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## SYNTHESIS AND BIOLOGICAL ACTIVITY EVALUATION OF IMIDAZOLE HETEROCYCLIC SULFONYLUREA COMPOUNDS

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**Abstract** – Sulfonylurea herbicides are the most widely used herbicides in the world. They have the advantages of high efficiency, good selectivity, and no toxicity to human and animals. In this study, sulfonylureas containing imidazole heterocycles were synthesized on the basis of computer simulation of molecular docking, and the biological activity was evaluated. It shows that the compound has a good inhibitory effect on the ALS and a certain inhibitory effect on the phytopathogenic fungi of *Curvularia lunata* and *Curvularia meibaldsii*. Its inhibitory rate at concentration of 50 mg/L is similar to that of the carbendazim. This research provides the basis for further optimization of the structure of imidazolium heterocyclic sulfonylurea and the synthesis of its derivatives.

### INTRODUCTION

Sulfonylurea compounds are a class of compounds with the basic structure of  $R^1-SO_2NHCONH-R^2$ . Such compounds are widely used in medicine and pesticides and have high research value. In medicine, it has anti-diabetic,<sup>1</sup> antibacterial,<sup>2</sup> anti-cancer,<sup>3</sup> anti-inflammatory,<sup>4</sup> diuretic<sup>5</sup> and other effects. In terms of pesticides, sulfonylurea compounds are the most widely used herbicides in the world. They have the advantages of ultra-high activity, broad spectrum, low dose, low toxicity, and high selectivity.<sup>6</sup> The structure of traditional sulfonylurea herbicides is generally composed of three parts: aryl, urea bridge and heterocycle. Among them, the urea bridge is mostly a sulfonylurea structure, and the activity is the highest without modification.<sup>7</sup>

There are many synthetic methods for sulfonylurea compounds, and the most common methods are isocyanate method and carbamate method.<sup>8</sup> The isocyanate method utilizes the nucleophilic substitution reaction between amino groups and active isocyanate groups to generate sulfonylurea structures.<sup>9</sup> The reaction is simple and rapid, but the isocyanate group is extremely sensitive to moisture, and it needs to

be carried out under nitrogen protection if necessary. Among them, the methods for preparing isocyanates include phosgene method, phosgene derivative method,<sup>10</sup> oxalyl chloride method,<sup>11</sup> cyanate method<sup>12</sup> and others.<sup>13</sup>

The carbamate method is another method for the synthesis of sulfonylurea compounds,<sup>14</sup> generally by the reaction of arylsulfonamide with ethyl chloroformate or phenyl chloroformate, or heterocyclic amine with ethyl chloroformate. Phenyl chloroformate reacts to obtain a substituted ester intermediate, which is then condensed with another amino compound. This method avoids the use of strongly irritating phosgene or its derivatives, and the target product is generally in the form of solid precipitation, with high purity and easy separation.<sup>15</sup>

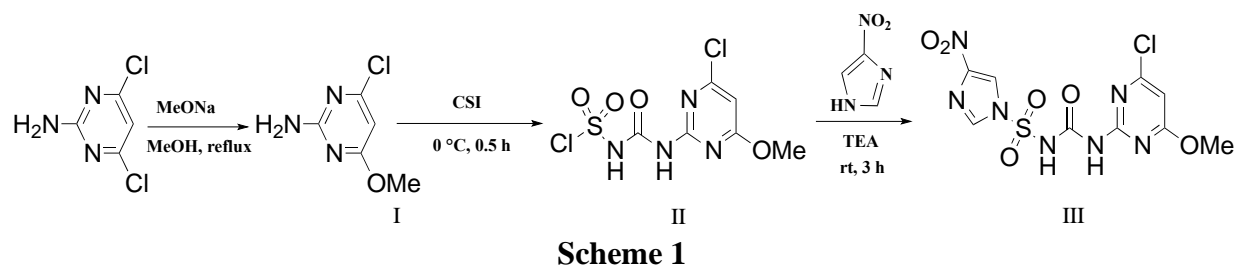
The herbicidal mechanism is to inhibit the activity of acetolactate synthase (ALS) in plants, thereby preventing the synthesis of branched-chain amino acids valine, leucine and isoleucine, preventing cell division and the normal growth of sensitive plants.<sup>16</sup> Furthermore, the ALS does not exist in mammals, so this type of herbicide is almost non-toxic to humans and animals.<sup>17</sup> Because some bacteria and fungi contain this enzyme, they also have a certain antibacterial effect. The dosage of sulfonylurea herbicides is very small, only a few grams to tens of grams per hectare can achieve good weeding effect, high efficiency and low amount, environmentally friendly,<sup>18</sup> and has great commercial value.

Through early computer simulation screening, based on the classic sulfonylurea structure, without changing the pyrimidine active group and sulfonylurea bridge, the aromatic ring group was replaced with an imidazole heterocyclic ring, and it was found that the new compound formed a more stable complementary structure with the active site of ALS. Therefore, we first synthesized the characterized nitroimidazole heterocyclic sulfonylurea, and determine their ALS inhibitory activity and phytopathogenic fungi inhibitory properties.

## RESULTS AND DISCUSSION

The target compound N-((4-chloro-6-methoxypyrimidin-2-yl)carbonyl)-4-nitro-1*H*-imidazole-1-sulfonamide (**III**) is different from traditional sulfonylurea herbicides. It used imidazole groups instead of aryl groups as hydrophobic groups, 2-amino-4,6-dichloropyrimidine as starting material to synthesize 2-amino-4-chloro-6-methoxypyrimidine, and then mixed with chlorosulfonyl isocyanate (**CSI**) reacted to produce compound **II**, which was then reacted with 4-nitroimidazole to finally obtain the target compound.

The synthetic route is as follows:

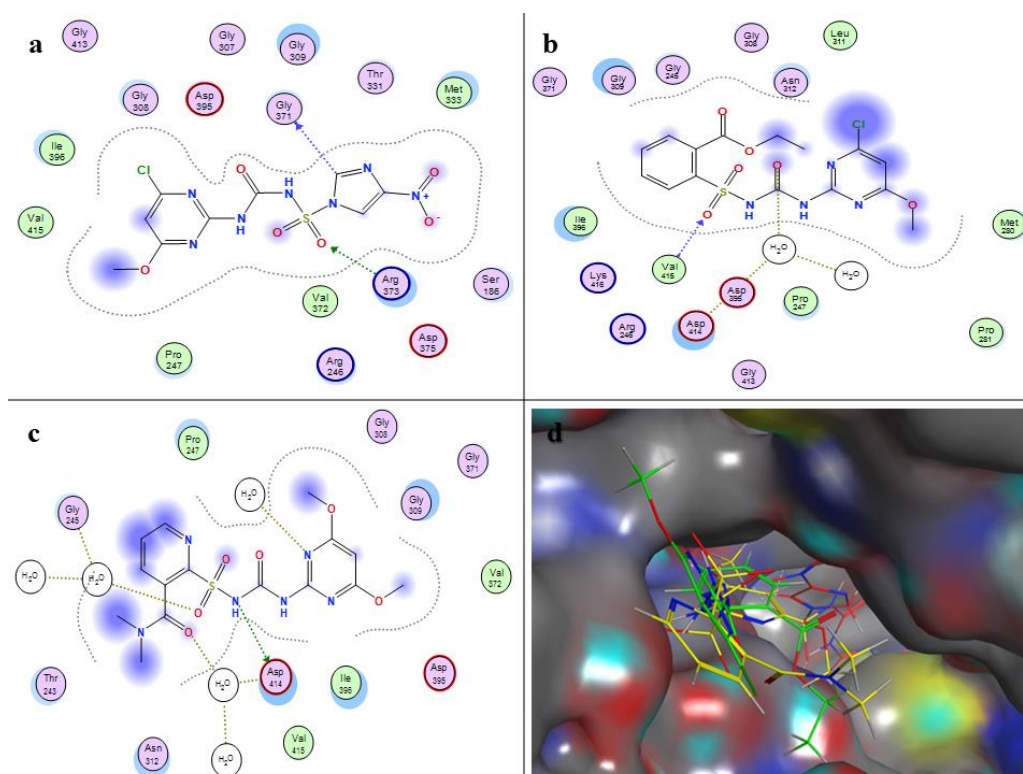


## Docking studies

Molecular docking is a process that small compounds bind to the active site of the protein by adjusting the conformation. Lower docking scores indicating stable complexes between ALS and compound, in other words, the conformational energy of their complexes is lower. Table 1 showed that target compound **III** has a lower score than chlorimuron and nicosulfuron, which indicate that it may have a greater inhibitory effect on ALS. The compound **III** acts as a hydrogen bond donor towards the residue GLY371 and a hydrogen bond acceptor towards the residue ARG 373. The O atom in chlorimuron -HNCONH- and -SO<sub>2</sub>- forms a hydrogen bond with HOH 4096 and VAL 415 respectively. In nicosulfuron, the N atom of the -SO<sub>2</sub>NHCO- and pyridinium ring could form H-bonds with the ASP 414 and HOH 4147, the O atom of -SO<sub>2</sub>- and -CON(Me)<sub>2</sub> is connected to the HOH 4116 and HOH 4096 by H-acceptor.<sup>19</sup> However, the atoms in the -NHCONH- groups in chlorimuron, the -SO<sub>2</sub>-, pyrimidine ring, -CON(Me)<sub>2</sub>-groups in nicosulfuron form hydrogen bonds with the associative water in ALS, and the bond is weaker than that formed directly with amino acid residues. All compounds are docked into almost same groove of the binding site of ALS (Figure 1), blocking the entry of substrates and achieving the purpose of inhibiting ALS. Among them, the carbon atoms of compound **III**, chlorimuron, and nicosulfuron are represented by red, green, and yellow, respectively.

**Table 1.** Docking results of ALS with target compound **III**, chlorimuron and nicosulfuron

Compounds	S (kcal/mol)	Ligand	Receptor	Interaction	Length (Å°)	E (kcal/mol)
Compound <b>III</b>	-6.1053	C(imidazole)	GLY371	H-donor	3.22	-2.2
		O(-SO <sub>2</sub> -)	ARG373	H-acceptor	3.10	-0.9
Chlorimuron	-5.0349	O(-HNCONH-)	HOH4096	H-acceptor	2.68	-1.2
		O(-SO <sub>2</sub> -)	VAL415	H-acceptor	2.81	-3.0
Nicosulfuron	-5.8128	N(-SO <sub>2</sub> NHCO-)	ASP414	H-donor	3.27	-0.7
		O(-SO <sub>2</sub> -)	HOH4116	H-acceptor	2.75	-1.9
		N(pyrimidine)	HOH4147	H-acceptor	2.64	-0.4
		O(-CON(Me) <sub>2</sub> )	HOH4096	H-acceptor	2.92	-1.7



**Figure 1.** 2D images of ALS docking of the target compound **III** (a), chlorimuron (b) and nicosulfuron (c), and 3D image of the above compounds (d).

### Synthesis of 2-amino-4-chloro-6-methoxypyrimidine (I)

When preparing sodium methoxide, pay attention that the kerosene on the surface of sodium metal should be absorbed with paper and quickly cut into small pieces and weigh in petroleum ether. The petroleum ether needs to be sucked dry again before feeding. What's more, we have simply optimized the synthetic route, the best feed ratio of 2-amino-4,6-dichloropyrimidine to sodium methoxide is 1:1.2, and the best solvent is methanol.

### Synthesis of N-((4-chloro-6-methoxypyrimidin-2-yl)carbamoyl)-4-nitro-1H-imidazole-1-sulfonamide (III)

In the synthesis of intermediate compound **II**, the isocyanate group (-NCO) and chlorosulfonyl group (-SO<sub>2</sub>Cl) contained in the chlorosulfonyl isocyanate (CSI) are extremely active and sensitive to heat and humidity. Compound **II** is also easy to hydrolyze. Therefore, the reaction process should ensure anhydrous conditions. The acetonitrile needs to be re-evaporated after absorbing water with anhydrous calcium chloride to reduce the occurrence of side reactions. What's more, the reaction time and temperature should be strictly controlled.

The synthesis process has been optimized. The best reaction time, reaction temperature and acid binding agent for the synthesis of compound **III** is 3 h, 25 °C and triethylamine, respectively. For the separation

and purification of compound **III**, we tried solvent extraction, acid-base sedimentation, column chromatography, preparative chromatography, and strongly acidic cation exchange resin method. Finally, the water-ethyl acetate extraction method has a better separation effect, and the residual triethylamine was further purified by a strong acid cation exchange resin with satisfactory results.

### ALS inhibitory activity

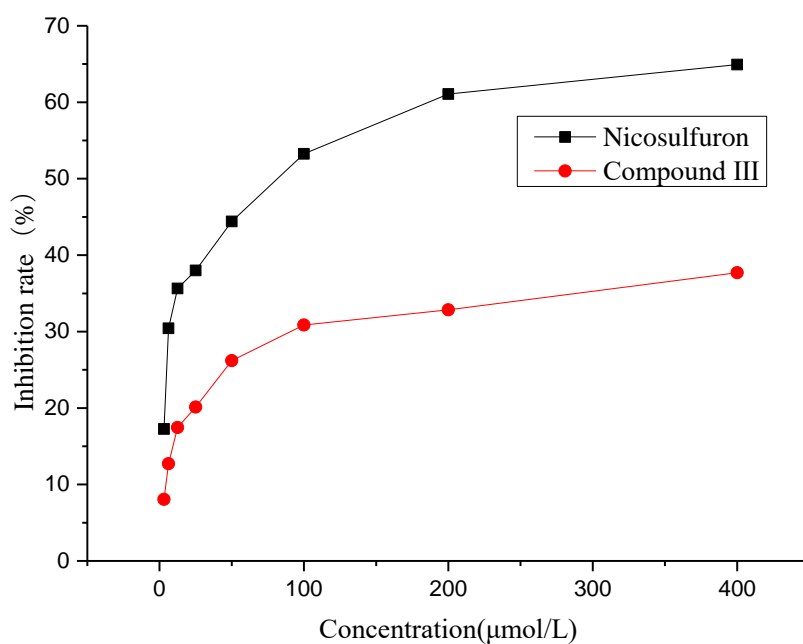
Under the action of ALS, pyruvate became acetolactate and then converted to 3-hydroxybutanone by decarboxylation, which further reacted with creatine and  $\alpha$ -naphthol to form a colored complex ( $A_{520\text{nm}}$ ).<sup>20</sup> The absorbance is proportional to the concentration. Under the condition of excessive sodium pyruvate, the stronger the compound inhibits ALS, the weaker the ALS activity, and less 3-hydroxybutanone is produced, the absorbance value is lower, vice versa. Inhibition rate and trend of compounds on ALS are shown in Table 2 and Figure 2.

**Table 2.** Inhibition rate of different concentrations of compounds on ALS

Concentration ( $\mu\text{mol/L}$ )	Inhibition rate (%)	
	Nicosulfuron	Compound <b>III</b>
3.125	17.26	8.06
6.25	30.43	12.71
12.5	35.64	17.45
25	37.99	20.13
50	44.41	26.20
100	53.26	30.87
200	61.08	32.85
400	64.93	37.70
800	68.59	44.72
1600	82.42	58.92

It can be seen from Figure 2 that the inhibition rate increases with the increase of the compound concentration. At the maximum concentration of 1600  $\mu\text{mol/L}$  (Table 2), the inhibition rate of compound **III** is 58.92%, while that of nicosulfuron is 82.42%. It shows that compound **III** has a certain inhibitory effect on ALS.

However, it is different from the computer simulation results, which is slightly weaker than nicosulfuron. The possible reason we think is that molecular docking is the optimal solution in an ideal state, so it may be different from the actual results.



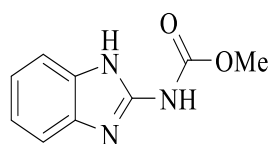
**Figure 2.** The effect of each compounds on ALS activity

### In vitro antifungal activity

After the initial screening of phytopathogenic fungi, it was found that the compound **III** has a certain inhibitory effect on *Curvularia lunata* and *Curvularia mebaldsii* at a concentration of 30 mg/L. The re-screening data is shown in Table 3.

**Table 3.** In vitro antifungal activity of compound **III** and positive drugs

Compounds	Concentration(mg/L)	Inhibition rate±SD(%)	
		<i>C. lunata</i>	<i>C. mebaldsii</i>
	5	4.40±0.63	4.38±0.89
	10	3.77±1.09	7.06±1.79
	20	6.29±0.63	6.17±0.00
	50	8.18±0.63	8.85±0.00
	100	7.55±1.09	10.63±0.89
	200	15.09±1.09	21.36±1.79
	5	100±0.00	28.96±0.78
	10	100±0.00	40.67±2.07
	20	100±0.00	48.48±1.35
	50	100±0.00	44.57±0.78
	100	100±0.00	47.70±2.07
	200	100±0.00	46.92±0.78
	5	3.45±0.70	6.32±1.35
	10	6.27±0.70	7.88±0.78
	20	11.91±2.54	12.57±2.07



50	6.98±1.22	9.45±3.90
100	18.96±0.70	17.25±2.81
200	25.30±0.70	13.35±3.58

According to the Table 3, the compound **III** has a mild inhibitory effect on *Curvularia lunata*. Under the concentration of 50 mg/L, its antifungal activity is equivalent to that of the carbendazim, which have similar imidazole heterocyclic structure. But chlorothalonil can almost completely inhibit the fungus.

For another fungus, *Curvularia meibaldsii*, the inhibitory rate of the compound **III** at low concentration is close to that of the positive control carbendazim. At concentration of 200 mg/L, the inhibitory effect is better than carbendazim, and the IC<sub>50</sub> value is much smaller than the positive drug carbendazim. Therefore, the introduction of nitro or sulfonylurea groups may enhance the antifungal effect of the compound. The antifungal effect of chlorothalonil at lower concentrations still has a higher advantage, but as the drug concentration increases, its inhibition rate does not rise significantly, inhibition capacity is limited, and the maximum is basically maintained between 40% to 48%. The addition of a large amount of electron-withdrawing group chlorine has obvious advantages for the antibacterial effect.

In summary, nitroimidazole heterocyclic sulfonylurea have certain inhibitory effects on these two phytopathogenic fungi, and it may be more suitable for corn and wheat fields. It is necessary to note that we found that the compound **III** is relatively easy to decomposed, which indirectly affects the level of its activity in experiment, although this may be beneficial for the residual problem of sulfonylurea. In the next step, we will further study and optimize the structure, considering improving its stability and antifungal ability.

## Conclusion

In this study, a novel type of ALS inhibitor was screened through computer simulation and synthesized. The ethyl acetate/water extraction method and the strong acid cationic resin method were used to remove trace amounts of triethylamine, with satisfactory results. In addition, in vitro activity evaluation was performed. Compound **III** with a good inhibition rate on ALS, but it is weaker than nicosulfuron, which is somewhat different from the molecular docking results. What's more, for two phytopathogenic fungi, compound **III** has a moderate antifungal effect which is close to carbendazim. Further studies on the structural optimization and more biological activity evaluations of imidazole heterocyclic sulfonylureas are in progress.

## EXPERIMENTAL

### Chemistry

All reagents and solvents were obtained from commercial suppliers and were dried by standard methods

in advance and distilled before use. The starting chemical materials were purchased from Shanghai Macklin or Sinopharm Group Chemical reagent.

Melting points were determined using an RY-1 digital melting point apparatus (Tianjin Analytical Instrument Factory) and were uncorrected. The absorbance was measured using a UV-600 ultraviolet-visible spectrophotometer (Beijing LabTech).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained using a 500 MHz Bruker spectrometer in  $\text{DMSO-}d_6$  with TMS as an internal standard. All the reaction was monitored through HPLC in an Agilent 1200 series system.

### Molecular docking

Docking experiments between compounds and acetolactate synthase (ALS) were carried out using the molecular docking software. The crystal structure of acetolactate synthase (PDB-ID:1Z8N)<sup>21</sup> was obtained from RCSB protein data bank (<http://www.rcsb.org/pdb>). The ligands were docked into the ALS cavity site by automatically finding the potential active site through Site Finder.<sup>22</sup> In this program, the structure of ALS always maintains rigidity, while the compound maintains complete flexibility for docking. The obtained docking score (S) was to evaluate the combination between the compound and the ALS.

### 2-Amino-4-chloro-6-methoxypyrimidine (I)

The sodium (0.828 g, 0.036 mol) was cut into small pieces, added them to anhydrous MeOH (30 mL), stirred and refluxed for 30 min to obtain a white sodium methoxide solution. 2-Amino-4,6-dichloropyrimidine (4.92 g, 0.03 mol) in a 250 mL three-necked flask, was added 30 mL of anhydrous MeOH, stirred and refluxed. The prepared sodium methoxide solution was slowly dropped into a three-necked flask with a constant pressure funnel for 10 min, and then refluxing for 15 min. The progress of the reaction was monitored by HPLC. The conditions of HPLC: stationary phase: Kromasil C18-5 $\mu$ -100A 250 mm $\times$ 4.6 mm; mobile phase: MeCN: H<sub>2</sub>O (70:30); flow rate: 0.8 mL/min; detection wavelength: 232 nm, injection volume: 20  $\mu$ L; Column temperature: 25  $^\circ\text{C}$ .

After the reaction was over, the solution was filtered while hot, washed the filter with MeOH (15 mL $\times$ 3). The filtrate was dried under vacuum, and the obtained solid was washed with H<sub>2</sub>O, filtered, and dried in vacuo. The crude product was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to obtain yellow needles 4.53 g, yield: 94.72%, mp 165-166  $^\circ\text{C}$ ,  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 500 MHz),  $\delta$ : 7.09 (s, 2H, NH<sub>2</sub>), 6.10 (s, 1H, Pyridine-H), 3.81 (s, 3H, CH<sub>3</sub>).

### N-((4-Chloro-6-methoxypyrimidin-2-yl)carbonyl)-4-nitro-1H-imidazole-1-sulfonamide (III)

The solution of compound I (0.96 g, 6 mmol) in anhydrous MeCN (20 mL) was stirred at 0  $^\circ\text{C}$  for 10 min, and followed by the dropwise addition of chlorosulfonyl isocyanate (0.78 mL, 9 mmol) in anhydrous MeCN (5 mL), and reacted at 0  $^\circ\text{C}$  for 0.5 h. The compound II was directly subjected to the next reaction without treatment.

To the above solution were added dropwise 4-nitroimidazole (0.69 g, 6 mmol) and triethylamine (2.5 mL, 18 mmol) in anhydrous MeCN (5 mL), and reacted at 25 °C for 3 h with HPLC monitoring (The conditions of HPLC were the same as above). After the reaction, the reaction solution was placed at refrigerator overnight to produce a large amount of white precipitate, filtered, and the filtrate was dried under vacuum at low temperature. Then washed with H<sub>2</sub>O (30 mL), extracted with EtOAc (30 mL×3), water phase dried under vacuum to obtain the target compound **III** 1.83 g, yield: 80.97%. Finally purified by the strong-acid cation exchange resin. <sup>1</sup>H NMR (DMSO<sub>d</sub><sub>6</sub>, 400 MHz), δ:10.09 (s, 1H, NH), 8.32 (s, 1H, imidazole-H), 7.85 (s, 1H, imidazole-H), 6.71 (s, 1H, pyrimidine-H), 3.93 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO<sub>d</sub><sub>6</sub>, 126 MHz), δ:171.02, 160.33, 157.67, 150.22, 148.02, 136.44, 119.61, 100.28, 55.35.

### ALS inhibitory activity-preparation of experimental solution

Enzyme extraction solution: accurately measured 50 mL of 0.1 mol/L K<sub>2</sub>HPO<sub>4</sub>-KH<sub>2</sub>PO<sub>4</sub> buffer solution (pH 7.5), accurately weighed MgCl<sub>2</sub> (0.0235 g), sodium pyruvate (0.0055 g), 0.0125 g of thiamine pyrophosphate (TPP), 0.0750 g of dithiothreitol (DTT) and added them to the buffer solution, stirred to make it fully dissolved, placed at 4 °C for later use.

Enzymatic reaction solution: accurately measured 50 mL of 0.1 mol/L K<sub>2</sub>HPO<sub>4</sub>-KH<sub>2</sub>PO<sub>4</sub> buffer solution (pH 7.0), accurately weighed MgCl<sub>2</sub> (0.0047 g), sodium pyruvate (1.1000 g), 0.0250 g of thiamine pyrophosphate (TPP) and added them to the buffer solution, stirred to make it fully dissolved, placed at 4 °C for later use.<sup>20</sup>

Dissolved the nicosulfuron (0.0066 g) and compound **III** (0.0061 g) with an appropriate amount of DMSO, diluted to 10 mL with deionized water, prepared their solution with a concentration of 1600 μmol/L, and then diluted it to 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.125 μmol/L.

### Evaluation of ALS inhibitory activity

After soaking an appropriate amount of corn seeds at 40 °C for 4 h, buried them in the soil and cultivated at 28 °C to ensure that the soil was moist. When the corn buds grew to about 3 cm, took the white buds, washed and drained, weighed and took about 20 g, putted them into a mortar, placed the mortar in an ice bath, and added the enzyme extraction solution at a ratio of 1 g : 2 mL in a mortar, quickly grinded and then filtered with gauze. The filtrate was centrifuged at 4000 rpm for 20 min, and the supernatant was decanted to obtain the crude enzyme solution, which was placed at 4 °C for later use.

The test group and blank control group have been created. Added 1 mL of enzymatic reaction solution, 1 mL of treatment agent (drug solution or water) and 2 mL of crude enzyme solution in sequence to each group, shaken evenly, wrapped in tin foil and placed at 37 °C for 1 h in the dark. The reaction was terminated by adding 100 μL of 3 mol/L sulfuric acid aqueous solution, followed by a decarboxylation reaction at 60 °C. Took it out after 15 min, and added 2 mL of 0.083% creatine and 2 mL of 0.83% α-naphthol to each group in sequence. After that, the color reaction was performed at 60 °C for 15 min.

Finally, measured the absorbance at 520 nm at room temperature.<sup>20</sup>

Inhibition rate for ALS( $\%$ ) $= (A_b - A_t) / A_b \times 100\%$ , where  $A_b$  and  $A_t$  were the absorbance of blank group and test group, respectively.

### **In vitro antifungal activities**

The antifungal activity of compound **III** against phytopathogenic fungi was determined by the mycelial growth rate method. The compound was dissolved in an appropriate amount of DMSO, and then added to PDA medium that was prepared and sterilized to obtain a series of concentrations (5, 10, 20, 50, 100, and 200 mg/L). The same amount of DMSO was added to the sterile medium as a blank control. Chlorothalonil and carbendazim were used as positive controls. Inoculate the mycelial disc (5 mm) of the fungus on the PDA plate, and did it 3 times in parallel for the control group and the treatment group. Cultivated them in incubator at 28 °C for 5-7 days. When the blank control group mycelium grew to the edge of the petri dish, the growth inhibition rate was calculated by measuring the colony diameter.<sup>23</sup>

Inhibition rate formula: mycelial growth inhibition( $\%$ ) $= (D_b - D_t) / (D_b - 5 \text{ mm}) \times 100\%$ , where  $D_b$  and  $D_t$  were average diameters of the fungal colony of blank control and treatment, respectively.

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