HETEROCYCLES, Vol. 91, No. 6, 2015, pp. 1256 - 1268. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 13th April, 2015, Accepted, 13th May, 2015, Published online, 26th May, 2015
DOI: 10.3987/COM-15-13225

SYNTHESIS AND SAFENER ACTIVITY OF NOVEL SUBSTITUTED 4-PHENOXYACETYL-1,4-BENZOXAZINES

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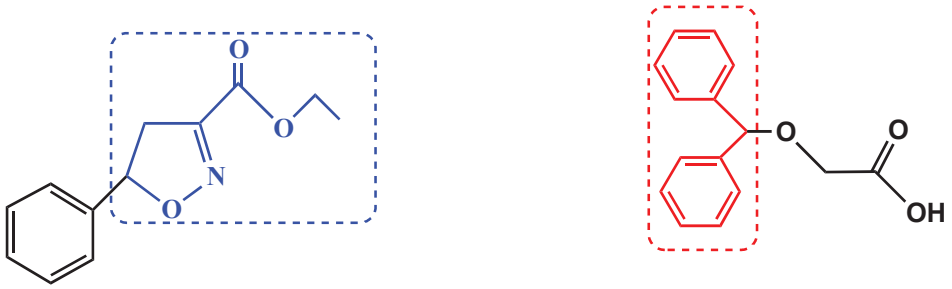
Abstract — A novel class of 3-methyl-4-phenoxyacetyl-3,4-dihydro-2*H*-1,4-benzoxazine **3** were synthesized *via* reduction, cyclization, and acylation reactions. The structures of the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analyses. The configuration of **3f** was determined by X-ray crystallography. The bioassay results demonstrated that most of these compounds could alleviate 2,4-D butylate injury to maize.

1,4-Benzoxazine derivatives have received great attention in chemical and medicinal research because of their natural occurrence and important biological activities.[1] Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives have been reported as potassium channel openers (PCOs) in vascular smooth muscle. Some 1,4-benzoxazine derivatives are known to be central nervous system depressants, antibacterial agents,[2] antipsychotic agents,[3] calcium antagonists,[4] and antimicrobial agents agonists,[5] and so on. In particular, benzoxazine derivatives with particular biological activities were applied widely in the agrochemicals fields, including herbicide safener benoxacor.[6]

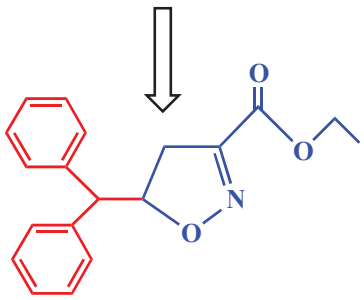
Structure-activity correlations (SAR) are very important in the search for biological activity because they provide useful information about chemical substituents that are necessary for the required bioactivity.[7] Base on the SAR, fenoxaprop-ethyl was used as the target herbicide, and replacing the pyrazoline core from mefenpyr-diethyl by a similar substituted isoxazoline resulted in the safener 5-phenyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester, which were not sufficiently active for commercialization. However, combining the structural features of 5-phenyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester and the safener diphenyl acid led to the strong rice safener isoxadifen-ethyl (**Scheme 1**).[8] Using strategies of active substructure combination and bioisosteric replacement, Guan et al.

designed and synthesized novel dihalopropene derivatives with insecticidal activity.[9] Recently many successful cases have been reported.[10]

As part of our ongoing work on the synthesis of nitrogen-containing heterocyclic herbicide safeners,[11] herein 4-phenoxyacetylbenzoxazine derivatives were design and synthesized based on the SAR and active substructure combination keeping the benzoxazine as the parent skeleton structure (**Scheme 2**). Several approaches had been developed to benzoxazine derivatives with Mo/Fe/Al/Cr,[12] $AlCl_3$,[13] CuI,[14] pyridinium chlorochromate,[15] $[Ir(COD)Cl]_2$ with (S)-Segphos,[16] $HSiCl_3$,[17] or 1,10-phenanthroline[18] as catalysts. Most of these reported methods required harsh reaction conditions, expensive catalysts, or poor yields. However, simple benzoxazines ring closure could also been obtained by a tandem reduction-reductive amination reaction with Pd/C as catalyst in good yields.[19-21] In view of the facts mentioned above and continuous of our previous work, the novel target molecules with potential herbicide safener activity, substituted 3-methyl-4-phenoxyacetyl-3,4-dihydro-2*H*-1,4-benzoxazine **(3)**, were designed and synthesized with *o*-nitrophenoxyl ketone and phenoxyacetyl chloride as the starting material *via* reduction, cyclization, and acylation reactions (**Scheme 3**).

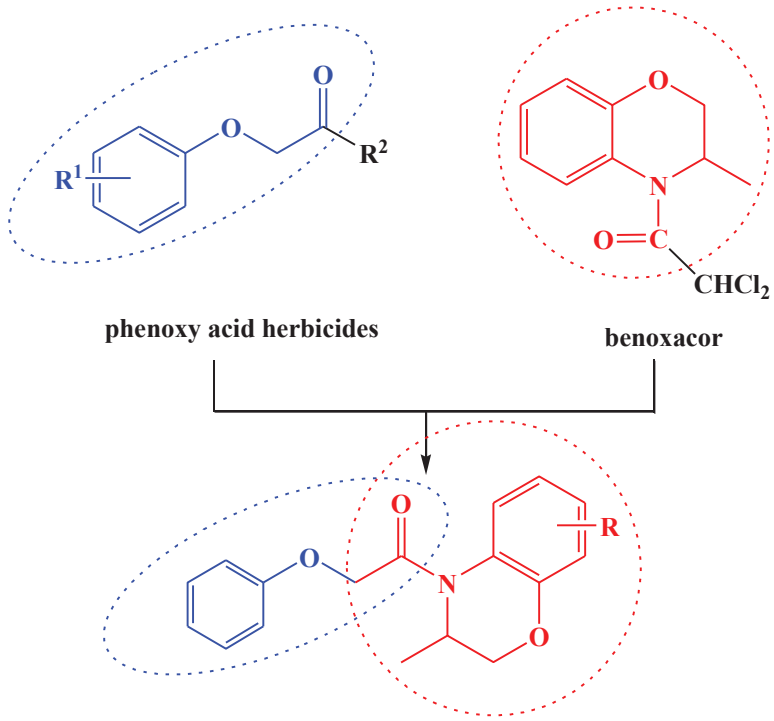


5-phenyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester **diphenyl acid**

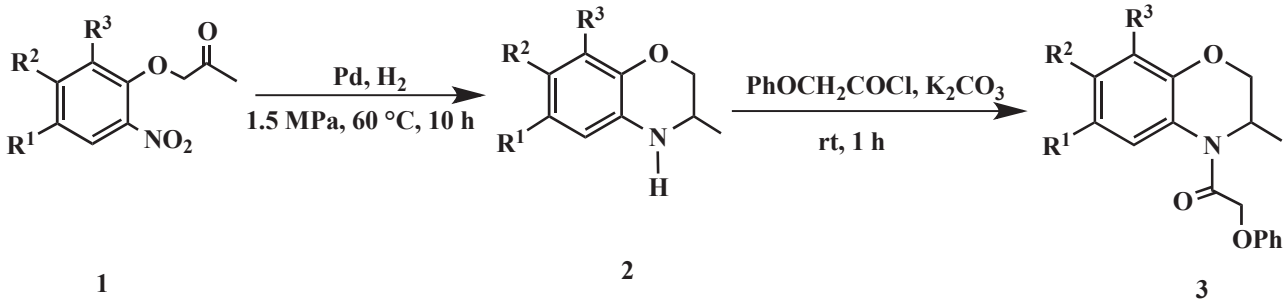


isoxadifen-ethyl

Scheme 1. Design of isoxadifen-ethyl



Scheme 2. Design of the target compound



Scheme 3. Route for synthesis of 4-phenoxyacetyl-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine

3-Methyl-3,4-dihydro-2*H*-1,4-benzoxazines **2** were prepared by reduction and cyclization at 55-60 ℃ with the pressures of 1.5 MPa for 10-25 h, and Pt/C was used as catalyst. Isopropanol and toluene were used as solvent. Herein was used as co-solvent and dehydrating agent. Isopropanol increased the solubility of the reactants in toluene. Series of 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**2**) were obtained in 68%-91% yields (**Table 1**). The target compounds **3** were obtained by acylation of **2** with phenoxyacetyl chloride in benzene by stirring the mixture for 1-1.5 h at room temperature. The process was monitored by TLC. The substitute group structure affected the yields significantly. According to the yields of **3**, it was found that the electron-donating on the benzene ring increased the yields of **3**. The compounds **3h** gave the better yield than others with tert-butyl on position 6. However, the yield of **3d** was the best for there was another chloride on position 8.

Table 1. Structure and yields of compounds **2** and **3**

Product	R^1	R^2	R^3	Yields of 2(%)	Yield of 3(%)
a	H	H	H	72	60
b	Me	H	H	87	77
c	MeO	H	H	91	72
d	^{t}Bu	H	H	89	76
e	Cl	H	H	85	64
f	Cl	H	Cl	68	78
g	Et	H	H	71	72
h	Br	H	H	75	70
i	H	Me	H	84	63

Finally, the single crystal of **3f** was obtained by dissolving it in ethyl acetate and light petroleum, followed by slow evaporation. The X-ray data were collected on a Bruker AXS Ⅱ CCD area-detector diffractometer using graphite monochromated Mo *K*a radiation (λ=0.71073 Å) at 293(2) K. The structure was solved by direct methods using SHELXS-97,[22] and refined by full matrix least squares on F^2, SHELXL-97.[23]

The compound, $C_{20}H_{21}Cl_2NO_3$, contained a six-membered and two benzene rings. The C5/C6/O1/C7/C8/N1 composed of the oxazine ring with the torsion angle of N1/C5/C6 and O1 being -1.58(72)°, which states N1/C5/C6 and O1 are almost coplanar. While the atom C7 and C8 deviated from the selected plane, just as what was shown in **Figure 1**. The oxazine ring adopted a half-chair

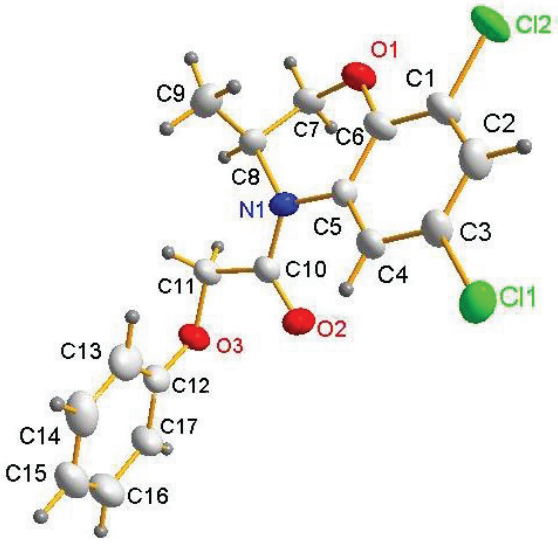


Figure 1. Molecular structure for compound **3f**

conformation. The dihedral angles between the oxazine ring and the adjacent benzene ring (C1/C2/C3/C4/C5/C6) were 4.93(14)°, which indicated two ring are close to coplanar. Besides, the dihedral angles of two benzene ring are 70.11(16)°.

The compound crystallized in the monoclinic space group $P\bar{1}$, with two molecules in the unit cell. The packing view of the compound was shown in **Figure 2**. In the crystal structure, molecules were linked by weak intermolecular C-H…O hydrogen bonds and C-H…π interactions to form one-dimension chains, which stabilized the crystal structure (**Figure 3**). No significant π-π interactions were found in the crystal structure.

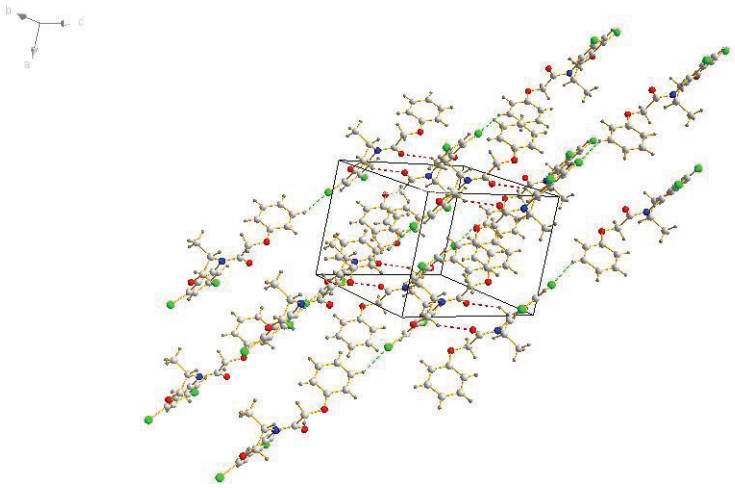


Figure 2. Packing view of the compound **3f,** hydrogen bonds are described as dashed lines

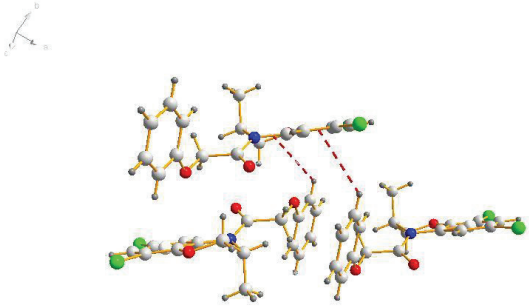


Figure 3. C-H…π interactions of the compound **3f**

All the novel compounds **3a-i** were evaluated for their protection of maize *in vivo* against the injury of 2,4-D butylate at the concentration of 0.244 g/m^2 (**Table 2)**. The recovery rates of the growth index could be attained almost 50%. Among the compounds tested, compound **3h** showed the best activity against the injury of 2,4-D butylate, even better than the commercialized safener, benoxacor. That indicated the

compound with bulk group link to benzene led to good activity. However, compounds **3b**, **3c**, and **3i** did not show protection, they inhibited the root growth. They might be used as the candidate of herbicide because they are similar as phenoxy acid herbicide. The further bioassay was still investigated.

Table 2. Effect of detoxification of compounds **3a-i** to growth index of maize [a,b,c]

Compound	**Recovery of root length (%)**	**Recovery of plant height (%)**	**Recovery of root weight (%)**	**Recovery of plant weight (%)**
Benoxacor	28.42±1.21	7.46±0.52	88.00±1.54	28.2±0.58
3a	18.69±0.83	-16.92±0.82	80.39±2.01	9.6±0.87
3b	-5.92±0.55	43.10±1.84	-17.60±0.45	16.27±1.17
3c	-10.00±1.08	36.99±1.09	8.10±0.74	37.41±1.56
3d	42.00±0.96	94.48±2.13	112.06±2.83	51.56±1.83
3e	12.27±0.67	74.62±1.42	43.15±1.65	17.47±1.12
3f	9.37±0.51	29.40±0.63	42.46±1.48	35.37±1.24
3g	2.13±0.32	66.51±1.15	55.01±1.86	21.23±1.69
3h	25.31±1.04	45.56±1.05	86.14±0.78	32.08±1.57
3i	-6.68±0.73	28.68±1.32	58.79±1.69	17.06±0.98

[a] data are means of three replicates

[b] $\text{Recovery Rate}\,(\%) = \dfrac{\text{Treated with compounds - Treated with 2,4 - D butylate}}{\text{Contrast - Treated with 2,4 - D butylate}}$

[c] water treated was used as contrast

In conclusion, we have developed an efficient, fast and convenient method for the preparation of 4-phenoxyacetyl-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine derivatives base on SAR and active substructure combination. The advantages of this method were readily available starting materials, mild reaction conditions, and good yields. The preliminary bioactivity results showed that compound **3d** attained the best herbicide safener activity to 2,4-D butylate.

EXPERIMENTAL

The IR spectra were taken on a ALPHA-T infrared spectrophotometer in KBr pellets or film. The NMR

spectra were recorded on Bruker AVANVE 300 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer. The mass spectrum was recorded on a Waters Xevo TQ spectrometer. X-Ray diffraction data were collected on a Brukcr AXSII CCD area-detector diffractometer, Mo K_α. The melting points were determined on a Beijing Taike melting point apparatus(X-4) and are uncorrected. All the reagents were of analytical reagents grade.

General procedure for the preparation of 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (2a-i)[21]

Pt/C (2 g) was added to solution of compounds **1** (50 mmol) in mixture of toluene (200 mL) and isopropanol (100 mL). The reaction mixture was stirred in H_2 at 60 °C, 1.5 Mpa for 10 h. Then the mixture was filtered, and the filtrate was dried over magnesium sulfate anhydrous, and the toluene was removed under vacuum. The crude product was separated on silica gel by column chromatography [*V* (EtOAc): *V* (light petroleum) = 1:4] until the compounds **2** were collected. The physical and spectra data of the compounds **2** were as follows:

3-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine (2a). Yield 72%. Light yellow oil. IR(film, cm^{-1}): *v*3371(N-H), 2970-2871(C-H), 1608-1427(C=C). ^{1}H-NMR(DMSO-d_6, 300 MHz): δ 6.24-6.67(m, 4H, Ar-H), 5.63(m, 1H, N-H), 4.05-4.12, 3.58-3.63(m, 2H, O-CH_2), 2.11(s, 1H, N-CH), 1.08(m, 3H, CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 143.71, 133.49, 121.36, 118.84, 116.52, 115.45, 70.75, 45.17, 17.83. *Anal.* Calcd for $C_9H_{11}NO$: C 72.44, H 7.44, N 9.39. Found: C 72.42, H 7.48, N 9.35.

3,6-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (2b). Yield 87%. Light yellow oil. IR(film, cm^{-1}): *v*3369(N-H), 2970-2869(C-H), 1614-1454(C=C). ^{1}H-NMR(DMSO-d_6, 300 MHz): δ 6.24-6.52(m, 3H, Ar-H), 5.59(m, 1H, N-H), 4.05-4.08, 3.55-3.57(m, 2H, O-CH_2), 3.34-3.35(m, 1H, N-CH), 2.11(s, 3H, Ar-CH_3), 1.05-1.07(d, 3H, *J*=6.4Hz, CH_3); ^{13}C-NMR(DMSO-d_6, 75 MHz): δ 141.20, 134.72, 129.99, 117.69, 115.86, 115.63, 70.46, 44.89, 20.96, 17.80. *Anal.* Calcd for $C_{10}H_{13}NO$: C 73.57, H 8.03, N 8.59. Found: C 73.61, H 8.05, N 8.64.

3-Methyl-6-methoxyl-3,4-dihydro-2*H*-1,4-benzoxazine (**2c**). Yield 91%. White solid, mp 60-61 °C. IR(KBr, cm^{-1}): *v*3373(N-H), 2968-2833(C-H), 1620-1456(C=C). ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.18-6.73(m, 3H, Ar-H), 4.14-4.18(m, 1H, N-H), 3.71-3.77(m, 5H, O-CH_2- and Ar-O-CH_3), 3.53-3.58(m, 1H, N-CH), 1.18-1.20(m, 3H, CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 154.47, 137.84, 133.97, 116.66, 103.49, 101.17, 70.61, 55.62, 45.32, 17.82. *Anal.* Calcd for $C_{10}H_{13}NO_2$: C 67.00, H 7.32, N 7.82. Found:

C 67.08, H 7.41, N 7.75.

3-Methyl-6-*tert*-butyl-3,4-dihydro-2*H*-1,4-benzoxazine (2d). Yield 89%. Light yellow oil. IR(film, cm^{-1}): *v*3369 (N-H), 2962-2867(C-H), 1610-1446(C=C). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.65-6.77(m, 3H, Ar-H), 4.17-4.21(m, 1H, N-H), 3.74-3.81(m, 2H, O-CH_2), 3.55-3.58(m, 1H, N-CH), 1.27-1.35(m, 9H, Ar-C(CH_3)$_3$), 1.19-1.21(d, 3H, *J* = 6.4 Hz, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.38, 141.55, 132.58, 115.93, 115.93, 112.77, 70.82, 45.33, 34.10, 31.54, 31.54, 31.54, 17.86. *Anal.* Calcd for C_9H_7NO: C 76.04, H 9.33, N 6.83. Found: C 76.09, H 9.38, N 6.80.

3-Methyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine (2e). Yield 85%. White solid, mp 80-81 °C. IR (KBr, cm^{-1}): *v*3365(N-H), 2975-2871(C-H), 1596-1442(C=C). ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.56-6.72(m, 3H, Ar-H), 4.16-4.21(m, 1H, N-H), 3.72-3.78(m, 2H, O-CH_2), 3.51-3.57(m, 1H, N-CH), 1.18-1.21(m, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 142.17, 134.46, 125.95, 118.18, 117.35, 114.69, 70.56, 44.98, 17.72. *Anal.* Calcd for $C_9H_{10}ClNO$: C 59.00, H 5.51, N 7.65. Found: C 59.06, H 5.46, N 7.62.

3-Methyl-6,8-dichloro-3,4-dihydro-2*H*-1,4-benzoxazine (2f). Yield 68%. White solid; mp 75-76 °C. IR(KBr, cm^{-1}): *v*3398(N-H), 2966-2854(C-H), 1595-1456(C=C). ^{1}H-NMR($CDCl_3$, 300 MHz,): δ 6.47-6.73(m, 2H, Ar-H), 4.28-4.32(m, 1H, N-H), 3.78-3.84(m, 2H, O-CH_2), 3.53-3.59(m, 1H, N-CH), 1.19-1.24 (m, 3H, CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 138.16, 135.26, 125.74, 121.82, 118.52, 113.07, 70.93, 44.88, 17.57. *Anal.* Calcd for $C_9H_9Cl_2NO$: C 49.77, H 4.18, N 6.45. Found: C 49.82, H 4.25, N 6.39.

3-Methyl-6-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine (2g). Yield 71%. Yellow liquid. IR(film, cm^{-1}): *v*3370(N-H), 2965-2871(C-H), 1612-1456(C=C); ^{1}H-NMR($CDCl_3$, 300 MHz)：δ 6.46-6.75(m, 3H, Ar-H), 4.16-4.20(m, 1H, O-CH_2)，3.74-3.80(m, 1H, O-CH_2-,), 3.33-3.58(m, 2H, N-CH-, N-H)，2.54-2.51(m, 2H, Ar-CH_2-Me), 1.23-1.18(m, 6H, Ar-C-CH_3, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 141.76, 137.42, 133.24, 118.17, 116.30, 114.89, 70.82, 45.34, 28.32, 17.89, 15.92.

3-Methyl-6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine (2h). Yield 75%. White solid, mp 85-86 °C; IR(KBr, cm^{-1}): *v*3364(N-H), 3034-2869(C-H), 1597-1498(C=C); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.63-6.75(m, 3H, Ar-H), 4.15-4.20 (m, 1H, O-CH_2-), 3.71-3.77 (m, 2H, O-CH_2-, N-CH-), 3.48-3.58 (m, 1H, N-H), 1.17-1.12 (d, *J*=9.0 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 142.73, 134.78, 121.22, 117.86, 117.61, 113.26, 70.52, 45.00, 17.70.

3,7-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (2i). Yield 84%. White solid, mp 37-38 °C; IR (KBr,

cm^{-1}): *v*3364(N-H)，3024-2869(C-H), 1623-1515(C=C); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.48-6.61(m, 3H, Ar-H), 4.14-4.17 (m, H, O-CH_2-)，3.72-3.76 (m, 1H, O-CH_2-), 3.41-3.51(m，2H，N-CH-, N-H)，2.21(s, 3H, Ar-CH_3)，1.16-1.14(d, *J*=8.0 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 143.67, 130.84, 128.61, 121.77, 117.02, 115.57, 70.87, 45.29, 20.60,17.76.

General procedure for the preparation of 3-methyl-4-acetyl-3,4-dihydro-2*H*-1,4–benzoxazine (3a-i)

Phenoxyacetyl chloride (21 mmol) was dropwise added to the mixture of K_2CO_3 (15.2 mmol, 1.6 g), 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (14 mmol) and benzene (34 mL) at room temperature for 1 h. Then the mixture was filtered, and the filtrate was washed and dried over magnesium sulfate anhydrous. The benzene was removed under vacuum. The crude products were recrystallized with EtOAc and light petroleum. The physical and spectra data of the compounds **3a-i** were as follows:

3-Methyl-4-phenoxyacetyl-3,4-dihydro-2*H*-1,4-benzoxazine (3a). Yield 60%. White solid, mp 56-57 °C; IR(KBr, cm^{-1}): *v*3061-2893(C-H)，1655(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.90-7.32(m, 9H, Ar-H)，4.83-4.96(m, 3H, N-CH-, O-CH_2-C=O), 4.13-4.20 (m, 2H, O-CH_2-), 1.23-1.27(d, *J*= 9.0 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.40, 157.77, 146.10, 129.67, 129.67, 126.60, 124.30, 122.79 121.83, 120.66, 117.12, 114.67, 114.67, 70.04, 67.50, 44.57, 15.43. ESI-MS: 284 [M+H^+]. *Anal.* Calcd for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94. Found: C 72.11, H 6.12, N 4.89.

3,6-Dimethyl-4-phenoxyacetyl-3,4-dihydro-2*H*-1,4-benzoxazine (3b). Yield 77%. White solid；mp 95-96 °C IR(KBr, cm^{-1}): *v*3059-2900 (C-H)，1659(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 7.27-7.33(m, 3H, Ar-H), 6.81-7.00(m, 5H, Ar-H), 4.83-4.94(m, 3H, N-CH-, O-CH_2-C=O), 4.08-4.18(m, 2H, O-CH_2-), 2.26(s, 3H, Ar-CH_3)，1.25-1.23(d, *J*=9.0 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.34, 157.82, 143.88, 130.06, 129.66, 129.66, 127.24, 124.48, 122.42, 121.80, 116.75, 114.68, 114.68, 69.93, 67.65, 45.18, 20.81, 15.45. ESI-MS: 298 [M+H^+]. *Anal.* Calcd for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71. Found: C 72.68, H 6.45, N 4.78.

3-Methyl-4-phenoxyacetyl-6-methoxy-3,4-dihydro-2*H*-1,4-benzoxazine (3c). Yield 72%. White solid, mp 102-103 °C; IR(KBr, cm^{-1}) *v*3050-2851(C-H), 1654(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 7.27-7.32(m, 3H, Ar-H), 6.67-7.02(m, 5H, Ar-H), 4.81-4.94(m, 3H, N-CH-, O-CH_2-C=O), 4.05-4.16(m, 2H, O-CH_2-)，3.70(s, 3H, Ar-O-CH_3)，1.24-1.26(d, *J*=9.0 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz)：δ 166.28, 157.80, 153.34, 140.09, 129.688, 129.69, 123.06, 121.87, 117.43, 114.64, 114.64, 112.90, 109.05, 69.70, 67.69, 55.77, 45.23, 15.50. ESI-MS: 314 [M+H^+]. *Anal.* Calcd for $C_{18}H_{19}NO_4$: C 68.99, H 6.11, N 4.47. Found: C 68.87, H 6.08, N 4.52.

3-Methyl-4-phenoxyacetyl-6-tert-butyl-3,4-dihydro-2*H*-1,4-benzoxazine (3d). Yield 76%. White solid；mp 95-96 °C; IR(KBr, cm^{-1}): *v*3063-2869(C-H), 1675(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.85-7.31(m, 8H, Ar-H)，4.80-4.96(m, 3H, N-CH-, O-CH_2-C=O), 4.19-4.13(m, 2H, O-CH_2-), 1.27(s, 12H, oxazine-CH_3, Ar-C(CH_3)$_3$); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.27, 157.87, 143.64, 129.61, 129.61, 123.68, 122.17, 121.74, 121.74, 121.03, 116.35, 114.59, 114.59, 70.10, 67.35, 45.08, 34.28, 31.42, 31.42, 31.42, 15.35. ESI-MS: 340 [M+H^+]. *Anal.* Calcd for $C_{21}H_{25}NO_3$: C 74.31, H 7.42, N 4.13. Found: C 74.28, H 7.45, N 4.18.

3-Methyl-4-phenoxyacetyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine (3e). Yield 64%. White solid, mp 85-86 °C, IR(KBr, cm^{-1}): *v*3065-2893(C-H), 1652(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.83-7.33(m, 8H, Ar-H), 4.87(s, 2H, O-CH_2-C=O), 4.78(m, 1H, N-CH-), 4.09-4.19(m, 2H, O-CH_2-) 1.26-1.24(d, *J*=9.0Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.36, 157.58, 144.54, 129.76, 129.76, 126.23, 125.30, 124.05, 123.59, 122.04, 118.04, 114.62, 114.62, 69.73, 68.00, 46.75, 15.68. ESI-MS: 318 [M+H^+]. *Anal.* Calcd for $C_{17}H_{16}ClNO_3$: C 64.26, H 5.08, N 4.41. Found: C 64.30, H 5.02, N 4.38.

3-Methyl-4-phenoxyacetyl-6,8-dichlor-3,4-dihydro-2*H*-1,4-benzoxazine (3f). Yield 78%. White solid, mp 49-50 °C; IR(KBr, cm^{-1}): *v*2972-2892(C-H), 1677(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.87-7.69(m, 7H, Ar-H), 4.84(s, 2H, O-CH_2-C=O), 4.71(m, 1H, N-CH-), 4.11-4.31(m, 2H, O-CH_2-)，1.24-1.23(d, *J*=4.5 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 M Hz): δ 166.53, 157.40, 140.87, 129.81, 129.81, 126.41, 124.94, 124.53, 122.78, 122.34, 122.17, 114.52, 114.52, 70.27, 68.05, 45.99, 15.70. ESI-MS: 352 [M+H^+]. *Anal.* Calcd for $C_{17}H_{15}Cl_2NO_3$: C 57.97, H 4.29, N 3.98. Found: C 57.92, H 4.21, N 4.05.

Crystal data for compound 3f: $C_{17}H_{15}Cl_2NO_3$, triclinic, space group $P\bar{1}$, *a*=9.0786(18) Å, *b*=10.568(2) Å, *c*=10.798(2) Å, *V*=3025.6(10) $Å^3$, *α*=106.88(3), *β*=97.94(3), *γ*=93.77(3), *Z*=2, D_c=1.342 cm^{-3}, *μ*=0.352 mm^{-1}, *F*(000)= 412. Independent reflections were obtained in the range of 3.22° < *θ* < 25.00, 1464. The final least-square cycle gave R_1= 0.0648, ωR_2 = 0.1209 for 3413 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.306 and -0.297 e/$Å^3$, respectively.

3-Methyl-4-phenoxyacetyl-6-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine (3g). Yield 72%. White solid, mp 95-96 °C; IR(KBr, cm^{-1}): *v*3052-2870(C-H), 1673.23(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.83-7.32(m, 8H, Ar-H), 4.82-4.95(m, 3H, N-CH-, O-CH_2-C=O), 4.09-4.18(m, 2H, O-CH_2-), 2.52-2.60(q, 2H, J_1=7.5 Hz, J_2=15.0 Hz, Ar-CH_2-), 1.16-1.26(m, 6H, Ar-C-CH_3, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.33, 157.82, 144.02, 136.58, 129.64, 129.64, 126.08, 123.29, 122.48, 121.79, 116.78, 114.64, 114.64, 69.97, 67.69, 44.83, 28.20, 15.67, 15.67. ESI-MS: 312 [M+H^+]. *Anal.* Calcd for $C_{19}H_{21}NO_3$: C 73.29, H

6.80, N 4.50. Found: C 73.32, H 6.75, N 4.42.

3-Methyl-4-phenoxyacetyl-6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine (3h). Yield 70%. White solid, mp 95-96 °C; IR(KBr, cm^{-1}): *v*3060-2932(C-H), 1654(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.78-7.34(m, 8H, Ar-H), 4.83-4.95(m, 3H, N-CH-, O-CH_2-C=O), 4.09-4.20(m, 2H, O-CH_2-), 1.24-1.26(d, *J*=6.6 Hz, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.35, 157.55, 145.03, 129.77, 129.14, 126.87, 124.00, 122.04, 120.65, 118.49, 117.11, 114.60, 112.33, 69.74, 67.91, 46.85, 15.67. ESI-MS: 364 [M+2]. *Anal.* Calcd for $C_{17}H_{16}BrNO_3$: C 56.37, H 4.45, N 3.87. Found: C 56.42, H 4.52, N 3.81.

3,7-Dimethyl-4-phenoxyacetyl-3,4-dihydro-2*H*-1,4-benzoxazine (3i). Yield 63%. White solid, mp 43-44 °C; IR(KBr, cm^{-1}): *v*2966-2931(C-H)，1684(C=O); ^{1}H-NMR($CDCl_3$, 300 MHz): δ 6.71-7.29(m, 8H, Ar-H), 4.81-4.92(m, 3H, N-CH-Me, O-CH_2-C=O), 4.09-4.15(m, 2H, O-CH_2-C), 2.29(s, 3H, Ar-CH_3), 1.20(s, 3H, oxazine-CH_3); ^{13}C-NMR($CDCl_3$, 75 MHz): δ 166.24, 157.81, 145.86, 129.61, 129.61, 123.94, 121.75, 121.47, 121.47, 120.17, 117.36, 114.67, 114.67, 70.04, 67.02, 26.95, 20.97, 15.29. ESI-MS: 298 [M+1]. *Anal.* Calcd for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71. Found: C 72.65, H 6.41, N 4.78.

Biological activity: Maize (Dongnong 253) seeds were moistened with warm water about 30 min. The untreated or safener-treated maize were soaked by title compounds (10mg/kg) for 12 h, and then germinated for 24 h at 26.5 °C. The seeds were planted 1.5 cm deep in plastic trays, in which soil was treated with 0.244 g/m^2 2,4-D butylate. Trays were incubated at 28 °C for 7 days. The effects of the title compound on the detoxification of 2,4-D butylate in soil were determined by testing the growth level.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis of **3f** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1040927). These data can be obtained free of charge from The Cambridge Crystallographic Datavia www.ccdc.cam.ac.uk/data_request/cif.

ACKNOWLEDGMENT

This work was supported by the National Nature Science Foundation of China (No. 31401787), China Postdoctoral Science Foundation（2014M551208), Natural Science Foundation of Heilongjiang Province (B201212), and the Science and Technology Research Project of Heilongjiang Education Department (No. 12531027).

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