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Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Yan Wei, Shi-qiang Li & Shuang-hong Hao (2017): New angular oxazole-fused coumarin derivatives: synthesis and biological activities, Natural Product Research, DOI: 10.1080/14786419.2017.1405408

To link to this article: https://doi.org/10.1080/14786419.2017.1405408

NATURAL PRODUCT RESEARCH, 2017
https://doi.org/10.1080/14786419.2017.1405408

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New angular oxazole-fused coumarin derivatives: synthesis and biological activities

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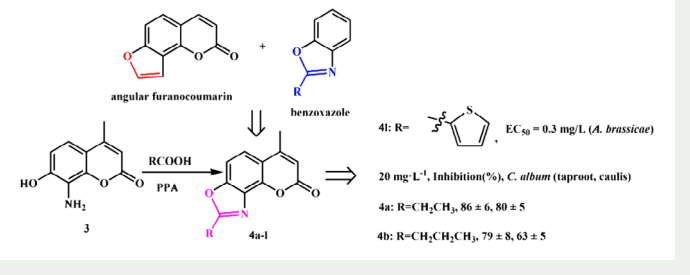
ABSTRACT

Twelve angular oxazole-fused coumarin derivatives were designed, synthesised and characterised by ^{1}H NMR, ^{13}C NMR and HRMS. The structure of compound **4a** was further confirmed by X-ray single-crystal diffraction. The bioassay experiment results indicated that compounds **4f** and **4l** have high antifungal activity on the mycelium growth of 4 plant disease fungi. Especially, compound **4l** has a stronger antifungal activity compare to the commercial fungicide, Carbendazim. The herbicidal activity experiment showed that **4a** and **4b** can significantly inhibit the taproot and caulis development of *Chenopodium album* seedling and have better activities than the commercial herbicide, Acetochlor.



ARTICLE HISTORY
Received 18 August 2017
Accepted 3 November 2017

KEYWORDS
Angular oxazole-fused coumarin; synthesis; antifungal activity; herbicidal activity

1. Introduction

Furanocoumarins constitute a subfamily of coumarin compounds that widely exist in a number of plant families, e.g. Rutaceae and Umbelliferae. Angular furanocoumarins are one important category of furanocoumarins with versatile pharmacological effects of antitumor and antioxidant (Zhou et al. 2011; Shokoohinia et al. 2014), antipsoriatic (Morison 1999), anti-HIV (Shikishima et al. 2001), antiplatelet (Xiao et al. 2007), antimycobacterial (Guo et al. 2014), as well as agronomical activities of antiphytopathogen, insecticide and allelopathy (Shimomura et al. 1982; Boulogne et al. 2012; Caboni et al. 2014; Villegas et al. 2015). These chemicals produced by plant may act as allelopathic defence compounds, i.e. phytoalexins

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Supplemental data for this article can be accessed at https://doi.org/10.1080/14786419.2017.1405408.

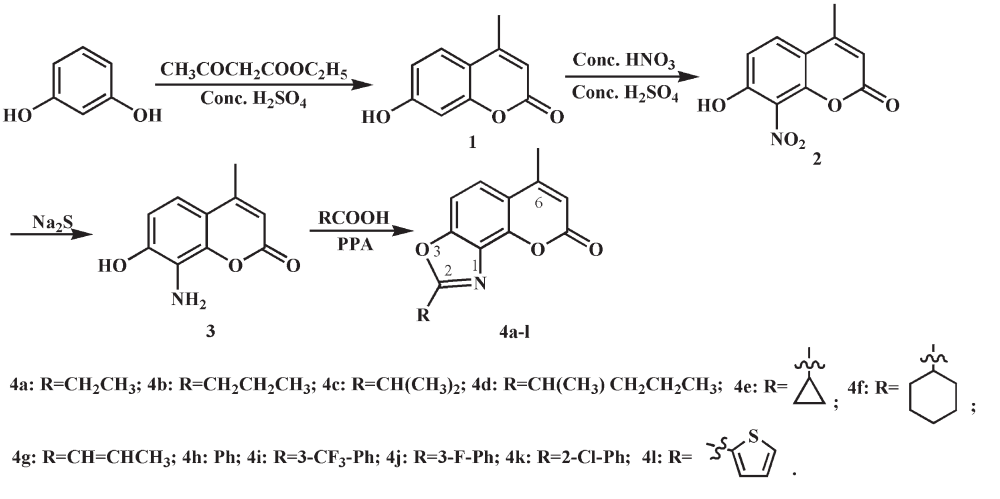
(Shimomura et al. 1982; Desjardins et al. 1989; Sardari et al. 1999; Khatune et al. 2004; Song et al. 2017).

The benzoxazole scaffold is a core structure which exists in a wide class of natural and synthetic compounds (Tugba et al. 2016; Belal and Khan 2016). Benzoxazole ring is one of the most common heterocycles in medicinal chemistry and plays an important role in drug design (Reddy et al. 2015). In fact, substituted benzoxazoles are associated with diverse pharmacological activities, viz. antitumor (Sommer et al. 2008), COX-2 inhibition (Srinivas et al. 2010), antifungal (Jyothi and Ramchander 2013), antibacterial (Balaswamy et al. 2012; Seenaiah et al. 2017) and anticancer (Kamal et al. 2010), as well as pesticidal activities of insecticide (Guan et al. 2013; Yang et al. 2015) and herbicide (Youssef et al. 2010; Imramovsky et al. 2014). The potential bioactivities of these heterocyclic compounds inspire us to design and synthesise a serial of fused oxazole-containing coumarin derivatives. And the antifungal and herbicidal activities of these new compounds were tested.

2. Results and discussion

2.1. Synthesis of angular oxazole-fused coumarin derivatives

The synthetic route of title compounds is depicted in Scheme 1. Compound **1** was prepared by Pechmann reaction from resorcinol and ethyl acetoacetate in the presence of H_2SO_4. Compound **2** was obtained by nitration of compound **1** with Conc. HNO_3-Conc. H_2SO_4. Compound **3** was synthesised by reduction of compound **2** with Na_2S. The title compounds **4a**–**l** were prepared by cyclisation of compound **3** with a series of acids catalysed by PPA. The structures of all target compounds were well characterised by ^1H NMR, ^{13}C NMR, HRMS and mp. Additionally, to confirm the three-dimensional structural information of **4a**–**l**, the single-crystal structure of **4a** was determined by X-ray crystallography as illustrated in Figure 1. Crystallographic data (excluding structure factors) for the structure of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1558080.



Scheme 1. Synthetic route of target compounds.

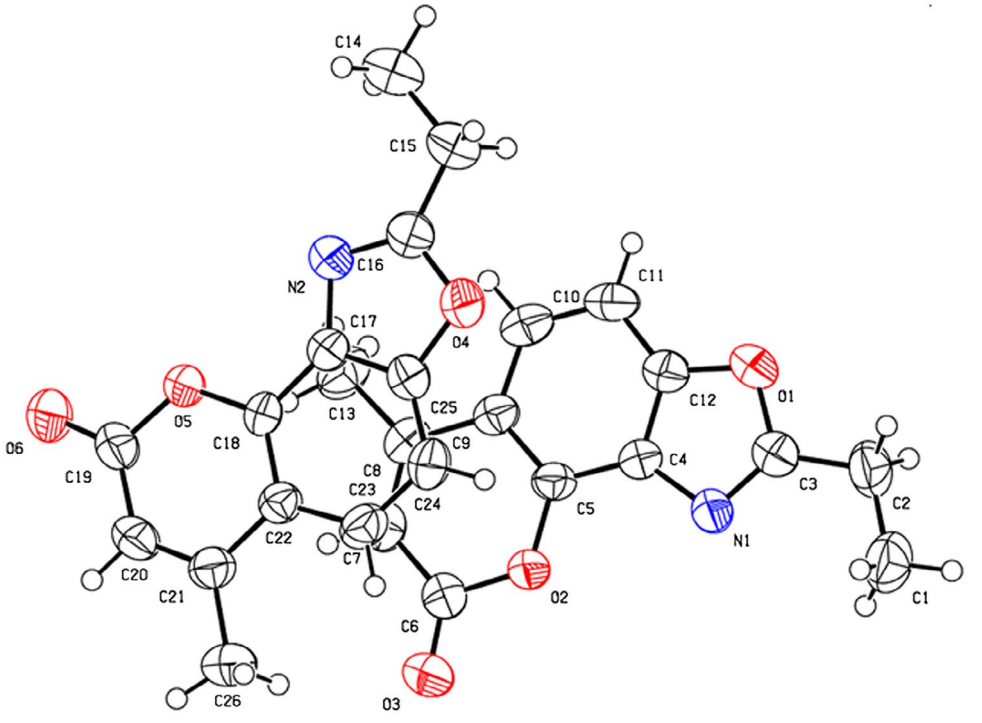


Figure 1. Molecular structure of compound **4a**.

2.2. Antifungal activities

The *in vitro* antifungal activities were evaluated against *Botrytis cinerea*, *Colletotrichum gloeosporioides*, *Alternaria brassicae* and *Gaeumannomyces gramini*. The results of antifungal screening test of these new compounds are given in Table 1. As shown, all the synthesised title compounds exhibited certain inhibition against at least one phytopathogen, especially, compounds **4f** and **4l** showed excellent antifungal activities. The EC_{50} of compound **4f** against the 4 tested phytopathogens are all less than 28 mg·L^{-1}. The EC_{50} of compound **4l** against *B. cinerea*, *A. brassicae* and *G. gramini* are near or less than 15 mg·L^{-1}. Compound **4l** showed the highest antifungal activity against *A. brassicae* with EC_{50} of 0.27 mg·L^{-1}, which are more active than the commercial fungicide Carbendazim. Furthermore, compounds **4k** and **4i** also exhibited good antifungal activity with EC_{50} of 11.72 mg·L^{-1} and 16.83 mg·L^{-1} against *C. gloeosporioides* and *G. gramini,* respectively.

For the 2-alkyl substituted compounds **4a**–**4d**, the bulky groups would be unfavourable for the antifungal activity against *C. gloeosporioides* but be favourable for the activity against *G. gramini*. On the contrary, 2-cyclohexyl substituted compound **4f** exhibited much higher activity than 2-cyclopropyl substituted compound **4e** to the test fungus. 2-thienyl-2 substituted compound **4l** showed the highest activity against *B. cinerea*, *A. brassicae* and *G. gramini*. For the 2-phenyl substituted compounds **4h**–**4k**, electron-withdrawing groups on the benzene ring would increase the activity to *C. gloeosporioides* and *G. gramini* but decrease the activity to *B. cinerea* and *A. brassicae*.

Table 1. Antifungal activity of the title compounds.

Compd.	EC_{50}/mg·L^{-1}			
	B. cinerea	*C. gloeosporioides*	*A. brassicae*	*G. gramini*
4a	74.8 ± 6.7	45.8 ± 1.2	110.3 ± 8.8	75.3 ± 5.7
4b	141.5 ± 11.8	47.8 ± 7.6	94.4 ± 7.3	59.7 ± 4.3
4c	134.7 ± 12.5	97.7 ± 6.8	223.5 ± 18.7	70.6 ± 5.3
4d	–	–	–	35.4 ± 2.9
4e	76.6 ± 5.3	76.1 ± 4.6	218.5 ± 16.3	54.0 ± 3.8
4f	21.3 ± 1.9	27.9 ± 1.7	26.3 ± 1.9	25.0 ± 1.4
4g	56.6 ± 3.3	–	52.6 ± 4.3	37.0 ± 2.6
4h	40.3 ± 2.8	127.2 ± 9.9	53.2 ± 5.0	128.4 ± 7.9
4i	190.3 ± 16.6	43.6 ± 3.1	96.3 ± 7.2	16.8 ± 1.3
4j	86.4 ± 5.9	78.1 ± 6.4	53.2 ± 4.4	39.4 ± 4.7
4k	102.1 ± 8.1	11.7 ± 7.1	109.0 ± 8.3	37.4 ± 2.7
4l	15.2 ± 1.3	70.8 ± 5.4	0.3 ± 0.0	14.2 ± 1.1
Carbendazim	26.8 ± 2.7	1.3 ± 0.1	47.0 ± 2.3	0.9 ± 0.2

(–) No activity.
(±) Standard deviation.

2.3. Herbicidal activities

As indicated in Table 2, the synthesised title compounds have certain degree of herbicidal activity against at least 1 kind of weeds *D. sanguinalis* and *C. album*. All the compounds except **4k** showed certain level of inhibition against the taproot and caulis development of dicotyledonous weed *C. album*. While the activities of the title compounds against monocotyledonous weed *D. sanguinalis* are weak or ineffective except compound **4j**, which has medium activity against the taproot and caulis development of *D. sanguinalis*. Compounds **4a**, **4f**, **4h** and **4k** exhibiting medium activity against the caulis development of *D. sanguinalis* at 100 mg·L^{-1}. 2-alkyl (C numbers < 4) substituted compounds **4a**–**4c** show good to excellent activities against *C. album*. And the activities decrease as the C numbers of alkyl substitute increase. The activities of compound **4a** and **4b** against *C. album* are higher than the commercial herbicide Acetochlor. Compound **4g** has similar toxic level against *C. album* as

Table 2. Herbicidal activity (%) of the title compounds.

Compd.	*D. sanguinalis*				*C. album*			
	20 mg·L^{-1}		100 mg·L^{-1}		20 mg·L^{-1}		100 mg·L^{-1}	
	taproot	caulis	taproot	caulis	taproot	caulis	taproot	caulis
4a	26 ± 3	43 ± 4	40 ± 5	56 ± 6	86 ± 6	80 ± 5	93 ± 3	85 ± 5
4b	4 ± 1	16 ± 2	22 ± 2	40 ± 3	79 ± 8	63 ± 5	83 ± 9	67 ± 6
4c	6 ± 1	7 ± 1	28 ± 2	25 ± 2	62 ± 2	45 ± 4	76 ± 5	58 ± 4
4d	–	–	–	–	7 ± 1	8 ± 1	38 ± 4	27 ± 4
4e	–	–	–	–	52 ± 6	28 ± 1	74 ± 7	25 ± 3
4f	33 ± 3	32 ± 6	27 ± 3	51 ± 4	19 ± 2	32 ± 3	40 ± 5	37 ± 2
4g	–	–	–	–	70 ± 8	59 ± 3	86 ± 5	75 ± 7
4h	8 ± 1	15 ± 1	35 ± 5	54 ± 5	36 ± 4	28 ± 3	53 ± 5	46 ± 4
4i	–	–	–	–	29 ± 3	26 ± 3	30 ± 2	37 ± 4
4j	25 ± 1	47 ± 5	60 ± 6	60 ± 3	32 ± 2	30 ± 2	47 ± 5	45 ± 3
4k	27 ± 2	23 ± 4	36 ± 4	55 ± 5	–	–	–	–
4l	9 ± 1	17 ± 1	25 ± 3	40 ± 2	34 ± 7	29 ± 3	52 ± 4	47 ± 3
Acetochlor	64 ± 6	70 ± 7	83 ± 7	78 ± 4	76 ± 2	61 ± 5	88 ± 8	80 ± 5

(–) No activity.
(±) Standard deviation.

herbicide Acetochlor. It is interesting that compound **4j** shows good activity against *D. sanguinalis* but less toxic against *C. album*.

3. Experimental

3.1. General

All chemicals were obtained from commercial sources and used without further purification. Resorcinol, ethyl acetoacetate, Na_2S and PPA were supplied by Sinopharm Chemical Reagent Co., Ltd. The inorganic acids and organic solvents were manufactured by Laiyang Kangde Chemical Co., Ltd. The organic acids were purchased from SA Chemical Technology (Shanghai) Co., Ltd. Analytical thin-layer chromatography (TLC) was performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a WRS-1B digital melting-point apparatus (Shanghai Precision Optical Instrument Co., Ltd.) and without further calibration. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance III HD 500 MHz instrument in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz) using tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were carried out with an IonSpec 4.7 T FTMS instrument. Single-crystal structure was determined by a Bruker AXS D8 QUEST X-ray single-crystal diffractometer.

3.2. General procedure for synthesis of angular oxazole-fused coumarin (4a–l)

4-Methyl-7-hydroxyl-6-amino-courmin (5 mmol), acid (6 mmol) and PPA (5 g) were stirred at 150 °C for 5.5 h. The reaction mixture was cooled at room temperature. Water (30 mL) was added, and the mixture was stirred for another 30 min. The resulting emulsion was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (30 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* sequentially. The residue was purified by silica gel column chromatography to give the target compounds **4a**–**4l**. The yield, appearance, m.p., NMR and HRMS date of the synthesised compounds are listed in the supplementary material of this article.

3.3. Procedure for antifungal and herbicidal activities

The antifungal activities of the title compounds against *B. cinerea*, *C. gloeosporioides*, *A. brassicae* and *G. gramini* were tested *in vitro* using the mycelium growth rate test. The test compound was dissolved in acetone to form a series of proper concentration solutions. Then, 1 mL of the solution was added to 100 mL melting potato dextrose agar (PDA) at 45 °C, and the mixture was shaken up to obtain the required concentration of poisoned medium; 5 mL of the poisoned medium was poured into 6 cm petri dish and cooled to room temperature to get a solid plate. After that, a 4 mm activated mycelium disk was inoculated on the PDA plate and incubated in dark at 28 °C for 48 h. The mycelium elongation radius (mm) of the fungus settlements was measured, and the growth inhibition rate related to the untreated control was calculated. Acetone was used as blank control, and Carbendazim was used as positive control. Each treatment was repeated for 3 times. Furthermore, the effective concentrations (EC_{50}) of the synthesised compounds that inhibited mycelium growth by 50% were obtained according to Finney's probability value method (Zhang et al. 2013).

The herbicidal activities of the synthesised compounds against the taproot and caulis development of dicotyledonous weed *C. album* and monocotyledonous weed *D. sanguinalis* were determined *in vitro* (Ma et al. 2010). A suspension of 5 g agar powder in 1 L distilled water was heated to melt, and then cooled to 40–50 °C. Each title compound was dissolved by acetone to give stock solution of 10 g·L^{-1}, and 0.1 or 0.5 mL of the stock solution was added to 50 mL of the melting agar at 45 °C to achieve the required concentrations. Then, 5 mL of the agar-containing compound was added to beaker (10 mL) and cooled, and uniform germinating seeds were placed on the surface of the agar mass. The beaker was sealed by a piece of plastic wrap with several small holes on it, and then, the cultivations were carried out in an illumination incubator set at 28 ± 1 °C and 50–55% relative humidity for 12 h in the light and 12 h in the dark alternatively for 3 days. Acetone was used as blank control, and Acetochlor was used as positive control. Each treatment was conducted in three replicates. After 3 days of cultivation, the taproot and caulis lengths were measured, and the growth inhibitory rate related to the untreated control was determined.

4. Conclusions

Twelve angular oxazole-fused coumarin derivatives were synthesised, and their antifungal and herbicidal activities were evaluated. 2-Cyclohexyl substituted product **4f** and 2-(Thienyl-2-) substituted product **4l** exhibited strong antifungal activity. The compound **4l** has good potential of inhibition on *A. brassicae* and showed the better results than the positive fungicide Carbendazim. While 2-ethyl substituted product **4a** and 2-propyl substituted product **4b** showed prominent inhibition against the seedling growth of *C. album*, which were more active than the commercial herbicide Acetochlor. It is worth mentioning that 2-(*m*-F-phenyl) substituted product 4i displayed better herbicidal activity against the seedling growth of *D. sanguinalis*.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Natural Science Foundation of China [Grant Number 31471808].

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