Chinese Chemical Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Design and synthesis of novel coumarin analogs and their nematicidal activity against five phytonematodes

Le Pan [a,b], Xiu-Zhuang Li [a], Di-An Sun [c], Hui Jin [a], Hong-Ru Guo [a], Bo Qin [a,*]

[a] Key Laboratory of Chemistry of Northwestern Plant Resources of CAS and Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China
[c] Institute of Medical Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, China

ARTICLE INFO

Article history:
Received 26 June 2015
Received in revised form 15 November 2015
Accepted 8 January 2016
Available online xxx

Keywords:
Coumarin analogs
Targeted design
Synthesis
Nematicidal activity
Structure–activity relationships

ABSTRACT

The presence of hydroxyl groups at the C4 and C7 positions in coumarin backbone has been proposed as a potential modification site for providing excellent bioactivity according to previous studies. A series of novel coumarin derivatives were rationally designed and synthesized by use of a complex catalytic system for a targeted modification at the above sites. These derivatives were assayed for nematicidal activity. As predicted, the derivatization enhanced the activity of the coumarins against five nematodes. Compounds **7b**, **9a**, **10c** and **11c** showed significant strong nematicidal broad spectrum activity against all tested nematodes. Compound **10c** was the most effective with the lowest LC_{50} values against *Meloidogyne incognita* (5.1 μmol/L), *Ditylenchus destructor* (3.7 μmol/L), *Bursaphelenchus mucronatus* (6.4 μmol/L), *Bursaphelenchus B. xylophilus* (2.5 μmol/L) and *Aphelenchoides besseyi* (3.1 μmol/L), respectively. A brief investigation on the structure–activity relationships (SAR) revealed that the targeted modification by a C7 hydroxyl was optimum compared with that of a C4 hydroxyl and that the coupling chain length was crucial for the nematicidal activity.

1. Introduction

Plant-parasitic nematodes have been one of the most notorious plant pathogens worldwide [1,2]. Thousands of crops and trees are susceptible and the disease caused by the phytonematodes results in billions of agricultural losses annually [3]. Chemical methods, combined with agriculture practice, have been the primary way for the nematode control [4–7]. To lessen environmental toxicity, pesticide residues and nematode resistance, the development of new control substitutes has become an urgent and challenging task [8]. Natural products and their derivatives provide a promising treasury for the identification of modern pesticides [9]. As an alternative to a large screening program for the identification of new active materials, a rational program of structural modification of known active compounds can be more efficient and equally useful.

Coumarins are widely available promising natural compounds for modification due to their broad bioactivities [10–12]. Some simple coumarins, furocoumarines and dicoumarolums, display excellent nematicidal activity and their skeletons have drawn interest for the development of efficient nematicides [13,14]. In our previous study, 7-hydroxycoumarin was isolated from *Stellera chamaejasme* and had been discovered to show nematicidal activity against *Bursaphelenchus xylophilus* and *Bursaphelenchus mucronatus.* In recent years, the structure–activity relationships (SAR) of hydroxycoumarin derivatives have been intensively conducted and indicated that C4 and C7 position modifications in the backbone could enhance their tumor cytotoxicity, termiticidal and bactericidal activities [15–18]. Therefore, we were prompted to design and develop coumarin-based nematicides by modification at these positions (Fig. 1). In a pilot study, we coupled 4-hydroxycoumarin (**1**) and 7-hydroxy-4-methylcoumarin (**2**) with alkyl bromides, and a significant difference in activity was observed. Based on this, we proposed to further develop modifications of 4-hydroxycoumarin (**1**) and 7-hydroxy-4-methylcoumarin (**2**) by coupling coumarin with functional moieties at the C4 and C7 hydroxyls, and five

* Corresponding author.
E-mail address: bqin@licp.cas.cn (B. Qin).

http://dx.doi.org/10.1016/j.cclet.2016.01.029

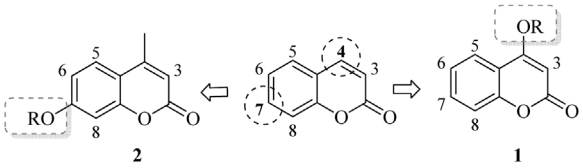

Fig. 1. Structures of coumarins and their modification sites.

phytonematodes were applied to evaluate their nematicidal activities.

2. Experimental

All starting chemicals were of analytical reagent and used without purification. Reactions were monitored by precoated TLC plates (Silica Gel 60 F_{254}. Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), and the spots were visualized by ultraviolet (UV) illumination. Silica gel (200–300 mesh) (Qingdao Haiyang Chemical Co., Ltd.) was used for column chromatography. Melting points were tested with a X-4 melting point apparatus (Beijing Tech Instrument Co., Ltd., China). The structural ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker AM-400BB instrument (Bruker, Karlsruhe, Germany) with TMS as internal standard, operating at 400 MHz. The chemical shift values are on a δ scale and the coupling constant values (J) are in Hertz. ESI-HRMS was recorded using a Bruker micrOTOF-Q II.

2.1. Synthesis of target compounds (*3a–12b*)

The general synthesis is illustrated in Scheme 1. Compounds **3a–c** were prepared by the reaction of 4-hydroxycoumarin (**1**) with 1, 2-dibromoethane, 1, 3-dibromopropane and 1, 4-dibromobutane, respectively, in the presence of an alkaline catalyst [19]. Compounds **9a–c** were similarly prepared with the dibromides. 6-Methoxy-4-methylquinolone (**5**) and 6-hydroxy-4-methylquinolone (**6**) were synthesized *via* a Knorr reaction of ethyl acetoacetate with anisidine in the presence of H_2SO_4 [20]. The bromoalkoxy derivatives of 4-hydroxycoumarins (**4a–c**) and 7-hydroxy-4-methylcoumarins (**10a–c**) were prepared through the bromoalkylation of 4-hydroxycoumarin (**1**) and 7-hydroxy-4-methylcoumarin (**2**) with 1, 2-dibromoethane, 1,3-dibromopropane and 1,4-dibromobutane, respectively. *N*-Alkylation is classically realized with halogen derivatives under alkaline condition, but with simply potassium hydroxide as a catalyst, the coupling reaction between alkyl bromides, coumarins (**4a–c**) and 6-methoxy-4-methylquinolone (**5**) was unsuccessful. Finally, a complex catalyst system of KOH, KI and tetrabutyl ammonium bromide (TBAB) was developed to prepare compounds **7a–c** in high yield. Compounds **11a–c** were then prepared by the reaction between 6-methoxy-4-methyl-quinolone (**5**) and 7-bromoalkoxy-4-methylcoumarins (**10a–c**). 6-Hydroxy-4-methylquinolone (**6**) coupled with appropriate 4-bromoalkoxycoumarins (**4a** and **b**) in the presence of K_2CO_3, KI and TBAB to yield compounds **8a** and **8b**, and the reaction with 7-bromoalkoxy-4-methylcoumarins (**10b** and **c**) gave **12a** and **b**. The coumarin analogs were analyzed by ^{1}H NMR, ^{13}C NMR and HR-ESI-MS. The purity of all test compounds was above 95% (determined by HPLC). All the compounds were characterized and the data was listed in Supporting information. Here, compound **11b** was taken as an example to show the typical structure of coumarin analogs.

4-Methyl-7-[3-(6-methoxy-4-methylquinolin-2-on-1-yl)propyloxy]benzopyran-2-one **(11b):** White solid, yield 63%. mp 184-185 °C. Its molecular formula was determined to be $C_{24}H_{23}NO_5$ from the HRESIMS data at m/z 406.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32-2.35 (m, 2H, H-12), 2.38 (s, 3H, CH_3-4′), 2.58 (s, 3H, CH_3-4), 3.92 (s, 3H, OCH_3-6), 4.23 (t, 2H, J =6.0 Hz, H-13), 4.63 (t, 2H, J =6.0 Hz, H-11), 6.12 (s, 1H, H-3′), 6.76 (s, 1H, H-3), 6.83 (d, 1H, J =2.4 Hz, H-8′), 6.87 (dd, 1H, J =8.8 Hz, 2.4 Hz, H-6), 7.14 (d, 1H, J =2.4 Hz, H-8), 7.25-7.28 (m, 2H, H-7′, H-5), 7.46 (d, 1H, J = 8.8 Hz, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.68, 18.89, 28.95, 30.95, 55.97, 65.46, 101.43, 103.39, 111.91, 112.07, 112.73, 113.12, 113.53, 120.26, 125.47, 125.57, 125.93, 128.95, 152.54, 155.29, 156.04, 160.44, 161.34, 162.07. The ^{1}H NMR spectrum showed the two methyl protons and one methoxyl protons. The protons at δ 6.12–7.46 indicated the moieties of coumarin and quinolone. The presence of the protons at δ 2.32-2.35 (H-12), 4.23 (H-13) and 4.63 (H-11) revealed the existence of linker between the two moieties. The results of ^{13}C NMR were in accordance with that of ^{1}H NMR spectrum. Therefore, the compound **11b** was elucidated as 4-Methyl-7-[3-(6-methoxy-4-methylquinolin-2-on-1-yl)propyloxy]-benzopyran-2-one.

2.2. Nematicidal assay

Five prevalent nematodes, *Meloidogyne incognita*, *Ditylenchus destructor*, *Bursaphelenchus xylophilus*, *Bursaphelenchus mucronatus* and *Aphelenchoides besseyi*, were used to evaluate the nematicidal spectrum and potential of the synthesized compounds. *B. xylophilus* and *B. mucronatus*, isolated from *Pinus massoniana*, were supplied by Dr. Han Zhengmin (College of Forest Resources and Environment, Nanjing Forestry University). *M. incognita*, *D. destructor* and *A. besseyi* were provided by Dr. Lin Maosong (College of Plant Protection, Nanjing Agricultural University). *D. destructor* was grown on potato dextrose Agar (PDA) media containing a strain of *Fusarium solani* in 9-cm Petri dishes. *M. incognita*, *B. xylophilus*, *B. mucronatus* and *A. besseyi* were cultured on PDA media with *Botrytis cinerea* Pers. All nematodes were stored at 28 °C and subcultured before bioassay. With successive observing under a microscope, J2s were collected and suspended in distilled water for the experiments. The tested compounds were dissolved in dimethylsulfoxide (DMSO) to obtain stock solutions, which were diluted with distilled water containing Tween-20 to prepare working solutions. 300 μL of dilutions and J2s suspension (containing about 60–80 J2s) were added into 24-well plates within 24 h. The final concentrations of DMSO and Tween-20 were kept under 0.5% and 0.05% of volume in each well, at which concentration levels, the motility of nematodes exposed was similar to those of a blank control. Distilled water and a solution of DMSO and Tween-20, at concentrations equivalent to those in the treatment wells, was used as a control. Abamectin was used as a positive control [21]. The plates were covered and parafilmed to prevent evaporation, and then incubated in the dark at 28 °C for 72 h. Juveniles were delivered to clean water and observed with a microscope at 40× magnification (Shanghai Optical Instrument Factory, Shanghai, China). Those immotile in a straight or "L" shape and not recovering in clean water were defined as dead. (Fig. 2) The experiment was conducted twice with three replicates. The values were determined as percentage corrected mortality (±standard deviation) according to the Schneider-Orelli formula:

Corrected mortality% = [(mortality% in treatment – mortality% in control)/(100 – mortality% in control)] × 100.

The compounds with strong activity were tested further under a series of concentrations to calculate their LC_{50} values. Probit analysis was used to estimate LC_{50} [22,23].

3. Results and discussion

The target coumarin analogs were efficiently prepared in the presence of the complex catalytic system. Their nematicidal activity was evaluated under a series of concentration and the LC_{50}

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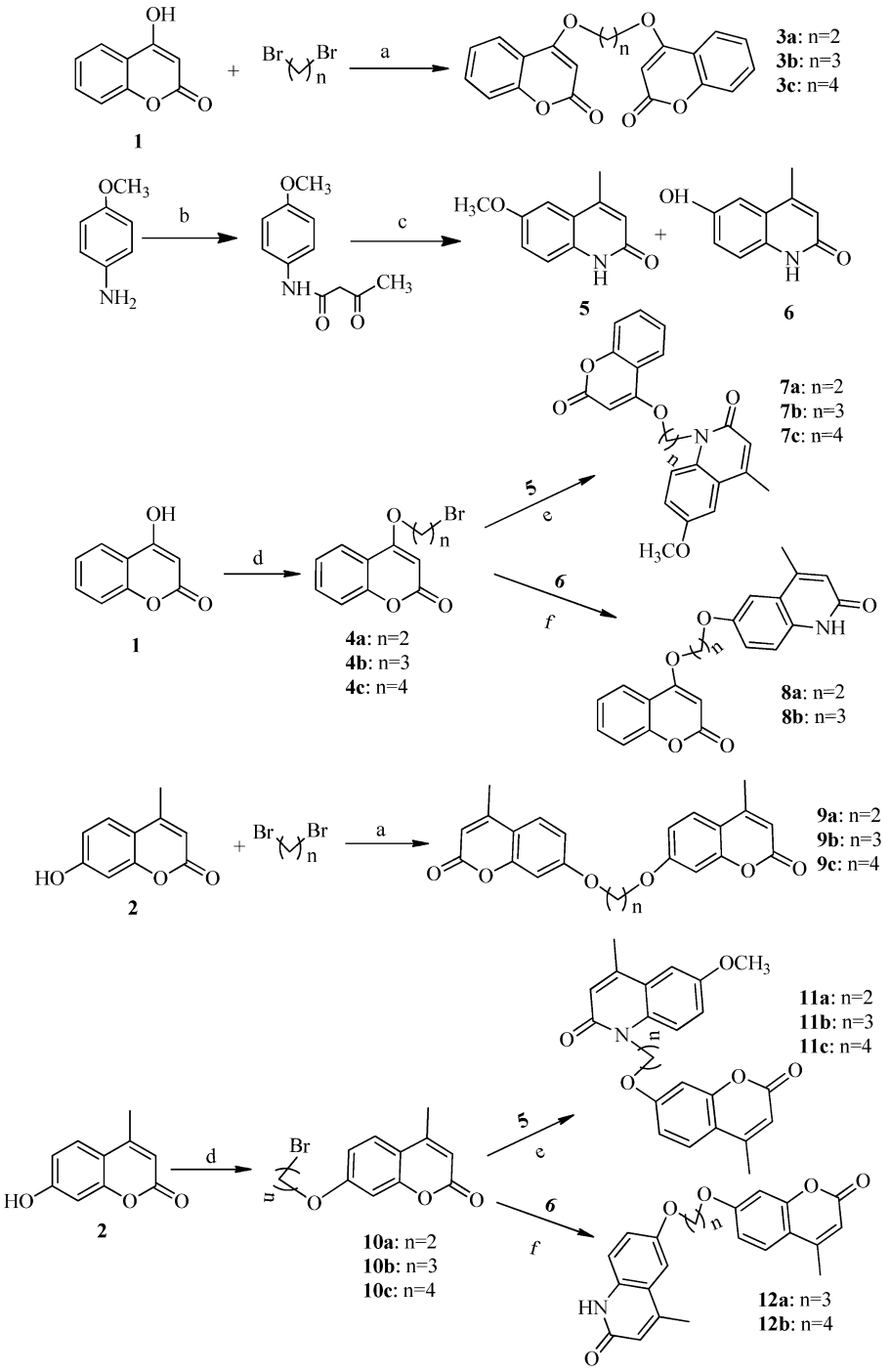

Scheme 1. Synthesis of coumarin derivatives. Reagents and conditions: (a) K_2CO_3/KOH/acetone, reflux; (b) ethyl acetoacetate, reflux; (c) 80% H_2SO_4, 95 °C; (d) K_2CO_3/acetone, reflux; (e) KOH/KI/TBAB/methylbenzene, 90 °C; (f) K_2CO_3/KI/TBAB/methylbenzene, 90 °C.

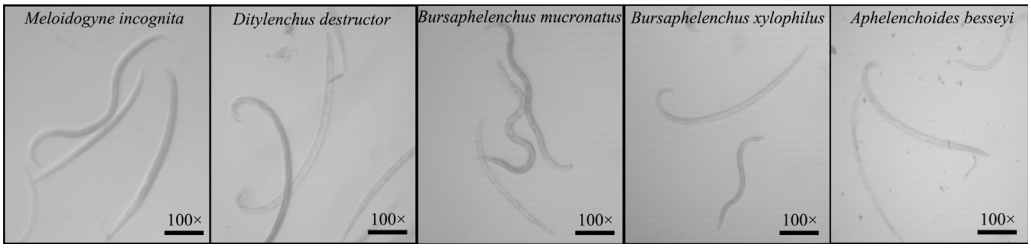

Fig. 2. Representative pictures of five plant-parasitic nematodes immersed in the solution of compound **9a** at the concentration of 100 μmol/L for 72 h (observed with microscope at 100× magnification).

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Table 1
Nematicidal activity of coumarin analogs against five plant-parasitic nematodes (calculated at 72 h).

Comp.	LC_{50} values (95% CI)/μmol/L				
	M. incognita	*D. destructor*	*B. mucronatus*	*B. xylophilus*	*A. besseyi*
1	261.1 (150.0–318.7)	333.5 (220.2–412.1)	329.7 (262.3–483.0)	168.9 (92.1–251.9)	406.7 (307.0–539.8)
2	>1000	>1000	>1000	>1000	>1000
3a	>1000	>1000	>1000	>1000	>1000
3b	>1000	>1000	>1000	>1000	>1000
3c	940.3 (737.0–1043.5)	286.2 (140.8-351.1)	>1000	744.9 (612.1-955.4)	>1000
4a	>1000	>1000	>1000	>1000	>1000
4b	>1000	>1000	>1000	>1000	>1000
4c	>1000	>1000	>1000	>1000	>1000
7a	544.4 (195.7–893.2)	436.2 (284.5–663.9)	329.4 (152.6–556.3)	812.9 (464.3–1241.1)	>1000
7b	64.0 (20.5–127.0)	52.9 (38.8–84.7)	97.9 (72.7–123.2)	103.2 (112.9–427.3)	95.2 (29.4–276.9)
7c	>1000	>1000	>1000	>1000	>1000
8a	883.5 (786.8–980.3)	761.8 (510.5–913.8)	>1000	913.1 (565.5–1260.8)	>1000
8b	>1000	>1000	>1000	>1000	>1000
9a	37.4 (10.9–67.2)	35.8 (15.7–75.3)	60.9 (31.3–86.7)	190.9 (75.9–260.2)	121.2 (63.9–184.6)
9b	>1000	>1000	>1000	>1000	>1000
9c	>1000	>1000	>1000	>1000	>1000
10a	491.1 (233.1–785.3)	907 (555.0–1255.2)	652.8 (385.8–819.6)	910.5 (486.6–1334.5)	893.7 (618.8–1168.5)
10b	762.6 (432.2–955.1)	593.7 (247.6–912.1)	256.6 (221.2–535.9)	731.6 (386.7–944.0)	907.9 (555.0–1293.7)
10c	5.1 (2.0–9.3)	3.7 (1.2–8.5)	6.4 (2.4–9.2)	2.5 (0.3–6.2)	3.1 (1.0–7.3)
11a	>1000	>1000	>1000	>1000	>1000
11b	114.5 (98.8–196.3)	214.2 (126.8–301.5)	367.6 (302.6–432.5)	410.2 (333.6–566.4)	384.5 (337.8–453.9)
11c	42.4 (19.8–70.2)	68.0 (41.2–86.9)	77.8 (42.1–101.4)	145.5 (72.6–232.1)	120.7 (65.4–201.2)
12a	385.0 (343.3–447.8)	380.6 (343.2–433.9)	430.0 (385.9–497.6)	381.8 (322.2–495.1)	441.6 (400.3–502.5)
12b	335.9 (279.5–430.4)	275.3 (233.1–335.3)	330.6 (288.8–391.5)	393.3 (315.2–561.3)	>1000
Abamectin[a]	0.50 (0.15–1.08)	0.62 (0.12–1.36)	0.38 (0.12–0.94)	0.47 (0.11–0.94)	0.26 (0.14–1.22)

[a] Abamectin was used as a positive control.

values were calculated (Table 1). As predicted, the modification on the hydroxyl at C4 and C7 positions led to the identification of promising lead compounds. Among the derivatives, compounds **7b**, **9a, 10c** and **11c** showed significant strong nematicidal activity, with a broad spectrum against all tested nematodes. Compound **10c** was the most effective with lowest LC_{50} values against *M. incognita* (5.1 μmol/L), *D. destructor* (3.7 μmol/L) and *B. mucronatus* (6.4 μmol/L), *B. xylophilus* (2.5 μmol/L) and *A. besseyi* (3.1 μmol/L) respectively. The rest of the derivatives exhibited moderate or weak nematicidal activity. Clearly, the type and position of the substituents were intensively responsible for the activity expression. Different substituents resulted in varied activity. When the coumarin moiety was replaced with that of a quinolone, a change of activity occurred. For the C4 position, substitution of the coumarin moieties with quinolone groups significantly increased (**7b**) or decreased (**7a** and **c**) the nematicidal activity. For the C7 position, compounds **9a–c** showed significantly different activity compared with their quinolone derivatives (**11a–c**). Beside the effect of a particular functional group, the position effect was also significant. Most 7-hydroxy-4-methylcoumarin derivatives showed improved nematicidal activity, whereas only one among all the 4-hydroxycoumarin derivatives (**7b**) exhibited better activity. Thus, the C7 hydroxyl is more likely to be a better modification site for the preparation of promising compounds.

It is notable that the length of linkers between two terminal moieties was intensively responsible for the activity. For the linkers between two 4-hydroxycoumarins (**1**), the change of chain length had little impact on the activity of compounds (**3a–c**), with **3a** and **3b** exhibiting none activity and **3c** just showing weak nematicidal activity to specific species. Three-carbon chain lengths (**7b**) were most active among the linkers between 4-hydroxycoumarin (**1**) and quinolone, and four-carbon atom lengths (**7c**) induced the loss of activity. For the coupling of two 7-hydroxy-4-methylcoumarins (**2**), the chain length of two carbon atoms (**9a**) was optimum, and chain lengths of three carbon atoms (**9b**) or four (**9c**) resulted in the great loss of activity. However, concerning to compounds **10–12**, it was found a positive correlation between linker lengths and activities among quinolone coupled 7-hydroxy-4-methylcoumarins (**11a–c**). This was not observed among compounds **10a-c**, but they all showed strong activities with four carbon chains. The chain length had little influence on the activity expression of compounds **12a** and **b**. It was worth noting that brombutyl substituted 7-hydroxy-4-methylcoumarin (**10c**) exerted outstanding nematicidal activity, whereas bromopropyl (**10b**) and bromoethyl (**10a**) derivatives showed weak activity, which suggested that the four-carbon chain length was the most active. About mono-coumarin analogs and bi-coumarin ones, it was found that, as a mono-coumarin analog, brombutyl coumarin (**10c**) exhibited better activities than its bi-coumarin analog (**9c**), but the different results were observed between bromoethyl analog (**10a**) and bi-coumarin one (**9a**). This indicated that the better activity of compound **10c** was determined by the combination of coumarin moiety, bromo atoms and butyl chain. Taken together, the length of the alkyl chain was a key factor for the activity, but the optimum length was not fixed and was depended upon the moiety to which it was linked.

4. Conclusion

In summary, a series of coumarin-based compounds were designed and synthesized with a targeted derivatization of the C4 and C7 hydroxyl groups. Their activity against five prevalent nematodes was systematically investigated to reveal structure–activity relationship (SAR). The results showed that the expression of activity was determined by a combination of carbon chain link lengths and functional moieties, and that an optimum link chain length has been established. Compounds **7b**, **9a**, **10c** and **11c** exhibited the most efficient broad spectrum activity and could be promising for development as novel nematicides.

Acknowledgments

We thank Dr Frank Stermitz for his valuable help in English editing. The authors are thankful to the National Natural Science Foundation of China (Nos. 31070386, 21302195 and 31300290),

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135 Key Cultivation Program of the Chinese Academy of Sciences, and the Province-Academy Cooperation Program of Henan Province of China (No. 102106000021) for financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.01.029.

References

[1] N.G. Ntalli, P. Caboni, Botanical nematicides: a review, J. Agric. Food. Chem. 60 (2012) 9929–9940.
[2] J.T. Pechacek, T.M. Bargar, M.R. Sabol, Inhibition of nematode induced root damage by derivatives of methylenecyclopropane acetic acid, Bioorg. Med. Chem. Lett. 7 (1997) 2665–2668.
[3] D.J. Chitwood, Research on plant-parasitic nematode biology conducted by the United States Department of Agriculture–Agricultural Research Service, Pest. Manag. Sci. 59 (2003) 748–753.
[4] T.C. Thoden, M. Boppré, J. Hallmann, Effects of pyrrolizidine alkaloids on the performance of plant-parasitic and free-living nematodes, Pest. Manag. Sci. 65 (2009) 823–830.
[5] I.O. Giannakou, I.A. Anastasiadis, S.R. Gowen, et al., Effects of a non-chemical nematicide combined with soil solarization for the control of root-knot nematodes, Crop. Prot. 26 (2007) 1644–1654.
[6] D.J. Chitwood, S.L.F. Meyer, Phytochemically based nematode control: opportunities and challenges, J. Nematol. 46 (2014), 145-145.
[7] J. Kearn, E. Ludlow, J. Dillon, et al., Fluensulfone is a nematicide with a mode of action distinct from anticholinesterases and macrocyclic lactones, Pestic. Biochem. Phys. 109 (2014) 44–57.
[8] S.M. Seo, J. Kim, S.H. Koh, et al., Nematicidal activity of natural ester compounds and their analogues against pine wood nematode, *Bursaphelenchus xylophilus*, J. Agr. Food. Chem. 62 (2014) 9103–9108.
[9] D.J. Chitwood, Phytochemical based strategies for nematode control, Annu. Rev. Phytopathol. 40 (2002) 221.
[10] M.E. Riveiro, N. De Kimpe, A. Moglioni, et al., Coumarins: old compounds with novel promising therapeutic perspectives, Curr. Med. Chem. 17 (2010) 1325–1338.
[11] B.R. Vijay Avin, P. Thirusangu, V. Lakshmi Ranganatha, et al., Synthesis and tumor inhibitory activity of novel coumarin analogs targeting angiogenesis and apoptosis, Eur. J. Med. Chem. 75 (2014) 211–221.
[12] M.E. Riveiro, D. Maes, R. Vázquez, et al., Coumarins: old compounds with novel promising therapeutic perspectives, Bioorg. Med. Chem. 17 (2009) 6547–6559.
[13] H. Cui, H. Jin, Q. Liu, et al., Nematicidal metabolites from roots of *Stellera chamaejasme* against *Bursaphelenchus xylophilus* and *Bursaphelenchus mucronatus*, Pest. Manag. Sci. 70 (2014) 827–835.
[14] Z. Yang, Z. Yu, L. Lei, et al., Nematicidal effect of volatiles produced by *Trichoderma* sp, J. Asia-Pac. Entomol. 15 (2012) 647–650.
[15] K. Takaishi, M. Izumi, N. Baba, et al., Synthesis and biological evaluation of alkoxycoumarins as novel nematicidal constituents, Bioorg. Med. Chem. Lett. 18 (2008) 5614–5617.
[16] S. Lee, K. Sivakumar, W.S. Shin, et al., Synthesis and anti-angiogenesis activity of coumarin derivatives, Bioorg. Med. Chem. Lett. 16 (2006) 4596–4599.
[17] M. Kawase, H. Sakagami, K. Hashimoto, et al., Structure-cytotoxic activity relationships of simple hydroxylated coumarins, Anticancer. Res. 23 (2003) 3243–3246.
[18] M. Adfa, Y. Hattori, T. Yoshimura, et al., Antitermite activity of 7-alkoxycoumarins and related analogs against *Coptotermes formosanus* Shiraki, Int. Biodeterior. Biodegrad. 74 (2012) 129–135.
[19] Y. Chen, S.L. Wang, X.Q. Xu, et al., Synthesis and biological investigation of coumarin piperazine (piperidine) derivatives as potential multireceptor atypical antipsychotics, J. Med. Chem. 56 (2013) 4671–4690.
[20] N. Priya, A. Gupta, K. Chand, et al., Characterization of 4-methyl-2-oxo-1, 2-dihydroquinolin-6-yl acetate as an effective antiplatelet agent, Bioorg. Med. Chem. Lett. 18 (2010) 4085–4094.
[21] Q.L. Dang, W.K. Kim, C.M. Nguyen, et al., Nematicidal and antifungal activities of annonaceous acetogenins from *Annona squamosa* against various plant pathogens, J. Agr. Food. Chem. 59 (2011) 11160–11167.
[22] P. Caboni, L. Tronci, B. Liori, et al., Tulipaline A: structure-activity aspects as a nematicide and V-ATPase inhibitor, Pestic. Biochem. Phys. 112 (2014) 33–39.
[23] J.O. Kong, S.M. Lee, Y.S. Moon, et al., Nematicidal activity of plant essential oils against *Bursaphelenchus xylophilus* (Nematoda: Aphelenchoididae), J. Asia-Pac. Entomol. 9 (2006) 173–178.

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