Synthesis, Structures, and Herbicidal Activity of Isoxazole Derivatives

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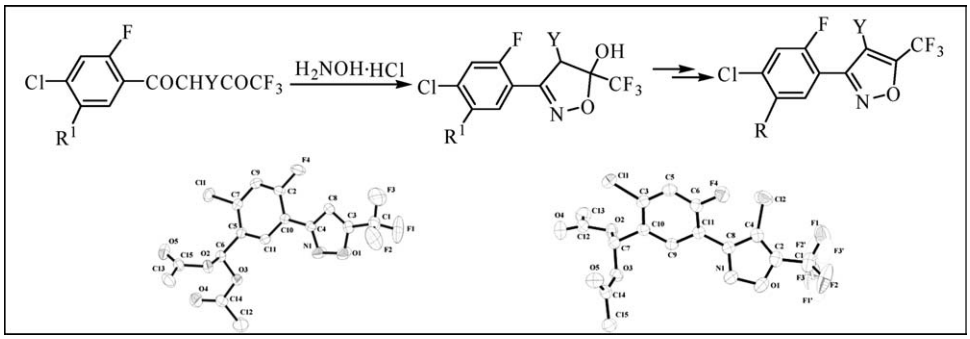

The several novel 3-substituted phenyl isoxazole derivatives were prepared from substituted phenyl-butan-1,3-dione. Their structures were confirmed by element analysis, IR, MS, and ^{1}H NMR. X-ray structure analysis indicated that the dihedral angles of the phenyl ring with the isoxazole ring in compounds **4a** and **4b** were 19.46° and 49.18°, respectively. Preliminary bioassay showed that the title compounds had good activity to various weeds, and **4a** exhibited almost the same activity with **4b**. This was different from the former works, which showed that the big dihedral angle of the phenyl ring with the heterocyclic moiety was necessary for high-herbicidal activity.

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INTRODUCTION

Herbicides inhibiting protoporphyrinogen oxidase (Protox) are the ones of the most important class of herbicides. Targeting the porphyrin pathway, these herbicides have shown high-activity and low-toxicity, and thus have become a hot-point of novel pesticides research [1]. Besides di-phenylether-type herbicides, which have been commercialized for more than 30 years, many other chemical classes belong to this family, such as azafenidin, oxadiazon, carfentrazone, etc. Substituted phenyl heterocyclic compounds are thought to be potent Protox-inhibitors, because they are similar to one half of the protoporphyrinogen IX, which is the target of Protox. Research on heterocyclic Protox inhibitors has been actively pursued, and a large number of compounds with high-bioactivity were reported [2–6]. Some samples of commercial Protox inhibitors are shown in Figure 1. Substituted phenyl isoxazoline derivatives have been reported, and some of them have high-activities [7]. We have also reported several novel 3-(substituted phenyl) isoxazole in a previous letter [8], considering that some isoxazole derivatives have displayed good biological activity [9–12], and that isoxazole moiety is more similar to the substructure of protoporphyrinogen IX than isoxazoline moiety. More importantly, a further study shows these isoxazole derivatives exhibit different structure-activity relationship from other phenyl heterocyclic compounds. Herein, details of the study, including the synthesis, their X-ray structures and the herbicidal activity of these isoxazole derivatives, are reported.

RESULTS AND DISCUSSION

The title compounds were prepared from substituted phenyl-butan-1,3-dione. At first, the isoxazole cycle was built via a ring closure reaction of phenylbutan-1,3-dione with hydroxylamine chloride [13]. In this reaction, what we obtained were isoxazolines (**2**), which could be changed into isoxazoles via a dehydration reaction in hot concentrated sulfuric acid (98%). When **2c** was employed as the substrate, the C—O band of the methoxy group was cleaved and **3c** was obtained (Scheme 1). From compounds **3a** or **3b**, different aimed compounds can be obtained by derivation of the methyl group on Position 5 of the phenyl cycle. It can be transformed into an aldehyde through a diester, via an oxidation reaction and a hydrolytic reaction. Otherwise, the methyl group on Position 5 of the phenyl cycle can be oxidized into a carboxyl group with chromium trioxide/

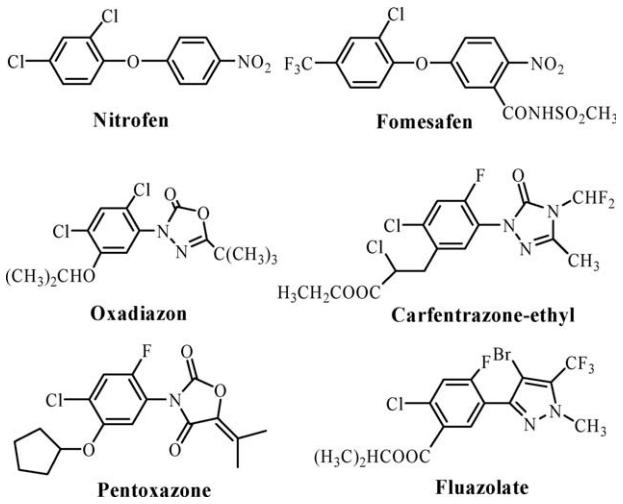


Figure 1. Samples of commercial Protox inhibitors.

sulfuric acid, and further transformed to an ester or amide via an acyl chloride intermediate. From compounds **3c**, different aimed compounds can be obtained via an alkylation reaction (Scheme 2).

To investigate further the structure-activity relationship of the aimed compounds, the single crystals of compounds **4a** and **4b** were prepared, and their structures were determined. The details of crystals, data collections and final refinement for compounds **4a** and **4b** are listed in Table 1. The selected bond distances (Å), angles (°) and torsion angles (°) of compounds **4a** and **4b** were given in Table 2. Both of the compounds have two planar rings, that is, the phenyl ring and the isoxazole moiety. However, the dihedral angle in **4a** [shown as C(2)—C(10)—C(4)—C(8)] is much different from that in **4b** [shown as C(5)—C(11)—C(8)—C(4)]. In compound **4a** (Fig. 2), it is 19.46°, whereas 49.18° in compound **4b** (Fig. 3). It indicated that the chlorine substitution could increase the dihedral angle of the two rings for the steric effect, which agreed with our former work [14].

Preliminary bioassay showed that compounds **4**, **5**, **7**, **8** have good activity to various weeds. Compared with fomesafen, which was a high-activity herbicide widely used, the herbicidal activity of these compounds to different weeds by stem and leaf treatment at a dosage of 1.5 kg/hm^2 and 150 g/hm^2, were shown in Table 3. Some of them have higher activity than fomesafen, especially at a lower dosage.

Here, we noticed that both compounds with chlorine substitution on isoxazole (**4b**, **5b**, **7a**∼**e**) and those without chlorine substitution on isoxazole (**4a**, **5a**, **8a**∼**f**) have high-activity.

It was reported that the ortho-position (to the phenyl ring) substituted groups on the heterocyclic moiety was necessary for high-activity to force the heterocyclic moiety out of planarity with the attached phenyl ring and to match closely the angle of the methylene bridge between two pyrrole rings of the protoporphyrinogen structure [15]. And it was reported recently that the dihalopyrrole nucleus was important for biological activity in 3-arylpyrroles [16]. However, in this research, the result was different from these former works. The tested isoxazole derivatives had high-activity no matter that Y was hydrogen or chlorine. Although the compounds with chlorine substituted had higher activity than those unsubstituted, the difference was quite little. Meanwhile, our former work indicated that the dihedral angle of the phenyl ring and the isoxazole moiety in the compound with chlorine on isoxazole ring was much bigger than those without chlorine substitution in solution [14]. These results suggest that the big dihedral angle of the phenyl ring and the isoxazole moiety may be not a key point for high-activity. We think a molecule may adjust the angle to fit closely the Protox in cells in bio-assaying. However, it needs further research.

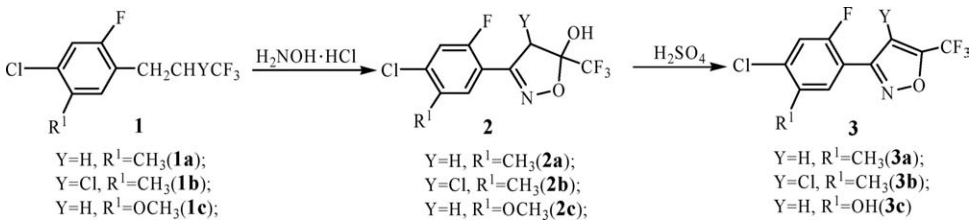
EXPERIMENTAL

^{1}H NMR spectra were measured on a Varian VA400MHz spectrometer with TMS as an internal standard. ^{13}C NMR spectra were obtained with broadband proton decoupling. MS was performed on a HP1100 high-performance liquid chromatography/mass selective detector. Melting points were determined using a YanacoMP-500 apparatus and were uncorrected. IR spectra were run on Nicolet 20DBX FT-IR. Elemental analysis was measured on MOD.1106 elemental analysis instrumentation.

Compounds **1a** and **1c** were synthesized by methods described in [17]. Compounds **1b** were prepared from **1a** following the procedure given in [7].

General procedure for the preparation of compound 2. To a solution of **1** (34 mmol) in acetic acid (100 mL), hydroxylamine chloride (5 g, 72 mmol) was added. Then the

Scheme 1. Building of isoxazole cycle.



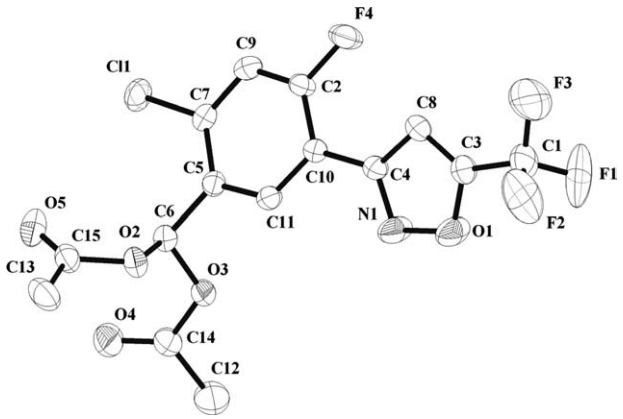


Figure 2. ORTEP (ellipsoids at 30% probability) diagram of compound **4a**. All hydrogen atoms are omitted for clarity.

mixture was heated to 100°C for 30 min. After the solution was cooled, it was poured into water, resulting in a white solid precipitate.

3-(4-Chloro-2-fluoro-5-methyl)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2a). This compound was obtained as a white solid, yield 92%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 128.0∼130.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, 1H, J = 8.0 Hz, Ph), 7.18 (d, 1H, J = 10.4 Hz, Ph), 3.91 (br, 1H, OH), 3.77 (dd, 1H, J = 18.6 Hz, 2.0 Hz, CH), 3.57 (d, 1H, J = 18.6 Hz, CH), 2.36 (s, 3H, CH_3); MS (API-ES, negative), m/z: 296.0 ($[M-H]^-$).

Anal. Calcd. for $C_{11}H_8O_2NClF_4$ (297.6): C, 44.39; H, 2.71; N, 4.71. Found: C, 44.51; H, 2.58; N, 4.52.

4-Chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2b). This compound was obtained as a white solid, yield 86%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 84.0∼86.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, 1H, J = 7.6 Hz, Ph), 7.24 (d, 1H, J = 10.8 Hz, Ph), 5.70 (s, CH), 4.2∼4.4(br, 1H, OH), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9 (d, J = 253.4 Hz), 153.9 (s, 138.0 (d, J = 10.1 Hz), 132.9 (s), 130.9 (s), 121.8 (q, J = 286.1 Hz), 117.2 (d, J = 24.9 Hz), 113.4 (d, J = 11.9 Hz), 104.1 (q, J = 33.1 Hz), 61.1 (d, J = 4.8 Hz), 19.2(s); MS (API-ES, negative), m/z: 330.0 ($[M-H]^-$).

Anal. Calcd. for $C_{11}H_7O_2NCl_2F_4$ (332.1): C, 39.79; H, 2.12; N, 4.22. Found: C, 40.01; H, 2.15; N, 4.01.

3-(4-Chloro-2-fluoro-5-methoxy)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2c). This compound was obtained as a white solid, yield 99%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 149.0∼151.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (br, 1H, OH), 7.41 (d, 1H, J = 6.0 Hz, Ph), 7.20 (d, 1H, J = 10.4 Hz, Ph), 3.91 (s, 3H, CH_3), 3.71 (d, 1H, J = 18.4 Hz, 1/2CH_2), 3.54 (d, 1H, J = 18.4 Hz, 1/2CH_2); ^{13}C NMR (100 MHz, broadband proton decoupling, $CDCl_3$) δ: 153.2 (d, J = 248.0 Hz), 152.5(s), 151.5 (s), 125.9 (d, J = 10.7 Hz), 122.1 (q, J = 283.8 Hz), 118.3 (d, J = 27.1 Hz), 115.0 (d, J = 12.7 Hz), 109.8 (d, J = 3.1 Hz), 104.4 (q, J = 33.6 Hz), 56.6 (s), 44.1 (d, J = 8.3 Hz); MS (API-ES, negative), m/z: 312.0 ($[M-H]^-$), 348.0 ($[M+Cl]^-$).

Anal. Calcd. for $C_{11}H_8O_3NClF_4$ (313.6): C, 42.12; H, 2.57; N, 4.47. Found: C, 41.95; H, 2.51; N, 4.39.

General procedure for the preparation of compound 3. A solution of **2** (16 mmol) in concentrated sulfuric acid (98%, 35 mL) was heated to 110, and maintained at that temperature for 3 h. After the solution was cooled, it was poured into ice-water, resulting in a white solid precipitate. The yields of all compounds were about 100%.

3-(4-Chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (3a). This compound was obtained as a white solid. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 34.0∼34.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, 1H, J = 7.6 Hz, Ph), 7.25 (d, J = 10.4 Hz, Ph), 7.13 (d, J = 3.2 Hz, 1H, isoxazole), 2.40 (s, 3H, CH_3); MS (API-ES, negative), m/z: 278.0 ($[M-H]^-$).

Anal. Calcd. for $C_{11}H_6ONClF_4$ (279.6): C, 47.25; H, 2.16; N, 5.01. Found: C, 46.96; H, 2.07; N, 4.83.

4-Chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (3b). This compound was obtained as an oily residue; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, 1H, J = 7.2 Hz, Ph), 7.27 (d, 1H, J = 9.6 Hz, Ph), 2.35 (s, 3H, CH_3); MS (API-ES, negative), m/z: 312.0 ($[M-H]^-$).

Scheme 2. Synthesis of aimed compounds.

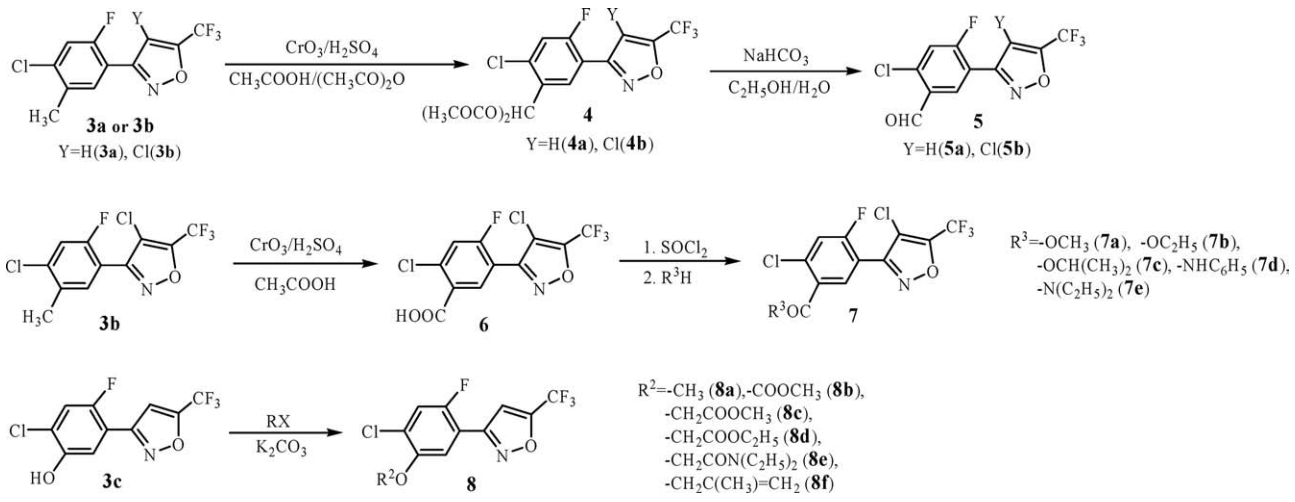


Table 1

Crystallographic parameters of compounds **4a** and **4b**.

Complex	**4a**	**4b**
Empirical formula	$C_{15}H_{10}ClF_4NO_5$	$C_{15}H_9Cl_2F_4NO_5$
Formula weight	395.69	430.13
Crystal system	Orthorhombic	monoclinic
Space group	Pbca	C2/c
a, (Å)	13.8903(6)	26.3306(9)
b, (Å)	7.6624(3)	8.1761(3)
c, (Å)	31.3155(12)	19.8365(6)
β, (deg)	90	124.992(2)
V, (Å^3)	3333.0(2)	3498.5
Z	8	8
D_{calcd}, (g/cm^3)	1.577	1.633
T, (K)	273(2)	273(2)
μ (mm^{-1}),	0.299	0.440
F(000)	1600	1728
θ, (deg)	1.96–27.58	2.10–29.12
limiting indices	$^{-}17 \leq h \leq 14$	$-35 \leq h \leq 35$
	$^{-}9 \leq k \leq 9$	$-10 \leq k \leq 10$
	$^{-}38 \leq l \leq 40$	$-24 \leq l \leq 26$
Reflns collected/unique	20813/3645	10565/4417
GOF(F^2)	1.039	1.013
R_1/wR_2 [I > 2sigma(I)]	0.0548/0.1477	0.0485/0.1280
R_1/wR_2 (all data)	0.0996/0.1735	0.0829/0.1509
Largest diff. peak and hole, e. Å^{-3}	0.389, −0.268	0.350, −0.383

Anal. Calcd. for $C_{11}H_5ONCl_2F_4$ (313.0): C, 42.07; H, 1.60; N, 4.46. Found: C, 41.96; H, 1.67; N, 4.53.

3-(4-Chloro-2-fluoro-5-hydroxy)phenyl-5-trifluoromethylisoxazole (3c). This compound was obtained as a white solid. A sample suiting for analysis was obtained by recrystallization with a mixture of petroleum ether and ethyl acetate (3:1); mp 49.0∼50.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, 1H, J = 6.4 Hz, Ph), 7.26 (d, J = 9.6 Hz, Ph), 7.13 (s, 1H, isoxazole), 5.4∼6.0(br, 1H, OH); MS (API-ES, negative), *m*/*z*: 280.0 ([M-H]$^-$).

Anal. Calcd. for $C_{10}H_4O_2NClF_4$ (281.6): C, 42.65; H, 1.43; N, 4.97. Found: C, 42.96; H, 1.37; N, 4.85.

General procedure for the preparation of compound 4. To a mixture of **2** (18 mmol), acetic acid (15 mL), acetic anhydride (40 mL) and concentrated sulfuric acid (98%, 4.5 mL), was added chromium oxide (about 3 g, 30 mmol) in small portion, maintaining the temperature under 25. The reaction was monitored by TLC. After the reaction was completed, it was poured into water, recrystallized from alcohol to give **4**.

2-Chloro-4-fluoro-5-(5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde diacetate (4a). This compound was obtained as a white solid, yield 57%, mp 87.0∼88.5; IR (KBr): 1768 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, 1H, J = 8.0 Hz, Ph), 7.97 (s, 1H, CH), 7.34 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 2.4 Hz, isoxazole), 2.16 (s, 6H, $2CH_3$); MS (API-ES, positive), *m*/*z*: 417.7 ([M+Na]$^+$).

Anal. Calcd. for $C_{15}H_{10}O_5NClF_4$ (395.7): C, 45.53; H, 2.55; N, 3.54. Found: C, 45.86; H, 2.67; N, 3.39.

2-Chloro-4-fluoro-5-(4′-chloro-5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde diacetate (4b). This compound was obtained as a white solid, yield 68%, mp 97.0∼98.5°C; IR (KBr): 1773, 1759 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (s, 1H, CH),7.81 (d, 1H, J = 6.8 Hz, Ph), 7.37 (d, 1H, J = 9.2 Hz, Ph), 2.14 (s, 6H, CH_3); MS (API-ES, positive), *m*/*z*: 451.7 ([M+Na]$^+$).

Anal. Calcd. for $C_{15}H_9O_5NCl_2F_4$ (430.1): C, 41.89; H, 2.11; N, 3.26. Found: C, 42.03; H, 2.17; N, 3.31.

General procedure for the preparation of compound 5. A slurry of **4** (5 mmol), sodium bicarbonate (2 g, 24 mmol), alcohol (10 mL) and water (2 mL) was refluxed for 2 h. After the solution was cooled, it was poured into water, resulting in **5** as a white solid precipitate.

2-Chloro-4-fluoro-5-(5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde (5a). This compound was obtained as a white solid, yield 82%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 78.5∼80.0°C; IR (KBr): 1621 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.42 (s, 1H, CHO), 8.56 (d, 1H, J = 7.2 Hz, Ph), 7.40 (d, 1H, J = 10.0 Hz, Ph), 7.14 (s, 1H, isoxazole); MS (API-ES, negative), *m*/*z*: 359.6 ([M+CH_3OH+Cl]$^-$).

Anal. Calcd. for $C_{11}H_4O_2NClF_4$ (293.6): C, 45.00; H, 1.37; N, 4.77. Found: C, 44.86; H, 1.31; N, 4.95.

2-Chloro-4-fluoro-5-(4′-chloro-5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde (5b). This compound was obtained as a white solid, yield 78%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 77.5∼78.5°C; IR (KBr): 1694 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.44 (s, 1H, CHO), 8.21 (d, 1H, J = 7.2 Hz, Ph), 7.43 (d, 1H, J = 8.8 Hz, Ph); MS (API-ES, negative), *m*/*z*: 393.6 ([M+CH_3OH +Cl]$^-$).

Anal. Calcd. for $C_{11}H_3O_2NCl_2F_4$ (228.0): C, 40.28; H, 0.92; N, 4.27. Found: C, 40.55; H, 0.97; N, 4.49.

Procedure for the Preparation of 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoic acid (6). To a

Table 2

Selected bond distances (Å), angles (deg) and torsion angles (deg) of compounds **4a** and **4b**.

4a		**4b**	
Cl(1)—C(7)	1.725(3)	Cl(1)—C(3)	1.727(2)
F(4)—C(2)	1.349(3)	C(5)—F(4)	1.350(3)
O(1)—N(1)	1.401(3)	N(1)—O(1)	1.398(3)
O(1)—C(3)	1.325(4)	O(1)—C(2)	1.339(3)
C(10)—C(4)	1.475(4)	C(8)—C(11)	1.472(3)
C(4)—C(8)	1.401(4)	C(4)—C(8)	1.415(3)
C(4)—N(1)	1.299(4)	N(1)—C(8)	1.300(3)
C(8)—C(3)	1.320(4)	C(2)—C(4)	1.327(3)
C(6)—C(5)	1.495(4)	C(7)—C(10)	1.504(3)
C(3)—C(1)	1.483(4)	C(1)—C(2)	1.488(4)
		Cl(2)—C(4)	1.691(3)
O(2)—C(6)—O(3)	106.2(2)	O(2)—C(7)—O(3)	105.40(16)
C(7)—C(5)—C(6)	122.7(2)	C(3)—C(10)—C(7)	120.9(2)
F(4)—C(2)—C(10)	118.3(2)	F(4)—C(5)—C(11)	118.5(2)
N(1)—C(4)—C(10)	118.1(3)	N(1)—C(8)—C(11)	119.8(2)
C(4)—N(1)—O(1)	105.6(2)	C(8)—N(1)—O(1)	106.2(2)
C(3)—O(1)—N(1)	107.6(2)	C(2)—O(1)—N(1)	107.94(19)
C(8)—C(3)—O(1)	111.1(3)	C(4)—C(2)—O(1)	110.4(2)
C(3)—C(8)—C(4)	104.5(3)	C(2)—C(4)—C(8)	104.8(2)
C(8)—C(3)—C(1)	133.5(3)	C(4)—C(2)—C(1)	133.6(3)
C(9)—C(7)—Cl(1)	117.8(2)	C(6)—C(3)—Cl(1)	118.32(17)
C(2)—C(10)—C(4)—C(8)	19.46	C(5)—C(11)—C(8)—C(4)	49.18
C(11)—C(5)—C(6)—O(2)	63.33	C(9)—C(10)—C(7)—O(3)	27.12

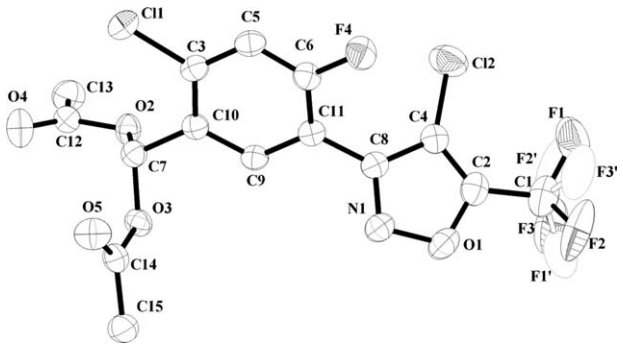


Figure 3. ORTEP (ellipsoids at 30% probability) diagram of compound **4b**. All hydrogen atoms are omitted for clarity.

mixture of 4-chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (**3b**) (12 g, 38 mmol), acetic acid (150 mL) and concentrated sulfuric acid (98%, 15 mL), was added chromium oxide (about 10 g, 0.1 mol) in small portion, maintaining the temperature under 25. The reaction was monitored by TLC. After the reaction was completed, it was poured into water, recrystallized from alcohol, resulting in a white solid precipitate 10 g (79%).

General procedure for the preparation of compound 7. To a solution of 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoic acid (**6**) (1.8 g, 5.2 mmol) in toluene (10 mL), thionyl chloride (1 mL, 14 mmol) and *N*,*N*-dimethyllformamide (3 drops) were added. Then, after the mixture was refluxed for 2 h, the solvent was removed in vacuum. After the oil obtained was cooled, methanol (10 mL) was added and refluxed for 2 h. After the solution was cooled, it was poured into water, resulting in a white solid precipitate.

Methyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7a). This compound was obtained as a white solid, yield 89%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 60.5∼61.5°C; IR (KBr): 1711 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, 1H, J = 7.2 Hz, Ph), 7.42 (d, 1H, J = 9.2 Hz, Ph), 3.95 (s, 3H, CH_3); MS (API-ES, positive), m/z: 379.8 ($[M+Na]^+$).

Anal. Calcd. for $C_{12}H_5O_3NCl_2F_4$ (358.1): C, 40.25; H, 1.41; N, 3.91. Found: C, 40.01; H, 1.50; N, 4.13.

Ethyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7b). This compound was obtained as a white solid, yield 83%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 25.5∼26.0°C; IR (KBr): 1793 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, 1H, J = 7.2 Hz, Ph), 7.41 (d, 1H, J = 9.6 Hz, Ph), 4.42 (q, 2H, J = 7.2 Hz, CH_2), 1.41 (t, 3H, J = 7.2 Hz, CH_3); MS (API-ES, positive), m/z: 393.7 ($[M+Na]^+$).

Anal. Calcd. for $C_{13}H_7O_3NCl_2F_4$ (372.1): C, 41.96; H, 1.90; N, 3.76. Found: C, 42.09; H, 1.98; N, 3.84.

Isopropyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7c). This compound was obtained as a white solid, yield 84%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 40.0∼40.5°C; IR (KBr): 1735 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, 1H, J = 7.6 Hz, Ph), 7.41 (d, 1H, J = 9.6 Hz, Ph), 5.29 (sept, 1H, J = 6.4 Hz, CH), 1.40 (d, 6H, J = 6.4 Hz, $2CH_3$); MS (API-ES, positive), m/z: 407.7 ($[M+Na]^+$).

Anal. Calcd. for $C_{14}H_9O_3NCl_2F_4$ (386.1): C, 43.55; H, 2.35; N, 3.63. Found: C, 43.28; H, 2.27; N, 3.42.

N-phenyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzamide (7d). This compound was obtained as a yellow solid, yield 86%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 173.0∼175.0°C; IR (KBr): 1651 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.0∼8.1(m, 8H, Ph+NH); MS (API-ES, positive), m/z: 440.8 ($[M+Na]^+$).

Anal. Calcd. for $C_{17}H_8O_2N_2Cl_2F_4$ (419.2): C, 48.71; H, 1.92; N, 6.68. Found: C, 48.53; H, 2.01; N, 6.86.

N,N-diethyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzamide (7e). This compound was obtained as a yellow solid, yield 80%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 87.5∼88.5°C; IR (KBr): 3272 (N—H), 1640 (C=O) cm^{-1}; ^1H

Table 3

Herbicidal activity of aimed compounds (% inhibition).

	Echinochloa crusgalli/%		*Setaria viridis*/%		*Abutilon theophrasti*/%		*Acalypha australis*/%	
Compound	1.5 kg/hm^2	150 g/hm^2	1.5 kg/hm^2	150 g/hm^2	1.5 kg/hm^2	150 g/hm^2	1.5 kg/hm^2	150 g/hm^2
4a	95.17	76.22	94.56	86.21	87.09	87.09	61.90	35.90
4b	99.40	80.95	97.73	93.52	92.28	91.34	61.54	36.63
5a	79.41	74.82	96.89	49.62	92.04	87.39	33.70	19.80
5b	99.67	79.85	98.15	97.31	94.11	93.22	50.55	46.15
7a	98.50	68.21	98.64	91.91	89.51	54.15	98.06	96.98
7b	99.20	87.84	98.90	98.25	100.00	82.89	100.00	100.00
7c	99.04	68.25	98.03	95.43	92.42	45.69	100.00	90.21
7d	74.48	63.68	54.76	9.68	77.70	38.22	78.29	65.50
7e	99.27	76.70	98.44	73.25	77.13	64.69	100.00	97.54
8a	81.95	80.95	66.69	64.51	92.28	79.79	49.08	42.49
8b	80.85	80.08	77.38	68.04	97.58	91.22	40.66	26.37
8c	85.61	78.01	96.80	70.56	90.69	89.51	89.01	36.99
8d	91.77	81.51	92.77	77.04	95.05	83.97	64.21	52.01
8e	75.72	74.15	92.68	60.81	91.99	90.81	40.66	15.75
8f	82.31	80.78	81.16	49.62	93.75	82.38	51.28	17.95
fomesafen	96.39	56.96	95.85	48.29	79.06	71.98	100.00	64.55

NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 1H, J = 7.2 Hz, Ph), 7.36 (d, 1H, J = 9.6 Hz, Ph), 3.3∼3.9 (bd, 2H, CH_2), 3.2 (br, 2H, CH_2), 1.28 (m, 3H, CH_3), 1.12 (m, 3H, CH_3); MS (API-ES, positive), m/z: 398.9 ($[M+H]^+$).

Anal. Calcd. for $C_{15}H_{12}O_2N_2Cl_2F_4$ (399.17): C, 45.14; H, 3.03; N, 7.02. Found: C, 45.13; H, 2.96; N, 6.91.

General procedure for the preparation of compound 8. To a slurry of 3-(4-chloro-2-fluoro-5-hydroxy)phenyl-5-trifluoromethylisoxazole (**3c**) (1.5 g, 5 mmol), anhydrous potassium carbonate (1.7 g, 25 mmol) in acetone (15 mL), was added dimethyl sulfate (0.75 mL, 7.5 mmol) or corresponding chlorides. The mixture reacted at room temperature or refluxed, allowed to cool and poured into water, resulting in a white solid precipitate.

3-(4-Chloro-2-fluoro-5-methoxy)phenyl-5-trifluoromethylisoxazole (8a). This compound was obtained as a white solid (reacted at room temperature for 3 h), yield 89%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 80.0∼80.5°C; ^{1}H NMR (400 MHz, CDCl3) δ: 7.54 (d, 1H, J = 6.4 Hz, Ph), 7.28 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 3.2 Hz, isoxazole), 3.96 (s, 3H, OCH_3); MS (API-ES, negative), m/z: 329.6 ($[M + Cl]^-$).

Anal. Calcd. for $C_{11}H_6O_2NClF_4$ (295.6): C, 44.69; H, 2.05; N, 4.74. Found: C, 44.61; H, 2.00; N, 4.54.

Ethyl 2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenyl carbonate (8b). This compound was obtained as a white solid (refluxed for 2 h), yield 96%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 97.0∼98.0°C; IR (KBr): 1772 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ: 7.94 (d, 1H, J = 7.2 Hz, Ph), 7.37 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 2.4 Hz, isoxazole), 4.37 (q, 2H, J = 7.2 Hz, CH_2), 1.42 (t, 1H, J = 7.2 Hz, CH_3); MS (API-ES, positive), m/z: 375.8 ($[M+Na]^+$).

Anal. Calcd. for $C_{13}H_8O_4NClF_4$ (353.7): C, 44.15; H, 2.28; N, 3.96. Found: C, 44.43; H, 2.31; N, 3.87.

Methyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetate (8c). This compound was obtained as a white solid (refluxed for 2 h), yield 88%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 92.0∼94.0°C; IR (KBr): 1735 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 1H, J = 6.0 Hz, Ph), 7.32 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 2.4 Hz, isoxazole), 4.78 (s, 2H, OCH_2COO), 3.83 (s, 3H, CH_3); MS (API-ES, positive), m/z: 375.8 ($[M+Na]^+$).

Anal. Calcd. for $C_{13}H_8O_4NClF_4$ (353.7): C, 44.15; H, 2.28; N, 3.96. Found: C, 44.39; H, 2.38; N, 4.07.

Ethyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetate (8d). This compound was obtained as a white solid (refluxed for 2 h), yield 91%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 72.5∼73.0°C; IR (KBr): 1729 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51(d, 1H, J = 6.0 Hz, Ph), 7.32 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 2.4 Hz, isoxazole), 4.76 (s, 2H, OCH_2COO), 4.29 (q, 2H, J = 7.2 Hz, Et-CH_2), 1.32 (t, 3H, J = 7.2 Hz, Et-CH_3); MS (API-ES, positive), m/z: 368.0 ($[M+H]^+$).

Anal. Calcd. for $C_{14}H_{10}O_4NClF_4$ (367.7): C, 45.73; H, 2.74; N, 3.81. Found: C, 45.50; H, 2.66; N, 3.86.

N,N-diethyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetamide (8e). This compound was obtained as a white solid (refluxed for 2 h), yield 84%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 78.5∼80.0°C; IR (KBr): 1647 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 1H, J = 6.0 Hz, Ph), 7.28 (d, 1H, J = 9.6 Hz, Ph), 7.12 (d, 1H, J = 2.8 Hz, isoxazole), 4.82 (s, 2H OCH_2CO), 3.3∼3.5 (m, 4H, 2Et—CH_2), 1.26 (t, 3H, J = 7.2 Hz, Et—CH_3), 1.13 (t, 3H, J = 7.2 Hz, Et—CH_3); MS (API-ES, positive), m/z: 416.9 ($[M+Na]^+$).

Anal. Calcd. for $C_{16}H_{15}O_3N_2ClF_4$ (394.7): C, 48.68; H, 3.83; N, 7.10. Found: C, 49.04; H, 3.59; N, 7.01.

3-[4-Chloro-2-fluoro-5-(2′-methyl)allyl]phenyl-5-trifluoromethylisoxazole (8f). This compound was obtained as a white solid (refluxed for 6 h), yield 88%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 82.0∼82.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 1H, J = 6.4 Hz, Ph), 7.28 (d, 1H, J = 10.0 Hz, Ph), 7.15 (d, 1H, J = 3.6 Hz, isoxazole), 5.18 (s, 1H, =CH), 5.05 (s, 1H, =CH), 4.55(s, 2H, OCH_2), 1.87 (s, 3H, CH_3); MS (API-ES, negative), m/z: 333.9 ($[M-H]^-$).

Anal. Calcd. for $C_{14}H_{10}O_2NClF_4$ (335.7): C, 50.09; H, 3.00; N, 4.17. Found: C, 49.89; H, 2.90; N, 3.98.

Crystal structure determination. Saturated solution of **4a** and **4b** in EtOAc were covered with n-hexane, and stand in air at room temperature to give single crystals. The data were obtained on a Bruker SMART APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Empirical absorption corrections were performed using the SADABS program. Structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2 using shelx97. All of the non-hydrogen atoms were refined anisotropic ally. All of the hydrogen atoms were generated and refined in ideal positions.

Post-emergence herbicidal activity test. Compounds were formulated as 22 g/L emulsible concentrates, which were diluted with water to the required concentration and applied to pot-grown plants in a greenhouse.

Seeds of assayed weeds (*Echinochloa crusgalli*, *Setaria viridis, Abutilon theophrasti*, and *Acalypha australis*) were germinated in water at 30°C under dark conditions for 48 h. The germinated seeds were placed in a pot (0.1 m^2) as 10 seeds per-pot. While *Echinochloa crusgalli* was in the third-leaf stage, *Setaria viridis* was in the second-leaf stage, *Abutilon theophrasti* and *Acalypha australis* had two or three leaves, the diluted formulation was applied. Fifteen days after treatment, the upper-soil parts of the plants were cut off, and their weights were measured freshly (*FW*). The degree of weeds control by the test compounds was calculated with the following formulation:

$$\text{Inhibition} = \frac{CK - FW}{CK} \times 100\%$$

where *CK* is the fresh weight of untreated weed.

Each test was repeated three times.

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