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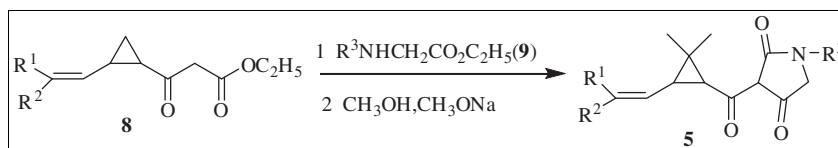
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A variety of novel 3-(α -hydroxymethylene)pyrrolidine-2,4-dione derivatives containing a cyclopropane moiety were designed and synthesized in satisfactory yields. Their structures were confirmed by ¹H NMR and HRMS. The bioassays indicated that most of the title compounds displayed some extent herbicidal activities at 100 mg/mL.

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INTRODUCTION

Heterocyclic compounds are significant in modern organic and agrochemical chemistry due to their presence in a majority of well-known pharmaceutical preparations [1]. For these reasons, we have for a long time been interested in the synthesis of new heterocycles of potential pharmaceutical value. Recently, our attentions were focused on the preparation of compound **1** through a modification of the natural product **2** [2–7], which was inhibitory toward 4-hydroxyphenylpyruvate dioxygenase (HPPD, EC 1.13.11.27) with an IC₅₀ = 18 μ M [8]. The bioassay results showed that when *R*¹ was electron-donating, compound **1** exhibited better herbicidal activities [3–7]. In particular, when *R*¹, *R*², and *R*³ were 2,4-dimethoxy, *iso*-propyl, and hydrogen, respectively, compound **1** provided 93% control of *Echinochloa crus-galli* at pre-emergence at 187.5 g/ha.

It was also noticed that α -ketoisocaproate (**3**) serve as natural substrates for HPPD [9]. In light of these findings and subsequent comparisons of the molecular structures of both HPPD enzyme substrates and triketone type inhibitors, Lin and co-workers reported 2-cyclopropanoylcyclohexane-1,3-dione (**4**) exhibited higher *in vitro* inhibition activity against HPPD (IC₅₀ = 6 μ M) [10]. In order to find valuable new lead compounds with high herbicidal activities, compounds **5** were designed and synthesized through replacement of the aryl group of compound **1** by different cyclopropyl groups. In this paper, we described the synthesis and herbicidal activities of some 3-[(α -hydroxy(cyclopropyl)methylene]pyrrolidine-2,4-diones **5** (Figure 1, Scheme 1).

RESULTS AND DISCUSSION

Preparations. Among the many methods for synthesizing β -keto esters of the type RCOCH₂CO₂C₂H₅, three classical

syntheses via acetoacetic esters [11], via Meldrum's acid [12,13], and via mixed malonic esters [14] are practically useful, although not always satisfactory in yield. In this paper, considering the properties of acyl chlorides (**6**) and the starting materials' availability, β -keto esters (**8**) were synthesized through a general and versatile method based on the noteworthy reactivity of Meldrum's acid.

Compound **5** can be synthesized by acetylation of pyrrolidine-2,4-dione followed by the acyl group's migration [15] or reaction of acyl acetates with *N*-alkyl aminoacetates [16]. We preferred the latter method to prepare the target products **5** for its less toxic reagents and greater convenience. Intermediate **8** was reacted with **9** in refluxing absolute xylene to give the target compound **5** (Scheme 1). This reaction was assumed to go through a nucleophilic addition/elimination reaction. During this process, an intermediate amide's formation and a cyclizative condensation were involved.

Structure–activity relationship. A series of the related target products **5** were prepared and their herbicidal activities were tested, and the results listed in Table 4 shows that most of the target products **5** exhibited a higher inhibition rate for *Brassica campestris* than that for *E. crus-galli* at 100 μ g/mL and this result indicated the selectivity of this kind compounds was effected by the halogen's introduction (such as **5s**).

For *B. campestris* at 100 μ g/mL, when the substituent *R*³ was *iso*-propyl, propyl, allyl, and cyclo-propyl, the corresponding compounds **5** (except for **5m**, **5p**) generally exhibited better herbicidal activity than those compounds **5** (*R*³ = butyl and *sec*-butyl) **2**, as a result of substituent steric hindrance.

For *E. crus-galli* at 100 μ g/mL, most of the target compounds **5** exhibited moderate herbicidal activity, but

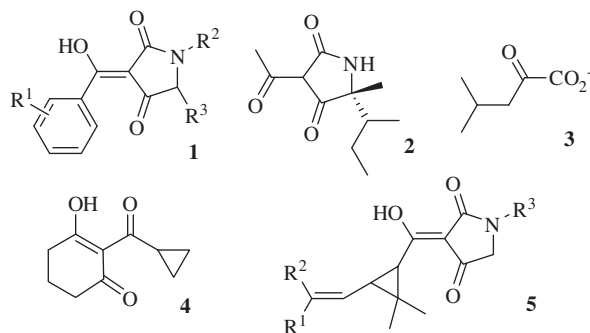
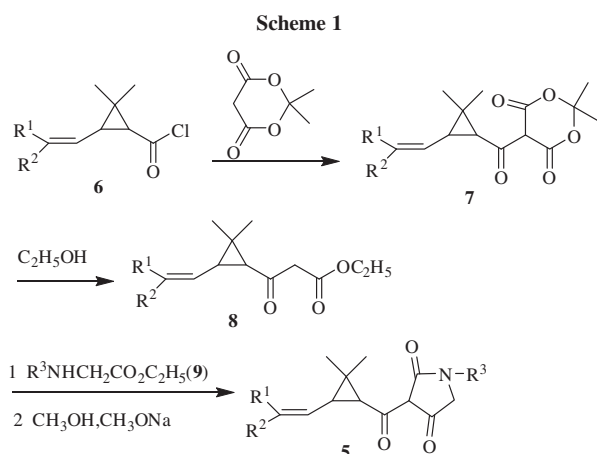


Figure 1. Chemical structures of compounds 1–5.



when R^1 , R^2 , and R^3 were methyl, methyl, and iso-propyl, respectively, compound **5s** showed about 89% inhibiting rate. Considering that compound **5s** also possessed excellent herbicidal activity (about 95%) for *B.campestris*, compound **5** (R^1 , R^2 =methyl) will be our next research emphasis.

In summary, a variety of novel 3-(α -hydroxymethylene)pyrrolidine-2,4-dione derivatives were designed and synthesized in satisfactory yields and the bioassays indicated that most of the title compounds displayed some extent herbicidal activities.

EXPERIMENTAL

All chemicals were purchased from commercial sources and purified by recrystallization or distillation. NMR spectra were recorded on a Bruker DPX 400 spectrometer (Bruker BioSpin AG industriestrasse 26CH-8117, Fallanden, Switzerland.); data for ^1H are reported as follows: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad), coupling constant (Hz), and number. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. High resolution mass spectra were recorded on a VARIAN 7.0 T direct inlet instrument (IonSpec Corporation, Lake Forest, USA). Solvents were fractionally distilled before use.

Compounds 8a–8d were synthesized as the literature described [12,13,17,18]. Meldrum's acid (0.01 M) was dissolved in 75 mL of methylene chloride, and the reaction mixture was placed under nitrogen and brought to 0°C with an ice bath; pyridine (0.02 M) was then added by means of a dropping funnel. The appropriate acid chloride (0.01 M) was added over a 30-min period to the vigorously stirred mixture. After the final addition, the solution was allowed to rise to room temperature and allowed to stand for 3 h. The reaction was monitored by TLC (silica gel). Upon termination, the mixture was then washed with 30 mL of 4 N HCl, 2% sodium bicarbonate, and distilled water saturated with sodium chloride. The dried (MgSO_4) organic phase was filtered and crude **7a–7d** was obtained by solvent removal *in vacuo* and not further purified. The residue crude **7a–7d** was resolved in 10 mL of ethanol and refluxed for 2 h. The solvent was removed, and the residue was purified by flash silica gel chromatography using petroleum ether ($60\text{--}90^\circ\text{C}$) and ethyl acetate as the eluent to yield **8a–8d**. All of the compounds were identified by ^1H NMR spectroscopy. Their yields of compounds **8a–8d** are listed in Table 1.

General synthetic procedure for 5a–5s. Compounds **5a–5s** were synthesized as the literature described [6,7,16].

A mixture of **8** (3 mmol) and **9** (3.13 mmol) in dry xylene (5 mL) was heated at $125\text{--}130^\circ\text{C}$ with stirring for 24 h. The cooled solution was added to methanolic CH_3ONa , prepared from Na metal (3.35 mmol) and methanol (4 mL) at room temperature with stirring. After the aforementioned mixture was stirred at room temperature for 48 h, water (20 mL) was added to the reaction mixture and the organic layer was separated and extracted twice with water. The original water layer and the extracts were combined and acidified to pH 2–3 with 2N HCl under cooling. The acidic solution was extracted three times with chloroform (30 mL), and the extracts were washed with saturated brine and then dried over Na_2SO_4 . The solvent was removed under reduced pressure to give crude product **5**, which was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether as the eluent to afford the pure target product. The melting points and yields of compounds **5a–5s** are listed in Table 2, and their ^1H NMR are listed in Table 3.

Bioassays. The herbicidal activities of the title compounds (**5a–5s**) were evaluated using a previously reported procedure [4,5].

Treatment. The emulsions of purified compounds were prepared by dissolving them in 100 μL of *N,N*-dimethylformamide with the addition of a little Tween 20 and proper water. There were two

Table 1

Yields and ^1H NMR data of compound **8**.

	R^1	R^2	Yield (%)	mp ($^\circ\text{C}$)
8a	Cl	Cl	88	liquid
8b	Br	Br	82	liquid
			1.21 (s, 3H), 1.28–1.31 (m, 6H), 2.12 (t, $J=8.2$ Hz, 1H), 2.25 (d, $J=8.0$ Hz, 1H), 3.54 (q, $J=15.1$ Hz, 2H), 4.21 (q, $J=7.1$ Hz, 2H), 6.80 (d, $J=8.5$ Hz, 1H)	
8c	CH_3	CH_3	44	liquid
8d	CF_3	Cl	85	liquid
			1.16 (s, 3H), 1.22 (t, $J=7.1$ Hz, 3H), 1.27 (s, 3H), 2.24 (t, $J=8.5$ Hz, 1H), 2.31 (d, $J=8.0$ Hz, 1H), 3.47 (q, $J=14.7$ Hz, 2H), 4.14 (q, $J=7.1$ Hz, 2H), 6.88 (d, $J=9.1$ Hz, 1H)	

Table 2
Melting points, yields, and mass data of compounds **5a–5s**.

	R^1	R^2	R^3	mp/°C	Yield (%)	MS (ESI, m/z):
5a	Cl	Cl	C ₃ H ₇	liquid	58	330.0675[(M – H) [–] ,100%]
5b	Cl	Cl	<i>iso</i> -C ₃ H ₇	113–114	58	330.0669[(M – H) [–] ,100%]
5c	Cl	Cl	<i>cyclo</i> -C ₃ H ₅	liquid	18	328.0515[(M – H) [–] ,100%]
5d	Cl	Cl	<i>allyl</i>	liquid	58	328.0513[(M – H) [–] ,100%]
5e	Cl	Cl	C ₄ H ₉	liquid	47	344.0826[(M – H) [–] ,100%]
5f	Cl	Cl	<i>sec</i> -C ₄ H ₉	liquid	56	344.0826[(M – H) [–] ,100%]
5g	Br	Br	C ₃ H ₇	liquid	43	419.9639[(M – H) [–] ,100%]
5h	Br	Br	<i>iso</i> -C ₃ H ₇	liquid	51	443.9587[(M + Na) ⁺ ,100%]
5i	Br	Br	<i>cyclo</i> -C ₃ H ₅	liquid	27	417.9485[(M – H) [–] ,100%]
5j	Br	Br	<i>allyl</i>	liquid	50	417.9482[(M – H) [–] ,100%]
5k	Br	Br	C ₄ H ₉	liquid	30	433.9795[(M – H) [–] ,100%]
5l	Br	Br	<i>sec</i> -C ₄ H ₉	liquid	28	435.9931[(M + H) [–] ,100%]
5m	Cl	CF ₃	C ₃ H ₇	54–55	60	364.0930[(M – H) [–] ,100%]
5n	Cl	CF ₃	<i>iso</i> -C ₃ H ₇	82–84	54	388.0898[(M + Na) ⁺ ,100%]
5o	Cl	CF ₃	<i>cyclo</i> -C ₃ H ₅	liquid	37	362.0772[(M – H) [–] ,100%]
5p	Cl	CF ₃	<i>allyl</i>	liquid	41	362.0771[(M – H) [–] ,100%]
5q	Cl	CF ₃	C ₄ H ₉	liquid	32	378.1089[(M – H) [–] ,100%]
5r	Cl	CF ₃	<i>sec</i> -C ₄ H ₉	72–74	45	378.1089[(M – H) [–] ,100%]
5s	CH ₃	CH ₃	<i>iso</i> -C ₃ H ₇	liquid	54	290.1762[(M – H) [–] ,100%]

Table 3
¹H NMR of compounds **5a–5s**.

	¹ H NMR δ (ppm)
5a	0.94 (t, $J=7.3$ Hz, 3H), 1.35 (s,3H), 1.36(s,3H), 1.56–1.67(m,2H), 2.42(t, $J=8.8$ Hz,1H), 3.23(d, $J=8.5$ Hz, 1H), 3.40 (t, $J=7.2$ Hz,2H), 3.72 (s, 2H),6.23 (d, $J=9.3$ Hz,1H)
5b	1.14 (s, 3H), 1.15 (s, 3H), 1.28 (d, $J=5.4$ Hz, 6H), 2.34 (t, $J=8.7$ Hz, 1H), 3.15 (d, $J=8.4$ Hz, 1H),3.61 (s, 2H), 4.38–4.45 (m, $J=6.6$ Hz, 1H), 6.16 (d, $J=9.1$ Hz, 1H)
5c	0.72–0.80 (m, 4H), 1.26 (s, 3H), 1.28 (s, 3H), 2.34 (t, $J=9.0$ Hz, 1H), 2.62–2.68 (m, 1H), 3.14 (d, $J=8.4$ Hz, 1H), 3.61 (s, 2H), 6.15 (d, $J=9.1$ Hz, 1H)
5d	1.35 (s, 3H), 1.36 (s, 3H), 2.43 (t, $J=8.8$ Hz, 1H), 3.24 (d, $J=8.4$ Hz, 1H), 3.71 (s, 2H), 4.04–4.06 (m, 2H), 5.19–5.22 (m, 1H), 5.26–5.28 (m, 1H), 5.73–5.81 (m, 1H), 6.22 (d, $J=9.2$ Hz, 1H)
5e	0.96 (t, $J=7.3$ Hz, 3H), 1.31–1.40 (m, 2H), 1.35 (s, 3H), 1.36 (s, 3H), 1.53–1.60 (m, 2H), 2.42 (t, $J=8.7$ Hz, 1H), 3.23 (d, $J=8.5$ Hz, 1H), 3.44 (t, $J=7.2$ Hz, 2H), 3.72 (s, 2H), 6.23 (d, $J=9.2$ Hz, 1H)
5f	0.82 (t, $J=7.4$ Hz, 3H), 1.12 (d, $J=6.7$ Hz, 3H), 1.25–1.29 (m, 6H), 1.42–1.51 (m, 2H), 2.34 (t, $J=8.8$ Hz, 1H), 3.16 (d, $J=8.5$ Hz, 1H), 3.49–3.62 (m, 2H), 4.11–4.20 (m, 1H), 6.15–6.19 (d-d, $J_1=4.8$, $J_2=9.2$, 1H)
5g	0.95 (t, $J=7.4$ Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.57–1.66 (m, $J=7.3$ Hz, 2H), 2.34 (t, $J=8.7$ Hz, 1H), 3.24 (d, $J=8.4$ Hz, 1H), 3.40 (t, $J=7.3$ Hz, 2H), 3.72 (s, 2H), 6.75 (d, $J=8.9$ Hz, 1H)
5h	1.14 (s, 3H), 1.15 (s, 3H), 1.26–1.28 (m, 6H), 2.26 (t, $J=8.6$ Hz, 1H), 3.16 (d, $J=8.4$ Hz, 1H), 3.60(s, 2H), 4.37–4.46 (m, $J=6.7$ Hz,1H), 6.68 (d, $J=8.8$ Hz, 1H)
5i	0.72–0.80 (m, 4H), 1.26 (s, 3H), 1.28 (s, 3H), 2.26 (t, $J=8.6$ Hz, 1H), 2.64–2.70 (m, 1H), 3.15 (d, $J=8.5$ Hz, 1H), 3.60 (s, 2H), 6.66 (d, $J=8.8$ Hz, 1H)
5j	1.34 (s, 3H), 1.36 (s, 3H), 2.37 (t, $J=8.6$ Hz, 1H), 3.25 (d, $J=8.4$ Hz, 1H), 3.71 (s, 2H), 4.04–4.06(m, 2H), 5.19–5.22 (m, 1H), 5.26–5.29 (m, 1H), 5.72–5.81 (m, 1H), 6.74 (d, $J=8.8$ Hz,1H)
5k	0.88 (t, $J=7.3$ Hz, 3H), 1.24–1.33 (m, 8H), 1.46–1.53 (m, 2H), 2.27 (t, $J=8.6$ Hz, 1H), 3.16 (d, $J=8.4$ Hz, 1H), 3.37 (t, $J=7.1$ Hz, 2H), 3.65 (s, 2H), 6.67 (d, $J=8.9$ Hz, 1H)
5l	0.83 (t, $J=7.4$ Hz, 3H), 1.12 (d, $J=6.5$ Hz, 3H), 1.27–1.29 (m, 6H), 1.42–1.51 (m, 2H), 2.26 (t, $J=8.6$ Hz, 1H), 3.17 (d, $J=8.5$ Hz, 1H), 3.50–3.64 (m, 2H), 4.78–4.82 (m, 1H), 6.69 (d, $J=5.3$ Hz, 1H)
5m	0.95 (t, $J=7.3$ Hz, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.56–1.68 (m, $J=7.2$ Hz, 2H), 2.53 (t, $J=9.0$ Hz,1H), 3.36 (d, $J=8.4$ Hz, 1H), 3.41 (t, $J=7.2$ Hz, 2H), 3.74 (s, 2H), 6.89 (d, $J=9.6$ Hz, 1H)
5n	1.14 (s, 3H), 1.15 (s, 3H), 1.31 (d, 6H), 2.44 (t, $J=8.8$ Hz, 1H), 3.27 (d, $J=8.4$ Hz, 1H), 3.62 (s, 2H),4.38–4.44 (m, $J=6.5$ Hz, 1H), 6.81 (d, $J=9.6$ Hz, 1H)
5o	0.72–0.81 (m, 4H), 1.30 (s, 3H), 1.32 (s, 3H), 2.44 (t, $J=9.0$ Hz, 1H), 2.64–2.70 (m, 1H), 3.26 (d, $J=8.4$ Hz, 1H), 3.62 (s, 2H), 6.79 (d, $J=9.6$ Hz, 1H)
5p	1.30 (s, 3H), 1.33 (s, 3H), 2.46 (t, $J=9.0$ Hz, 1H), 3.28 (d, $J=8.4$ Hz, 1H), 3.64 (s, 2H), 3.96–3.98 (m, 2H), 5.11–5.20 (m, 1H), 5.63–5.73 (m, 1H), 6.80 (d, $J=9.6$ Hz, 1H)
5q	0.96 (t, $J=7.32$ Hz, 3H), 1.29–1.41 (m, 8H), 1.53–1.60 (m, 2H), 2.52 (t, $J=9.0$ Hz, 1H), 3.35 (d, $J=8.4$ Hz, 1H), 3.45 (t, $J=7.40$ Hz, 2H), 3.74 (s, 2H), 6.88 (d, $J=9.6$ Hz, 1H)
5r	0.83 (t, $J=7.4$ Hz, 3H), 1.12 (d, $J=6.8$ Hz, 3H), 1.27–1.29 (m, 6H), 1.41–1.51 (m, 2H), 2.44 (t, $J=8.9$ Hz, 1H), 3.28 (d, $J=8.5$ Hz, 1H), 3.51–3.63 (m, 2H), 4.11–4.20 (m, 1H), 6.80–6.84 (m, 1H)
5s	1.19 (s, 3H), 1.21 (s, 3H), 1.30 (d, $J=18.3$ Hz, 6H), 1.69 (s, 3H), 1.72 (s, 3H), 2.51 (t, $J=6.7$ Hz, 1H), 2.76 (d, $J=5.6$ Hz, 1H), 3.65 (s, 2H), 4.46–4.53 (m, $J=6.8$ Hz, 1H), 5.02 (d, $J=7.9$ Hz, 1H)

Table 4

Herbicidal activity of compounds **5a–5s** (percent inhibition; concentration 100 mg/mL).

	<i>Brassica campestris</i>	<i>Echinochloa crus-galli</i>
5a	94.8	30.0
5b	94.8	44.3
5c	92.2	42.0
5d	94.8	44.3
5e	75.9	41.4
5f	87.0	40.0
5g	74.0	35.0
5h	83.7	22.0
5i	79.8	15.0
5j	92.8	74.1
5k	60.3	12.8
5l	66.8	12.8
5m	0	39.2
5n	92.2	32.3
5o	85.7	43.1
5p	0	35.0
5q	5.7	33.1
5r	60.3	23.7
5s	94.8	89.4

replicates for each treatment. The mixture of the same amount of water, *N,N*-dimethylformamide and Tween 20 was used as control.

Inhibition of the root growth of rape (*B. campestris* L).

Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6-cm Petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 15 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 65 h at 28 (± 1) °C. The lengths of 10 rape roots selected from each plate were measured, and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. The herbicidal activity is summarized in Table 4.

Inhibition of the seedling growth of barnyard grass (*E. crus-galli* L. BeauV). Ten *E. crus-galli* seeds were placed into a 50-mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup was placed in a bright room, and the seeds were allowed to germinate for 65 h at 28 (± 1) °C. The heights of the aboveground parts of the seedlings in each cup were measured and the means calculated. The percentage

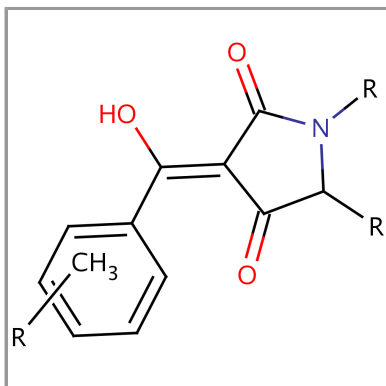
inhibition was used to describe the control efficiency of the compounds. The herbicidal activity is summarized in Table 4.

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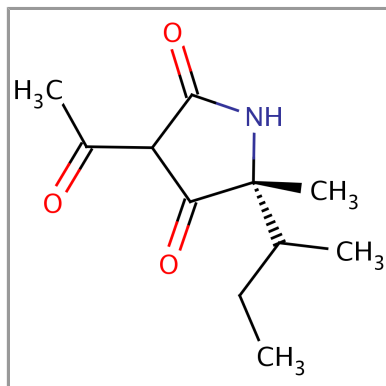
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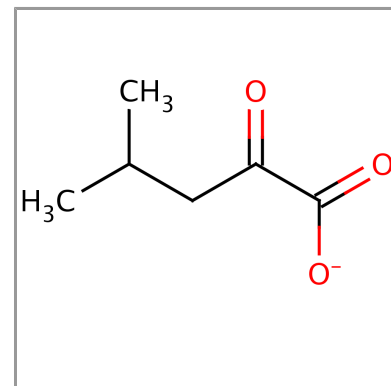
2



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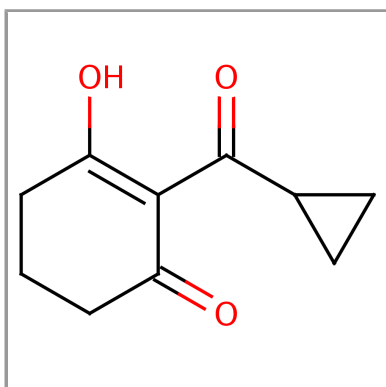
3



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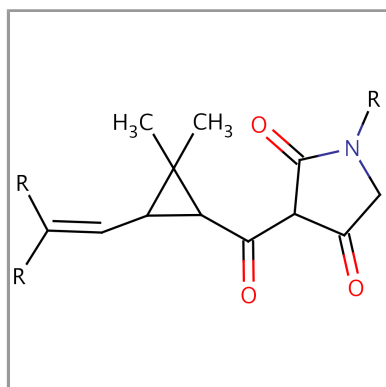
4



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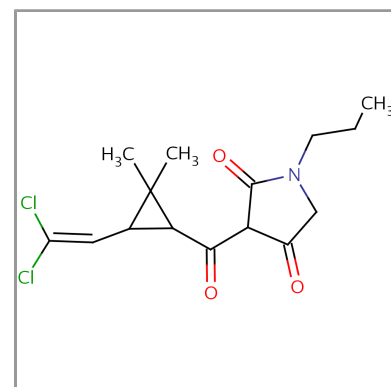
5



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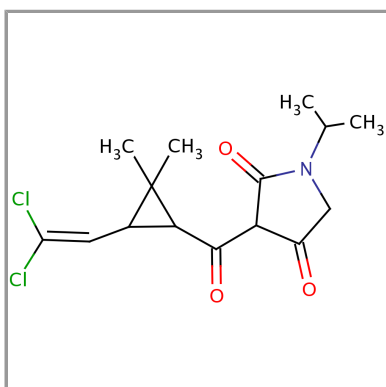
5a



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[Structure Search](#)

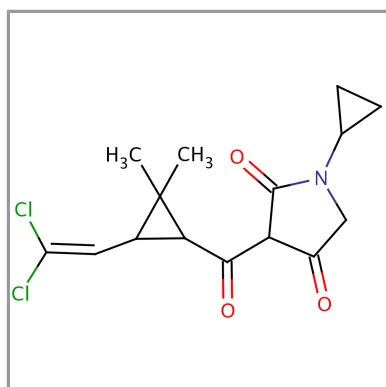
5b



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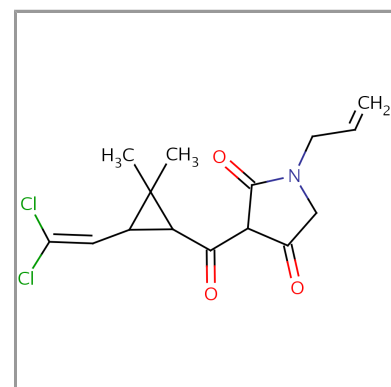
5c



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[Structure Search](#)

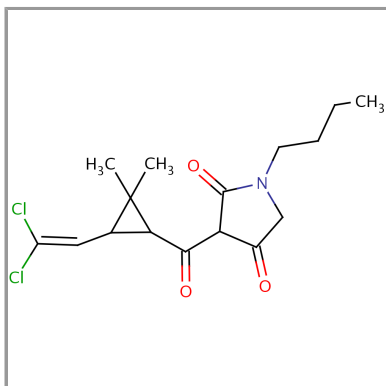
5d



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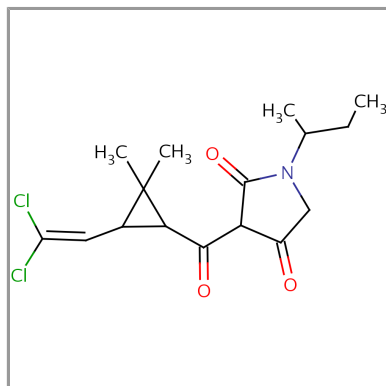
5e



[Compound Details](#)

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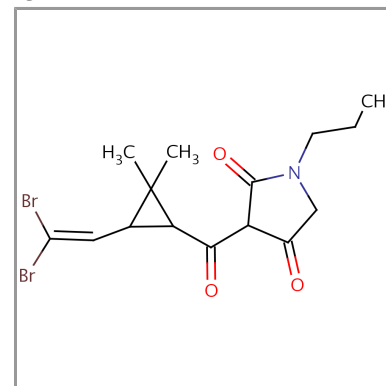
5f



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[Structure Search](#)

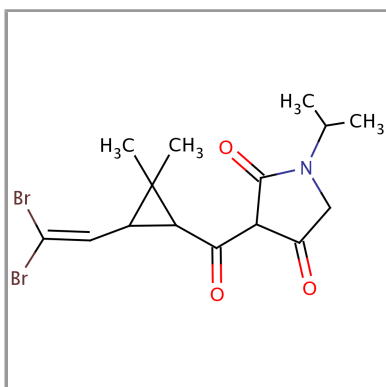
5g



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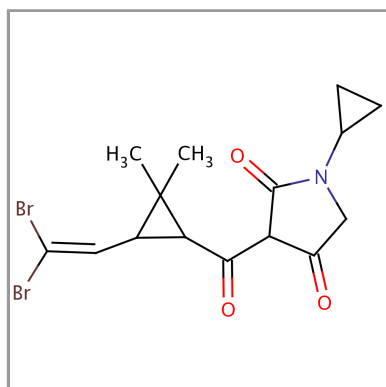
5h



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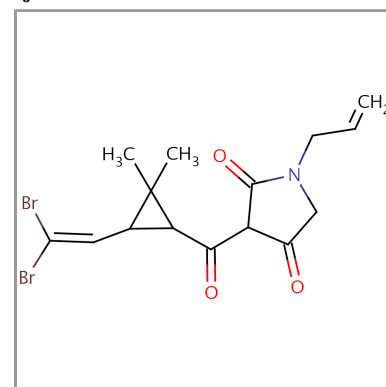
5i



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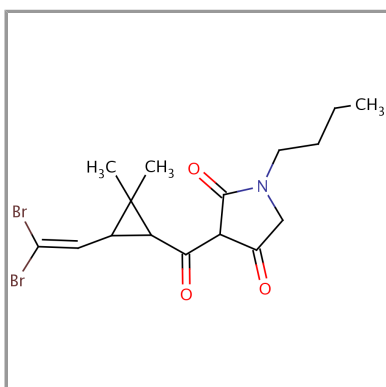
5j



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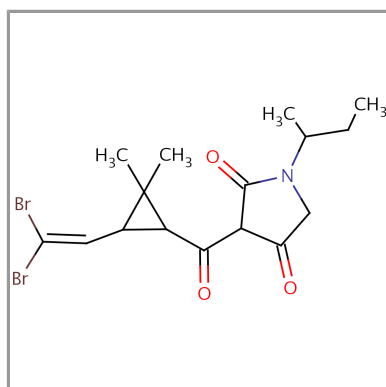
5k



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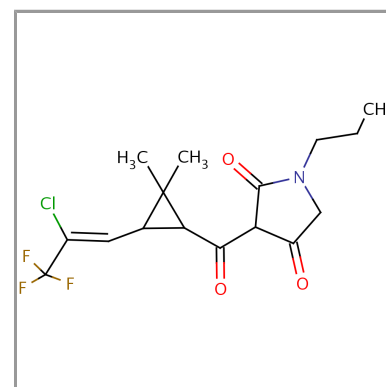
5l



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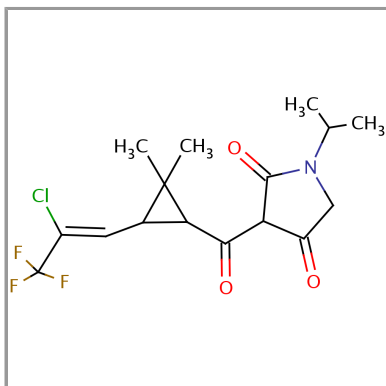
5m



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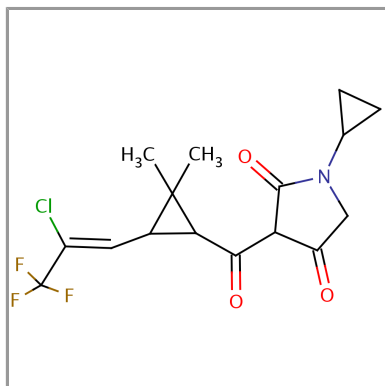
5n



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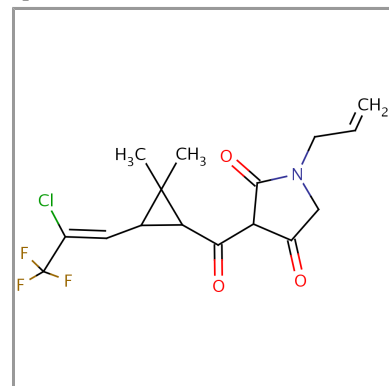
5o



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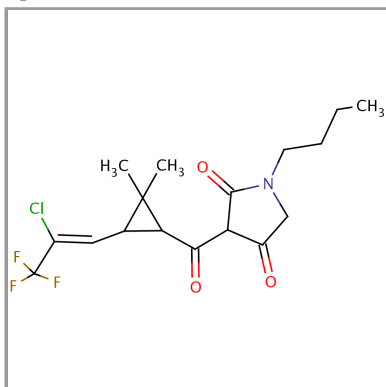
5p



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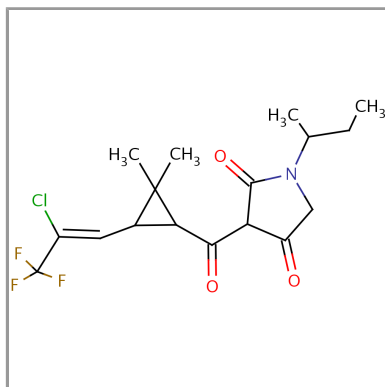
5q



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[Structure Search](#)

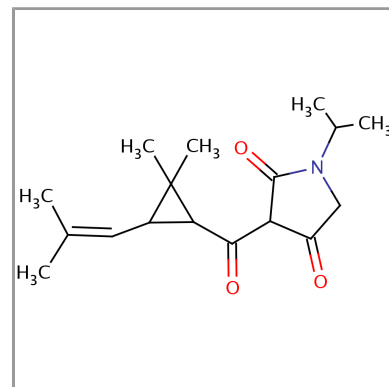
5r



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[Structure Search](#)

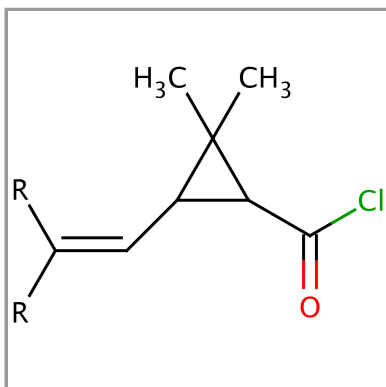
5s



[Compound Details](#)

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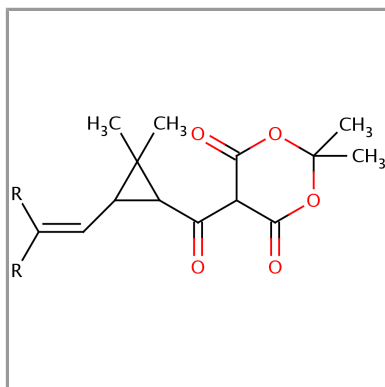
6



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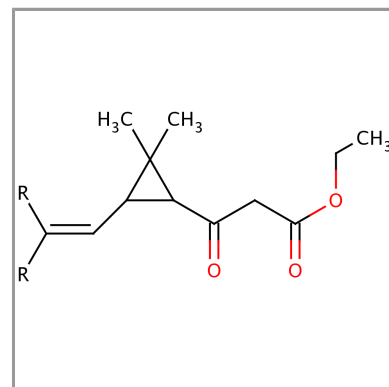
7



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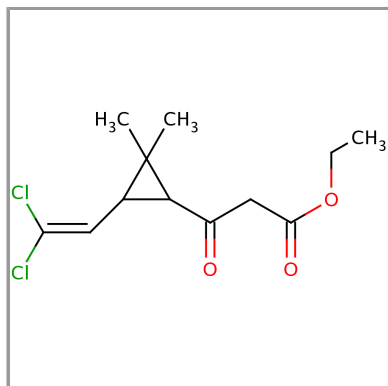
8



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[Structure Search](#)

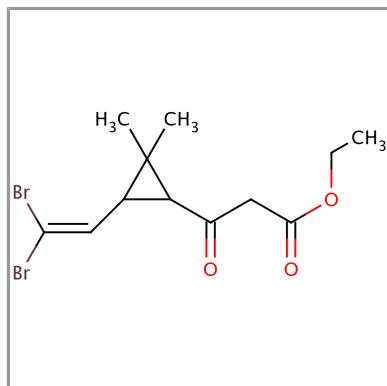
8a



[Compound Details](#)

[Structure Search](#)

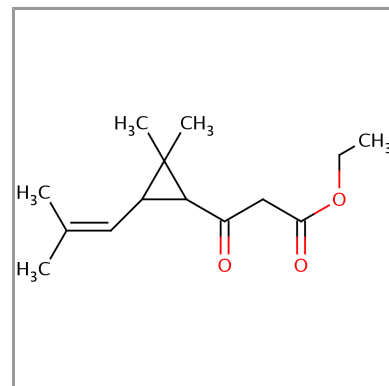
8b



[Compound Details](#)

[Structure Search](#)

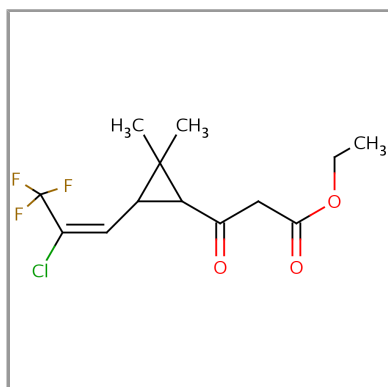
8c



[Compound Details](#)

[Structure Search](#)

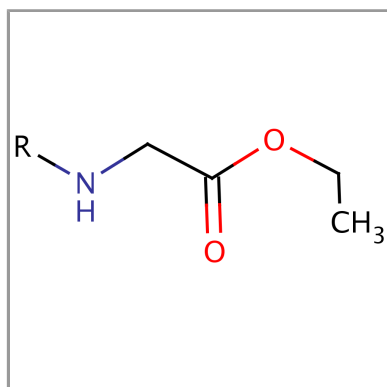
8d



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9



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