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Synthesis, Crystal Structure, and Herbicidal Activity of 3-(2-Chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole

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ABSTRACT A novel *N*-aroyl diketone derivative, 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole ($C_{14}H_{10}ClFN_2O_4$, M_r=324.69), was designed via fragment analysis and coupling strategy that led to highly potent and bio-selective herbicide. The title compound was prepared by a multistep-reaction, including nucleophilic addition and *N*-acylation reaction using 2-chloro-6-fluorobenzaldehyde as the starting materials in 83.4% yield. The product was characterized by infrared, proton nuclear magnetic resonance, Carbon-13 nuclear magnetic resonance, human resource management system, and X-ray diffraction. The title compound crystallized in the monoclinic system, space group $P2_1/n$ with a=10.7119(4) Å, b=17.5875(7) Å, c=11.5151(7) Å, β=100.927(2)°, Z=8, V=2870.0(2) Å^3, $F(000)$=1328, D_c=1.503 Mg/m^3, crystal size: 0.130 × 0.120 ×0.100 mm. The herbicidal activity was tested against the gramineous weed *Echinochloa crus-galli* and broadleaf *Abutilon juncea*.

KEYWORDS 3-(2-Chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole, Synthesis, Characterization, Single-crystal structure, Herbicidal activity.

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INTRODUCTION

The phytotoxicity and resistance problems occur continuously with the extensive use of herbicides. Thus, the exploration for novel herbicides is imminent, which is also an important measure for the pesticide industry to enter the prostate of the world. 4-Hydroxyphenylpyruvate dioxygenase (HPPD) is an important target enzyme for the development of green herbicides after the discovery of protoporphyrinogen oxidase and acetohydroxyacid synthase.[1] It catalyzes the conversion of 4-hydroxyphenylpyruvate acid to homogentisic acid (HGA), which plays a key role in the tyrosine degradation pathway.[2,3] HGA can be catalyzed into plastoquinone and tocopheryl in plant, and the former is an essential synthetic precursor for carotenoid which quenches sunlight-dependent singlet oxygen against degrading photosynthetic pigments.[4] The latter manifests a primary antioxidant effect in metabolism and firms the functions and structure of photosystem II.[5] Therefore, the inhibition of HPPD provokes unique bleaching symptoms, which is followed by necrosis and death. Based on the trait, varieties of HPPD-inhibiting compounds are designed, synthesized, and applied to control weed in the agricultural field.[6-8] To date, HPPD inhibitors, such as triketone derivatives, pyrazoles, isoxazoles, and others, have also been commercialized as herbicides and widely used in agriculture.[9-12] Most of the HPPD inhibitors possess a range of advantages, such as low application rate, outstanding crop selectivity, low toxicity, broad-spectrum weed control, and environmental safety. In continuation of our efforts to find novel HPPD-inhibiting compounds,[13-15] herein, a novel *N*-aroyl diketone derivative was synthesized and characterized by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), Carbon-13 nuclear magnetic resonance (^{13}C NMR), and human resource management system

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(HRMS). The single-crystal structure was confirmed by X-ray diffraction. The bioactivity evaluation showed that the target compound exhibited good herbicidal activity toward the test weeds at 0.045 and 0.090 mmol/m^2, respectively.

RESULTS AND DISCUSSION

Synthesis

The synthetic route for the title compound, 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole, was depicted in **Scheme 1**. 2-Chloro-6-fluorobenzaldehyde **1** on the treatment with a solution containing hydroxylamine hydrochloride, 10% aq. Na_2CO_3 and EtOH yielded 2-chloro-6-fluorobenzaldehyde oxime **2**. A mixture of compound **2**, pyridine, and *N*-chlorosuccinimide was stirred to obtain 2-chloro-6-fluoro-*N*-hydroxybenzimidoyl chloride **3**. Compound **3** was added dropwise to a solution including methyl acetoacetate, Et_3N, and EtOH and stirred to give 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid **4**. Compound **4** and $SOCl_2$ were refluxed in toluene to get 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride **5**.[16] Compound **5**, NaOH, and oxazolidine-2-one was stirred in acetone to get the final product, 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole **6**.[17]

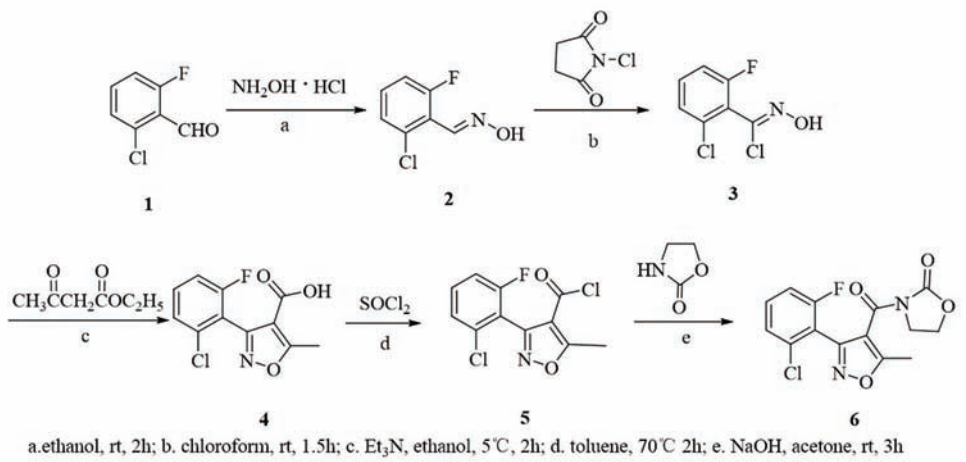
Spectroscopic studies

The title compound was characterized through IR, ^{1}H NMR, ^{13}C NMR, and HRMS. IR spectrum confirmed the presence of two carbonyl groups at 1764 and 1668 cm^{-1} and C=C at 1602 cm^{-1}. The ^{1}H NMR data indicate the possible structure. The signals at δ 7.40-7.12 ppm correspond to the three hydrogen atoms of benzene ring. The signals at δ 4.28-4.02 ppm belong to the two methylenes of oxazolidone. The signal observed at δ 2.66 ppm is characteristic of the methyl group of the isoxazole. The ^{13}C NMR data show that the signals at 161.38 ppm and 152.30 ppm belong to two C=O groups. The signals at δ 159.53-114.62 ppm (not including 154.39 ppm) relate to the six carbons of the benzene ring. The signals at δ 173.55, 154.39, and 112.22 ppm correspond to three carbons of the isoxazole ring. The signals at δ 62.45 and 43.16 ppm relates two carbons in the oxazolidone ring, which connect with N and O atom, respectively. The signal observed at δ 12.81 ppm is characteristic of methyl of the isoxazole. The compound is further confirmed by the positive ion source of ESI-MS to determine the molecular weight of the compound. The excimer ion peak is 325.0386 and the theoretical value is 325.0386, which is in line with the molecular weight of the compound within the allowable error range (−0.1 ppm error).

Crystal structure studies

The target compound **6** was dissolved in ethyl acetate to form an almost saturated solution and then filtered to obtain the filtrate. Under darkness, the crystal appeared in the progress of slow volatilization of ethyl acetate. The block-shaped colorless single crystals of the title compound were obtained by slow diffusion in ethyl acetate. The crystal with dimensions of 0.130 × 0.120 × 0.100 mm was mounted on a Bruker AXSII CCD area-detector diffractometer using graphite monochromator Mo *K*α radiation (λ = 0.71073 Å) at 300(2) K in the range of $2.674° \leq \theta \leq 28.282°$. Selected crystallographic and experimental details are summarized in **Table 1**. The structure was solved by direct methods using *SHELXL-2014/7*, and refined by full-matrix least squares on F^2, *SHELXL-2014/7*. Symmetry equivalent reflections were used to optimize crystal shape and size. H atoms were then constrained to an ideal geometry, with C-H distances of 0.93–0.98 Å. The U_{iso} values were set to $1.2U_{eq}$(C). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1998499. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [www.ccdc.cam.ac.uk/data_request/cif].

The molecular structure of the title compound with atom-numbering is shown in **Figure 1**. Selected bond lengths and bond angles of the title compound are listed in **Table 2**. According to X-ray analysis, the title compound crystallized in the monoclinic space group $P2_1/n$. The bond length of C11-N2 (1.387(5) Å) and C12-N2 (1.387(5) Å) is shorter than the typical C-N bond (1.49 Å)[17] due to π-*p*-π conjugation formed of the corresponding two carbonyls (C11-O2, C12-O4) with lone pair electrons on N2 atom.



Scheme 1: Route for synthesis of the title compound

The oxazolidone ring is like an envelope conformation with the torsion angle of −22.75°. The isoxazole ring adopts an almost planar with a torsion angle of −0.58°. The molecule is not co-planar because the dihedral angles between the isoxazole ring A, the benzene ring B, and the oxazolidone ring C are 59.51° (A/B), 54.09° (A/C), and 33.08° (B/C). The Van Der Waals forces connect molecules into a one-dimensional chain structure, as shown in **Figure 2**. No significant π-π packing and hydrogen-bond interactions are found between the molecules.

Herbicidal activity

The herbicidal activity of the title compound was evaluated against the gramineous weed *Echinochloa crus-galli* (EC) and broadleaf weed *Abutilon juncea* (AJ) in the greenhouse environment. The chlorophyll levels were tested after spraying with compound **6** and mesotrione. The treated grass displayed unique bleaching symptoms followed by necrosis after 15 days. The herbicidal activity was basically consistent with the levels of chlorophyll a (C_a) and chlorophyll b (C_b). As shown in **Table 3**, the target compound exhibited similar herbicidal activity as mesotrione toward the test weeds at 0.045 and 0.090 mmol/m^2, respectively. The aromatic ring(s) moiety in herbicide structure can form π-π interaction with the amino residue of *Arabidopsis thaliana* HPPD enzyme in the active site. The π electron cloud density of pyridine and isoxazole is lower, which made the π-π interaction with amino residue was not as stable as the benzene of mesotrione in the active pocket. Moreover, the pyridine and isoxazole are alkalescent, and the pKa of the inhibitors is also increased and made the inhibition decreased.

Table 1: Crystal data of the title compound

Item	Value
CCDC	1998499
Empirical formula	$C_{14}H_{10}ClFN_2O_4$
Formula weight	324.69
Temperature	300 (2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a=10.7119 (4) Å α=90°
	b=17.5875 (7) Å β=100.927 (2)°
	c=15.5151 (7) Å γ=90°
Volume	2870.0 (2) Å^3
Z	8
Calculated density	1.503 Mg/m^3
Absorption coefficient	0.97 mm^{-1}
F (000)	1328
Crystal size	0.130×0.120×0.100 mm
Theta range for data collection	2.674°–28.282°
Limiting indices	$-14\leq h\leq 142$, $-23\leq k\leq 23$, $-20\leq l\leq 20$
Reflections collected/unique	5848/7113 [R (int) = 0.0355]
Completeness to theta=25.242	99.8%
Absorption correction	Semi-empirical from equivalents
Absorption correction T_{min} and T_{max}	0.971 and 0.962

EXPERIMENTAL

Materials and instrumentation

All reagents were of analytical grade. The melting point was measured on a Shanghai INESA melting point instrument (WRS-3) (INESA Company, CHN) and are uncorrected. The IR spectra were recorded in KBr on ALPHA-T (Bruker Company, DEU). The ^{1}H-NMR and ^{13}C-NMR spectrum was recorded on Bruker AV-400 (Bruker Company, DEU) spectrometer using $CDCl_3$ as a solvent and TMS as an internal

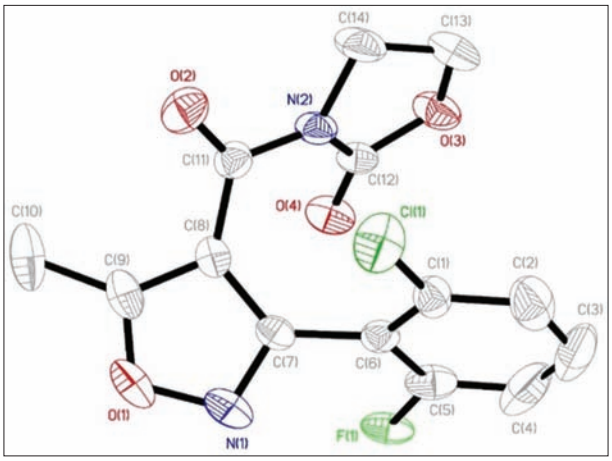


Figure 1: Structure of the title compound

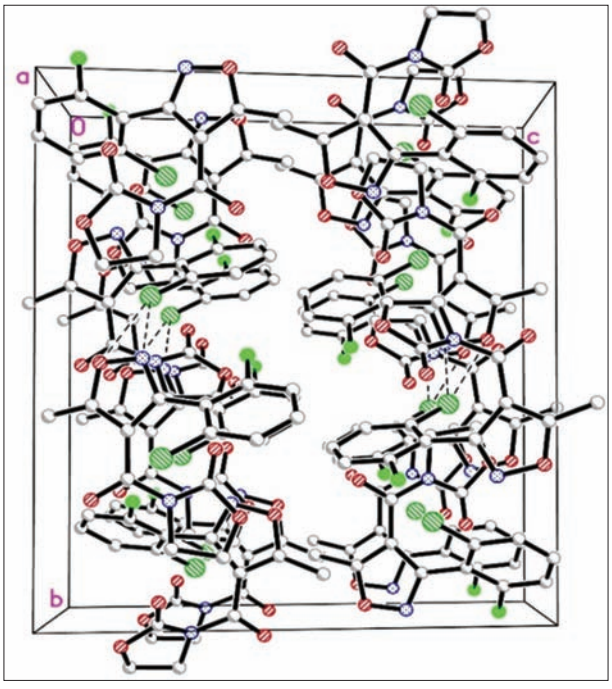


Figure 2: Packing of the title compound

Table 2: Bond lengths (Å) and angles (°) of the title compound

Bond	Lengths(Å)	Bond	Lengths(Å)	Bond	Lengths(Å)
C1-C6	1.374 (6)	C1-C2	1.403 (7)	C1-Cl1	1.611 (5)
C2-C3	1.434 (11)	C3-C4	1.330 (12)	C4-C5	1.325 (9)
C5-F1	1.465 (6)	C5-C6	1.405 (6)	C6-C7	1.477 (5)
C7-C8	1.427 (5)	C7-N1	1.308 (5)	C8-C9	1.364 (5)
C8-C11	1.468 (5)	C9-C10	1.482 (7)	C9-O1	1.333 (6)
C11-O2	1.209 (5)	C11-N2	1.387 (5)	C12-O3	1.337 (5)
C12-O4	1.184 (4)	C12-N2	1.387 (5)	C13-O3	1.450 (6)
C13-C14	1.493 (7)	C14-N2	1.456 (5)	N1-O1	1.404 (5)
N3-O5	1.402 (4)				
Bond	Angles(°)	Bond	Angles(°)	Bond	Angles(°)
C6-C1-C2	122.0 (5)	C6-C1-Cl1	119.2 (3)	C2-C1-Cl1	118.7 (5)
C1-C2-C3	116.3 (6)	C2-C3-C4	122.1 (6)	C3-C4-C5	119.0 (6)
C4-C5-C6	124.6 (6)	C4-C5-F1	111.5 (5)	C6-C5-F1	123.8 (4)
C1-C6-C5	116.0 (4)	C1-C6-C7	122.2 (3)	C5-C6-C7	121.7 (4)
N1-C7-C6	118.2 (3)	N1-C7-C8	111.6 (3)	C6-C7-C8	130.2 (3)
C7-C8-C9	104.0 (4)	C9-C8-C11	124.9 (4)	C7-C8-C11	130.5 (3)
O1-C9-C8	109.3 (4)	O1-C9-C10	116.7 (4)	C8-C9-C10	134.0 (5)
O2-C11-N2	119.7 (4)	O2-C11-C8	122.2 (4)	N2-C11-C8	117.8 (3)
O3-C12-O4	123.7 (3)	O3-C12-N2	107.9 (3)	O4-C12-N2	128.5 (3)
O3-C13-C14	104.5 (4)	N2-C14-C13	100.6 (3)	C9-N1-O1	110.0 (3)
C7-N1-O1	105.1 (3)	C11-N2-C14	121.9 (3)	C12-N2-C11	126.5 (3)
C12-N2-C14	110.6 (3)				

Table 3: The chlorophyll content of EC and AJ treated with target compound*

Compound	EC		AJ	
	C_a (mg/g)	C_b (mg/g)	C_a (mg/g)	C_b (mg/g)
CK	1.838±0.027	0.994±0.015	1.905±0.037	1.372±0.046
mesotrione	0.738±0.013	0.260±0.006	0.683±0.013	0.345±0.021
6	0.836±0.005	0.336±0.012	0.847±0.009	0.456±0.019

*Data are presented as the mean±standard deviation of triplicate experiments. EC: *Echinochloa crus-galli*, AJ: *Abutilon juncea*

standard. High-resolution mass spectrometry (HRMS) data were obtained by Fourier transform ion cyclotron resonance mass spectrometry (Bruker Company, DEU).

Synthesis of 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole 6

All reactions were monitored by thin-layer chromatography. 2-Chloro-6-fluorobenzaldehyde **1** was dissolved in EtOH (50 mL) containing hydroxylamine hydrochloride (94 mmol) and 10% aq. Na_2CO_3 (50 mL). The mixture was stirred for 2 h at room temperature and afforded 2-chloro-6-fluorobenzaldehyde oxime **2** in 97.0% yield. A mixture of compound **2** (90 mmol), pyridine (135 mmol), and *N*-chlorosuccinimide (90 mmol) was stirred at room temperature for 1.5 h in 30 mL $CHCl_3$. The solvent was removed under vacuum to obtain 2-chloro-6-fluoro-*N*-hydroxybenzimidoyl chloride **3** in 87.0% yield. Compound **3** (75 mmol) was added dropwise to a solution including methyl acetoacetate (80 mmol), Et_3N (85 mmol), and EtOH (50 mL) and stirred for 12 h at 5 °C. The product was recrystallized from hexane/ethyl acetate to obtain white solid, 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid **4** in yield 72.0%. Compound **4** (40 mmol) and $SOCl_2$ (10 mL) were mixed in toluene (15 mL) and refluxed for 2 h at 70 °C. After cooling to room temperature, the mixture was concentrated under vacuum to obtain 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride **5**. Compound **5** (15 mmol) was stirred with oxazolidine-2-one (12 mmol) for 3 h at room temperature, NaOH was used (15 mmol) as attaching acid agent in acetone (45 mL). The product was purified on silica gel by column chromatography [*V*(EtOAc):*V*(petroleum ether) =1:3] to obtain 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole **6**. Yield: 83.4%, white solid, m.p. 144.2–145.5°C. IR (KBr, cm^{-1}) ν: 3069-2900 (-CH_3, -CH_2-, =CH), 1764-1668 (C=O), 1560-1449 (Ph, C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.40-7.12 (m, 3H, Ph-H), 4.28-4.02 (m, 4H, O-$(CH_2)_2$-N), 2.66 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:173.55,

161.38, 159.53, 154.39, 152.30, 134.64, 134.60, 131.87, 131.77, 125.40, 125.37, 114.84, 114.62, 112.22, 62.45, 43.16, 12.81. HRMS (ESI): calculated for $C_{14}H_{10}ClFN_2O_4$ $[M+H]^+$325.0386, found 325.0386.

Determination of herbicidal activity

The synthesized compound was evaluated against gramineous weed EC and broadleaf AJ by postemergence application.[18] The commercial herbicide mesotrione was used as control. The test compounds were prepared by using dimethyl sulfoxide (DMSO) as the solvent and Tween 80 (0.1 g/mL) as the emulsifier. The solutions were diluted with water to the desired concentration and sprayed onto the plants in a greenhouse. Clay soil was Mollisols−Cryolls clay loam-type with a pH of 7.3. Approximately 15 seeds of EC and AJ were planted in pots, covered with soil to a thickness of 1.5 cm, and grown at the temperature of 18−28 °C in a greenhouse, and air humidity was 78%. Broadleaf weeds were treated at the two-leaf stage, and monocotyledon weeds were treated at the one-leaf stage. When the weeds (EC and AJ) grew approximately to the one-leaf and two-leaf stages, they were treated by the inhibitors at the dosage of 0.045 and 0.090 mmol/m^2 (approximately 150 and 300 g of ai/ha), respectively. The solvent control group weeds were treated by water. After 15 days of treatment by inhibitors, the chlorophyll levels were surveyed and evaluated, with three duplicates per experiment. A bulk extract of chlorophyll from the grass leaves was made in semi-darkness using the formulation [*V*(acetone):*V*(ethanol):*V*(H_2O)=16:19:5]. The contents of C_a and C_b were determined as the following.[19,20]

$$C_a = A_{663} \times 12.72 – A_{645} \times V / (W \times 100)$$

$$C_b = A_{645} \times 22.88 – A_{663} \times V / (W \times 100)$$

where C_a and C_b are the contents of chlorophyll a and chlorophyll b (mg/g), respectively, A_{645} and A_{663} are optical densities at 645 and 663 nm, respectively, V is the constant volume (mL), and W is the weight of the sample (g).

CONCLUSION

In summary, the title compound, 3-(2-chloro-6-fluorophenyl)-4-(2-oxooxazolidine-3-carbonyl)-5-methylisoxazole, as a novel HPPD inhibitor was designed and synthesized in a good yield. The synthetic approach is efficient, fast, and facile. The structure was characterized by IR, ^{1}H-NMR ^{13}C-NMR, HRMS, and X-ray diffraction. Bioactivity evaluation indicated good herbicidal activity toward EC and AJ.

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