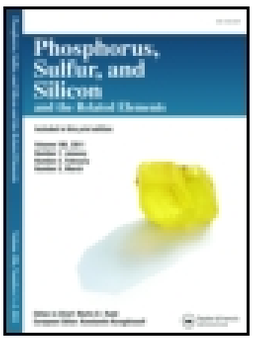

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Synthesis and nematicidal activities of 1,2,3-benzotriazin-4-one containing 4,5-dihydrothiazole-2-thiol derivatives against *Meloidogyne incognita*

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ABSTRACT

A series of novel 1,2,3-benzotriazin-4-one derivatives containing 4,5-dihydrothiazole-2-thiol were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. The bioassay results showed that compounds 3-(3-((4,5-dihydrothiazol-2-yl)thio)propyl)-7-methoxybenzo[d][1–3]triazin-4(3H)-one, 3-(3-((4,5-dihydrothiazol-2-yl)thio)propyl)-6-nitrobenzo[d][1–3]triazin-4(3H)-one, 7-chloro-3-(3-((4,5-dihydrothiazol-2-yl)thio)propyl)benzo[d][1–3]triazin-4(3H)-one exhibited good control efficacy against the cucumber root-knot nematode disease caused by *Meloidogyne incognita* at the concentration of 10.0 mg L^{-1} *in vivo*. Compound 7-chloro-3-(3-((4,5-dihydrothiazol-2-yl)thio)propyl)-benzo[d][1–3]triazin-4(3H)-one showed excellent nematicidal activity with inhibition 68.3% at a concentration of 1.0 mg L^{-1}. It suggested that the structure of 1,2,3-benzotriazin-4-one containing 4,5-dihydro-thiazole-2-thiol could be optimized further.

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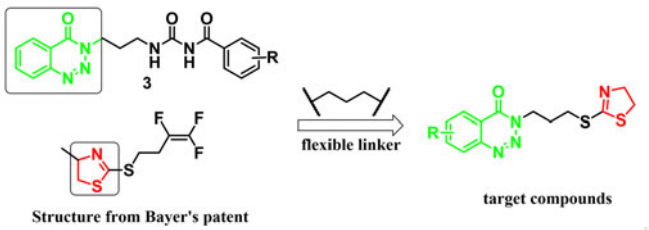
1,2,3-benzotriazin-4-one; 4,5-dihydrothiazole-2-thiol; *M. incognita*; nematicidal activity

GRAPHICAL ABSTRACT



Introduction

Root-knot nematodes (*Meloidogyne spp.*) interact with more than a thousand plant species in a remarkable manner.[1] Most plant parasitic nematodes develop from juvenile stage until reaching the adult stage (stage 1–4, J1–J4). J2 invade and feed on living plants through a protrusible oral stylet.[2] Root symptoms, root-gall, or root-necrosis indices, produced at mid-season or at harvest, also can be correlated with yield losses caused by *Meloidogyne spp.* and associated fungi.[2] Nematode control is becoming more difficult for growers in many regions of the world. Massive organophosphates and carbamates compounds relying upon single mode of action have been restricted.[3] For example, in Europe, most of the chemical nematicides previously available have been banned in recent years, due to their intrinsic toxicity, human health and environmental concerns (European Community directive 2007/619/EC).[4] In recent years, the newly developed fluensulfone, fluopyram and fluazaindolizine (Figure 1) have been brought into market.[5–7] In a broader context, achieving safe and effective nematicides is a key part of the move toward environmentally sustainable agriculture.

To the end of 2017 a total of 23 unique sulfur-containing structures were approved by the FDA.[8] More than 30% of today's agrochemicals contain at least one sulfur atom, mainly in fungicides, herbicides and insecticides (Figure 2).[9] Moreover, 75% of nematicides have at least one sulfur atom.[9] Thiazole ring is an important pharmacologically active heterocyclic ring and its reduced analogs such as thiazolines have been widely studied in medicinal chemistry.[10,11] For example, many compounds containing a thiazoline (4,5-dihydro-1,3-thiazole) fragment exhibited antibacterial, anticancer, antifungal, etc.[12,13] 4,5-Dihydrothiazole structure was included in the commercial carbapenems medicine tebipenem pivoxil and marine natural product with anti-cancer activity (Figure 3).[14,15] 4-Methyl-2-((3,4,4-trifluorobut-3-en-1-yl) thio)-4,5-dihydrothiazole containing 4,5-dihydrothiazole-2-thiol showed more than 90% inhibitory activity against *M. incognita* at a concentration of

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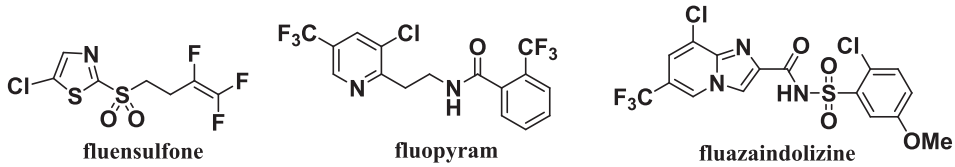


Figure 1. Nematicidal chemicals developed in recent years.

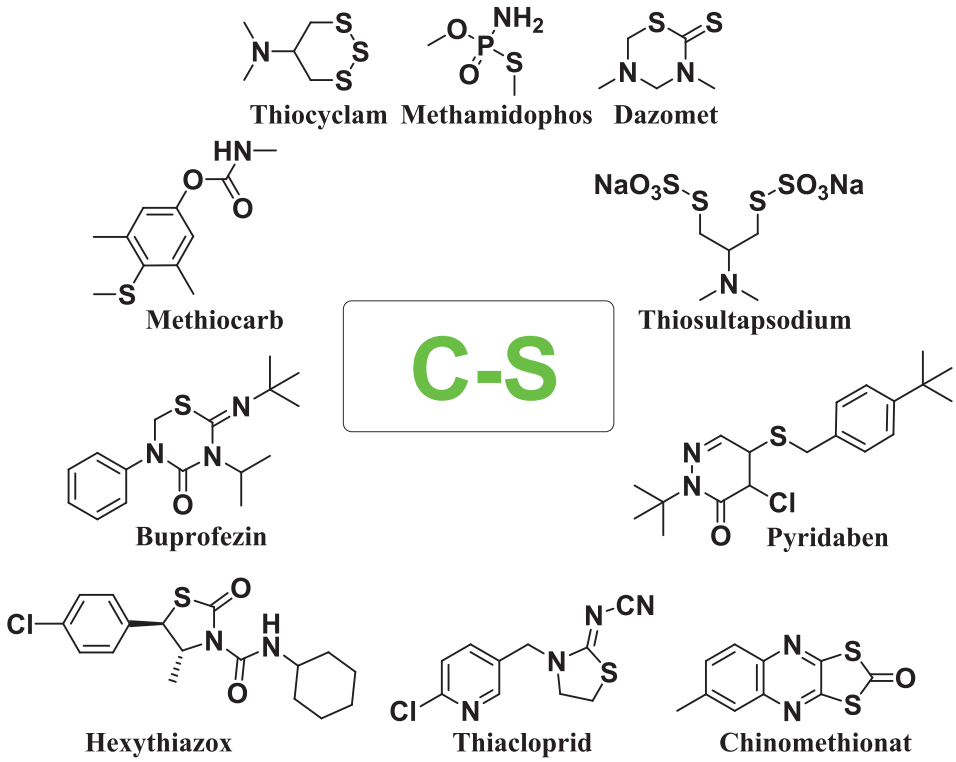


Figure 2. Examples of agrochemicals containing sulfur atom.

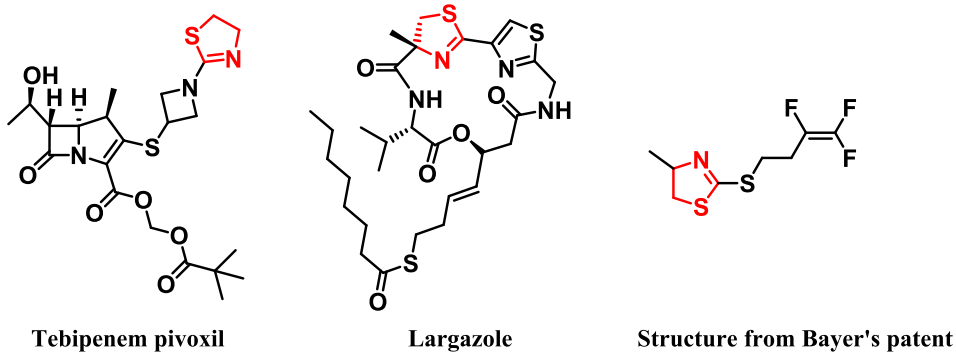


Figure 3. The structure of Tebipenem pivoxil, Largazole and Structure from Bayer's patent.

10.0 mg L^{-1} in Bayer's patent (Figure 3).[16–18] 4,5-Dihydrothiazole-2-thiol as a structure containing two S atoms absorbs our attention (Scheme 1).

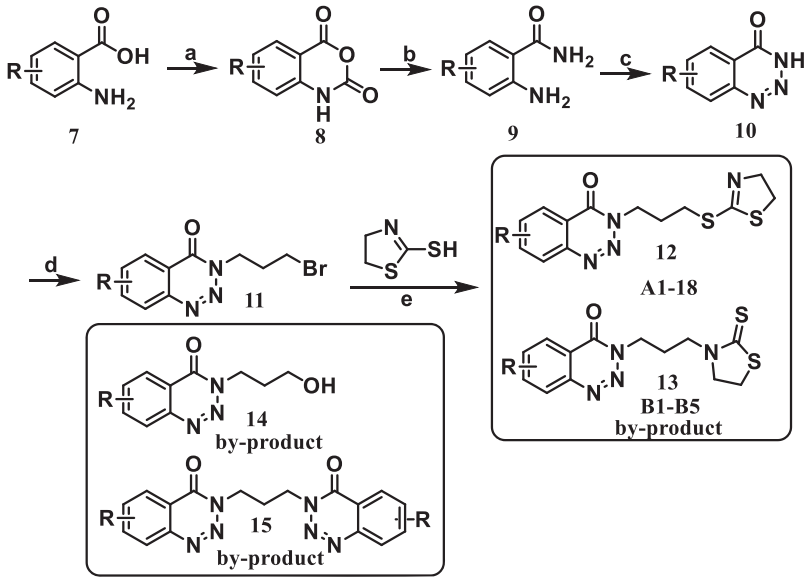
Recently, we have reported that 1,2,3-benzotriazin-4-one derivatives **1**–**4** (Figure 4) had significant inhibitory activities against *M. incognita*.[19–21] Sulfur-containing 1,2,3-benzotriazin-4-one derivative **5** and **6** were also reported to have antiparasitic activity against arthropod pest and nematicidal activity against Anguillula nematodes, respectively (Figure 5).[22,23]

Based on the reports above, in this study, we introduced 4,5-dihydrothiazole-2-thiol into title compounds and investigated the biological activities of the new molecules against *M. incognita in vivo* (Figure 6).

Results and discussion

Synthesis

In our research, all of target compounds with various substituents can be obtained easily though the reported method. During the synthetic process of intermediates substituted 3-bromoalkyl-1,2,3-benzotriazin-4-ones (**11**), substituted 3-(3-hydroxypropyl) benzo[d][1–3] triazin-4(3H)-one (**14**) and



Scheme 1. Synthetic procedure for title compounds. Reagents and conditions: (a) triphosgene (BTC), THF, −5 °C, 5h. (b) $(NH_4)_2CO_3$, 1,4-dioxane, 60 °C, 8h. (c) i. $NaNO_2$, 1.0 M HCl, H_2O, 0 °C, 2 h; ii. 30% NaOH, pH = 8, 15 min; (d) 1,2-dibromoethane, K_2CO_3, acetone, reflux 5–8 h, (e) K_2CO_3, acetone, reflux 5–8 h.

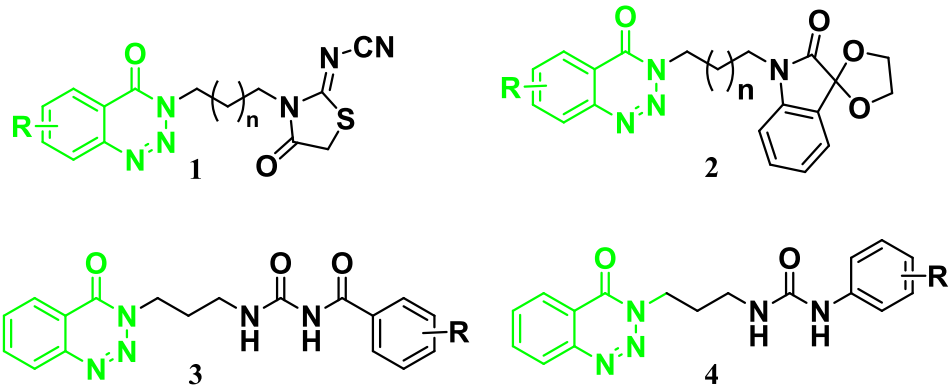


Figure 4. Compounds reported in our previous studies.

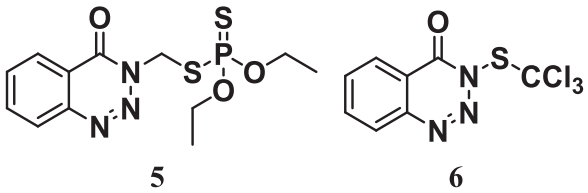


Figure 5. Bioactive agrochemicals containing triazinone skeletons.

substituted 3,3′-(propane-1,3-diyl) bis (benzo[d][1–3] triazin-4 (3H)-one) (**15**) were also obtained as by-products.[24] Water should be reduced as less as possible in the reaction system in order to decrease the production of by-product (**14**) due to the hydrolysis. The amount of 1,3-dibromopropane was three times than substituted 1,2,3-benzotriazin-4-one (**10**) to decrease the production of **15**. Detailed data was described in the Supplementary Material.

The other isomer of 4,5-dihydrothiazole-2-thiol is thiazolidine-2-thione, it was reasonably foreseeable thing that keto form of title compounds was also obtained. The structures were well-characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (Original spectrum of the compounds were in Supplementary materials, and ^{1}H NMR of A3 and ^{13}C NMR of A1 were assigned as examples.). Compound **A1** was obtained and confirmed by the X-ray diffraction (Figure 7) (Data was shown in Table S2 and S3, Supplementary Materials).[25] Some substituted 3-(3-(2-thioxothiazolidin-3-yl)propyl)benzo[d] [1–3]-triazin-4 (3H)-one (**13**) were obtained as by-products in yield of 0–40%. But the other by-products were not obtained due to the effect of different substituents. As the starting material 4,5-dihydrothiazole-2-thiol and the title compounds were hard to separate with flash chromatography on silica gel and the reaction process was difficult to be monitored by TLC, the content of the 4,5-dihydrothiazole-2-thiol should be less than substituted 3-bromoalkyl-1,2,3-benzotriazin-4-ones in the reaction system.

Biological activity

As shown in Table S1 (Supplementary Materials), the *in vivo* nematicidal activities of title compounds (**A1**–**A18**) against *M. incognita* were initially evaluated at a concentration of 20.0 mg L^{-1}. The preliminary bioassays indicated that some of the target compounds had good inhibitory activity against *M. incognita* at 20 mg L^{-1}. The inhibitory rate of compound **A4**, **A7** and **A12** reached 80%, 70% and

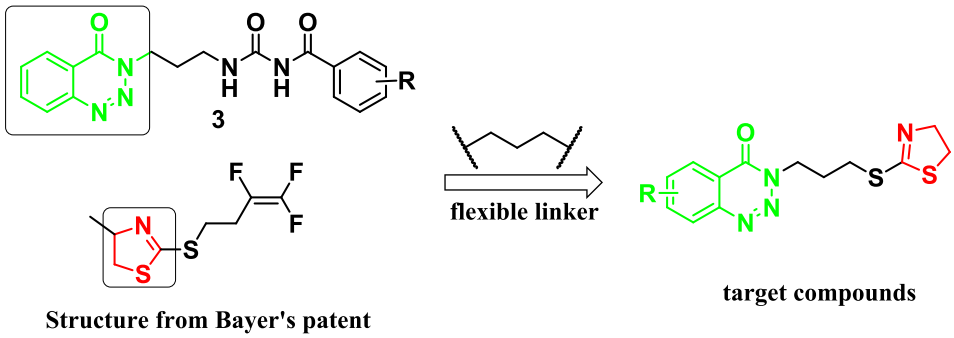


Figure 6. Design of target compounds.

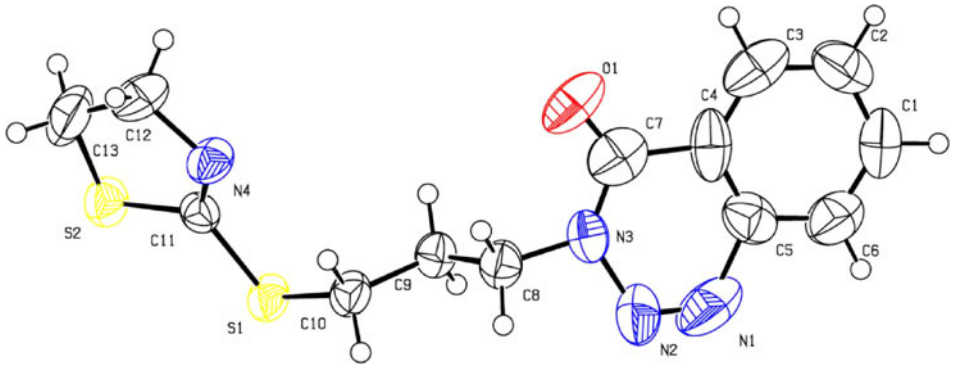


Figure 7. X-ray crystal structure of **A1** (Data was shown in Table S2 and S3).

100%, respectively. But compound **A16** was toxic to the plants and resulted in the death of plant at this concentration. All the by-products (**B1**–**B5**) had no inhibitory activity against *M. incognita* at 20 mg L^{-1}. When the concentration decreased to 10 mg L^{-1}, **A12** and **A16** kept more than 50% inhibition, then when the concentration decreased to 1 mg L^{-1} further, only compound **A12** exhibited 68.3% inhibition.

Analyzing the influence of substituents, it was found that when electron-donating group OCH_3, electron-withdrawing group NO_2 or Cl, were introduced into the 1,2,3-benzotriazin-4-one, compound **A4** (7-OCH_3) and **A12** (7-Cl) showed higher inhibitory activity than others at 20 mg L^{-1}, which indicated that 7 position of 1,2,3-benzotriazin-4-one played a positive role in promoting the nematicidal activity of the target compounds. To evaluate the effect of substituents at 7 position of the 1,2,3-benzotriazin-4-one ring, different types of substituted groups were introduced into 7 position of 1,2,3-benzotriazin-4-one. **A12** (7-Cl) showed better inhibitory activity than **A14** (7-CH_3), **A15** (7-F), **A17** (7-I) and **A18** (7-CF_3). But **A16** exhibited toxic to the plant at this concentration.

In addition, the *in vitro* nematicidal evaluation of compounds **A1**–**A18** and **B1**–**B5** against *M. incognita* was conducted. As a positive control, avermectin had the LC_{50} of 1.0 ± 0.1 mg L^{-1}. Unexpectedly, all synthesized compounds showed only <5% corrected mortalities at 50.0 mg L^{-1} (not listed here), which indicated that these compounds had no contact activity against *M. incognita*. The significant difference between *in vivo* and *in vitro* data attracted our attention. Root-knot nematodes are obligate biotrophic pathogens that can only feed on living cells. There is no evidence that they feed before invading the root.[26] So it is hard for compounds to get into the nematode before the feeding behavior. Thus, these compounds could not kill the nematodes directly like some nervous toxicants such as avermectin and organophosphate nematicides. We supposed that the active compounds may affect the movement of nematodes and host finding or they could change the rhizosphere microbiology of the plant, strengthening antagonism against nematodes.[27,28]

Experimental

Chemistry

*Synthesis of substituted Anthranilamides (**9**).* A suspension of substituted isatoic anhydride (35 mmol), ammonium carbonate (140 mmol), and 1,4-dioxane (150 mL) was heated at 60 °C. After stirring for 8 h, the reaction mixture was cooled to room temperature and evaporated under reduced pressure, and then water (200 mL) was added to the residue, which was extracted with CH_2Cl_2 (3 × 80 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give compounds **9** in yields of 63–94%.

*Synthesis of substituted 1,2,3-benzotriazin-4-ones (**10**) (except 8-nitrobenzo[d][1–3]triazin-4(3H)-one).*[29] A solution of anthranilamide (30 mmol) in 1 N HCl (120 mL) was stirred at 0 °C for 20 min. Then, sodium nitrite (60 mmol) dissolved in deionized water (100 mL) was added dropwise to the above solution for 40 min. After another 2 h of stirring at 0 °C, 30% NaOH solution was added slowly to adjust pH value to 8.0. The reaction mixture was allowed to stir

vigorously for 15 min. The precipitated product was filtered, washed with deionized water (200 mL), and dried to afford compounds **10** in yields of 40–92%.

*Synthesis of substituted 3-bromoalkyl-1,2,3-benzotriazin-4-ones (**11**).* A stirring suspension of substituted 1,2,3-benzotriazin-4-one (6 mmol), 1,3-dibromopropane (18 mmol), potassium carbonate (12 mmol), and acetone (50 mL) was refluxed for 5–8 h and then cooled to room temperature. The reaction solution was concentrated under reduced pressure, and water (100 mL) was added to the residue, which was extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified with flash chromatography on silica gel, eluting with petroleum ether (60–90 °C)/EtOAc to afford compounds **11** in yields of 36–62%.

*General synthetic procedure for target compounds (**12**).* To a mixture of compound **11** (2 mmol), potassium carbonate (2 mmol), and acetone (20 mL), 4,5-dihydrothiazole-2-thiol (1.9 mmol) was added, and then refluxed. The reaction process was monitored by TLC. After the complete consumption of 4,5-dihydrothiazole-2-thiol, the reaction was cooled to room temperature. The reaction mixture was evaporated under reduced pressure, and water (100 mL) was added to the residue, which was extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified with flash chromatography on silica gel, eluting with petroleum ether (60–90 °C)/EtOAc to afford compounds **12** in yields of 56–70%. And some of the by-products **13** were also obtained in yields of 0–40%. (Other data of target compounds and by-products are presented in the Supplemental Materials together with ^1H and ^{13}C NMR spectra)

*3-(3-((4,5-dihydrothiazol-2-yl)thio)propyl)benzo[d][1–3]-triazin-4(3H)-one (**A1**):* white solid, yield 50%; mp: 92.4–93.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 8.0, 1.2 Hz, 1H, Ph-H), 8.15 (d, J = 8.0 Hz, 1H, Ph-H), 7.99–7.91 (m, 1H, Ph-H), 7.85–7.77 (m, 1H, Ph-H), 4.59 (t, J = 6.9 Hz, 2H, CH_2), 4.13 (t, J = 8.0 Hz, 2H, CH_2), 3.36 (t, J = 8.0 Hz, 2H, CH_2), 3.21 (t, J = 7.2 Hz, 2H, CH_2), 2.36 (p, J = 7.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.94 (C = N), 155.54 (C = O), 144.26 (Ph-C), 134.78 (Ph-C), 132.33 (Ph-C), 128.27 (Ph-C), 125.06 (Ph-C), 119.81 (Ph-C), 64.10 (CH_2), 48.56 (CH_2), 35.45 (CH_2), 29.61 (CH_2), 28.80 (CH_2) ppm. HRMS *m/z* (ES+) calcd. for $C_{13}H_{14}N_4NaOS_2$ $(M + Na)^+$, 329.0507; found, 329.0500.

Biological assay

The second-stage juveniles (J2) of *M. incognita* used in all tests were cultured by Huzhou Modern Agricultural Biotechnology Innovation Center, Chinese Academy of Sciences, China.

Nematicidal activity in vivo

All compounds (**A1**–**A18** and **B1**–**B5**) were dissolved with DMSO, then diluted with distilled water to obtain series concentrations of 20.0, 10.0, 5.0, and 1.0 mg L^{-1} for bioassays. The final concentration of DMSO in each treatment never exceeded 1% v/v. The one-week age cucumber seedlings were replanted in sterilized sand in test tubes (one seedling per test tube, tube size: 20 × 250 mm), and the roots of each seedling were treated with 3 mL of test solution. Then approximately 2000 living J2 nematodes were inoculated into the rhizosphere sand of each host plant. Fenamiphos and avermectin (B1) at concentrations of 20.0, 10.0, 5.0 and 1.0 mg L^{-1} served as positive control, and the negative control group was prepared in the same way but lacked the tested compound. Distilled water without nematodes served as blank control. Each treatment was replicated four times and the experiment was repeated three times. All the above test tubes were incubated at 20–25 °C for 45 d, with 10 h in the daylight and 14 h in the dark per day. The number of root knots in each test tube was counted and recorded a score. The inhibition on J2 of *M. incognita* was calculated by comparison with the negative control group (Computing formula 1):

1. Computing formula

$$\text{Inhibition (\%)} = [(\text{score of negative control} - \text{score of treatment})/(\text{score of negative control})] \times 100.$$

Scoring criteria: 0: 0–5 knots; 5: 6–10 knots; 10: 11–20 knots; 20: more than 20 knots.

Nematicidal activity in vitro

Pure compounds (**A1**–**A18** and **B1**–**B5**) were dissolved in DMSO and diluted with distilled water to obtain stock solutions of double the treatment concentration. Then, 2 mL of J2 aqueous suspension containing approximately 200 living nematodes was added to a 6 cm diameter Petri dish and treated with 2 mL of the above solution, meanwhile providing series concentrations of 50.0, 25.0, 10.0, 5.0, and 1.0 mg L^{-1}. The final concentration of DMSO in each treatment never exceeded 1% (v/v). Avermectin (B1) at the above same treatment concentrations served as a positive control, and the negative control group was prepared in the same way but lacked the tested compound. Distilled water served as a blank control. All of the above test dishes were covered with the laboratory parafilm to avoid the possible evaporation or pollution. Each treatment was incubated at 25 °C for 24 h and had three repetitions. Nematodes in each test dish were collected after washing in sterile water through a 500-mesh sieve, and finally, the activities of tested compounds were monitored under a microscope by recording the death rates of tested nematodes. Nematodes that did not move when prodded with a needle were considered to be dead. The LC_{50} values of tested compounds were calculated using the probit method.

Conclusion

In conclusion, a series of novel 1,2,3-benzotriazin-4-one derivatives bearing 4,5-dihydrothiazole-2-thiol were synthesized, the nematicidal activities against *M. incognita* were evaluated *in*

vivo and *in vitro*. Some of them exhibited good in vivo inhibitory activities at 10.0 mg L^{-1}, which implied that 1,2,3-benzotriazin-4-one with 4,5-dihydrothiazole-2-thiol is a potential active structure worth studying further.

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