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Synthesis, Crystal Structure, and Safener Activity of Some New *N*-Dichloroacetylindole Derivatives

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ABSTRACT Seven new *N*-dichloroacetyl indole derivatives were designed and synthesized by the theory of active fragment splicing. The title compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry. The structure of 2,2-dichloro-1-(5-fluoro-1H-indol-1-yl)ethanone (**2c,** $C_{10}H_6Cl_2FNO$) was determined by single-crystal X-ray diffraction. Compound **2c** crystallizes in the monoclinic system, space group $P2_1/n$ with a = 9.2047(6) Å, b = 10.6564(7)Å, c = 9.9906(6) Å, β = 90.629(2)°, V = 979.91(11) Å^3, D_c = 1.668 Mg/m^3, Z = 4, F(000) = 496, μ(MoKα) = 0.644 mm^{-1}, R_1 = 0.0347, and wR_2 = 0.0915. Biological assay indicated all the compounds could protect maize under acetochlor toxicity stress in different degree, particularly the compound **2c** exhibited similar effects as commercial herbicide safener AD-67.

KEYWORDS *N*-Dichloroacetyl indole derivatives, Synthesis, Crystal structure, Safener activity.

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INTRODUCTION

Acetochlor, an chloroacetamide herbicide, was one of the most widely used herbicides in China to control annual graminaceous weeds and some broadleaf weeds in many fields such as corn, peanut, and soybean on account of its broad spectrum and high efficiency.[1,2] However, the use of herbicides as acetochlor has been reported negative effect on crop growth, development and yield, especially under adverse weather conditions.[3] To prevent and alleviate the phytotoxicity of herbicide to crop plants, herbicide safener has been adopted as the most cost-effective solution.

Herbicide safeners are chemicals that could reduce herbicide damage to crops and improve the selectivity of herbicides without affecting the herbicide activity to weed.[4] Safeners give new vigor to some traditional herbicides with high efficiency, broad spectrum but harmful effects on crops. More than 30 kinds of herbicide safeners and their commercial composition with herbicide have been launched on the market. Up to now, nearly ten commercial herbicide safeners belong to dichloroacetamides, such as dichlormid, acetamide, and AD-67. They were applied to crops (e.g., corn, sorghum, and cereal) to protect them from the damage of chloroacetanilide, thiocarbamate, and imidazolinone herbicides. Although the detoxifying mechanism of safener is still not entirely definite, the present studies showed that it appeared to be related to a range of enzymes.[5-7] For example, R-28725 can raise the activity of glutathione-S-transferase (GST) and promote the conjugation between herbicide and glutathione (GSH) in plant to enhance the detoxification to herbicide.[8]

Heterocyclic compounds act a significant part in the field of medicinal chemistry due to the physiological and pharmacological properties. About 70% of pesticides contain heterocyclic rings in their molecular structures,[9] and N, S, containing heterocyclic molecule have drawn especially interests. Indole derivatives as a remarkable nitrogen-containing heterocyclic compounds have extraordinary physiological activity and hold significant status in pestcide chemistry, medical science, and materials science.[10-12] In agriculture, indole-3-acetic acid and indole-3-butyric acid are plant growth regulators,[13,14] and 5-iodoindole was proved to have insecticidal activity

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The maize seedlings treated with distilled water (the control), acetochlor only, and safener + acetochlor were measured at 7 d after treatment. Moreover, the injury recovery rates of plant height, plant weight, root height, and root weight were calculated by the following equation to determine the biological activity of the potential safeners.[29]

$$IRR(\%) = \frac{Treated\ with\ compounds\ and\ acetochlor - Treated\ with\ acetochlor}{Control - Treated\ with\ acetochlor} \times 100$$

Determination of GSH Content and GST Activity

Growth conditions were the same as described above, and the maize seeds treated with the target compounds (100 μM) and AD-67 (100 μM) was applied in determination of GSH content and GST activity. The content of GSH was measured as described by Gao's method[30] and improved in this study. The extraction and activity assay of GST was based on Zhao[31] and modified, and all steps were performed at 0 ~ 4°C.

0.2 g plant root were added to the mortar, an appropriate amount of liquid nitrogen and 1.2 mL of 5% TCA were poured the mortar, plant root in the mortar were ground and transferred to the centrifugal tube and were centrifuged at a centrifugal force of 15,000 g for 20 min. 0.8 mL of supernatant was obtained after centrifugation, 1.6 mL of 0.5 mol·L^{-1} pH = 8 phosphoric acid buffer, and 16 μL of 10 mmoL/L DTNB were added to the supernatant. OD value was measured at 412 nm, and GSH content in root and leaves were calculated according to the standard curve.

0.2 g plant root to be tested were ground with appropriate amount of liquid nitrogen and 1 mL of enzyme GST extract. Centrifugation was performed as above. The supernatant was the enzyme liquid to be measured. 0.5 mL 3.0 mmoL/L GSH, 2.3 mL 0.1 mol/L buffer with pH=6.5 potassium phosphate, and 0.5 mL 20 mmoL/L in CDNB of 96% ethanol were added to 10 μL of the enzyme solution to be tested. The absorbance changes within 6 min were measured at 340 nm. The amount of enzyme catalyzed to produce 1 μmoL GS-DTNB within 1 min was taken as one unit of enzyme activity. The specific activity of GST was calculated as shown in the formula.

$$The\ specific\ activity\ of\ GST\ (\mu mol \cdot \min^{-1} \cdot mg^{-1}\ protein) = \frac{\text{The activity of GST}}{The\ amount\ of\ enzyme\ protein\ used\ was\ determined}$$

CONCLUSION

Seven new *N*-dichloroacetyl indole derivatives were successfully designed, synthesized, and characterized. The crystal structure of **2c** was determined by single-crystal X-ray diffraction. It had been confirmed that the compounds **2a** ~ **2g** have safener activity protecting maize from the damage of acetochlor in different degrees. Compound **2c** displayed excellent effects against acetochlor toxicity by improving the content of GSH and the activity of GST. Experiment shows that the protective effects of **2c** were similar to **AD-67**. This study provided a kind of promising potential safeners for maize protection; further, study will be carried out about this series of derivatives.

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