powder was purified using column chromatography to give a white solid 2-(2-hydroxyethoxy)-benzenesulfonamide **2-3** in 80% yield.

Synthesis of ***2-4****.* This preparation was carried out according to a method reported previously with slight modifications.[34] Sulfoxide chloride (0.95 g, 7.5 mmol) was added slowly to dimethylacetamide (DMAc, 1.065 g, 12.25 mmol) under an ice bath before the mixture was stirred at 15 °C for 30 min. 2-(2-Hydroxyethoxy) benzenesulfonamide **2-3** (1.10 g, 5 mmol) and dichloromethane (DCM, 2.5 mL) were then added to the reactants and the reaction continued at room temperature for 1 h. Then, the mixture was transferred into a mixed liquid of iced water (25 mL) and DCM (25 mL). Liquid separation was performed after the mixture was stirred to a homogeneous condition. The organic phase was washed with iced water until no DMAc could be detected. Following evacuation and column chromatography, 2-(2-chloroethoxy)benzenesulfonamide **2-4** was purified as a white powder in 61% yield.

Synthesis of ***2-6*** *and* ***2-7****.* 2-(2-Hydroxyethoxy)-benzenesulfonamide **2-4** (1.6 g, 7.4 mmol), DCM (20 mL), and anhydrous pyridine (1.7 mL) were mixed together. Subsequently, methanesulfonic anhydride (Ms_2O, 1.53 g, 8.8 mmol) was added to the mixture under an ice bath. The reaction was stopped after 4 h, and the solvent was removed under vacuum. After being washed with water, filtered, and then dried by infrared light without further purification, 2-(2-sulfamoylphenoxy)ethyl methanesulfonate **2-5** was obtained as a white solid with a yield of 85%.

2-(2-Sulfamoylphenoxy)ethyl methanesulfonate **2-5** (1.714 g, 5.5 mmol), LiBr or NaI (23mmol), and acetone (16 mL) were mixed together and the reactants were then stirred at 60 °C for 2 h. The solvent was removed under vacuum and the resulting solid was washed with water. After recrystallization, 2-(2-bromoethoxy)-benzenesulfonamide **2-6** or 2-(2-iodoethoxy)benzenesulfonamide **2-7** was purified in an excellent yield.

Synthesis of ***4****.* The synthesis of these compounds is basically according to a published method.[35,36] After **3** (50 mmol) was dissolved in tetrahydrofuran (THF, 80 mL), potassium carbonate (11.7g, 84 mmol) was added to the mixture. Then, phenyl carbonochloridate (9.4 mL, 50 mmol) was added to the reactants, and the mixture was stirred for 18 h at room temperature. In the next step, the reacting mixture was filtered, and THF was evacuated from the filtrate. Compound **4** was then purified by column chromatography in low-to-good yield.

Synthesis of ***6-1*** *to* ***6-14****.* For the target sulfonylurea compounds **6-1** to **6-14**, compound **4** (0.4 mmol) was dissolved in acetonitrile (5 mL) and compound **2** (0.44mmol) was added to the solution. Then, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 65μL, 0.44mmol) was added to the mixture under stirring and the reaction continued overnight at room temperature. Subsequently, water (10 mL) was added to the solution and 50% hydrochloric acid was added to adjust the pH value to 2.0 when precipitants started to appear. The precipitants were collected after filtration and washed with water to give the pure final product **6** in desirable yields.

Synthesis of ***6-15*** *to* ***6-42****.* The target sulfonylurea compounds **6-15** to **6-42** were synthesized using another conventional route. Compound **2** (4 mmol) and 1,4-diazabicyclo[2.2.2]octane (DBACO, 4 mmol) were mixed in anhydrous toluene (20 mL). Oxalyl chloride

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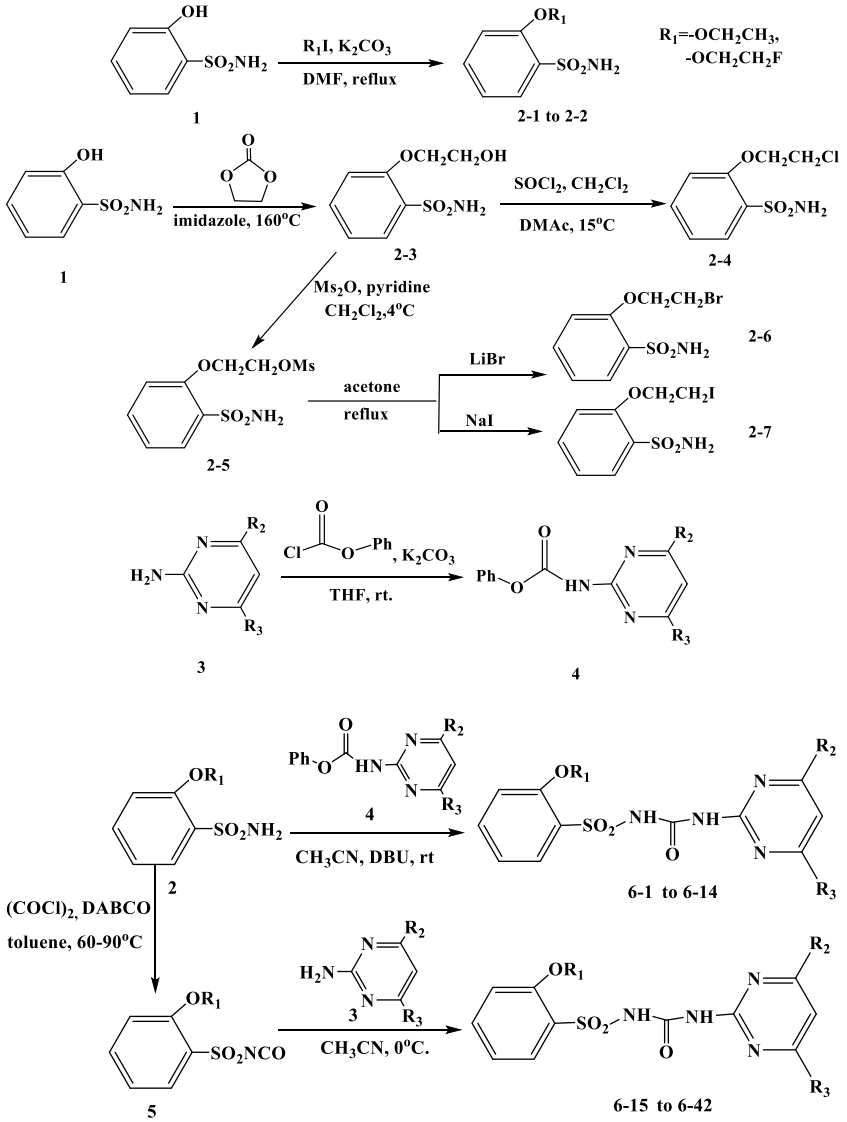

Figure 3. Synthetic routes of the intermediates and the target sulfonylurea compounds.

(1.35 mL, 20 mmol) was then added dropwise to the mixture. The reaction continued for 6 h at 60 °C, and then the temperature was increased to 90 °C for 12 h. The solid was then separated from the mixture by filtration, the solvent was removed by evacuation from the remaining liquid, and phenyl sulfonyl isocyanate **5** was left as a sticky oil without further purification. Subsequently, anhydrous acetonitrile (10 mL) was added to the sticky oil, and compound **3** (4 mmol) was added to the mixture at the ice temperature. Then, the reaction continued for 12 h at room temperature and acetonitrile was removed with evacuation. Next, a solution of sodium hydroxide (1 M, 20 mL) was mixed with the remaining sticky substance and the mixture was filtered, and the clear solution was kept. Further, 5% hydrochloric acid was added slowly to the solution until there were no more precipitants, and the mixture was kept still for 1 h. The final step was filtration, and the filter residue was washed with water and dried under infrared light to give the pure product **6** in medium-to-high yields.

Analytical data and the unreported intermediates and new target compounds **6-1** to **6-42** are detailed in the Supporting Information.

X-ray Diffraction. The crystal structure of compound **6-21** (0.20 ×0.18 × 0.12 mm size) was determined, and X-ray intensity data were recorded on a Rigaku Saturn 724 CCD diffractometer using graphite monochromated Mo KR radiation (λ = 0.71073 Å). "Direct methods" techniques of the Bruker software package SHELXTL were used to solve the chemical structure.[37] All calculations were refined anisotropically.

Biological Assays. *In Vitro Inhibition of Arabidopsis thaliana AHAS (AtAHAS).* The expression and purification of wild-type *AtAHAS* have been detailed previously.[38] The activity of this plant AHAS enzyme was measured using the colorimetric assay in a buffer (pH 7.0) that contained 50 mM potassium phosphate, 50 mM pyruvate, 1 mM thiamine diphosphate, 10 mM magnesium chloride, and 10 μM flavin adenine dinucleotide (FAD). The compounds to be tested were dissolved in DMSO at a concentration of 5 mM and diluted using MilliQ water to different concentrations. The reaction mixture was incubated at 37 °C for 30 min before the reaction was stopped by adding 25 μL of 10% sulfuric acid. Then, the mixture was heated at 60 °C for 15 min to convert acetolactate into acetoin. The acetoin formed was quantified by incubation with 0.5% creatine and a-naphthol (5%, w/v) for 15 min at 60 °C, and A_{525} was measured.

For the measurement of inhibition constants, trial experiments with a wide range of inhibitor concentrations were used to establish an appropriate concentration scope. Subsequently, the AHAS activity was measured in a series of inhibitor concentrations within this window. K_i values were analyzed by fitting the data with nonlinear regression using eqs 1 or 2, where v is the inhibited rate, v_0 is the uninhibited rate, v_∞ is the small residual activity for some cases, and $[I]$ is the total inhibitor concentration.

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$$v = v_o/(1 + [I]_o/K_i) \quad (1)$$

$$v = (v_o - v_\infty)/(1 + [I]_o/K_i) + v_\infty \quad (2)$$

In Vivo Inhibition of Rage (Brassica campestris L.) Root Growth. Preliminary herbicidal activity of the sulfonylurea compounds was evaluated using the rape root growth inhibition method.[25] Briefly, a 0.1% water emulsion was prepared by mixing 1 g of emulsifier with distilled water to a final volume of 1 L. The target compounds were made into a DMSO stock solution of 30 mg mL^{-1} concentration and diluted to different concentrations using the 0.1% water emulsion. Rape seeds were soaked in distilled water for 4 h and then placed on a filter paper in a 6 cm Petri plate, to which 2 mL of the inhibitor solution had been added beforehand. Usually, 10 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 72 h at 28 °C. The lengths of rape roots were measured, and the means were calculated. Percentage inhibition was calculated relative to controls using distilled water. Each trial was conducted in duplicate to obtain a reliable result.

Greenhouse Herbicidal Activity against Monocotyledon and Dicotyledon Weed Species. The pre-emergence and postemergence greenhouse herbicidal activities of the target compounds were evaluated against representative monocotyledon grasses (*Echinochloa crus-galli* and *Digitaria adscendens*) and dicotyledon weeds (*Brassica campestris* and *Amaranthus retroflexus*) using methods reported previously.[39,40] For compounds with promising activity, more weed species (*Eragrostis curvula* (Schrad.) Nees, *Bromus inermis* Leyss., *Eleusine indica* (L.) Gaertn., *Setaria viridis* (L.) Beauv., *Puccinellia distans* (L.) Parl., *Elymus dahuricus* Turcz., *Flaveria bidentis* (L.) Kuntze., *Ixeris polycephala* Cass., *Portulaca oleracea* L., *Pharbitis nil* (Linn.) Choisy, *Abutilon theophrasti* Medicus, *Medicago sativa*, *Capsella bursa-pastoris*, *Chenopodium album* Linn, *Taraxacum mongolicum* Hand.-Mazz., and *Polygonum* L., among which the top six belong to monocotyledon species and the last 10 belong to dicotyledon species) were selected to assess the broad-spectrum herbicidal activity. Soybean, peanut, and wheat were chosen for a preliminary crop safety test using the same bioassay technique. Triasulfuron, nicosulfuron, and penoxsulam were used as the control in different conditions.

In detail, the solution of compounds was prepared using the same procedure for the above rape root growth inhibition assay. A 0.1% water emulsion was prepared by mixing 1 g of emulsifier with distilled water to a final volume of 1 L. The target compounds were made into a DMSO stock solution of 30 mg mL^{-1} concentration and diluted to different concentrations using the 0.1% water emulsion. A 3WPSH-500E spray tower (from Nanjing Institute of Agricultural Mechanization, Ministry of Agricultural and Rural Affairs) was utilized to spray the aqueous samples.

For pre-emergence herbicidal activity, sandy clay (100 g) in a plastic box (11 cm × 7.5 cm × 6 cm) was wetted with water. Sprouting seeds of the weed under test were planted in fine earth (0.6 cm depth) in a greenhouse and sprayed with the test compound solution at certain dosages. For postemergence herbicidal activity, seedlings (one leaf and one stem) of the weed were sprayed with the test compound solutions at different dosages. For both treatments, the fresh weights of the aboveground portions were determined 3 weeks later, and the percent inhibition relative to the controls was calculated. Two replicates for each experiment were given.

Molecular Simulation. *Comparative Field Analysis (CoMFA).* The three-dimensional (3D) structures of the target sulfonylurea compounds were constructed using Sybyl 7.3 software (Tripos Inc., St Louis, MO) based on the crystal structures of chlorsulfuron and tribenuron methyl in complex with *At*AHAS (pdb entry 1YHZ and 1YI1).[7] The molecules were assigned Gasteiger-Hückel charges and fully minimized by the Tripos force field with a convergence of 0.01 kcaL mol^{-1} $Å^{-1}$. For CoMFA analysis,[41] all of the 42 molecules were put into a database and included in the training set. All of the parameters used the default values within the CoMFA module and the column filtering was set to 2.0 kcaL mol^{-1}. The "leave-one-out" (LOO) cross-validation method was applied to determine the optimum number of partial least squares (PLS) components. The non-cross-validated method was used to produce the steric and electrostatic model to depict the quantitative structure−activity relationship (3D-QSAR).

Density Functional Theory (DFT) Calculation. Compounds **6-11**, **6-21**, and triasulfuron were chosen for DFT geometry optimization by the SCF method using the B3LYP (Becke, three-parameter, Lee_Yang_Parr) function with a basis set of 6-31G to describe their molecular properties.[42,43] Gaussian03 was used to perform the calculations.[44] Conformations of **6-11** and **6-12** were taken from the molecular database from CoMFA analysis, and the 3D structure of triasulfuron was built based on the **6-11** model.

RESULTS AND DISCUSSION

Chemistry. As shown in Figure 3, the target sulfonylurea compounds were synthesized using two different routes. Generally, when OR_1 was an ethoxy or a fluoroethoxy group, the substituted benzenesulfonamide (compound **2**) reacted with different phenyl (pyrimidin-2-yl)carbamates (compound **4**) to give the corresponding title compounds (**6-1** to **6-14**) in good yields. When OR_1 was switched to the chloroethoxy, bromoethoxy, iodoethoxy, or hydroxyethoxy substituent, after compound **2** reacted with oxalyl chloride to produce sulfonyl isocyanate (compound **5**), the intermediate further reacted with different pyrimidin-2-amines to obtain the desired compounds (**6-17** to **6-42**). It should be noted that **6-15** and **6-16** had the fluoroethoxy substituent in the phenyl ring; however, these two compounds could only be prepared using the second method. For ^1H NMR data, the $-SO_2NH-$ proton signals were always in the range of δ 12−13 ppm, no matter which solvent the sample was in. Meanwhile, for the −CONH− proton, the signals were in the range of δ 7−8 ppm if the solvent was $CDCl_3$ or acetone-d_6, and such signals moved to the δ 10−13 range in the case of DMSO-d_6. For the HRMS data, all of the compounds displayed a $[M + H]^+$ result within a reasonable error of the theoretical data. Moreover, after attempts on several compounds, we successfully obtained the crystal of compounds **6-21** and determined the chemical structure using single-crystal X-ray diffraction. From Figure 4, it is clear that the phenyl ring is attached with a chloroethoxy group, which confirms the structure of this family. Notably, **6-21** is highly similar to triasulfuron, with a very minor difference in the heterocycle. For this compound, it is a pyrimidine ring while for triasulfuron it is a triazine ring instead. Another

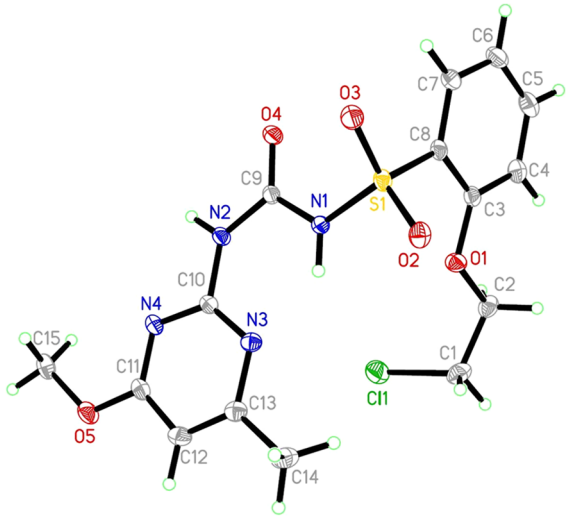

Figure 4. Molecular structure of **6-21** from X-ray diffraction.

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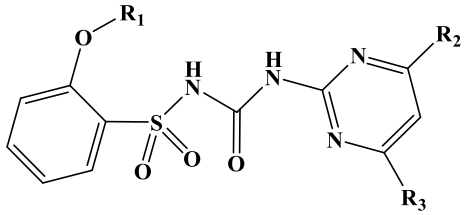
Table 1. Chemical Structures, in Vitro *At*AHAS Inhibition, and Rape Root Growth Inhibition of the Target Compounds



					rape root growth inhibition (%)		
no.	R_1	R_2	R_3	*At*AHAS inhibition K_i (nM)	10 $\mu g\ \mu L^{-1}$	1 $\mu g\ \mu L^{-1}$	0.1 $\mu g\ \mu L^{-1}$
6-1	$-CH_2CH_3$	$-CH_3$	$-CH_3$	950 ± 110	68.4	59.0	54.8
6-2	$-CH_2CH_3$	$-CH_3$	$-H$	1322 ± 208	60.6	65.8	44.9
6-3	$-CH_2CH_3$	$-CH_3$	$-Br$	205 ± 25	61.9	60.3	62.7
6-4	$-CH_2CH_3$	$-OCH_3$	$-CH_3$	85 ± 18	71.0	62.9	56.1
6-5	$-CH_2CH_3$	$-CH_3$	$-Cl$	650 ± 77	62.9	58.7	45.4
6-6	$-CH_2CH_3$	$-OCH_3$	$-Cl$	766 ± 40	69.2	61.4	59.8
6-7	$-CH_2CH_2F$	$-OCH_3$	$-OCH_3$	55 ± 8.3	70.2	64.5	65.5
6-8	$-CH_2CH_2F$	$-CH_3$	$-CH_3$	835 ± 108	59.0	59.8	53.5
6-9	$-CH_2CH_2F$	$-CH_3$	$-H$	2354 ± 155	64.0	59.5	50.1
6-10	$-CH_2CH_2F$	$-CH_3$	$-Br$	228 ± 18	61.1	60.3	55.2
6-11	$-CH_2CH_2F$	$-OCH_3$	$-CH_3$	36 ± 6.4	82.5	75.8	72.3
6-12	$-CH_2CH_2F$	$-OCH_3$	$-Br$	145 ± 36	65.2	52.2	44.8
6-13	$-CH_2CH_2F$	$-CH_3$	$-Cl$	358 ± 20	64.6	53.3	50.4
6-14	$-CH_2CH_2F$	$-OCH_3$	$-Cl$	444 ± 40	65.3	58.2	54.6
6-15	$-CH_2CH_2F$	$-CH_3$	$-I$	725 ± 64	66.5	65.3	34.7
6-16	$-CH_2CH_2F$	$-OCH_3$	$-I$	88 ± 13	69.2	65.7	64.6
6-17	$-CH_2CH_2Cl$	$-OCH_3$	$-Br$	72 ± 9.0	70.4	67.9	67.0
6-18	$-CH_2CH_2Cl$	$-OCH_3$	$-Cl$	605 ± 89	68.2	59.2	58.6
6-19	$-CH_2CH_2Cl$	$-CH_3$	$-I$	490 ± 74	71.5	63.7	48.0
6-20	$-CH_2CH_2Cl$	$-OCH_3$	$-I$	723 ± 63	67.6	66.5	59.8
6-21	$-CH_2CH_2Cl$	$-OCH_3$	$-CH_3$	33 ± 5.1	79.3	74.3	68.1
6-22	$-CH_2CH_2Br$	$-CH_3$	$-Br$	145 ± 25	61.0	58.6	50.8
6-23	$-CH_2CH_2Br$	$-CH_3$	$-Cl$	340 ± 44	64.2	55.0	43.0
6-24	$-CH_2CH_2Br$	$-OCH_3$	$-Cl$	882 ± 96	67.6	63.1	55.0
6-25	$-CH_2CH_2Br$	$-CH_3$	$-I$	718 ± 60	62.8	53.9	18.4
6-26	$-CH_2CH_2Br$	$-CH_3$	$-H$	2215 ± 310	62.6	52.8	0
6-27	$-CH_2CH_2Br$	$-OCH_3$	$-CH_3$	90 ± 4.6	75.7	72.6	62.9
6-28	$-CH_2CH_2Br$	$-OCH_3$	$-OCH_3$	182 ± 36	64.0	62.8	57.1
6-29	$-CH_2CH_2I$	$-CH_3$	$-Br$	105 ± 19	53.6	36.0	0
6-30	$-CH_2CH_2I$	$-OCH_3$	$-Br$	600 ± 210	62.0	59.0	32.7
6-31	$-CH_2CH_2I$	$-CH_3$	$-Cl$	469 ± 152	60.6	53.8	29.9
6-32	$-CH_2CH_2I$	$-OCH_3$	$-Cl$	895 ± 103	58.6	53.6	50.0
6-33	$-CH_2CH_2I$	$-CH_3$	$-I$	1480 ± 195	46.1	36.0	0
6-34	$-CH_2CH_2I$	$-OCH_3$	$-I$	950 ± 249	57.3	51.4	38.0
6-35	$-CH_2CH_2I$	$-CH_3$	$-H$	3590 ± 445	63.7	40.8	0
6-36	$-CH_2CH_2I$	$-OCH_3$	$-CH_3$	320 ± 83	64.2	62.8	51.7
6-37	$-CH_2CH_2I$	$-OCH_3$	$-OCH_3$	135 ± 45	59.8	55.9	48.9
6-38	$-CH_2CH_2OH$	$-OCH_3$	$-Br$	613 ± 158	66.5	62.6	57.9
6-39	$-CH_2CH_2OH$	$-CH_3$	$-Cl$	420 ± 67	63.1	57.5	35.8
6-40	$-CH_2CH_2OH$	$-OCH_3$	$-Cl$	326 ± 86	64.8	60.9	52.0
6-41	$-CH_2CH_2OH$	$-CH_3$	$-I$	431 ± 60	85.5	57.8	0
6-42	$-CH_2CH_2OH$	$-CH_3$	$-H$	5729 ± 1190	70.4	39.1	0
triasulfuron				31 ± 5.4	78.7	76.5	73.2

interesting observation is that the hydrogen atom connected with the N1 atom is at a distance of a hydrogen bond with an N3 atom, similar to our earlier result.[45]

Biological Activity. *In Vitro Plant AHAS Inhibition.* All of the synthesized sulfonylureas were subjected to the *At*AHAS inhibition bioassay. From Table 1, it can be seen that the K_i values are in a wide range of 33−5729 nM, although these compounds share very close chemical structures. As a comparison, triasulfuron was also included in this study, with an inhibition constant of 31 nM. For the compounds with a monosubstituent at the pyrimidine ring (**6-2**, **6-9**, **6-26**, **6-35**, and **6-42**), the weakest K_i values have been observed (from 1322 to 5729 nM). Seven of the compounds (**6-4**, **6-7**, **6-11**, **6-16**, **6-17**, **6-21**, and **6-27**) have K_i values below 100 nM, with a

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Table 2. Herbicidal Activity of Selected Compounds from the Greenhouse Pot Bioassay[a]

		pre-emergence activity (%)				postemergence activity (%)			
no.	dosage g ha^{-1}	Bc	Ar	Eg	Da	Bc	Ar	Eg	Da
6-1	30	89.1	81.9	65.4	12.9	24.0	89.9	15.2	17.7
6-2	30	33.2	41.1	22.5	0	52.0	19.8	0	0
6-3	30	61.2	69.1	0	0	0	40.3	6.9	0
6-4	30	95.4	97.2	88.7	78.3	95.7	96.4	75.0	74.8
	15	87.1	90.6	63.6	67.4	94.8	87.1	67.1	56.0
	7.5	79.4	85.0	58.2	54.2	90.0	46.0	46.8	49.0
6-5	30	11.2	21.1	13.4	0	0	5.6	0	0
6-6	30	86.4	93.1	53.5	13.7	18.0	28.8	36.3	20.9
6-7	30	91.0	93.1	64.1	24.7	79.6	77.7	27.4	23.8
6-8	30	94.6	81.9	81.4	63.8	19.7	61.2	28.0	38.8
	15	83.9	70.0	65.5	61.6	NT	NT	NT	NT
	7.5	78.8	58.8	58.2	55.3	NT	NT	NT	NT
6-9	30	38.1	40.8	7.5	0	79.9	34.9	0	21.9
6-11	30	96.4	93.7	95.9	84.5	100	100	92.9	84.6
	15	93.2	92.9	94.7	78.0	100	98.7	90.9	80.8
	7.5	83.4	91.3	93.1	71.7	100	87.3	88.8	65.2
6-13	30	60.1	75.0	16.3	17.3	1.5	0	4.2	1.5
6-14	30	89.1	91.7	39.5	18.8	80.5	100	51.2	33.2
6-17	30	75.2	61.5	38.0	8.5	33.0	16.0	7.8	18.1
6-21	30	91.3	90.4	90.8	50.4	95.7	94.5	82.0	65.2
	15	84.6	75.6	90.3	49.3	93.9	97.3	75.1	59.3
	7.5	80.7	70.0	85.5	46.9	93.7	80.7	73.8	45.6
6-27	30	69.8	73.1	75.5	25.6	30.6	25.4	86.7	29.3
	15	62.5	50.5	62.3	0	20.1	21.4	61.2	15.1
	7.5	60.3	45.1	20.4	0	0	0	35.0	0
6-36	30	93.3	51.0	33.7	29.9	26.1	7.2	42.7	14.9
6-40	30	7.4	38.5	13.5	39.3	28.5	16.6	33.5	26.9
TRSU	30	99.3	96.1	45.0	20.0	100	100	45.2	25.3
	15	95.0	90.8	43.6	24.3	100	92.3	41.3	19.7
	7.5	88.6	81.5	30.1	15.6	93.2	40.4	15.2	12.3
PNSL	15	92.1	85.0	65.9	48.1	98.3	99.1	85.8	55.9
	7.5	89.1	81.3	56.4	33.6	92.0	96.9	79.4	36.8
NISU	30	71.4	64.1	12.3	17.0	100	100	94.9	1.7
	15	58.6	48.7	6.7	4.1	100	100	69.5	0
	7.5	52.0	28.2	0	2.1	92.0	100	44.1	0

[a]Bc = *Brassica campestris*, Ar = *Amaranthus retroflexus*, Eg = *Echinochloa crus-galli*, Da = *Digitaria adscendens*, NT = no test, TRSU = triasulfuron, PNSL = penoxsulam, and NISU = nicosulfuron.

methoxy group at the *meta* position of the pyrimidine ring and a methyl, methoxy, bromo- or an iodo group at another *meta* position. If we only compare the in vitro *At*AHAS inhibition, none of the target compounds in this study is more potent than triasulfuron. Among all of the novel sulfonylureas in this study, **6-11** and **6-21** showed even potency to triasulfuron, and their K_i values were 36 and 33 nM, respectively. The chemical structures of **6-11** and **6-21** are close to that of triasulfuron, with the same substituents (a methyl group and a methoxy group) at the heterocycle ring. For these two compounds, **6-11** has a fluorine atom in the *ortho*-alkoxy group and **6-21** has a chlorine atom instead, as detailed in the crystal structure.

Rape Root Growth Inhibition. It has been proven to be a quick protocol to estimate the in vivo herbicidal activity preliminarily for the sulfonylurea compounds using rape root growth inhibition bioassay.[25] This method takes only 3 days, much shorter than the greenhouse pot assay method, which needs several weeks. As can be seen from Table 1, all of the target compounds exhibited promising activity at 10 μg μL^{-1} concentration. When the concentration dropped to 1.0 and 0.1μg μL^{-1}, the inhibitions generally became be less potent. Compounds **6-26**, **6-29**, **6-33**, **6-35**, **6-41**, and **6-42** displayed no herbicidal activity at 0.1 μg μL^{-1} treatment. This is not surprising because these compounds are very weak *At*AHAS inhibitors, except **6-29**, the K_i of which is 105 nM. In contrast, for compounds **6-3**, **6-7**, **6-11**, **6-16**, **6-17**, **6-21**, and **6-27**, the herbicidal activities were all >60% even at 0.1μg μL^{-1}. On the whole, these seven compounds have the best *At*AHAS inhibitions (**6-4** has a stronger K_i than **6-3**, yet **6-3** has slightly better rape root growth inhibition than **6-4**, which is the only exception). The herbicidal activities of **6-11** and **6-21** were 72.3 and 68.1% at 0.1 μg μL^{-1}, respectively, and the biological activity for triasulfuron is 73.2% at this condition. Taking together the best and the worst herbicidal activities, there is a basic but not absolute correlation of the in vivo rape root growth and the in vitro plant AHAS inhibitions.

Greenhouse Herbicidal Activity from Pot Assay. Despite the ideal herbicidal activities from rape root growth inhibition of most target sulfonylureas, it is more meaningful to evaluate the herbicidal activities in a greenhouse by both pre-emergence and postemergence application, through which different weed species can be tested and selectivity can be studied for a single

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compound. First, we chose all of the compounds bearing the ethoxy group (**6-1** to **6-6**) and six compounds with the fluoroethoxy group (**6-7**, **6-8**, **6-9**, **6-11**, **6-13**, and **6-14**) for the pot assay, regardless of their enzyme inhibition and rape root growth inhibition potency. From Table 2, compounds **6-2**, **6-3**, **6-5**, **6-9**, and **6-13** did not show good activities (<80% inhibition) at 30 g ha^{-1} against all of the tested weeds. Compounds **6-1**, **6-6**, **6-7**, and **6-14** exhibited promising activity upon *Brassica campestris* and *Amaranthus retroflexus*; however, these compounds were not attractive because their herbicidal activities against *Echinochloa crus-galli* and *Digitaria adscendens* were poor. Compounds **6-4** and **6-11** not only displayed desirable activities against the dicotyledon species but also showed excellent activities against monocotyledon grasses at both the pre-emergence and the postemergence treatments. For **6-8**, herbicidal activity against monocotyledon species could be observed in the pre-emergence condition. Therefore, these three compounds were further tested at decreased dosages. Excitingly, even at 7.5 g ha^{-1}, compound **6-11** still showed remarkable activity against barnyard grass (93.1% for pre-emergence and 88.8% for postemergence) and crab grass (71.7% for pre-emergence and 65.2% for postemergence), much stronger than the commercial AHAS-inhibiting herbicides penoxsulam and nicosulfuron, which are famous for the control of monocotyledon grasses. Since **6-4** and **6-11** both have a methyl group and a methoxy group at the heterocycle ring, we thus chose **6-21**, **6-27**, and **6-36** from the remaining compounds for the greenhouse assay. **6-17** was selected for this assay since its AHAS inhibition and rape root growth inhibition were both strong. **6-40** was also subjected to the pot assay after consideration of the enzyme inhibition and rape root inhibition to determine whether the hydroxyethoxy group in the compound provides good greenhouse activity. From the result, **6-21** displayed comparable activity to **6-11** against barnyard grass, but its activity against crab grass is less potent than **6-11**. Therefore, **6-21** was also tested at lower dosages, and Figure 5 illustrates the pre-emergence herbicidal activity of **6-21** against barnyard grass (90.3% at 15 g ha^{-1}). For **6-27**, the herbicidal activity against barnyard grass was around 80% at both conditions; however, when used at lower dosages, there was a significant loss of the herbicidal activity.

Figure 5. Pre-emergence herbicidal activity of **6-21** against barnyard grass at 15 g ha^{-1} dosage.

For **6-17** and **6-40**, no obvious weed control effect could be seen at all of the conditions. For **6-36**, it only exhibited 93.3% herbicidal activity for rape at the pre-emergence condition, which was not our emphasis in this study. Thus, from the results of *At*AHAS inhibition, rape root growth inhibition, and the greenhouse pot assay, **6-11** and **6-21** were always the best ones among all of the target compounds. To our surprise, although triasulfuron was equal to **6-11** and **6-21**, regarding AHAS inhibition potency and rape root inhibition data, its herbicidal activities against barnyard grass and crab grass were much weaker at the same conditions in the greenhouse.

Due to the outstanding behaviors of **6-11** and **6-21** in the pot assay, herbicidal activities of these two compounds were further evaluated against 16 other weed species, among which six were monocotyledon grasses (*Eragrostis curvula* (Schrad.) Nees, *Bromus inermis* Leyss., *Eleusine indica* (L.) Gaertn., *Setaria viridis* (L.) Beauv., *Puccinellia distans* (L.) Parl., and *Elymus dahuricus* Turcz) and the others belonged to dicotyledon weeds. For comparison, triasulfuron and nicosulfuron were also included to determine the weeding effects. Table 3 summarizes the broad-spectrum herbicidal activities of these compounds at 15 g ha^{-1} dosage. From the results, **6-11** displayed better herbicidal activities than triasulfuron and nicosulfuron for the monocotyledon weeds in most cases. The only exception is the activity against *Puccinellia distans* (L.) Parl., for which nicosulfuron had a better effect at the postemergence condition. **6-21** also showed stronger activity than nicosulfuron at pre-emergence conditions, except for the effect against *Eragrostis curvula* (Schrad.) Nees. For the control of the 10 dicotyledon weed species, **6-11** and **6-21** also had promising activities, which were basically comparable to triasulfuron and better than nicosulfuron for most weeds. Generally, **6-11** had better performances than **6-21** at all of the conditions, whether it was against monocotyledon or dicotyledon weeds. It can also be seen that **6-11** and **6-21** had better herbicidal activities when applied at the pre-emergence condition than at the postemergence condition. The results herein strongly suggest that **6-11** and **6-21** should be considered as possible herbicides to specifically defeat some troublesome monocotyledon weeds.

Biological safety toward certain crops is an important criterion for an agrochemical candidate to be used for crop protection; otherwise, it can only be used as a nonselective herbicide in lawns, forests, etc. An ideal herbicide usually selectively eliminates unwanted weeds in the field; however, it does no or little harm to the crops. For this purpose, we next preformed a crop safety test at 15 g ha^{-1} dosage to determine whether **6-11** or **6-21** could be used in wheat, peanut, and soybean fields. In principle, if a compound shows <10% inhibition of a certain crop, it is considered safe to the crop. As is known, triasulfuron is a herbicide used in wheat fields,[28,46] which shows 3.9% inhibition and 7.0% inhibition against wheat in this experiment (Table 4). In contrast, triasulfuron was not safe to soybean and peanut at the tested conditions. Meanwhile, nicosulfuron was safe for all of the tested crops at these conditions. It was encouraging that **6-11** exhibited no inhibition for peanut at the postemergence condition. For soybean, **6-11** displayed 9.3% inhibition and **6-21** displayed 7.0% inhibition at the pre-emergence condition. For wheat, **6-21** displayed the same inhibition with triasulfuron against the crop for the postemergence application. Hence, for primary consideration, it is most likely that **6-11** will be considered as a postemergence herbicide used in the peanut field based on the

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Table 3. Broad-Spectrum Weed Control Effect of 6−11 and 6−21 at 15 g ha^{-1} Dosage[a]

	6-11		6-21		TRSU		NISU	
weed species	A	B	A	B	A	B	A	B
Eragrostis curvula (Schrad.) Nees	99.1	37.3	92.9	0	18.5	0	97.3	5.6
Bromus inermis Leyss.	81.4	48.6	52.9	0	8.1	1.3	0	1.7
Eleusine indica (L.) Gaertn.	91.8	14.6	64.9	0	9.8	0	14.0	3.9
Setaria viridis (L.) Beauv.	80.4	35.3	42.5	30.2	23.7	18.1	31.7	15.0
Puccinellia distans (L.) Parl.	87.7	54.7	58.9	29.8	23.3	6.8	28.8	61.5
Elymus dahuricus Turcz.	NT	36.5	50.7	0	29.4	3.8	NT	18.9
Flaveria bidentis (L.) Kuntze.	45.1	26.7	18.9	33.8	0	73.5	85.1	48.5
Ixeris polycephala Cass.	77.0	0	68.5	3.6	80.3	46.4	36.5	0
Portulaca oleracea L.	63.3	8.2	16.7	1.6	52.7	32.3	0	0
Pharbitis nil (Linn.) Choisy	41.3	14.7	0	8.7	41.6	18.1	0	24.5
Abutilon theophrasti Medicus	65.0	20.6	25.7	0	61.4	46.6	0	0
Medicago sativa	82.7	90.0	66.8	56.0	79.7	95.3	18.5	0
Capsella bursa- pastoris	97.7	NT	97.9	NT	98.5	NT	54.1	NT
Chenopodium album Linn	80.3	NT	73.1	NT	88.4	NT	82.4	NT
Taraxacum mongo- licum Hand.-Mazz	64.0	59.3	62.2	34.7	64.4	96.4	54.9	28.2
Polygonum L.	NT	39.2	68.3	21.4	81.4	47.7	NT	15.5

[a]A = pre-emergence activity (%), B = postemergence activity (%),TRSU = triasulfuron, NISU = nicosulfuron, and NT = no test. This occurred when there were not enough grass seeds for some bioassay experiments.

Table 4. Biosafety Test of 6−11 and 6−21 upon Selected Crops at 15 g ha^{-1} Dosage[a]

	peanut		soybean		wheat	
no	A	B	A	B	A	B
6-11	26.7	0	9.3	34.6	80	39
6-21	30.9	11.1	7.0	25.3	66	7.0
triasulfuron	57.8	46.5	18.9	45.5	3.9	7.0
nicosulfuron	8.7	0	2	0	2.3	5.3

[a]A = pre-emergence activity (%) and B = postemergence activity (%).

current biosafety data upon these crops. More species of crop safety will be biologically screened for this compound in the near future.

***In Silico* Computational Modeling.** *QSAR from CoMFA Results.* CoMFA is a tool to generate 3D contour models to quantitatively analyze the structure−activity relationships of bioactive compounds by steric and electrostatic contributions.[41] As is known, the choice of the correct conformations is most critical for the establishment of the CoMFA model. A number of herbicidal sulfonylureas have been successfully co-crystallized with fungal AHAS or plant AHAS, and they share significant similarities in the conformations.[4,7,47] Accordingly, we built the chemical models of the inhibitors based on the bioactive poses. From the PLS, the leave-one-out q^2 value was 0.622 when the optimum number of components was 6, and none of the compounds were excluded from the training set, suggesting that the CoMFA model was successful. When subjected to a non-cross-validation, the r^2 value was 0.932 with a standard error of estimate of 0.151 and F values of 56.667. The steric and electrostatic contributions were 72.1 and 27.9%, respectively. The predictive biological activity versus the experimental biological activity has been listed in the Supporting Information.

The 3D-CoMFA contour maps have been exhibited in Figure 6. Compound **6-11** was used as the template to depict the steric and electrostatic contour maps, which were fitted on the *At*AHAS binding site. For the steric contour map (Figure 6A), a bulky group is favorable for enhanced AHAS inhibition in the green space while such a group decreases the potency in the yellow region. For the electrostatic contour map (Figure 6B), a positively charged group provides an increase of activity in the blue contour, whereas a negative charge is likely to reinforce the inhibition in the red-contour region. Based on this result, novel compounds bearing a difluoroethyl group ($-CH_2CF_2H$) or a trifluoroethyl group ($-CH_2CF_3$) have been designed and will be synthesized in the near future. The 3D-QSAR model has provided valuable clues for further discovery of novel inhibitors with improved binding affinity.

Theoretical DFT (B3LYP) Calculation. **6-11** and **6-21** possess significant similarities with triasulfuron, whether from their chemical structures or from K_i values of AHAS inhibition and rape root inhibitory data. However, it is a bit strange that **6-11** and **6-21** displayed excellent herbicidal activity against monocotyledon grasses such as barnyard grass, while triasulfuron only showed medium-to-weak herbicidal activity at the same conditions. The factors accounting for the difference in the greenhouse activity against the monocotyledon species should be discovered for some plausible explanation. As is known, for a plant that is not sensitive (in other words, displaying nontarget site resistance) to an AHAS-inhibiting herbicide, enhanced capacity of herbicide metabolism (metabolic resistance) is considered to be a major reason, in which cytochrome P450 is involved.[2] Therefore, it is likely that for the gramineous weeds, these compounds may have different metabolism rates. Frontier molecular orbital is regarded to play an important role in the related reactions of a compound and hence has an impact on the biological activity.[16,48,49] We accordingly performed DFT calculations for **6-11**, **6-21**, and triasulfuron to see if useful information could be observed. The bioactive conformation in the crystal structure was assumed to be the dominant conformation in the metabolic event. From Figure 7, HOMO maps for these three compounds are quite similar, which cover the heterocycle ring and the sulfonyurea bridge. Interestingly, LUMO maps for **6-11** and **6-21** locate on the heterocycle ring, the sulfonyurea urea bridge, and the phenyl ring; yet, the LUMO map for triasulfuron has very minor distribution at the phenyl ring. The difference in LUMO maps is likely to be a

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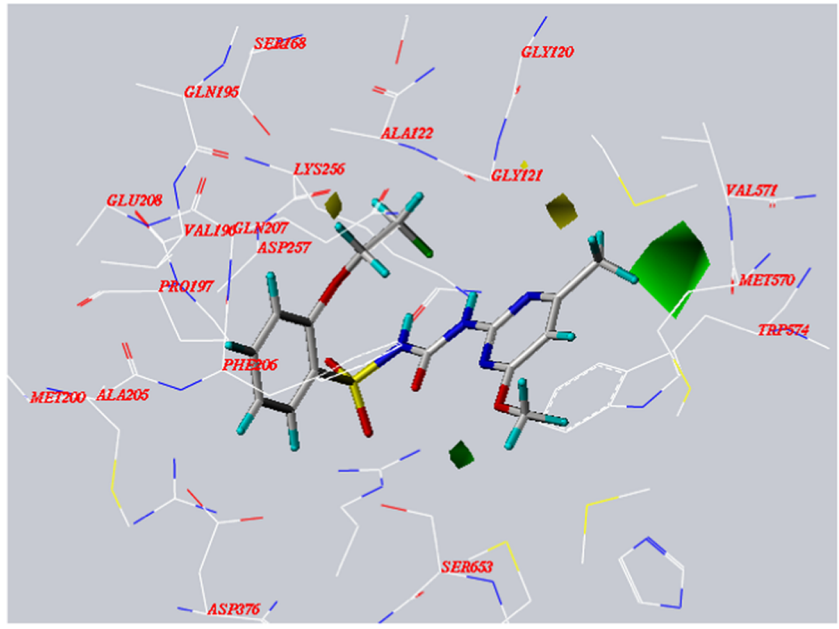
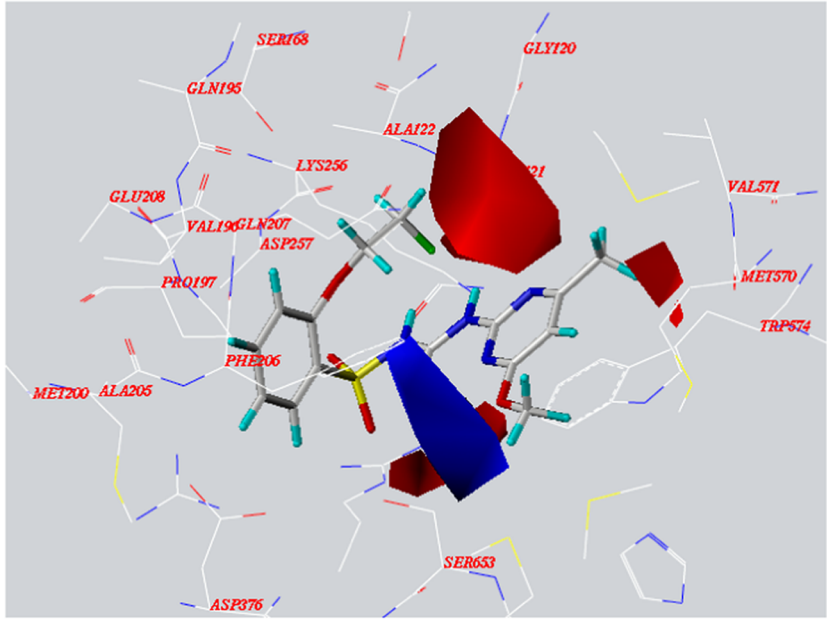


(A)



(B)

Figure 6. Steric contour map (A) and electrostatic contour map (B) for the CoMFA model mapped onto the binding site of *At*AHAS. **6-11** was chosen as a template to depict the structure−activity relationships.

possible reason leading to their different behaviors toward monocotyledon grasses.

In 2006, Xi and Yang et al. reported a density functional theory-based QSAR study of herbicidal sulfonylurea analogues, in which a general quantum-chemical descriptor was used by characterizing the volume of electron cloud for specific substituent using the method of density functional theory.[50] In our present study, we also found that frontier orbitals play an important role in the structure−activity relationships of the sulfonylurea herbicides. We therefore suggest that a quantum chemistry study is necessary for the design and discovery of novel AHAS-inhibiting sulfonylurea herbicides in the future.

We must admit the fact that herbicide resistance is likely to occur due to the overuse of all families of chemical herbicides, especially for the sulfonylurea herbicides. Therefore, at the very beginning stage of development of a new herbicide, some practical strategies should be proposed to postpone weed resistance toward this class of new sulfonylureas. One preferable solution is to prepare a mixed product with other commercial herbicides that have a distinct mode of action. Field efficacy trials of these two sulfonylurea compounds are currently in progress for some selected crop fields. Moreover, we will try to evaluate the herbicidal activity of **6-11** and **6-21** against some resistant weed species to see whether these new

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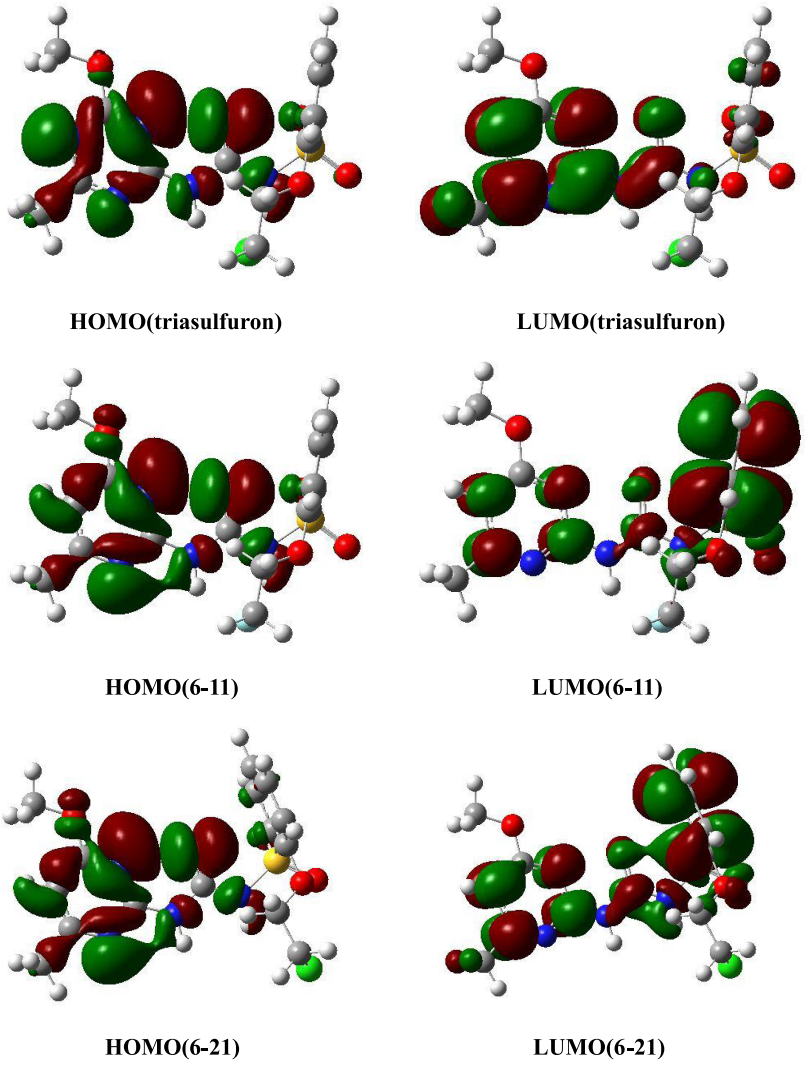

Figure 7. Frontier molecular orbital maps for triasulfuron, **6-11**, and **6-21** from DFT calculations.

candidates are also potent inhibitors toward these troublesome grasses in the near future.

In summary, we have designed and synthesized a series of *ortho*-alkoxy substituted novel sulfonylurea compounds and studied their herbicidal activities extensively. Compounds **6-11** and **6-21** showed strong inhibition of plant AHAS and outstanding herbicidal activity against the monocotyledon weed species. As a potential fluorine-containing herbicide candidate, **6-11** was superior to triasulfuron, penoxsulam, and nicosulfuron at all of the tested conditions regarding the weeding efficiency upon the gramineous species. **6-11** displayed zero postemergence herbicidal activity against peanut at 15 g ha^{-1}, indicating that it could be considered for weed control in such fields. Theoretical DFT calculation revealed that LUMO is a probable cause for the sensitivity to monocotyledon grasses for **6-11** and **6-21**. This study has provided valuable guidance for the discovery and development of green herbicides to control some malignant weeds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jafc.1c02081.

(CIF)

Predicted biological data versus determined biological data from CoMFA; ^{1}H NMR, ^{13}C NMR, HPLC (for 6-11 and 6-21) and HRMS data of intermediates and target compounds; and ^{1}H NMR, ^{13}C NMR, HPLC (for 6-11 and 6-21) and HRMS spectra of target compounds (from **6-1** to **6-42**) (PDF)

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Notes

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