Microwave-assistant Syntheses, Crystal Structures and Safener Activities of Two Substituted Phenyl Isoxazole Derivatives①

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ABSTRACT Two novel substituted phenyl isoxazole benzoxazine formamide derivatives were designed and synthesized with substituted *o*-aminophenol, 1,2-dibromoethane and different phenyl substituted isoxazole formyl chloride as the raw materials *via* microwave assistant synthesis. The target compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. Both single-crystal structures were further determined by X-ray diffraction. 3-(2′-Chloro-6′-fluoro-phenyl)-4-(2′,3′-dihydro-1′,4′-benzoxazine)-5-methyl-isoxazole formamide (**4a**) crystallizes in orthorhombic system, $P2_1$ space group with a = 8.9414(18), b = 10.834(2), c = 17.706(4) Å, V = 1715.1(6) Å^3, D_c = 1.444 Mg/m^3, Z = 4, F(000) = 768, μ(Mo$K\alpha$) = 0.255 mm^{-1}, R = 0.0406 and wR = 0.1171. 3-Phenyl-4-(6-methyl-2′,3′-dihydro-1′,4′-benzoxazine)-5-methyl-isoxazole formamide (**4b**) is of triclinic system, space group $P\bar{1}$ with a = 7.7659(16), b = 8.3626(17), c = 13.484(3) Å, α = 76.04(3)°, β = 100.63(3)°, γ = 82.01(3)°, V = 841.6(3) Å^3, D_c = 1.319 Mg/m^3, Z = 2, F(000) = 352, μ(Mo$K\alpha$) = 0.090 mm^{-1}, R = 0.0672 and wR = 0.2671. Both crystals are packed through C–H···O hydrogen bonding interaction. There is C–H···F hydrogen bond between **4a** molecules, and C–H···N between **4b** molecules. Bioassay results showed that compounds **4a** and **4b** exhibited detoxification on maize and restored maize growth index.

Keywords: isoxazole benzoxazine formamide, microwave-assistant synthesis, single-crystal structure, safener activity; DOI: 10.14102/j.cnki.0254–5861.2011–3142

1 INTRODUCTION

With the expansion of herbicides application, the safety issues have become serious, especially the excessive use of herbicides or damage to sensitive crops[1]. Herbicide safeners are regarded as a very effective way to solve these problems[2, 3]. In recent years, some safeners have been subsequently commercialized for different types of herbicides[4], such as isoxadifen-ethyl[5] and mefenpyr-diethyl[6].

Isoxadifen-ethyl, as a new safener for sulfonylurea herbicides, was launched by Bayer Crop Science AG in 2002[7]. It effectively alleviates the phytotoxicity of nicosulfuron to maize and increases the metabolism of nicosulfuron through non-cytochrome P450-catalyzed routes[8]. Andreas gave the mechanism of exogenous detoxification induced by isoxadifen-ethyl through multiple signaling channels in plants[9].

Benoxacor, which has been commercialized by Ciba-Geigy, is widely used to protect maize and sorghum from metolachlor and increases crops resistance to herbicides[10, 11]. As an effective ingredient of chloroa- cetamide herbicide safener, it usually induces the hydroxylation of primi- sulfuron-methyl and increases glutathione (GSH) conjugation of metolachlor, metazachlor and acetochlor to achieve the detoxification effect[12-14].

As a part of our ongoing interest in nitrogen-containing heterocyclic herbicide safeners[15-19], two novel substituted phenyl isoxazole derivatives were designed *via* active sub-units combination with isoxadifen-ethyl and benoxacor (Fig. 1). The synthesis was carried out under microwave irradiation (Scheme 1)[20-24]. The single crystal structure was confirmed by X-ray diffraction analysis. Biological activities as safener of the target compounds were evaluated on maize *in vivo*.

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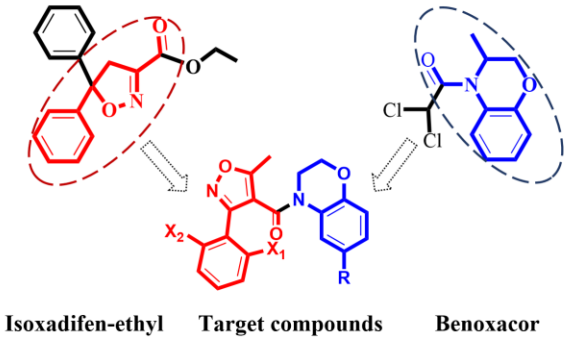


Fig. 1. Skeleton structure of the template compound

2 EXPERIMENTAL

2. 1 Materials and characterization

The chemicals involved in experiment were analytically pure and applied without purification. The melting points were obtained on a Beijing Taike point instrument (X-4) and uncorrected. IR spectra were measured on a Bruker ALPHA-T spectrometer (in KBr pallets). The NMR spectrum was collected on a Bruker AV-400 spectrometer with $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectrometry (HRMS) data were recorded using a Varian QFT-ESI instrument. Microwave irradiation was carried out with XH100A focused microwave. Crystallographic data of the compound were measured on a Rigaku R-AXIS RAPID area-detector diffractometer.

2. 2 Preparation of benzoxazine derivatives (3)

o-Aminophenol **1** (15 mmol), DMSO (40 mL) and K_2CO_3 (5 equivalents, 20 mmol) were added to 1,2-dibromoethane **2** (22 mmol) in sequence. The reaction conditions were optimized by a preliminary test (800 W, 85 ℃, and 20 min)[25]. When the reaction was completed (monitored by TLC), the solution was cooled to room temperature and filtered. The mixture was extracted with ethyl acetate and the organic phase was dried. Then the solvent was removed by rotary evaporation. The crude product was purified on silica gel by column chromatography (*V*(ethyl acetate):*V*(petroleum ether) = 1:9) to obtain compound **3**.

The infrared spectrum analysis of intermediates **3a** and **3b** shows that the absorption peaks at 3383 and 3356 cm^{-1} are the N–H stretching vibration peak of the benzoxazine ring, which indicates that the synthesis of the intermediate is correct.

2. 3 Preparation of phenyl isoxazole benzoxazine formamide derivative (4)

Compound **3** (0.05 mol), substituted phenyl isoxazole carbonyl chloride (0.06 mol) and anhydrous K_2CO_3 (5 *eq*., 0.38 g) were mixed in toluene (40 mL). Then, the mixture was placed in a microwave catalytic synthesizer (800 W, 40 ℃, and 25 min)[26]. After the reaction was completed, the solution was cooled to room temperature and filtered. The crude product was purified on silica gel by column chromatography (*V*(ethyl acetate):*V*(petroleum ether) = 1:6) to obtain the target compounds **4**.

3-(2′-Chloro-6′-fluoro-phenyl)-4-(2′,3′-dihydro-1′,4′-benzoxazine)-5-methyl-isoxazole formamide (**4a**) White crystal; m.p. 181.5～182.2 ℃; yield, 43.2%; IR (KBr, cm^{-1}) *v*: 3053～2870 (C–H), 1631 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 7.30～6.66 (m, 7H, Ar–H), 4.27～3.85 (m, 4H, O–CH_2CH_2–N), 2.58 (s, 3H, -CH_3); ^{13}C NMR (100MHz, $CDCl_3$, ppm) *δ*: 172.31, 161.59, 153.92, 145.94, 134.34, 131.71, 131.62, 126.10, 125.50, 125.47, 122.34, 120.78, 117.16, 114.72, 114.50, 113.46, 66.06, 41.04, 12.45; HRMS (ESI): $C_{19}H_{14}ClFN_2O_3$ calculated for $[M+H]^+$ 373.0750, found 373.0754.

3-Phenyl-4-(6-methyl-2′,3′-dihydro-1′,4′-benzoxazine)-5-methyl-isoxazole formamide (**4b**) White crystal; m.p. 125.8～127.6 ℃; yield, 75.5%; IR (KBr, cm^{-1}) *v*: 3004～2860 (C–H), 1638 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 7.40～7.34 (m, 4H, Ar–H), 7.29～6.46 (m, 4H, Ar–H), 4.15～3.57 (m, 4H, O–CH_2CH_2–N), 2.56 (s, 3H, -CH_3), 2.17 (s, 3H, -CH_3), ^{13}C NMR (100MHz, $CDCl_3$, ppm) *δ*: 171.18, 160.64, 160.61, 144.24, 129.99, 129.96, 129.42, 128.86, 128.21, 127.37, 127.37, 127.01, 127.01, 123.22, 112.12, 111.76, 65.61, 20.70, 12.08, 12.08; HRMS (ESI): $C_{20}H_{18}N_2O_3$ calculated for $[M+H]^+$ 337.1210, found 337.1213.

2. 4 Crystal structure determination

Crystals (**4a** and **4b**) suitable for X-ray analysis were obtained by the slow evaporation method with ethyl acetate as solvent at room temperature. The X-ray data were collected on a Rigaku RAXIS-RAPID diffractometer (Japan) with Mo*Kα*

radiation (λ = 0.71073 Å) at 293(2) K. The structure was solved by direct methods using SHELXS-97[26] and refined with SHELXL-97[27]. The hydrogen atoms were included in calculated positions, and refined in terms of riding model (U_{iso}(H) = 1.5U_{eq}(C) for the atoms of methyl and U_{iso}(H) = 1.2U_{eq}(C) for others). Selected bond lengths and bond angles are listed in Table 1, and hydrogen bond parameters are summarized in Table 2.

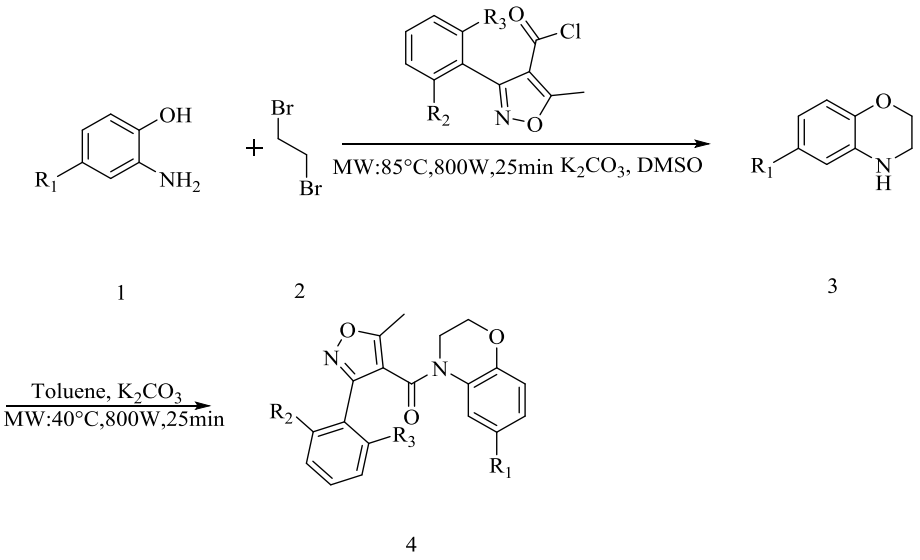
Table 1. Selected Bond Lengths (Å) and Bond Angles (°) for the Crystals of 4a and 4b

4a				4b			
Bond	Dist.	Bond	Dist.	Bond	Dist.	Bond	Dist.
C(1)–C(2)	1.373(4)	C(12)–N(2)	1.422(2)	C(1)–C(2)	1.399(6)	C(12)–N(2)	1.478(4)
C(1)–C(6)	1.391(3)	C(12)–C(13)	1.387(2)	C(1)–C(6)	1.370(5)	C(12)–C(13)	1.487(5)
C(1)–F(1)	1.386(3)	C(12)–C(17)	1.396(2)	C(2)–C(3)	1.384(6)	C(13)–O(3)	1.430(4)
C(2)–C(3)	1.371(5)	C(13)–C(14)	1.385(3)	C(3)–C(4)	1.375(7)	C(14)–O(3)	1.370(4)
C(3)–C(4)	1.366(4)	C(14)–C(15)	1.382(3)	C(4)–C(5)	1.399(6)	C(14)–C(15)	1.383(5)
C(4)–C(5)	1.379(4)	C(15)–C(16)	1.375(3)	C(5)–C(6)	1.404(5)	C(14)–C(19)	1.398(5)
C(5)–C(6)	1.396(3)	C(16)–C(17)	1.388(3)	C(6)–C(7)	1.471(5)	C(15)–C(16)	1.381(5)
C(5)–Cl(1)	1.707(2)	C(17)–O(3)	1.367(2)	C(7)–N(1)	1.312(4)	C(16)–C(17)	1.405(5)
C(6)–C(7)	1.472(3)	C(18)–O(3)	1.426(3)	C(7)–C(8)	1.436(5)	C(17)–C(18)	1.383(5)
C(8)–O(1)	1.348(2)	C(18)–C(19)	1.501(4)	C(8)–C(9)	1.362(5)	C(17)–C(20)	1.509(5)
C(8)–C(9)	1.355(3)	C(19)–N(2)	1.467(2)	C(9)–O(1)	1.345(4)	C(18)–C(19)	1.404(5)
C(9)–C(11)	1.485(2)	N(1)–O(1)	1.409(3)	C(9)–C(10)	1.469(6)	C(19)–N(2)	1.440(4)
C(11)–O(2)	1.225(2)	C(7)–N(1)	1.310(2)	C(11)–O(2)	1.231(4)	N(1)–O(1)	1.416(4)
C(11)–N(2)	1.359(2)	C(7)–N(9)	1.424(2)	C(11)–N(2)	1.351(4)		
Angle	(°)	Angle	(°)	Angle	(°)	Angle	(°)
C(6)–C(1)–C(2)	123.3(2)	O(2)–C(11)–C(9)	119.58(16)	C(6)–C(1)–C(2)	121.7(4)	C(18)–C(17)–C(16)	118.0(3)
C(2)–C(1)–F(1)	117.2(2)	N(2)–C(11)–C(9)	118.32(16)	C(3)–C(2)–C(1)	118.6(4)	C(18)–C(17)–C(20)	121.0(4)
F(1)–C(1)–C(6)	119.49(19)	C(13)–C(12)–C(17)	118.32(16)	C(4)–C(3)–C(2)	120.2(4)	C(16)–C(17)–C(20)	121.1(3)
C(3)–C(2)–C(1)	118.6(2)	C(13)–C(12)–N(2)	123.14(16)	C(3)–C(4)–C(5)	121.5(4)	C(17)–C(18)–C(19)	122.3(3)
C(4)–C(3)–C(2)	120.8(2)	C(17)–C(12)–N(2)	118.28(15)	C(4)–C(5)–C(6)	118.2(4)	C(14)–C(19)–C(18)	118.3(3)
C(3)–C(4)–C(5)	119.6(3)	C(14)–C(13)–C(12)	121.22(17)	C(1)–C(6)–C(5)	119.7(4)	C(14)–C(19)–N(2)	119.1(3)
C(4)–C(5)–C(6)	122.0(2)	C(15)–C(14)–C(13)	119.53(19)	C(1)–C(6)–C(7)	112.9(3)	C(18)–C(19)–N(2)	122.5(3)
C(4)–C(5)–Cl(1)	119.2(2)	C(16)–C(15)–C(14)	120.24(19)	C(5)–C(6)–C(7)	118.4(3)	C(7)–N(1)–O(1)	105.9(3)
C(6)–C(5)–Cl(1)	118.80(16)	C(15)–C(16)–C(17)	120.17(19)	N(1)–C(7)–C(8)	111.0(3)	C(11)–N(2)–C(19)	123.8(3)
C(1)–C(6)–C(5)	115.6(2)	O(3)–C(17)–C(16)	116.09(17)	N(1)–C(7)–C(6)	119.5(3)	C(11)–N(2)–C(12)	122.7(3)
C(1)–C(6)–C(7)	121.83(18)	O(3)–C(17)–C(12)	123.44(17)	C(8)–C(7)–C(6)	129.3(3)	C(19)–N(2)–C(12)	112.6(3)
C(5)–C(6)–C(7)	122.55(17)	C(16)–C(17)–C(12)	120.37(18)	C(9)–C(8)–C(7)	104.3(3)	C(9)–O(1)–N(1)	108.8(3)
N(1)–C(7)–C(9)	111.37(17)	O(3)–C(18)–C(19)	112.1(2)	C(9)–C(8)–C(11)	128.0(3)	C(14)–O(3)–C(13)	115.1(3)
N(1)–C(7)–C(6)	120.25(16)	N(2)–C(19)–C(18)	107.60(17)	C(7)–C(8)–C(11)	126.4(3)	N(2)–C(12)–C(13)	100.3(3)
C(9)–C(7)–C(6)	128.37(15)	C(7)–N(1)–O(1)	105.45(16)	O(1)–C(9)–C(8)	109.9(3)	O(3)–C(13)–C(12)	104.2(3)
O(1)–C(8)–C(9)	109.27(18)	C(11)–N(2)–C(12)	127.09(14)	O(1)–C(9)–C(10)	115.6(3)	O(3)–C(14)–N(2)	101.6(3)
O(1)–C(8)–C(10)	117.62(18)	C(11)–N(2)–C(19)	118.85(15)	C(8)–C(9)–C(10)	134.6(3)	O(3)–C(14)–C(16)	108.4(3)
C(9)–C(8)–C(10)	133.1(2)	C(12)–N(2)–C(19)	113.99(14)	O(2)–C(11)–N(2)	123.3(3)	N(2)–C(14)–C(16)	113.1(3)
C(8)–C(9)–C(7)	104.71(15)	C(8)–O(1)–N(1)	109.19(14)	O(2)–C(11)–C(8)	118.8(3)	O(3)–C(14)–C(15)	110.2(3)
C(8)–C(9)–C(11)	125.46(17)	C(17)–O(3)–C(18)	116.17(15)	N(2)–C(11)–C(8)	117.9(3)	N(2)–C(14)–C(15)	111.1(3)
C(7)–C(9)–C(11)	121.56(15)			N(2)–C(12)–C(13)	110.7(3)	C(7)–N(1)–O(1)	104.8(2)
				O(3)–C(13)–C(12)	109.8(3)	C(11)–N(2)–C(12)	126.2(3)
				O(3)–C(14)–C(15)	116.2(3)	C(11)–N(2)–C(14)	122.3(2)
				O(3)–C(14)–C(19)	123.9(3)	C(12)–N(2)–C(14)	110.7(3)
				C(15)–C(14)–C(19)	119.9(3)	C(9)–O(1)–N(1)	109.6(2)
				C(16)–C(15)–C(14)	121.0(4)	C(13)–O(3)–C(14)	107.4(3)
				C(15)–C(16)–C(17)	120.5(3)		

Table 2. Hydrogen Bond Parameters in the Structures of 4a and 4b

	D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
4a	C(11)–H(10A)···O(2)[a]	0.96	2.30	1.225(2)	169
	C(10)–H(10A)···F(1)[b]	0.96	2.60	1.386(3)	143
4b	C(3)–H(3)···O(2)[c]	0.93	2.70	3.463(21)	148
	C(12)–H(12B)···N(1)[d]	0.97	2.65	3.4080(48)	135

Symmetry codes: (a) *x*–0.5,1.5–*x*, –*z*; (b) 1–*x*, 0.5+*y*, 0.5–*z*; (c) 1–*x*, 2–*y*, 2–*z*; (d) 1–*x*, 1–*y*, 1–*z*



1 2 3

4

4a: R_1=H, R_2=Cl, R_3=F; 4b: R_1=CH_3, R_2=H, R_3=H

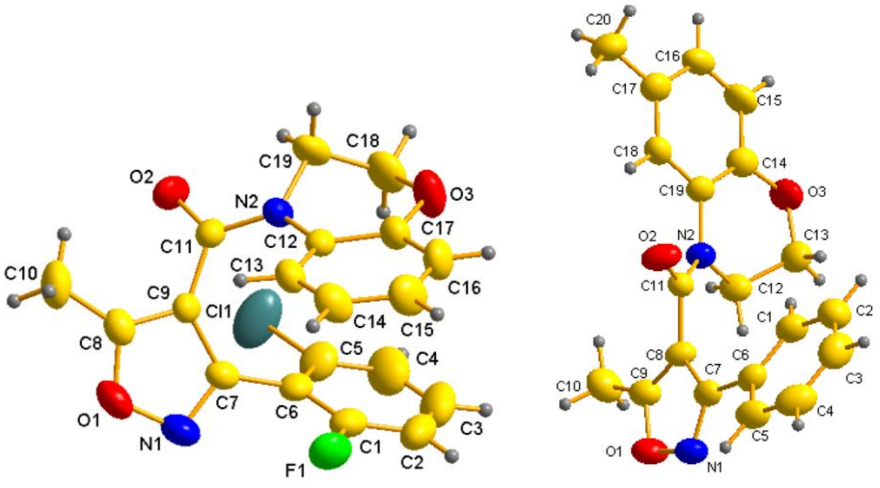
Scheme 1. Synthetic route of compounds 4a and 4b

2. 5 Biological activity assay

The title compounds (10 mg) were completely dissolved in ethanol (2 mL), and a small amount of emulsifier was added to make the solution uniform and transparent. The solution was prepared according to the principle of gradual dilution. Maize seeds (Dongnong 259) were soaked in solution (containing compounds 25 μM) overnight, and the control was treated with water. The seeds were then induced to germinate, and sown in paper cups with seven per cup with the soil mixed with acetochlor (20 mg/kg). They were incubated in an incubator (12 h of light, 26.5 ± 1 ℃, 75% relative humidity). The root length, plant height, root fresh weight and plant fresh weight of maize were measured after 7 days[28, 29].

3 RESULTS AND DISCUSSION

The molecular structures of compounds **4a** and **4b** with atom-numbering are shown in Fig. 2. The crystal structure of **4a** crystallizes in orthorhombic space group $P2_1$, and **4b** in triclinic space group $P\bar{1}$.

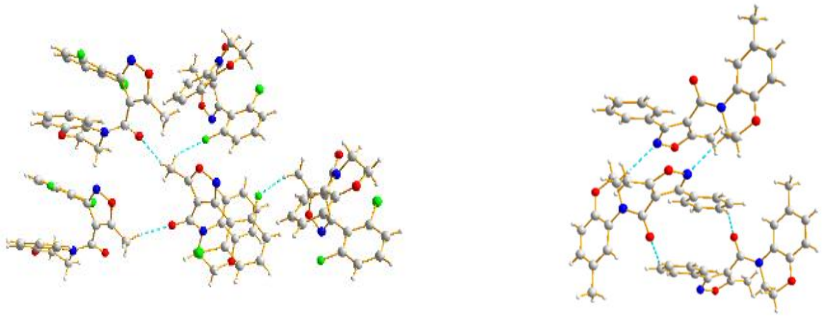


4a **4b**

Fig. 2. Molecular diagram of compounds 4a and 4b, showing 30% probability ellipsoids

Both of the crystal structures composed three parts: a benzoxazine skeleton (A), an isoxazole ring (B) and a benzene ring (C). For compound **4a**, the molecule is not coplanar. The dihedral angles between the benzoxazine skeleton (A), the isoxazole ring (B) and the benzene ring (C) are 60.66 ° (A/B), 18.57 ° (A/C), 61.08 ° (B/C). Obviously, there is π-π conjunctive effect between the isoxazole ring (B) and C(11)=O(2), which causes C(9)–C(11) (1.485(2) Å) shorter than the typical C–C bond (1.54 Å)[30]. And the bond C(11)–N(2) in 1.359(2) Å is shorter than the typical C−N (1.42 Å), indicating a p-π conjunction effect between N(2) and C(11)=O(2). The bond distance of C(12)–N(2) is 1.422(2) Å, similar to the typical C–N bond length, so there is no p-π conjunction effect between the benzene and N(2). There are similar crystal data for **4b**. The dihedral angles between the benzoxazine skeleton (A), isoxazole ring (B) and benzene ring (C) are 89.65 ° (A/B), 88.48 ° (A/C) and 28.00 ° (B/C), indicating rings B and C are almost perpendicular to the plane of A. The distances between A and C are 4.1334(6) Å for **4a** and 6.5455(18) Å for **4b**, longer than the typical π-π conjunction effect distance.

Hydrogen-bond interactions played a significant role in the crystal packing of **4a** and **4b**. Compound **4a** formed crystal packing *via* hydrogen bonds C(10)–H(10A)···F(1) and C(11)–H(10A)···O(2), and the crystal packing of **4b** was *via* the C(3)–H(3)···O(2) and C(12)–H(10B)···N(1) hydrogen bonds, as shown in Fig. 3. The presence of hydrogen bonds caused the target compounds to arrange in an ordered manner and form stable single crystal structures with high symmetry and regularity.



4a **4b**

Fig. 3. Molecular packing diagram of 4a and 4b. Hydrogen bonds are described as dashed lines

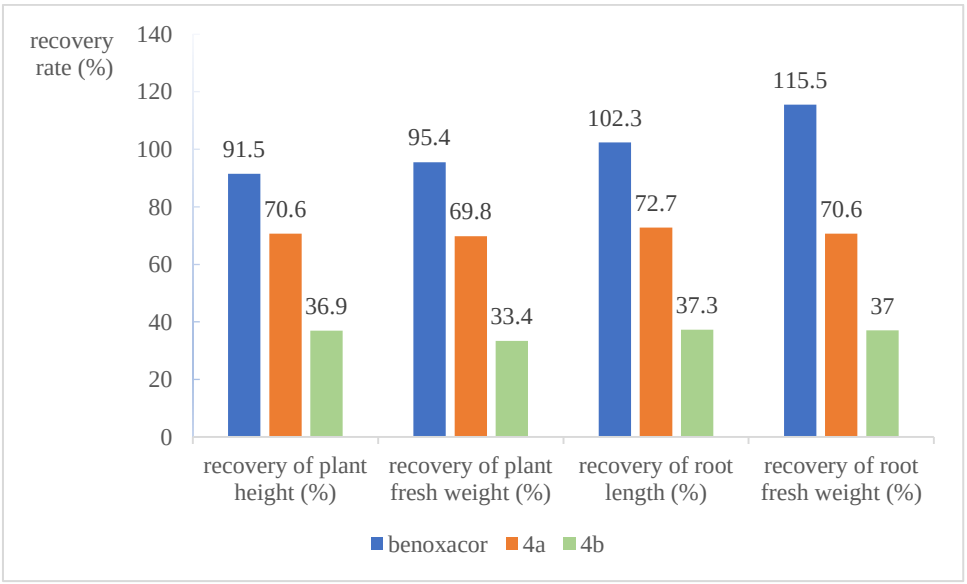


Fig. 4. Safener effects of 4a and 4b against the ACT-induced injury

4 BIOLOGICAL ACTIVITIES

The safener activity of the title compounds was tested with benoxacor selected as the control and acetochlor as the herbicide[31-33]. The recovery rate of various growth indicators of maize was evaluated after being treated with 20

mg/kg acetochlor in soil (Fig. 4). Compounds **4a** and **4b** showed detoxification effect on maize and could restore the maize growth to some extent. The root fresh weight recovery rates of **4a**, **4b** and benoxacor are 70.6%, 37.0% and 115.5%, respectively. The root length recovery rate of compound **4a** is 72.7%, however, that of **4b** is much lower, with the value to be only 37.3%. Compound **4a** has much better activity than **4b**, possibly caused by the halogen substituents (R_2 = Cl, R_3 = F) on the phenyl in **4a**. Halogen substitution usually enhances the bioactivity of compounds. Both title compounds show good safener activity, although they are not as active as benoxacor, indicating that the skeleton bears certain safener activity, and a new safener scaffold will be obtained with further structure modification.

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