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**Synthesis and herbicidal activity of aryloxyacetic acid derivatives as HPPD inhibitors**

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**Abstract**

A series of aryloxyacetic acid derivatives were designed and synthesized as HPPD inhibitors. The preliminary bioassay results indicated that these derivatives displayed promising *Arabidopsis thaliana* HPPD (*At*HPPD) inhibitory activity, such as compound **I12** ($K_i$ = 0.011 $\mu$M) and compound **I23** ($K_i$ = 0.012 $\mu$M), which were similar with commercial HPPD herbicide Mesotrione ($K_i$ = 0.013 $\mu$M). Furthermore, the newly synthesized compounds showed significant greenhouse herbicidal activities against tested weeds at dosages of 150 g ai/ha. In particular, compound **II4** exhibited highly herbicidal activity for pre-emergence treatment, even better than those of Mesotrione. Besides, compound **II4** was safe for weed control in maize fields at the rate of 150 g ai/ha. Therefore, compound **II4** was identified as the most potent candidate for novel HPPD inhibitor herbicide. Compounds described herein might provide useful ideas in the design and modification of new HPPD inhibiting-based herbicides.

**Keywords**: 4-hydroxyphenylpyruvate dioxygenase; herbicidal activity; aryloxy acetic acid; synthesis; modification

## Introduction

4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27, HPPD) is a vital enzyme for tyrosine catabolism, which belongs to the family of non-heme $Fe^{II}$-containing enzymes. In the catalytic process of HPPD, HPPA and $Fe^{II}$ form a chelate complex, then the substrate HPPA is converted to HGA. HPPD inhibitors competitively restrain HPPA chelating with $Fe^{II}$; If the transformation of HPPA to HGA is affected by HPPD inhibitors, the production of plastoquinone is inhibited and phytoene is accumulated [1, 2]. When exposing to sunlight, the plants are severely damaged. The results ultimately lead to bleaching symptoms followed by necrosis and death [3,4]. Therefore, HPPD inhibitors play an important role in the herbicide industry. Besides HPPD inhibiting-based herbicides have a range of advantages, such as low toxicity, high efficiency, broad-spectrum weed control, safety towards crops and the environment [5,6,7]. However, the abuse of HPPD inhibitors leads to increased weed resistance and damage to crops. Therefore, it's emergent to explore effective HPPD-inhibiting compounds to control resistant weeds.

Recently, a considerable number of HPPD inhibiting-based herbicides have been commercialized and applied in the agrochemical industry. These herbicides are mainly divided into three categories: triketones, pyrazoles, and isoxazoles [1,8,9]. As shown in **Figure 1**, there are some HPPD-inhibiting herbicides, including Mesotrione, Tefuryltrione, Isoxaflutole, Topramezone, and Pyrasulfotole. Among them, Mesotrione is a highly successful representative triketone HPPD herbicide. It can be seen from **Figure 1**, the structure of 1,3-dicarbonyl is almost contained in most cases of the HPPD inhibiting-based herbicides [3,7]. As reported, there are mainly two interactions between *Arabidopsis thaliana* HPPD (*At*HPPD) and its inhibitors: 1) 1,3-dicarbonyl forms bidentate interaction with the active center metal chelation. 2) The aromatic rings attach to residues Phe360, Phe403 of the active site and generate a favorable sandwich π−π stacking interaction. Thus,

1,3-dicarbonyl and aromatic moieties are indispensable pharmacophore for the potent HPPD-inhibiting compounds, which interplay with surrounding residues of *At*HPPD [9-12].

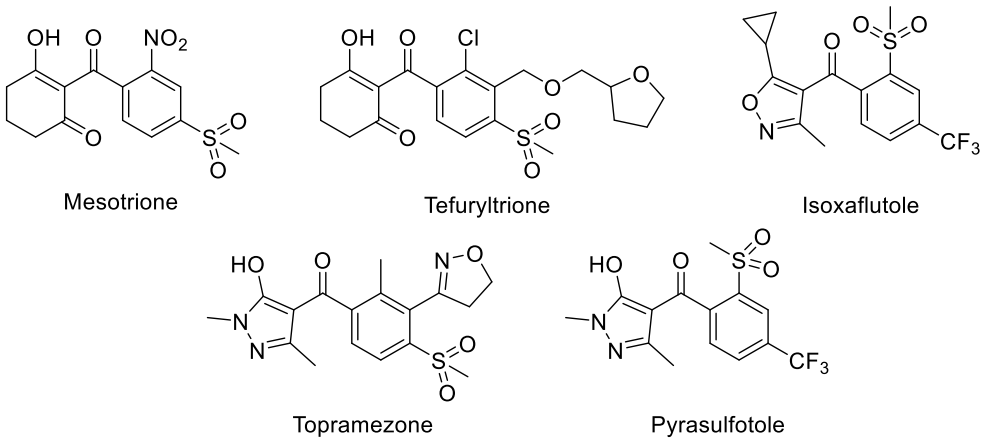



**Figure 1:** Chemical structures of the commercial HPPD inhibitors.

2,4-Dichlorophenoxyacetic acid (2,4-D) was synthesized, acting as a plant growth hormone n 1941. It is a selective pre- and post-emergence herbicide applied to several crops [10]. 2,4-D interferes with the balance of hormone and then destroys the metabolism of nucleic acids and proteins, especially being more effective in broadleaf weeds, such as *Amaranthus retroflexus* and *Alfalfa*. The application of 2,4-D causes excessive growth and ultimately results in the death of plants. 2,4-D has been one of the world's major herbicides, because of its low dosage and less investment cost.

Many types of research in HPPD inhibitors indicated that modification of the aromatic moieties is an eff ective way to get new HPPD inhibiting-based herbicides [13-16]. However, rare eff orts have been made on pyrazole derivatives. Inspired by the above opinions, we synthesized a group of new HPPD inhibitors, containing pyrazole and triketone to study their bioactivity. The design strategy was exhibited as **Figure 2**. Based on the principle of combining the two bioactive structures, the aromatic moieties of **2,4-D** and 1,3-dicarbonyl, a series of novel aryloxyacetic acid derivatives were designed and synthesized. The HPPD inhibition, herbicidal activity, structure-activity relationships (SAR) and crop safety of these derivatives were described in this context. As expected, many of the title compounds displayed promising inhibitory activity against *Arabidopsis thaliana* HPPD (*At*HPPD) in *vitro* and excellent herbicidal activity at the rate of 150 g ai/ha.

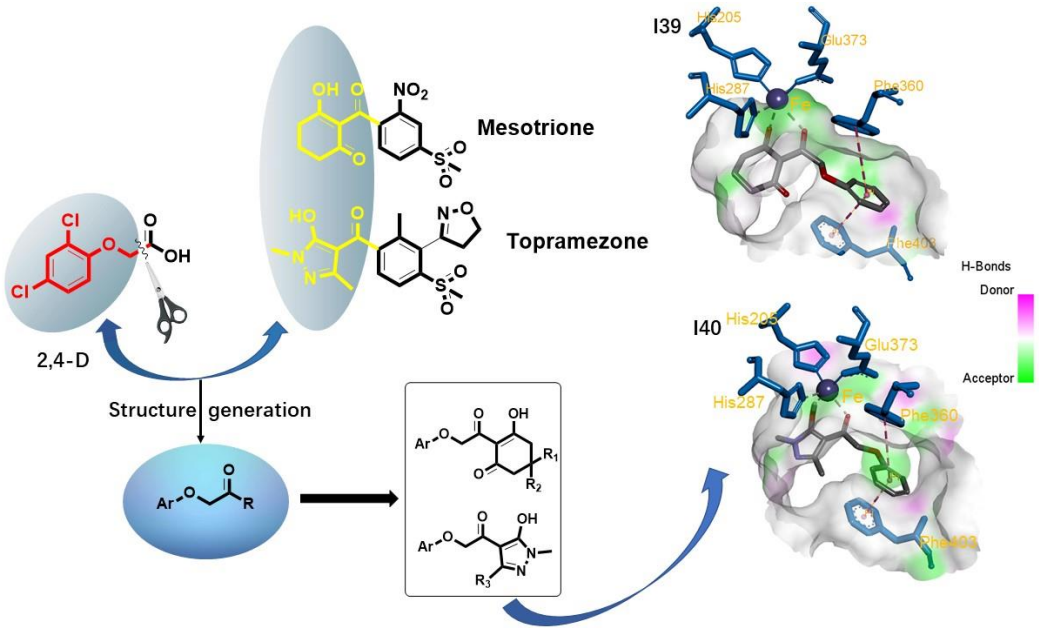
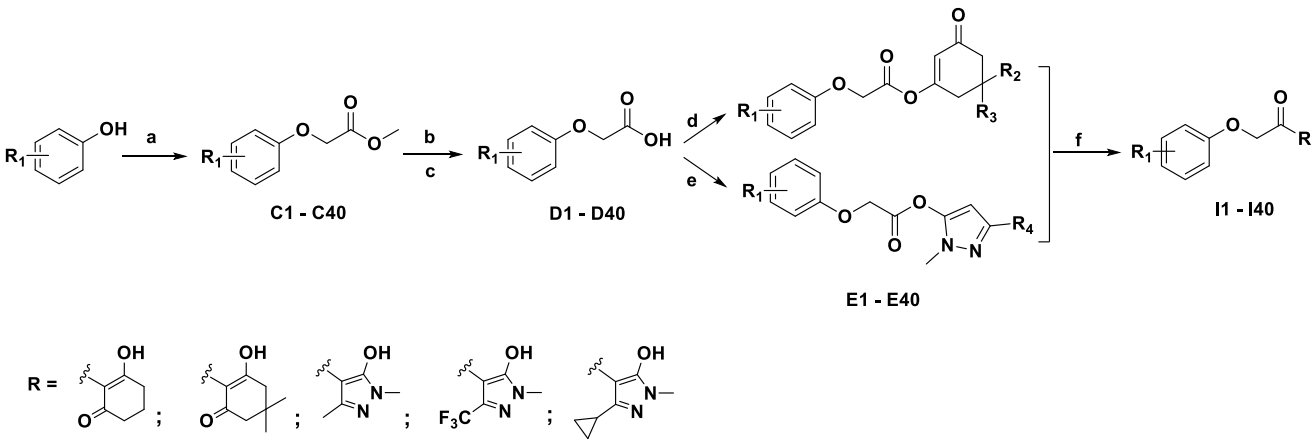



**Figure 2:** The design strategy of Aryloxy acetic acid derivatives as HPPD inhibitors and simulate the binding modes of compound **I39** and **I40** in a target enzyme (*At*HPPD). The key residues in the active site are shown in blue sticks, the $Fe^{II}$ is shown as a dark blue sphere, and compound **I39** and **I40** is shown in gray sticks.

## Results and discussion

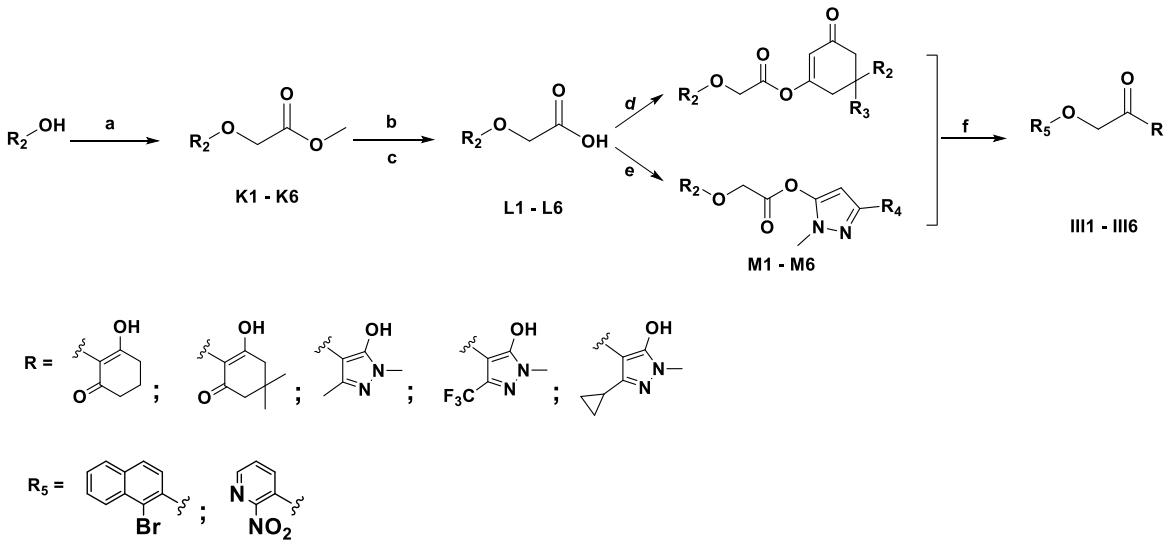
### Chemistry

Title compounds were classified into three series (I, II and III). The preparation of the title compounds was shown in **Scheme 1**, **Scheme 2** and **Scheme 3**. The synthesis of compounds **I** and **III** was depicted in **Scheme 1** and **Scheme 2**. The commercially available starting materials reacted with methyl chloroacetate in $CH_3CN$ and anhydrous potassium carbonate ($K_2CO_3$) as the base, and the corresponding products **C** and **K** were prepared. The products were hydrolyzed using $K_2CO_3$ as a base to yield the product **D** and **L** [17-21]. In the presence of 3-(ethyliminomethylideneamino)-N, N-dimethyl propane-1-amine, hydrochloride (EDCI), the aromatic oxyacetic acid reacted with substituted 1,3-cyclohexanediones or substituted 1,3-dimethyl-1H-pyrazole-5-ol, using DMAP as the catalyst. Subsequently, the key enol ester **E** and **M** were respectively obtained. Finally, Fries-type rearrangements were performed in anhydrous DCM at room temperature to afford the title compounds **I** and **III** [22]. All of the intermediates were synthesized and characterized as shown in **Supporting Information**.



**Reagents and conditions**:**(a)** methyl chloroacetate, $K_2CO_3$, $CH_3CN$, 65℃; **(b)** $K_2CO_3$, $H_2O$, 65℃; **(c)** aqueous HCl solution (10%), rt; **(d)** substituted 1,3-cyclohexanediones, EDCI, DMAP, DCM, rt; **(e)** substituted 1,3-dimethyl-1H-pyrazol-5-ol, EDCI, DMAP, DCM, rt; **(f)** $Et_3N$, acetone cyanohydrin, DCM, rt.

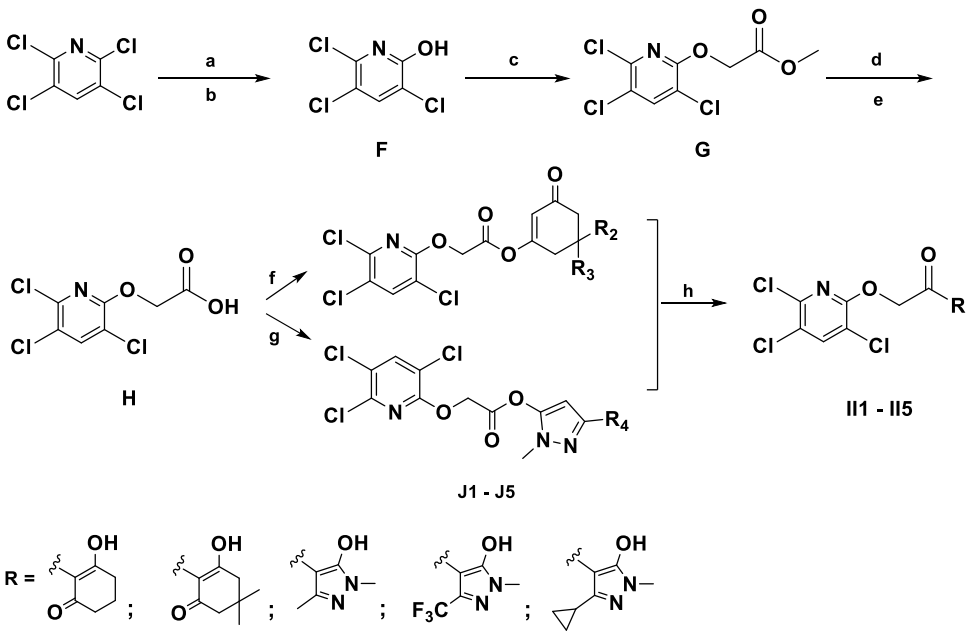
**Scheme 1:** Synthetic route of the title compounds **I**




**Reagents and conditions:(a)** methyl chloroacetate, $K_2CO_3$, $CH_3CN$, 65℃; **(b)** $K_2CO_3$, $H_2O$, 65℃; **(c)** aqueous HCl solution (10%), rt; **(d)** substituted 1,3-cyclohexanediones, EDCI, DMAP, DCM, rt; **(e)** substituted 1,3-dimethyl-1H-pyrazol-5-ol, EDCI, DMAP, DCM, rt; **(f)** $Et_3N$, acetone cyanohydrin, DCM, rt.

**Scheme 2:** Synthetic route of the title compound **III**

As shown in **Scheme 3**, the title compounds **II** were obtained by a five-step synthetic route using the commercially available 2,3,5,6-Tetrachloropyridine as the starting material. In the presence of TBAB, the starting material was hydrolyzed using NaOH in the water at 100℃. The resulting solution was cooled and hydrolyzed with HCl solution that yielded compound **F**. Subsequent preparations for compounds **G, H, J** and **II** were respectively the same as for compounds **C, D, E** and **I**.



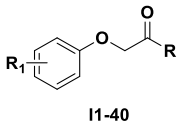

**Reagents and conditions**: **(a)** NaOH, TBAB, $H_2O$, 100℃; **(b)** concentrated HCl solution, rt; **(c)** methyl chloroacetate, $K_2CO_3$, $CH_3CN$, 65℃; **(d)** $K_2CO_3$, $H_2O$, 65℃; **(e)** aqueous HCl solution (10%), rt; **(f)** substituted 1,3-cyclohexanediones, EDCI, DMAP, DCM, rt; **(g)** substituted 1,3-dimethyl-1H-pyrazol-5-ol, EDCI, DMAP, DCM, rt; **(h)** $Et_3N$, acetone cyanohydrin, DCM, rt.

**Scheme 3.** Synthetic route of the title compounds **II**

## HPPD inhibition

The title compounds displayed promising *At*HPPD inhibitory activity. As shown in **Tables 1** and **2**, compound **I12** ($K_i$ = 0.011 $\mu$M), **I23** ($K_i$ = 0.012 $\mu$M) displayed similar inhibitor potency contrasting with that of Mesotrione ($K_i$ = 0.013 $\mu$M). There are mainly two interactions between compound **I12** and *At*HPPD active site (**Figure 3**), which was similar with Mesotrione. 1,3-Dicarbonyl parts could chelate the iron ion. The aromatic ring moiety formed π-π interaction with Phe403 and Phe360.

**Table 1:** Chemical structures of title compound I and their biological activity against *At*HPPD



| compound | $R_1$ | R | *At* HPPD inhibition $K_i$ ($\mu$M) | compound | $R_1$ | R | *At* HPPD inhibition $K_i$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| I1 | H |  | 1.542 ±0.031 | I22 | 2-Cl-4-$NO_2$ |  | 1.021±0.009 |
| I2 | H |  | 1.246 ±0.017 | I23 | 2-Cl-4-$NO_2$ |  | 0.012±0.009 |
| I3 | 2-Cl |  | 0.363 ±0.012 | I24 | 2-Cl-4-$NO_2$ |  | 0.258±0.012 |
| I4 | 2-Cl |  | 0.592 ±0.043 | I25 | 2-Cl-4-$NO_2$ |  | 0.206±0.043 |
| I5 | 4-Cl |  | 1.023±0.036 | I26 | 2-(2,4-Dichlorophenoxy)-4-Cl |  | 1.924±0.001 |
| I6 | 4-Cl |  | 0.934±0.032 | I27 | 2-(2,4-Dichlorophenoxy)-4-Cl |  | 2.240±0.041 |
| I7 | 2,4-diCl |  | 0.359±0.012 | I28 | 2-(2,4-Dichlorophenoxy)-4-Cl |  | 0.032±0.002 |
| I8 | 2,4-diCl |  | 0.216±0.023 | I29 | 2-(2,4-Dichlorophenoxy)-4-Cl |  | 1.253±0.022 |
| I9 | 2,4,6-tri-Cl |  | 0.311±0.048 | I30 | 2,4-di$CH_3$ |  | 2.203±0.034 |
| I10 | 2,4,6-tri-Cl |  | 0.240±0.003 | I31 | 2,4-di$CH_3$ |  | 3.091±0.343 |
| I11 | 2,4,6-tri-Cl |  | 0.081 0.001 | I32 | 2,4-di$CH_3$ |  | 2.013±0.009 |
| I12 | 2,4,6-tri-Cl |  | 0.011±0.012 | I33 | 2,4-di$CH_3$ |  | 2.754±0.045 |
| I13 | 2-$NO_2$ |  | 0.454±0.033 | I34 | 2,4-di$CH_3$ |  | 2.823±0.671 |
| I14 | 2-$NO_2$ |  | 0.213±0.042 | I35 | 4-$CH_3$-5-$OCH_3$ |  | 3.310±0.143 |
| I15 | 2-$NO_2$ |  | 0.273±0.004 | I36 | 4-$CH_3$-5-$OCH_3$ |  | 3.392±0.214 |
| I16 | 2-$NO_2$ |  | 0.439±0.013 | I37 | 4-$CH_3$-5-$OCH_3$ |  | 2.706±0.530 |
| I17 | 4-$NO_2$ |  | 0.227±0.004 | I38 | 4-$CH_3$-5-$OCH_3$ |  | 2.947±0.038 |
| I18 | 4-$NO_2$ |  | 0.934±0.006 | I39 | H |  | 1.314±0.056 |
| I19 | 4-$NO_2$ |  | 0.634±0.002 | I40 | H |  | 1.223±0.031 |
| I20 | 4-$NO_2$ |  | 0.496±0.003 | mesotrione | | | 0.013 ±0.001 |
| I21 | 4-$NO_2$ |  | 1.524±0.041 | | | | |

**Table 2:** Chemical structures of title compound **II**, **III** and their biological activity against *At*HPPD



**II1-5, III1-6**

| compound | $R_5$ | R | *At* HPPD inhibition $K_i$ ($\mu$M) | compound | $R_5$ | R | *At* HPPD inhibition $K_i$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| II1 | 2,3,5-trichloro-6-pyridyl |  | 0.093±0.007 | III2 | 2-Br-2-naphthyl |  | 2.231±0.090 |
| II2 | 2,3,5-trichloro-6-pyridyl |  | 0.097±0.010 | III3 | 2-Br-2-naphthyl |  | 2.157±0.125 |
| II3 | 2,3,5-trichloro-6-pyridyl |  | 0.021±0.004 | III4 | 2-Br-2-naphthyl |  | 1.965±0.012 |
| II4 | 2,3,5-trichloro-6-pyridyl |  | 0.023±0.006 | III5 | 2-nitro-3-pyridyl |  | 0.233±0.011 |
| II5 | 2,3,5-trichloro-6-pyridyl |  | 0.122±0.003 | III6 | 2-nitro-3-pyridyl |  | 0.214±0.042 |
| III1 | 2-Br-2-naphthyl |  | 2.495±0.011 | mesotrione | | | 0.013 ±0.001 |

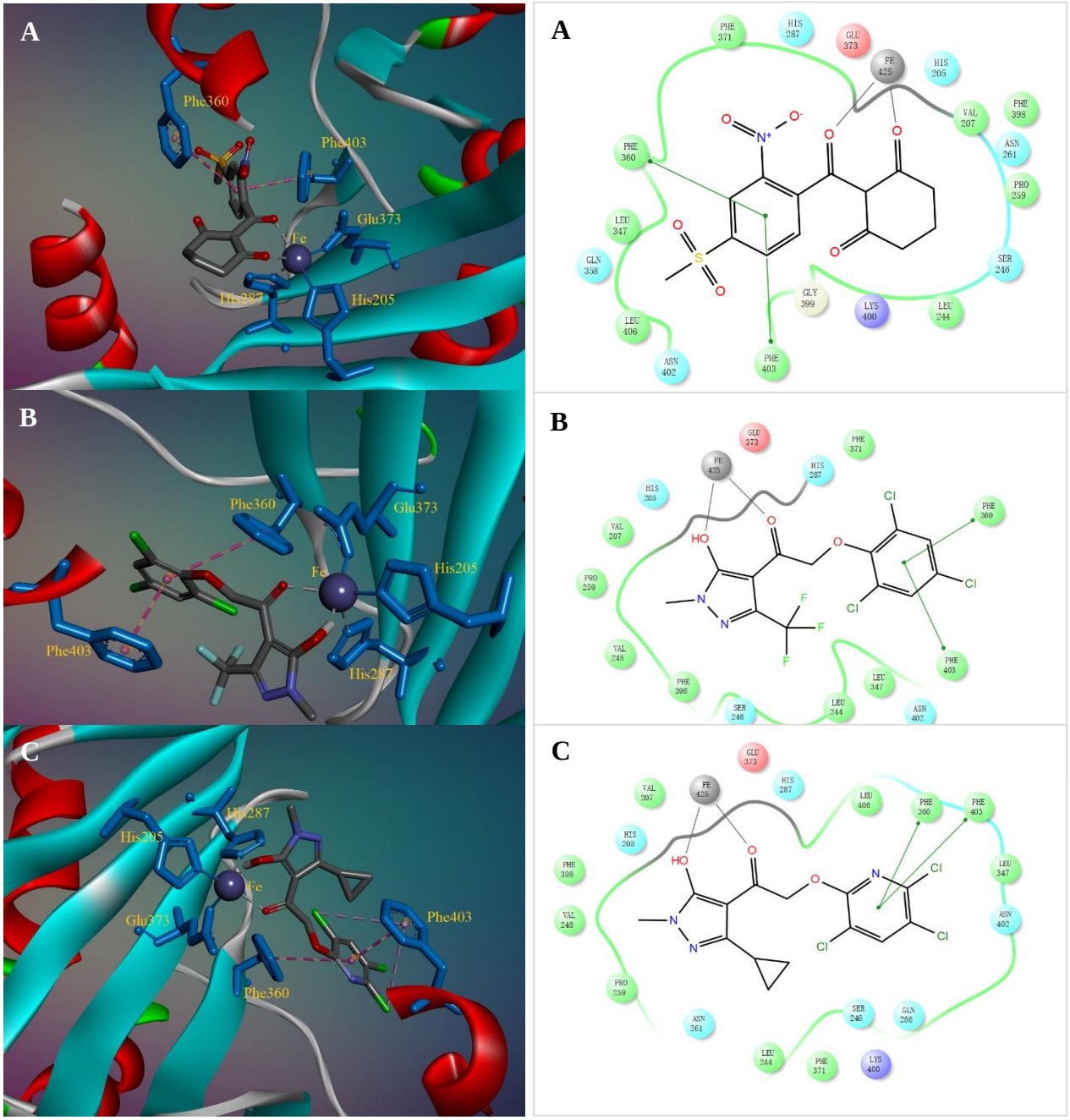



**Figure 3:** Simulated binding mode of **Mesotrione** (A), compound **I12** (B) and compound **II4** (C) with *At*HPPD. The key residues in the active site are shown in blue sticks, and $Fe^{II}$ is shown as a dark blue sphere. Mesotrione, compound **I12,** and **II4** are shown in gray sticks.

Electron withdrawing group and the electron-donating group were introduced to the benzene moiety of compound **I1**, which had a significant influence on HPPD inhibition activity. It was found that introducing electron-withdrawing groups would improve the activities. For example, **I3** ($K_i$ = 0.363 $\mu$M), **I4** ($K_i$ = 0.592 $\mu$M) showed a more potent activity than compound **I1** ($K_i$ = 1.542 $\mu$M); Also, the position of electron-withdrawing groups played an essential role in HPPD inhibitory activity. In most cases, when chlorine atom was introduced at the 2-position (**I4**, **I13**) or the 4-position (**I6**, **I18**), compound **I4** and **I13** showed improved activity than compound **I6** and **I18** (**I4**> **I6**, **I13**> **I8**). It indicated that electron-withdrawing groups at 2-position enhanced the eff ects compared to those with groups at 4-position. Besides, introducing electron-

donating groups were detrimental to HPPD inhibition activity (**I1**> **I33**, **I38**). It was found that the introduction of nitro atom exhibited more potent activity than chlorine atom (except **I6**, **I21**), such as compound **I15**> **I3**, **I18**> **I5**, **I24**> **I7**.

## Herbicidal activity

Post-emergence herbicidal activity of title compounds was summarized in **Figure 4**. Some of the synthesized compounds had better control efficiency to the test weed. Among them, compound **I28**, **I29**, **II3** and **II4** showed broad-spectrum herbicidal activity. Compound **II4** even exhibited a slightly more improved herbicidal activity than Mesotrione at the rate of 150 g ai/ha. When the compound **II4** was superimposed with positive control drug Mesotrione, it was observed that the compound was perfectly filled in the active pocket. (**Figure 5**)

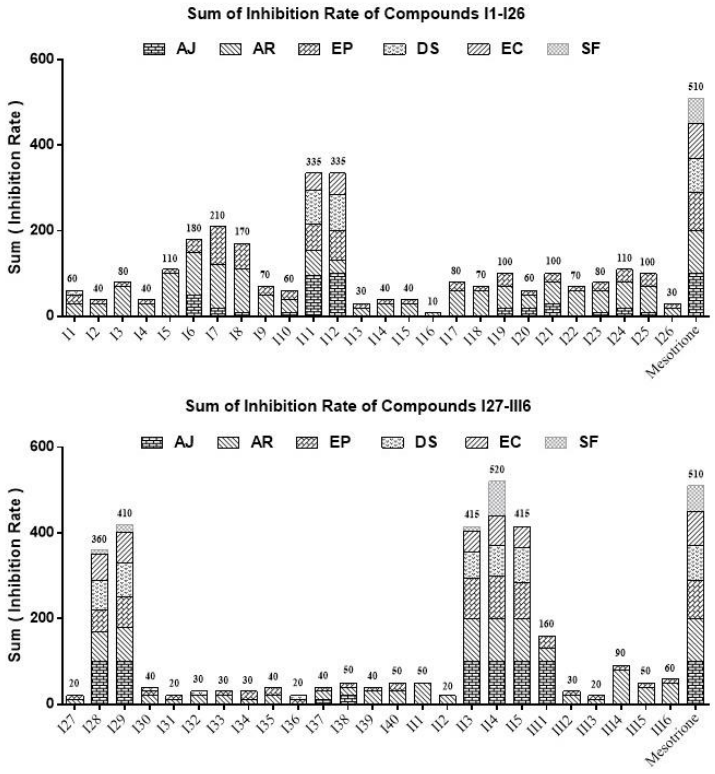



**Figure 4:** Sum of Inhibition rate of title compounds at 150 g ai/ha. (Abbreviations: AJ, Abutilon juncea; AR, Amaranthus retroflexus; EP, Eclipta prostrata; DS, Digitaria sanguinalis; EC, Echinochloa crus-galli; SF, Setaria faberi.)

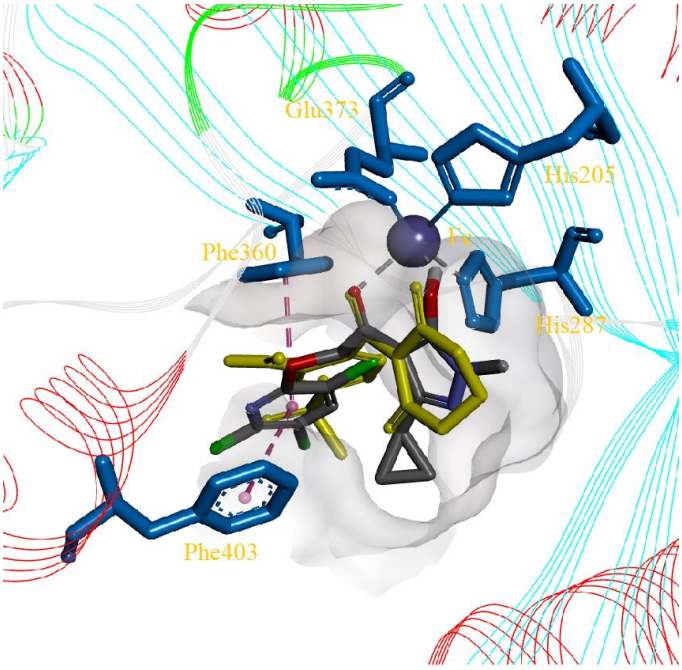



**Figure 5:** Simulated folding mode of Mesotrione (yellow sticks) and compound **II4** (gray sticks) with AtHPPD. The key residues in the active site are shown in blue sticks, and $Fe^{II}$ is shown as a dark blue sphere.

In this work, two categories of HPPD inhibitors were synthesized, including triketone and pyrazole derivatives. Compared with triketone derivatives, pyrazole-containing derivatives generally displayed more potent herbicidal activity. For instance, compound **I11**, **I12** with pyrazole ring displayed enhanced activity relative to compound **I9** with a cyclohexanedione ring. We also observed that introducing methyl groups to the 5-position of the 1,3-cyclohexane ring was detrimental to herbicidal activity (**I17**>**I18**, **I26**>**I27**, **II1**>**II2**). Compounds with electron-withdrawing groups at aromatic ring were found to displayed higher herbicidal activity than those with electron-donating groups, which was consistent with *At*HPPD inhibitory activity. Compound **I28** and **I29** had a significant improvement in herbicidal activity. Thus, the introduction of large groups on the benzene ring might be beneficial to the activity, deserving further structural optimization. Besides, the herbicidal activity of other aromatic rings, compound **II** and **III** with pyridine ring or naphthalene ring were tested. The results showed Chloro-substituted pyridine performed an improved herbicidal activity. It was found that some compounds having significant *At*HPPD inhibitory activity didn't exhibit promising herbicidal activity. For example, compound **I12** had the best AtHPPD inhibition activity with $K_i$=0.011 μM. However, its herbicidal activity was not as good as expected, which might be related to drug stability and metabolism in plants.

**Crop Safety**

Crop safety is one of the main indicators in herbicides discovery. Compound **II3**, **II4**, and **II5** with excellent herbicidal activity were chosen for further crop safety studies to evaluate whether they had the potential to be developed as herbicide or not (**Table 3**). The commercial HPPD herbicide Mesotrione was selected as a positive control. It was found that wheat and maize showed high tolerance to compound **II3** at the dosage of 150 g ai/ha, however, its herbicidal activity could not compete with that of Mesotrione. Besides, the results showed maize displayed tolerance to compound **II4**, indicating that **II4** had the potential to be developed as a postemergence herbicide for weed control in maize fields.

**Table 3:** Postemergence Crop safety of Compound **II3**, **II4** and **II5** (150 g ai/ha)

| compound | dosage (g ai/ha) | % injury | | | | | |
|---|---|---|---|---|---|---|---|
| | | rice | wheat | maize | cotton | soybean | canola |
| II3 | 150 | 40 | 10 | 10 | 60 | 50 | 90 |
| II4 | 150 | 30 | 50 | 10 | 60 | 30 | 100 |
| II5 | 150 | 50 | 50 | 30 | 90 | 70 | 100 |
| mesotrione | 150 | 50 | 40 | 10 | 80 | 50 | 100 |

## Conclusions

In summary, a series of novel aryloxyacetic acid derivates were synthesized for the novel HPPD inhibitors. Based on activity studies, some title compounds showed similar *At*HPPD inhibitor potency compared with Mesotrione ($K_i$ = 0.013 $\mu$M), such as compound **I12** ($K_i$ = 0.011 $\mu$M), **I23** ($K_i$ = 0.012 $\mu$M). Moreover, several newly synthesized compounds displayed a strong and broad spectrum of weed control at the rate of 150 g ai/ha. Most importantly, compound **II4,** with a good HPPD inhibition activity **(**$K_i$ = 0.023 $\mu$M**),** displayed slightly more potential than Mesotrione in the herbicidal activity. In addition, compound **II4** was safe for maize. These results suggested that compound **II4** might be a promising candidate as HPPD inhibiting-based herbicide, and well worth further optimization.

## Experimental

The experimental details and analytical data for intermediates **C** to **M** and title compounds were given in the **Supporting Information**. The chemical structures of all title compounds were confirmed by $^{1}$H NMR, $^{13}$C NMR spectroscopic and MS spectrometric.

## X-ray diffraction

The single crystal of compound **I18** and **III4** were cultivated for structure validation. Compound **I18** was recrystallized from a mixture of DCM/ methanol to afford a colorless transparent crystal. It crystallized in the monoclinic space group:
P 1 (2), Cell: a 6.425(4)Å, b 9.854(6)Å, c 13.205(8)Å, α 93.974(7)°, β 102.211(7)°, γ 107.567(7)°, Temperature: 298 K. Compound **III4** was recrystallized from a mixture of DCM/ methanol to afford a colorless transparent crystal. It crystallized in the monoclinic space group:
P 1 (2), Cell: a 5.191(5)Å, b 12.133(12)Å, c 13.576(14)Å, α 80.141(13)°, β 81.978(12)°, γ 79.496(12)°, Temperature: 296 K. X-ray crystal structure of compound **I18** and **III4** were shown in **Figure 6**.

Crystallographic data for crystal compounds **I18** and **III4** were deposited with the Cambridge Crystallographic Data Centre as supplementary publications with the deposition numbers CCDC 1959130 and CCDC 1959152 respectively. The data can be obtained free of charge from Http://www.ccdc.cam.ac.uk/.

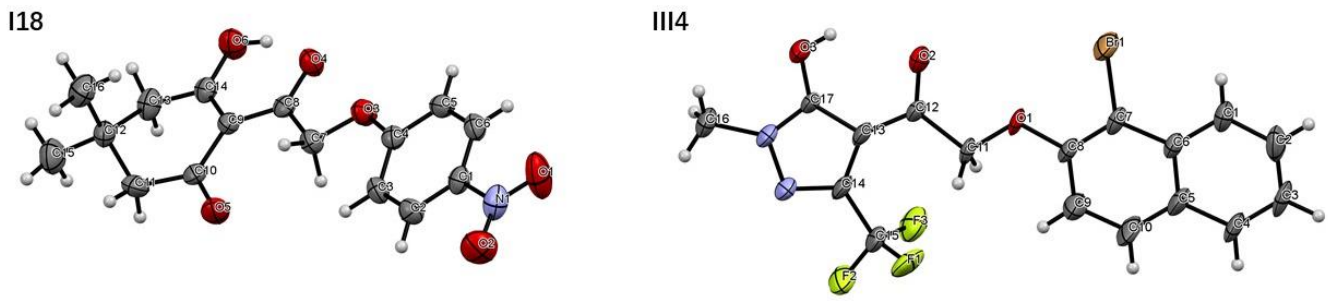



**Figure 6:** Crystal structures of **I18** and **III4**

## Docking studying

The docking study was conducted with the method reported previously [2, 23-26]. Crystal structures of *Arabidopsis thaliana* HPPD (PDB ID: 1TFZ) with the native ligand, named DAS869 were downloaded from the Protein Data Bank. The docking was carried out using Discovery Studio 4.0. During the docking process, all water molecules were removed. The ligand and protein were prepared with the Dock Ligands tool before docking. By using Define and Edit Binding Site tool to identify the active site. Then the center of the native ligand was deleted. Utilizing the CDOCKER, the prepared ligand was docked into the protein receptor binding site. After the docking calculations were performed, the best binding modes were determined by docking scores and also compared with the simulated binding mode of Mesotrione with *At*HPPD.

## Enzyme inhibition study

*At*HPPD was prepared and purified according to the reported methods in the literature [13, 26-29]. The inhibition constant ($K_i$) was obtained and shown in **Tables 1** and **2**.

## Herbicidal activities

The post-emergence herbicidal activities of the title compounds were evaluated against monocotyledon weeds (*E. crus-galli*, *S. faberii*, and *D. sanguinalis*) and broadleaf weeds (*A. retroflexus*, *E. prostrata*, and *A. juncea*) in the greenhouse experiments. The commercial HPPD herbicide Mesotrione was regarded as a control. All tested compounds were dissolved in DMF as 100 g/L emulsified concentrates, containing 1% Tween-80 as emulsifier. Then the solvent was diluted with distilled water. Flowerpots with an inner diameter of 7.5 cm were filled with complex nutrient soil to three-fourths of their height. The above six weed targets were respectively grown in the pots and covered with soil to a thickness of 0.2 cm and grown in the greenhouse. When the weeds grew to about the three-leaf stage, they were treated by the title compounds at the rate of 150 g ai/ha. After 18 days of treatment with inhibitors, the herbicidal activities were surveyed and evaluated [26]. (**Figure 4**)

## Crop Selectivity

The representative crops, rice, wheat, maize, cotton, soybean, and canola were selected to test the crop safety of compound **II3, II4,** and **II5**. The six crops were separately planted in flowerpots (12 cm diameter) containing the composite nutrient soil and grown at room temperature. When the crops had reached the four-leaf stage, the safety experiments were conducted at the rate of 150 g ai/ha. After 15 days, the final results of crop safety were evaluated with two duplicates per experiment (**Table 3**).

## Acknowledgments

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## Supporting information

Supporting information is available in the online version of this article.

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