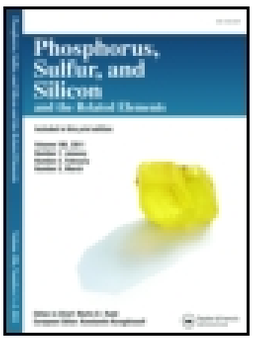


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Synthesis and herbicidal activity of new pyrazole ketone derivatives

Qing Fu , Sheng-Jie Kang , Liang-Kun Zhong , Jie Chen , Cheng-Xia Tan , Jian-Quan Weng , Tian-Ming Xu & Xing-Hai Liu

To cite this article: Qing Fu , Sheng-Jie Kang , Liang-Kun Zhong , Jie Chen , Cheng-Xia Tan , Jian-Quan Weng , Tian-Ming Xu & Xing-Hai Liu (2020): Synthesis and herbicidal activity of new pyrazole ketone derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2020.1828884

To link to this article: https://doi.org/10.1080/10426507.2020.1828884

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2020.1828884

Synthesis and herbicidal activity of new pyrazole ketone derivatives

Qing Fu[a,b], Sheng-Jie Kang[a,b], Liang-Kun Zhong[a,b], Jie Chen[c], Cheng-Xia Tan[a], Jian-Quan Weng[a], Tian-Ming Xu[b], and Xing-Hai Liu[a]

[a]College of Chemical Engineering, Zhejiang University of Technology, Hangzhou, China; [b]Zhejiang Base of National Southern Pesticide Research Centre, Zhejiang Research Institute of Chemical Industry, Hangzhou, China; [c]School of Forestry & Biotechnology, Zhejiang A & F University, Hangzhou, China

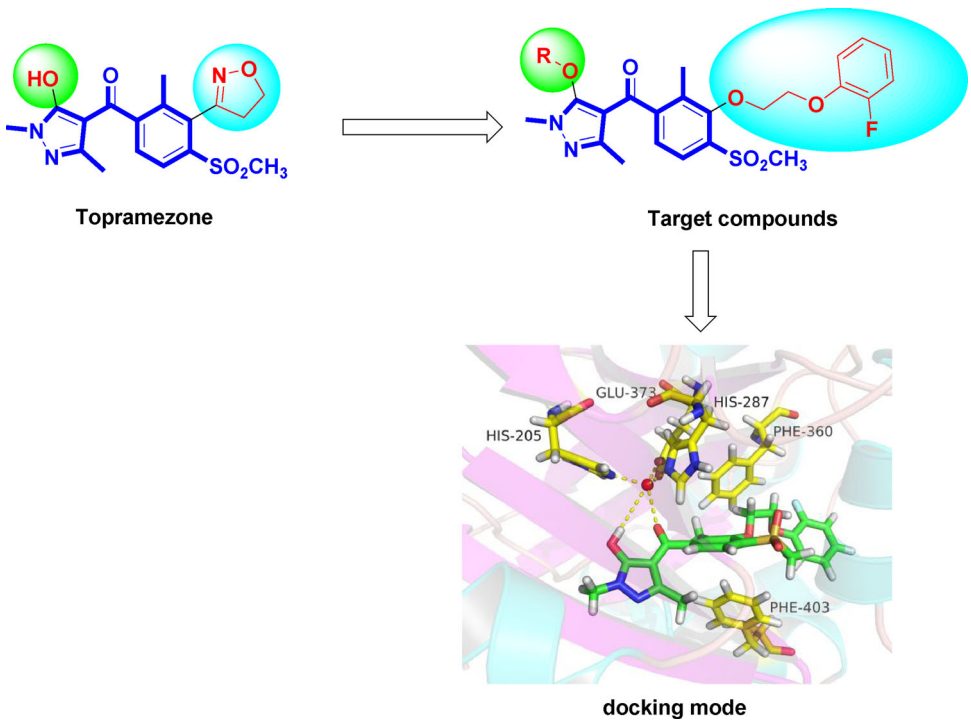
ABSTRACT

A series of pyrazole derivatives was designed according to prodrug strategy. These compounds were synthesized via eight steps and their structures were confirmed by ^{1}H NMR spectroscopy and MS. The preliminary herbicidal bioassay results indicated that the title pyrazole ketone compounds exhibited low herbicidal activity against six weeds at 150 g/ha, which is weaker than that of the commercial HPPD herbicide topramezone. The docking results showed that the binding mode of the key intermediate (3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)phenyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)methanone is the same as the reported inhibitor DAS689 in the complex.

ARTICLE HISTORY
Received 24 February 2020
Accepted 23 September 2020

KEYWORDS
Synthesis; pyrazole derivatives; molecular docking; herbicidal activity

GRAPHICAL ABSTRACT



Introduction

4-Hydroxyphenylpyruvate dioxygenase (HPPD) is an ideal herbicidal target[1] in green plants, because it catalyzes *p*-hydroxyphenylpyruvic acid conversion to homogentisic acid in plant photosynthesis.[2] Many different kinds of HPPD herbicides (Figure 1) have been discovered, such as pyrazole derivatives,[3,4] triketone derivatives [5] and isoxazole derivatives.[6] Among them, triketone HPPD herbicides have been widely used and studied.[7–12]

Prodrug strategy is an important method in drug design. Among these commercial HPPD herbicides, isoxaflutole, benzobicyclon, pyrazolynate, pyrazoxyfen and benzofenap belonged to prodrug HPPD herbicides. Topramezone is a

CONTACT Xing-Hai Liu xhliu@zjut.edu.cn College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China; Tian-Ming Xu xutianming@sinochem.com Zhejiang Base of National Southern Pesticide Research Centre, Zhejiang Research Institute of Chemical Industry, Hangzhou, China.

Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2020.1828884.

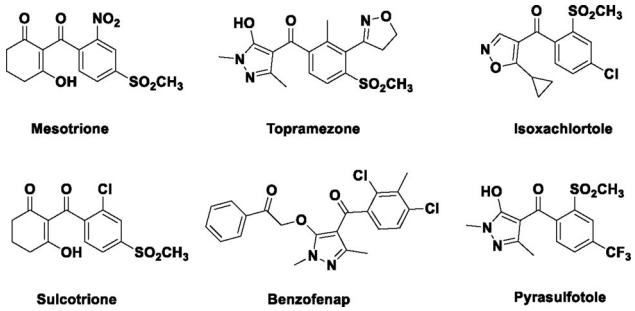


Figure 1. Representative some commercial HPPD herbicides.

good HPPD herbicide, which is used to control weeds in maize fields.[13] As a part of our research in pesticides,[14–32] many pyrazole compounds have been designed and synthesized. Herein, topramezone was used as a lead compound; the isoxazole ring of topramezone was opened and replaced by a flexible chain, and the hydroxyl group on the pyrazole ring was etherified or esterified. Ten pyrazole ketone derivatives were synthesized. The preliminary herbicidal activity indicated that the title compounds exhibited low herbicidal activity against six weeds. The design strategy of title compounds was shown in Figure 2.

Results and discussion

The synthetic procedure of title pyrazole ketone compounds is illustrated in Scheme 1. For the key intermediate 4, the thioether group was synthesized by using $NaSCH_3$. The reagent $NaSCH_3$ is smelly and must be strictly used in a fumehood. The solvent DMF must be anhydrous, otherwise it may lead to hydrolysis of the ester group. Then the thioether was oxidized by Na_2WO_4 to give CH_3SO_2 group. Another key process is the synthesis of pyrazole aromatic ketone. Several synthetic methods were reported.[33–35] The common method is using pyrazole-5-ol and RCOCl as starting materials, then rearranged to give a pyrazole aromatic ketone under base conditions. The second method is using methamiprid and pyrazole as starting materials, then hydrolyzed to give a pyrazole aromatic ketone. The most recent method is that CO was inserted between ArX and pyrazole under Pd catalyst. In this step, the key intermediate **9** was prepared by using acetone cyanohydrin as the base at room temperature.

The structures of compounds **B1~B8** were confirmed by ^{1}H NMR and ESI-MS. In the ^{1}H NMR spectra, three CH_3 proton signals of on the pyrazole and benzene ring can be found around at 2.20, 2.35 and 3.65 ppm respectively. The final CH_3 proton signals of SO_2CH_3 was observed around at 3.2 ppm. The mass spectra of pyrazol-4-one compounds showed molecular ion peak and consistent with the corresponding calculated values.

The postemergence herbicidal activities of compounds **B1∼B8** were tested against *Poa annua* (PA), *Chenopodium serotinum* (CS), *Alopecurus aequalis* (AA), *Polypogon fugax* (PF), *Brassica juncea* (BJ), *Stellaria media* (SM), at 150 g ai/ha in a greenhouse, topramezone is used as positive control. Most of them exhibited low herbicidal activities (Table S 1).

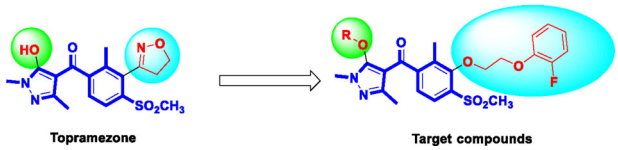


Figure 2. The design strategy of title compounds.

Among them, all the compounds showed no activity against *P. annua* and *P. fugax* under post mergence conditions. For the other monocotyledon weed *A. aequalis,* only compound B5 exhibited moderate herbicidal activity (∼40%). For the weed *C. serotinum,* most of them exhibited certain activity, only compound B5 (50%) and B8 (40%) possessed moderate herbicidal activity. For the weed *S. media,* most of the compounds displayed no herbicidal activity, except compound B8 (50%). For the weed *B. juncea,* only compounds B2 and B8 exhibited moderate herbicidal activity.

To study the binding mode of our intermediate and *At*HPPD complex(PDB code: 1TFZ) with pyrazole HPPD inhibitor DAS869,[36] the molecular docking was carried out by DS 2.5. As shown in Figure **3A** and **3B**, the binding site of DAS869 and intermediate **9** in the active pocket of *At*HPPD are well matched. The intermediate **9** was noticed to constitute a bidentate combination with the Fe^{2+}, forming twisted square-pyramidal complex with a mainly five-coordinate with the distances of 2.0 Å (Glu 373), 2.2 Å (His 205), 4.5 Å (OH of intermediate 9), 2.4 Å (Phe 360), 2.9 Å (CO of intermediate 9). It was the same as the binding mode of DAS869 in crystal of *At*HPPD with the distances of 2.0 Å (Glu 373), 2.2 Å (His 205), 2.2 Å (OH of DAS869), 2.4 Å (Phe 360), 2.3 Å (CO of DAS869). In the complex, there are two π-π stacking interactions between the DAS869 and Phe 360(4.5 Å), Phe 403(4.5 Å) respectively. But in our intermediate 9, the π-π stacking interaction was not observed. The molecular docking indicated that the π-π stacking interaction may increase the herbicidal activity.

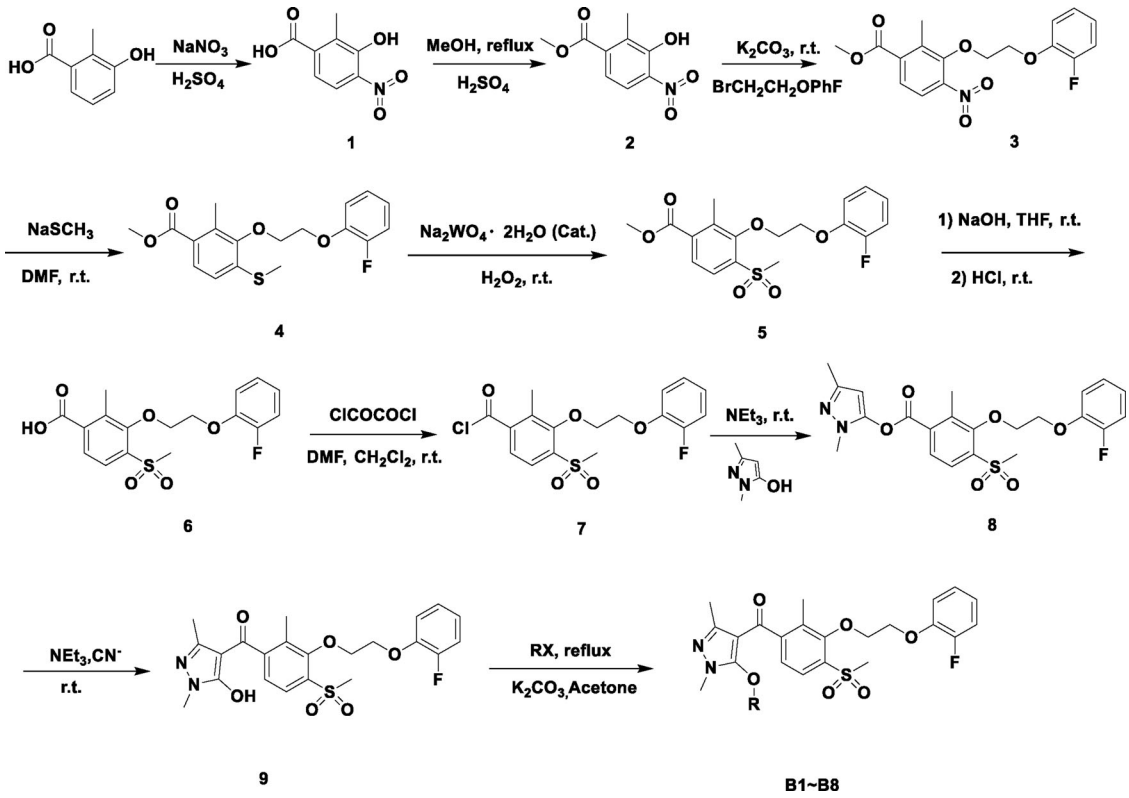
Experimental

Instrument and materials

^{1}H NMR spectra were recorded on a Bruker AV-600 instrument using TMS as an internal standard and $CDCl_3$ as the solvent. LRMS were measured on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. All the reagents are of analytical grade or freshly prepared before use. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF_{254}. The Supplemental Materials contains sample 1H NMR spectra for the products B1–B8 (Figures S1–S8).

General procedure

The intermediate **1** and **2** were published in our previous work.[4] The intermediates **3∼8** were synthesized by using the same method according to our previous work,[4] which changed the 4-Cl to 2-F on the phenyl ring.



Scheme 1. The synthetic route of title compounds.

Synthesis of intermediate 9

The intermediate **8** was dissolved in CH_3CN (100 mL), and then acetone cyanohydrin (0.11 g, 0.0013 mol) and Et_3N (1.42 g, 0.014 mol) was added at room temperature. After the mixture was stirred 6 h, the solvent was removed. The residue was dissolved in H_2O (65 mL), then acidified to pH = 7 using HCl, and the organic layer was exacted with ethyl acetate to give red brown liquid **9**, yield 43%.

General synthetic procedure for final compounds B

To a solution of intermediate **9** (1 g, 0.0022 mol) in dry acetone (50 mL), RX (0.0022 mol) and K_2CO_3 (0.33 g, 0.0024 mol) was added dropwise at room temperature, and then the mixture was refluxed for 5 h. The solution was evaporated and the residue was purified by column chromatography on silica gel with PE and EA as solvents to give product **B** (1:1).

1-((4-(3-(2-(2-Fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)ethyl methyl carbonate B1

Waxy solid, yield 44%, ^{1}H NMR (δ, ppm): 1.47 (d, 3H, J = 5.2 Hz, -CHC$\underline{H_3}$), 1.97 (s, 3H, Ar-CH_3), 2.40 (s, 3H, pyrazole-CH_3), 3.30 (s, 3H, -SO_2CH_3), 3.65 (s, 3H, pyrazole-CH_3), 3.73 (s, 3H, -OCH_3), 4.45-4.48 (m, 4H, -OCH_2CH_2O-), 6.24 (q, 1H, -C$\underline{H}$CH$_3$), 6.91-6.94 (m, 1H, Ar-H), 7.04-7.10 (m, 3H, Ar-H), 7.24 (d, 1H, J = 8.0 Hz, Ar-H), 7.92 (d, 1H, J = 8.0 Hz, Ar-H); ESI-MS: 564 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{26}H_{29}FN_2O_9S]$: 565.1651, found, 565.1655.

4-(3-(2-(2-Fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)-benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl furan-2-carboxylate B2

Waxy solid, yield 55%, ^{1}H NMR (δ, ppm): 2.30 (s, 3H, Ar-CH_3), 2.50 (s, 3H, pyrazole-CH_3), 3.14 (s, 3H, -SO_2CH_3), 3.65 (s, 3H, pyrazole-CH_3), 4.23-4.24 (m, 2H, -OCH_2-), 4.36-4.37 (m, 2H, -OCH_2-), 6.49-6.50 (m, 1H, oxole-H), 6.92-6.94 (m, 1H, Ar-H), 7.02-7.09 (m, 5H, Ar-H、oxole-H), 7.14 (d, 1H, J = 7.9 Hz, Ar-H), 7.63 (br, 1H, oxole-H), 7.69 (d, 1H, J = 7.9 Hz, Ar-H); ESI-MS: 556 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{27}H_{25}FN_2O_8S]$: 557.1388, found, 557.1390.

4-(3-(2-(2-Fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)-benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl methanesulfonate B3

Waxy solid, yield 65%, ^{1}H NMR (δ, ppm): 1.97 (s, 3H, Ar-CH_3), 2.41 (s, 3H, pyrazole-CH_3), 3.31 (s, 3H, -SO_2CH_3), 3.33 (s, 3H, -SO_2CH_3), 3.82 (s, 3H, pyrazole-CH_3), 4.46-4.48 (m, 4H, -OCH_2CH_2O-), 6.92-6.96 (m, 1H, Ar-H), 7.01-7.09 (m, 3H, Ar-H), 7.23 (d, 1H, J = 8.0 Hz, Ar-H), 7.92 (d, 1H, J = 8.0 Hz, Ar-H); ESI-MS: 540 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{23}H_{25}FN_2O_8S_2]$: 541.1109, found, 541.1108.

4-(3-(2-(2-Fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)-benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl methyl carbonate B4

Waxy solid, yield 48%, ^{1}H NMR (δ, ppm): 2.33 (s, 3H, Ar-CH_3), 2.35 (s, 3H, pyrazole-CH_3), 3.30 (s, 3H, -SO_2CH_3), 3.65 (s, 3H, pyrazole-NCH_3), 3.73 (s, 3H, -OCH_3), 4.44-4.49 (m, 4H, -OCH_2CH_2O-), 6.92-6.96 (m, 1H, Ar-H), 7.03-7.10 (m, 3H, Ar-H), 7.14 (d, 1H, J = 8.0 Hz, Ar-H), 7.89 (d, 1H,

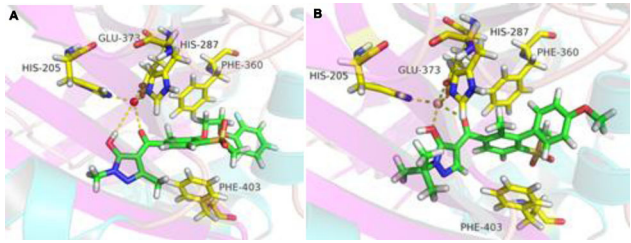


Figure 3. (A) binding mode of intermediate 9 with 1TFZ; (B) Crystal complex of 1TFZ with DAS869.

J = 8.0 Hz, Ar-H); ESI-MS: 520 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{24}H_{25}FN_2O_8S]$: 521.1388, found, 521.1389.

Benzyl (4-(3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl) carbonate B5

Waxy solid, yield 46%, ^{1}H NMR (δ, ppm): 2.29 (s, 3H, Ar-CH_3), 2.34 (s, 3H, pyrazole-CH_3), 3.19 (s, 3H, -SO_2CH_3), 3.61 (s, 3H, pyrazole-CH_3), 4.43-4.46 (m, 4H, -OCH_2CH_2O-), 5.09 (s, 2H, Bn), 6.92-6.96 (m, 1H, Ar-H), 7.02-7.09 (m, 5H, Ar-H), 7.14 (d, 1H, J = 8.0 Hz, Ar-H), 7.34-7.38 (m, 5H, Ar-H), 7.87 (d, 1H, J = 8.0 Hz, Ar-H); ESI-MS: 596 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{30}H_{29}FN_2O_8S]$: 597.1701, found, 597.1703.

4-(3-(2-(2-Fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)-benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl propyl carbonate B6

Waxy solid, yield 52%, ^{1}H NMR (δ, ppm): 0.92 (t, 3H, -CH_3), 1.67-1.68 (m, 2H, -CH_2CH_3), 2.28 (s, 3H, Ar-CH_3), 2.35 (s, 3H, pyrazole-CH_3), 3.29 (s, 3H, -SO_2CH_3), 3.65 (s, 3H, pyrazole-NCH_3), 4.03-4.05 (m, 2H, -OCH_2), 4.45-4.48 (m, 4H, -OCH_2CH_2O-), 6.92-6.96 (m, 1H, Ar-H), 7.01-7.09 (m, 3H, Ar-H), 7.15 (d, 1H, J = 7.9 Hz, Ar-H), 7.87 (d, 1H, J = 7.9 Hz, Ar-H); ESI-MS: 548 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{26}H_{29}FN_2O_8S]$: 549.1701, found, 549.1700.

Sec-butyl (4-(3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl) carbonate B7

Waxy solid, yield 47%, ^{1}H NMR (δ, ppm): 0.90 (t, 3H, -CH_3), 1.26 (d, 3H, J = 6.3 Hz, -$CHCH_3$), 1.57-1.67 (m, 2H, -$CHCH_2CH_3$), 2.21 (s, 3H, Ar-CH_3), 2.35 (s, 3H, pyrazole-CH_3), 3.28 (s, 3H, -SO_2CH_3), 3.66 (s, 3H, pyrazole-NCH_3), 4.45-4.47 (m, 4H, -OCH_2CH_2O-), 6.92-6.95 (m, 1H, Ar-H), 7.03-7.10 (m, 3H, Ar-H), 7.18 (d, 1H, J = 8.0 Hz, Ar-H), 7.88 (d, 1H, J = 8.0 Hz, Ar-H); ESI-MS: 562 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{27}H_{31}FN_2O_8S]$: 563.1858, found, 563.1860.

Ethyl (4-(3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)benzoyl)-1,3-dimethyl-1H-pyrazol-5-yl) carbonate B8

Waxy solid, yield 44%, ^{1}H NMR (δ, ppm): 1.28 (t, 3H, -CH_3), 2.31 (s, 3H, Ar-CH_3), 2.35 (s, 3H, pyrazole-CH_3), 3.29 (s, 3H, -SO_2CH_3), 3.65 (s, 3H, pyrazole-NCH_3), 4.11 (q, 2H, -OCH_2CH_3), 4.46-4.49 (m, 4H, -OCH_2CH_2O-), 6.93-6.95 (m, 1H, Ar-H), 7.03-7.11 (m, 4H, Ar-H), 7.15 (d, 1H, J = 7.9 Hz, Ar-H), 7.88 (d, 1H, J = 7.9 Hz, Ar-H); ESI-MS: 535 $[M+H]^+$. ESI-HRMS: m/z $[M+H]^+$ calcd for $[C_{25}H_{27}FN_2O_8S]$: 535.1545, found, 535.1550.

Greenhouse in vivo biological evaluation

The herbicidal activities of compounds **B1~B8** against monocotyledon weeds such as *P. annua*, *A. aequalis*, *P. fugax* and dicotyldon weeds such as *C. serotinum*, *S. media*, *B. juncea* were evaluated according to our previous work.[37,38] Topramezone was used as positive control. The herbicidal activities treated at three replicates are shown in Table S1 (Supplemental Materials).

Molecular docking

The molecular docking was carried out by using Discovery Studio 2.5 software according to the reported method.[39,40] The reference reported that the prodrug pyrazoxyfen is metabolized to active intermediate 5-hydroxypyrazole derivative in plants.[41] In this paper, the intermediate (3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)phenyl)(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)methanone **9** was selected as ligand to dock into the *At*HPPD structure. The structure of *At*HPPD (PDB ID: 1TFZ) was downloaded from the protein data bank (PDB). The The 3 D structure of intermediate 9 was constructed and optimized according to the standard methods by using Discovery Studio 2.5. Discovery Studio 2.5 was used to dock intermdiate 9 to the active site of *At*HPPD. The protein crystal structure *At*HPPD was prepared by standard methods using Discovery Studio 2.5. After molecular docking, the best binding modes were selected by the docking energy as well as by comparison with the cocrystal ligand. The force field used for protein and intermediate 9 was CHARMm. After energy minimization, PYMOL was used to analyze the binding modes.

Conclusions

In summary, ten pyrazole ketone derivatives were designed by using the prodrug method. The herbicidal activity indicated that these compounds possessed low herbicidal activity at 150 g/ha, compared with the positive control topramezone. The molecular docking showed that the binding mode of the key intermediate (3-(2-(2-fluorophenoxy)ethoxy)-2-methyl-4-(methylsulfonyl)phenyl)(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)methanone is the same as the reported inhibitor DAS689 in the complex. It provides a useful method for the discovery of new HPPD herbicides.

Funding

This work was funded by Zhejiang Provincial Natural Science Foundation of China (No. LY19C140002) and Research Fund of Department of Education of Zhejiang Province (Y201941832).

References

[1] Li, H. B.; Li, L.; Li, J. X.; Han, T. F.; He, J. L.; Zhu, Y. Q. Novel HPPD Inhibitors: Triketone 2H-Benzo[b][1,4]Oxazin-3(4H)-

One Analogs. *Pest Manage. Sci.* **2018**, *74*, 579–589. DOI: 10.1002/ps.4739.

[2] Hrens, H.; Lange, G.; Müller, T.; Rosinger, C.; Willms, L.; van Almsick, A. 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors in Combination with Safeners: Solutions for Modern and Sustainable Agriculture. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 9388–9398. DOI: 10.1002/anie.201302365.

[3] Adlington, R. M.; Baldwin, J. E.; Crouch, N. P.; Lee, M. H.; MacKinnon, C. H. Identification and Stereochemistry of the Product of 4-HPPD Catalyzed Oxidation of the Ketoacid of Methionine. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2003–2006. DOI: 10.1016/0960-894X(96)00362-9.

[4] Fu, Q.; Cai, P.-P.; Cheng, L.; Zhong, L.-K.; Tan, C.-X.; Shen, Z.-H.; Han, L.; Xu, T.-M.; Liu, X.-H. Synthesis and Herbicidal Activity of Novel Pyrazole Aromatic Ketone Analogs as HPPD Inhibitor. *Pest Manage. Sci.* **2020**, *76*, 868–879. DOI: 10.1002/ps.5591.

[5] Fu, Y.; Zhang, D.; Zhang, S. Q.; Liu, Y. X.; Guo, Y. Y.; Wang, M. X.; Gao, S.; Zhao, L. X.; Ye, F. Discovery of N-Aroyl Diketone/Triketone Derivatives as Novel 4-Hydroxyphenylpyruvate Dioxygenase Inhibiting-Based Herbicides. *J. Agric. Food Chem.* **2019**, *67*, 11839–11847. DOI: 10.1021/acs.jafc.9b01412.

[6] Viviani, F.; Little, J. P.; Pallett, K. E. The Mode of Action of Isoxaflutole II. Characterization of the Inhibition of Carrot 4-Hydroxyphenylpyruvate Dioxycides by the Diketonitrile Derivative of Isoxaflutole. *Pestic. Biochem. Physiol.* **1998**, *62*, 125–134. DOI: 10.1006/pest.1998.2375.

[7] Wang, D. W.; Lin, H. Y.; Cao, R. J.; Chen, T.; Wu, F. X.; Hao, G. F.; Chen, Q.; Yang, W. C.; Yang, G. F. Synthesis and Herbicidal Activity of Triketone-Quinoline Hybrids as Novel 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors. *J. Agric. Food Chem.* **2015**, *63*, 5587–5596. DOI: 10.1021/acs.jafc.5b01530.

[8] Fu, Y.; Zhang, S. Q.; Liu, Y. X.; Wang, J. Y.; Gao, S.; Zhao, L. X.; Ye, F. Design, Synthesis, SAR and Molecular Docking of Novel Green Niacintriketone HPPD Inhibitor. *Ind. Crop Prod.* **2019**, *137*, 566–575. DOI: 10.1016/j.indcrop.2019.05.070.

[9] Wang, D. W.; Lin, H. Y.; He, B.; Wu, F. X.; Chen, T.; Chen, Q.; Yang, W. C.; Yang, G. F. An Efficient One-Pot Synthesis of 2-(Aryloxyacetyl)Cyclohexane-1,3-Diones as Herbicidal 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors. *J. Agric. Food Chem.* **2016**, *64*, 8986–8993. DOI: 10.1021/acs.jafc.6b04110.

[10] Wang, D. W.; Lin, H. Y.; Cao, R. J.; Ming, Z. Z.; Chen, T.; Hao, G. F.; Yang, W. C.; Yang, G. F. Design, Synthesis and Herbicidal Activity of Novel Quinazoline-2,4-Diones as 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors. *Pest Manage. Sci.* **2015**, *71*, 1122–1132. DOI: 10.1002/ps.3894.

[11] Fu, Y.; Wang, K.; Wang, P.; Kang, J. X.; Gao, S.; Zhao, L. X.; Ye, F. Design, Synthesis, and Herbicidal Activity Evaluation of Novel Aryl-Naphthyl Methanone Derivatives. Front. Chem. **2019**, *7*, 2DOI: 10.3389/fchem.2019.00002.

[12] Wang, D. W.; Lin, H. Y.; Cao, R. J.; Yang, S. G.; Chen, Q.; Hao, G. F.; Yang, W. C.; Yang, G. F. Synthesis and Herbicidal Evaluation of Triketone-Containing quinazoline-2,4-diones. *J. Agric. Food Chem.* **2014**, *62*, 11786–11796. DOI: 10.1021/jf5048089.

[13] Hausman, N. E.; Singh, S.; Tranel, P. J.; Riechers, D. E.; Kaundun, S. S.; Polge, N. D.; Thomas, D. A.; Hager, A. G. Resistance to HPPD-Inhibiting Herbicides in a Population of Waterhemp (*Amaranthus Tuberculatus*) from Illinois, United States. *Pest Manage. Sci.* **2011**, *67*, 258–261. DOI: 10.1002/ps.2100.

[14] Cheng, L.; Zhao, W.; Shen, Z. H.; Xu, T. M.; Wu, H. K.; Peng, W. L.; Liu, X. H. Synthesis Nematocidal Activity and Docking Study of Novel Pyrazole-4-Carboxamide Derivatives against Meloidogyne incognita. *Lett. Drug Des. Discovery* **2019**, *16*, 29–35. DOI: 10.2174/1570180815666180326150827.

[15] Liu, X. H.; Zhao, W.; Shen, Z. H.; Xing, J. H.; Xu, T. M.; Peng, W. L. Synthesis, nematocidal activity and SAR study of novel difluoromethylpyrazole carboxamide derivatives containing flexible alkyl chain moieties. Eur. J. Med. Chem. **2017**, *125*, 881–889. DOI: 10.1016/j.ejmech.2016.10.017.

[16] Shen, Z. H.; Sun, Z. H.; Becnel, J. J.; Estep, A.; Wedge, D. E.; Tan, C. X.; Weng, J. Q.; Han, L.; Liu, X. H. Synthesis and Mosquiticidal Activity of Novel Hydrazone Containing Pyrimidine Derivatives against *Aedes aegypti*. *Lett. Drug Des. Discovery* **2018**, *15*, 951–956. DOI: 10.2174/1570180815666180102141640.

[17] Sun, N. B.; Zhai, Z. W.; Tong, J. Y.; Cai, P. P.; He, F. Y.; Han, L.; Liu, X. H. Synthesis, Crystal Structure and Fungicidal Activity of 3-(Difluoromethyl)-1-methyl-*N*-((2-(Trifluoromethyl)Phenyl) Carbamoyl)-1*H*-Pyrazole-4-Carboxamide. *Chin. J. Struct. Chem.* **2019**, *38*, 706–712. DOI: 10.14102/j.cnki.0254-5861.2011-2176.

[18] Fang, Y. M.; Zhang, R. R.; Shen, Z. H.; Tan, C. X.; Weng, J. Q.; Xu, T. M.; Liu, X. H.; Huang, H. Y.; Wu, H. K. Synthesis and Antifungal Activity of Some 6-*Tert*-Butyl-8-Chloro-2, 3-Dimethylquinolin-4-ol Derivatives against *Pyricularia Oryae*. *Lett. Drug Des. Discovery* **2018**, *15*, 1314–1318. DOI: 10.2174/1570180815666180313121735.

[19] Zhao, W.; Shen, Z. H.; Xing, J. H.; Xu, T. M.; Peng, W. L.; Liu, X. H. Synthesis, Characterization, Nematocidal Activity and Docking Study of Novel Pyrazole-4-Carboxamide Derivatives. *Chin. J. Struct. Chem.* **2017**, *36*, 423–428. DOI: 10.14102/j.cnki.0254-5861.2011-1353.

[20] Wang, H.; Zhai, Z. W.; Shi, Y. X.; Tan, C. X.; Weng, J. Q.; Han, L.; Li, B. J.; Liu, X. H. Novel Trifluoromethylpyrazole Acyl Urea Derivatives: Synthesis Crystal Structure Fungicidal Activity and Docking Study. *J. Mol. Struct.* **2018**, *1171*, 631–638. DOI: 10.1016/j.molstruc.2018.06.050.

[21] Liu, X. H.; Qiao, L.; Zhai, Z. W.; Cai, P. P.; Cantrell, L. C.; Tan, C. X.; Weng, J. Q.; Han, L.; Wu, H. K.; Liu, X. H. Novel 4-Pyrazole Carboxamide Derivatives Containing Flexible Chain Motif: Design, Synthesis and Antifungal Activity. *Pest Manage. Sci.* **2019**, *75*, 292–301. DOI: 10.1002/ps.3804.

[22] Zhao, W.; Shen, Z. H.; Xu, T. M.; Peng, W. L.; Liu, X. H. Synthesis Nematocidal Activity and Docking Study of Novel Chiral 1-(3-Chloropyridin-2-yl)-3-(Difluoromethyl)-1H-Pyrazole-4- Carboxamide Derivatives. *J. Heterocycl. Chem.* **2017**, *54*, 1751–1756. DOI: 10.1002/jhet.2753.

[23] Jin, T.; Zhai, Z. W.; Han, L.; Weng, J. Q.; Tan, C. X.; Liu, X. H. Synthesis, Crystal Structure, Docking and Antifungal Activity of a New Pyrazole Acylurea Compound. *Chin. J. Struct. Chem.* **2018**, *37*, 1259–1264. DOI: 10.14102/j.cnki.0254-5861.2011-1919.

[24] Liu, X. H.; Wang, Q.; Sun, Z. H.; Wedge, D. E.; Becnel, J. J.; Estep, A. S.; Tan, C. X.; Weng, J. Q. Synthesis and Insecticidal Activity of Novel Pyrimidine Derivatives Containing Urea Pharmacophore against Aedes aegypti. *Pest Manage. Sci.* **2017**, *73*, 953–959. DOI: 10.1002/ps.4370.

[25] Wang, H.; Zhai, Z. W.; Shi, Y. X.; Tan, C. X.; Weng, J. Q.; Han, L.; Li, B. J.; Liu, X. H. Novel Trifluoromethylpyrazole Acyl Thiourea Derivatives: Synthesis Antifungal Activity and Docking Study. *Lett. Drug Des. Discovery* **2019**, *16*, 785–791. DOI: 10.2174/1570180815666180704103047.

[26] Zhao, W.; Shen, Z. H.; Xing, J. H.; Xu, T. M.; Peng, W. L.; Liu, X. H. Synthesis and Nematocidal Activity of Novel Pyrazole Carboxamide Derivatives against *Meloidogyne incognita*. *Lett. Drug Des. Discovery* **2017**, *14*, 323–329. DOI: 10.2174/1570180813666160930164327.

[27] Zhao, W.; Shen, Z. H.; Xing, J. H.; Yang, G.; Xu, T. M.; Peng, W. L.; Liu, X. H. Synthesis and Nematocidal Activity of Novel 1-(3-Chloropyridin-2-yl)-3-(Trifluoromethyl)-1H- Pyrazole-4-Carboxamide Derivatives. *Chem. Pap.* **2017**, *71*, 921–928. DOI: 10.1007/s11696-016-0012-8.

[28] Zhao, W.; Xing, J. H.; Xu, T. M.; Peng, W. L.; Liu, X. H. Synthesis and *in Vivo* Nematocidal Evaluation of Novel N-Substituted 3-(Trifluoromethyl)-1*H*-Pyrazole-4-Carboxamide Derivatives. *Front. Chem. Sci. Eng.* **2017**, *11*, 363–368. DOI: 10.1007/s11705-016-1595-x.

[29] Liu, X. H.; Zhao, W.; Shen, Z. H.; Xing, J. H.; Yuan, J.; Yang, G.; Xu, T. M.; Peng, W. L. Synthesis, nematocidal activity and docking study of novel chiral 1-(3-chloropyridin-2-yl)-3-

(trifluoromethyl)-1H-pyrazole-4-carboxamide derivatives. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3626–3628. DOI: 10.1016/j.bmcl.2016.06.004.

[30] Liu, X. H.; Fang, Y. M.; Xie, F.; Zhang, R. R.; Shen, Z. H.; Tan, C. X.; Weng, J. Q.; Xu, T. M.; Huang, H. Y. Synthesis and in Vivo Fungicidal Activity of some new quinoline derivatives against rice blast. *Pest Manage. Sci.* **2017**, *73*, 1900–1907. DOI: 10.1002/ps.4556.

[31] Min, L. J.; Zhai, Z. W.; Shi, Y. X.; Han, L.; Tan, C. X.; Weng, J. Q.; Li, B. J.; Zhang, Y. G.; Liu, X. H. Synthesis and Biological Activity of Acyl Thiourea Containing Difluoromethyl Pyrazole Motif. *Phosphorus Sulfur Silicon Relat. Elem.* **2020**, *195*, 22–28. DOI: 10.1080/10426507.2019.1633530.

[32] Cheng, L.; Shen, Z. H.; Xu, T. M.; Tan, C. X.; Weng, J. Q.; Han, L.; Peng, W. L.; Liu, X. H. Synthesis and Nematocidal Activity of N-Substituted 3-Methyl-1H-Pyrazole-4-Carboxamide Derivatives against *Meloidogyne incognita*. *J. Heterocyclic Chem.* **2018**, *55*, 946–950. DOI: 10.1002/jhet.3123.

[33] Wang, B. L.; Wu, J.; Liu, Q. X.; Li, Y. H.; Song, H. B.; Li, Z. M. Synthesis, Structure, and Biological Activities of [5-(Arylthio/Sulfinyl/Sulfonyl)-3-Methyl-1-Phenyl-1H-Pyrazol-4-yl]-Arylmetha -Nones. *Phosphorus Sulfur Silicon Relat. Elem.* **2015**, *190*, 66–78. DOI: 10.1080/10426507.2014.919503.

[34] Evtushok, V. E.; Vorob'ev, A. Y. Synthesis of Pyrazolo- and [1,2,4]Triazolo-[1,5-a]Quinolin-9-Ols by Cycloaddition to 8-Hydroxyquinoline N-Imide. Chem. Heterocycl. Comp. **2019**, *55*, 229–234. DOI: 10.1007/s10593-019-02446-0.

[35] Balaneva, N. N.; Shestak, O. P.; Novikov, V. L. Trimethyl Orthoacetate as a Convenient Reagent for Selective Methylation of β-OH Groups of (Poly)Hydroxynaphthazarins. Russ. Chem. Bull. **2019**, *68*, 55–63. DOI: 10.1007/s11172-019-2415-5.

[36] Yang, C.; Pflugrath, J. W.; Camper, D. L.; Foster, M. L.; Pernich, D. J.; Walsh, T. A. Structural Basis for Herbicidal Inhibitor Selectivity Revealed by Comparison of Crystal Structures of Plant and Mammalian 4-Hydroxyphenylpyruvate Dioxygenases. *Biochemistry* **2004**, *43*, 10414–10423. DOI: 10.1021/bi049323o.

[37] Liu, X. H.; Zhai, Z. W.; Xu, X. Y.; Yang, M. Y.; Sun, Z. H.; Weng, J. Q.; Tan, C. X.; Chen, J. Facile and Efficient Synthesis and Herbicidal Activity Determination of Novel 1,2,4-triazolo[4,3-a]pyridin-3(2H)-one derivatives via microwave irradiation. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5524–5528. DOI: 10.1016/j.bmcl.2015.10.064.

[38] Liu, X. H.; Xu, X. Y.; Tan, C. X.; Weng, J. Q.; Xin, J. H.; Chen, J. Synthesis, crystal structure, herbicidal activities and 3D-QSAR study of some novel 1,2,4-triazolo[4,3-a]pyridine derivatives. *Pest Manage. Sci.* **2015**, *71*, 292–301. DOI: 10.1002/ps.3804.

[39] Liu, X.-H.; Yu, W.; Min, L.-J.; Wedge, D. E.; Tan, C.-X.; Weng, J.-Q.; Wu, H.-K.; Cantrell, C. L.; Bajsa-Hirschel, J.; Hua, X.-W.; Duke, S. O. Synthesis and Pesticidal Activities of New Quinoxalines. *J. Agric. Food Chem.* **2020**, *68*, 7324–7332. DOI: 10.1021/acs.jafc.0c01042.

[40] Fu, Y.; Liu, Y. X.; Yi, K. H.; Li, M. Q.; Li, J. Z.; Ye, F. Quantitative Structure Activity Relationship Studies and Molecular Dynamics Simulations of 2-(Aryloxyacetyl)Cyclohexane-1,3-Diones Derivatives as 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors. Front. Chem. **2019**, *7*, 556DOI: 10.3389/fchem.2019.00556.

[41] Jeschke, P. Propesticides and Their Use as agrochemicals. *Pest Manage. Sci.* **2016**, *72*, 210–225. DOI: 10.1002/ps.4170.