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DESIGN, SYNTHESIS AND BIOACTIVITY EVALUATION OF NOVEL PINOXADEN DERIVATIVE

Yang Zi-hui* Wang Ming-Liang Yang Gong Zheng

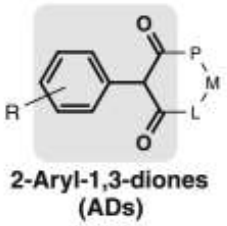
.Shan Dong Jinhuahai Biotechnology Co.,Ltd., Jinan Shandong,China
Email: *kih352870@163.com*

ABSTRACT: A novel compound was designed and synthesized with the bioisosteres rules, using commercial herbicide pinoxaden as the lead compound .The structure was confirmed by ^{1}H NMR and elemental analysis The herbicidal activity were also evaluated.. The herbicidal activity was in progress.

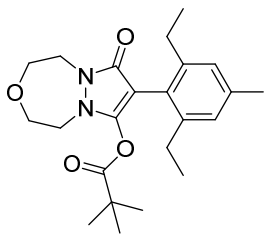
KEYWORDS: pinoxaden,herbicidal activity, monocotyledonous weeds

INTRODUCTION

2-(4-Aryloxyphenoxy)propanoates (APP), as one of the most important inhibitor of acetyl-CoA carboxylase (ACCase)[I], was found in 1970s. However, the application of APP herbicides to protect crops was still an important part of Integrated Pest Management (IPM)up to now, so the worldwide emergence of drug-resistant has been greatly increased with the abuse of various APP herbicides[II,III]. and it was necessary to attempt neotype chemical entities as potential herbicides .In 1990s, 2-Aryl-1,3-diones (ADs) and their enol derivatives had been found as a new class of acetyl-coenzyme A carboxylase (ACCase,EC 6.4.1.2) inhibitors.With its novel structure, 2-Aryl-1,3-diones (ADs) derivatives were used in cereal crop with no crossing resistences to APP herbicides. Pinoxaden, which was patented and launched in 1999, had been one of the ten best-seller herbicides in global market in 2013-2018, with its advantage of safety to cereal, low dosage and low residue.

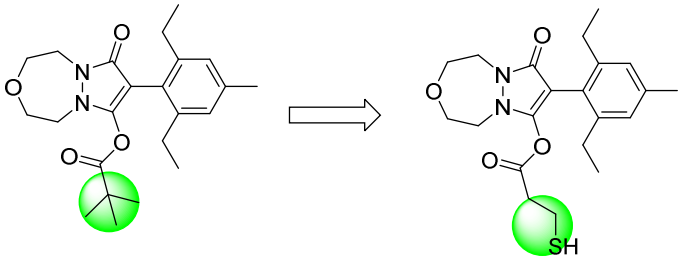


2-Aryl-1,3-diones
(ADs)



Pinoxaden

Fascinated by these findings and the structure-relationships of 2-Aryl-1,3-diones (ADs) and their enol derivatives[IV], A novel compound was designed and synthesized with the bioisosteres rules, by using thecommercial herbicide pinoxaden as the lead compound .The structure was confirmed by ^{1}H NMR and elemental analysis.Their herbicidal activity were evaluated in progress.The design route of the target compound were as follows.



Compound 6

Figure 1 The design route of compound 6

Experimental Section

Chemical Synthesis

General

All the reagents were of analytical grade and were used without further purification. Melting points were measured on an X-4 electrothermal digital melting point apparatus and uncorrected. All reactions were monitored by thin-layer chromatography on 0.25mm silica gel plates (60GF-254) and visualized with UV light. Flash chromatography was performed on silica gel (200–400 mesh) using commercially available petroleum ether and ethyl acetate. ^{1}HNMR spectra were recorded on a Bruker AV-300(USA) spectrometer with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed on a Vario EL III (Germany instrument

All the solvent and regaent were in chemical pure.

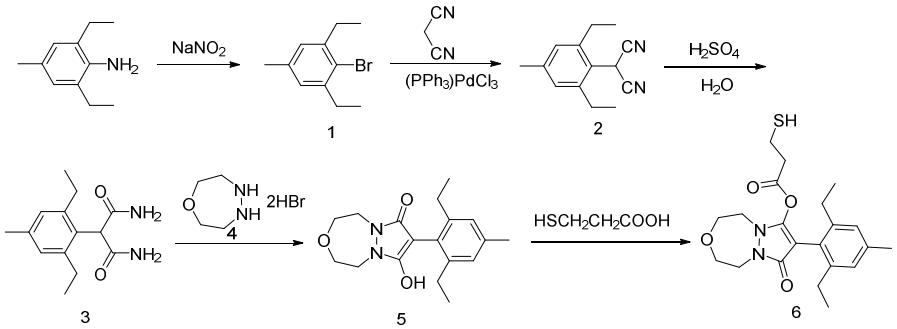


Figure 2 The synthetic route of compound 6

The compound 1-5 were prepared according to previously reported methods[V].

The synthesis procedure of Intermediate 1,

65.2 g(0.4 mol)2,6-diethyl-4-methylbenzeneamide was added into the 280 g 40% HBr aqueous, The reaction was cooled under 5 □The $NaNO_2$ aqueous33.1 g(0.48 mol) was dopwised.Then, the 262.2 g(0.2 mol) $CuBr_2$ was added, the mixture was heated to 60 □ for 4

h,While the reaction was completed, The mixture was droped into the 250 mL ice water, the CH_2Cl_2 was extracted three times, dried and condensed to give the crude product.liquid, boiling point 102-104□(Lit[V],102-106□) yield,88%.
Intermediate 2,yellow solid,m.p.82-83□(Lit[V],82-85□),yield 73%.
Intermediate 3, white solid, yield,90%,(Lit[V],yield95%.)
Intermediate 4, white solid, yield 68%,(Lit[V],yield70%.)
Intermediate 5, dark yellow solid. m.p.163-165 □, (Lit[V],160-165□)
General synthesis of target compound 6

The intermediate 5（158 mg，0.5 mmol）was dissolved in 30 ml DCM, and the $SOCl_2$(0.1 ml)was added into the mixture,the reaction was stirred for 2 h, While the reaction was completed ,the solvent was removed, the $HSCH_2CH_2COOH$ was dissolved in 30 ml THF, and the DMAP catalyst(,20mg) and TEA(101 mg) were treated into the following mixture, the mixture was added dropwised into the mixture,and the reaction was stirred overnight. The solvent was removed ,and 30 ml DCM was dissolved with the crude product, the organic phase was washed with $NaHCO_3$(a.q.)and NaCl(a.q.),dried with Na_2SO_4, and it was to give the white product 120 mg by removing the solvent,yield 59%.

Copmpound 6,white solid, m.p.130-133^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ:6.90-6.92(m,2H,phenyl),4.72(s,1H,CH_2),4.25-4.32(m,3H,O(CH_2)$_2$),3.76-4.03(m,8H,2X(CH$_2$$CH_3$),$CH_2SH$),2.21-2.29(m,5H,$CH_2COO$),1.42(s,1H,SH),1.10-1.27(m,6H,2XCH_3)
Anal.calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93; found C, 62.30; H, 6.93; N, 6.90.

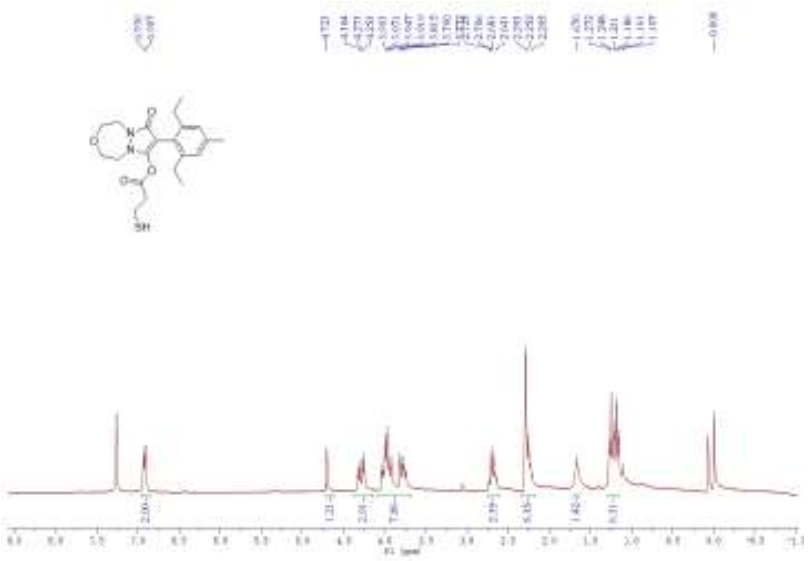


Figure **3** ^{1}H NMR spectra of compounds of **6**

The Procdeure of Herbicidal activity

The herbicidal activity assay of the compound was in progress.

RESULTS AND DISCUSSION

Synthesis of the target compound. The synthesis method of intermediate 1-5 was referred according the previous reports[5].

The synthesis of target compound 6 was using the method ,the chloride and alochloic by using the organic base. This method has the advantage of high yield.

CONCLUSION

A novel compound was designed and synthesized with the bioisosteres rules, using commercial herbicide pinoxaden as the lead compound .The structure was confirmed by ^{1}H NMR and elemental analysis The herbicidal activity was in progress.

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