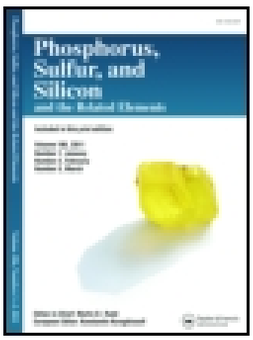

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Synthesis of novel azabicyclo derivatives containing a thiazole moiety and their biological activity against pine-wood nematodes

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ABSTRACT

To explore a new skeleton with nematicidal activity, a series of novel azabicyclo derivatives containing a thiazole moiety were designed, synthesized and evaluated for their nematicidal activities. The bioassay results against pine-wood nematodes (*Bursaphelenchus xylophilus*) showed that most of the title compounds displayed nematicidal activity at a concentration of 40 mg/L. Especially, the title compounds2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-4-(4-chlorophenyl)thiazole (**7e**), 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thio)-4-phenylthiazole (**10a**) and 2-((8-methyl-8-azabicyclo [3.2.1]octan-3-yl)thio)-4-(4-chlorophenyl)thiazole (**10e**) exhibited more than 90% mortality against *Bursaphelenchus xylophilus*.

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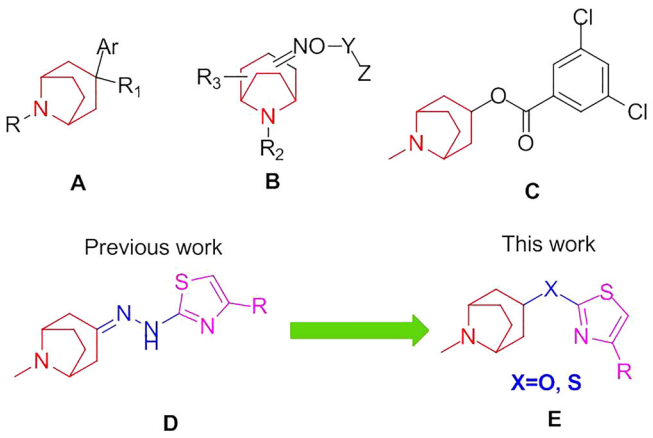
Azabicyclo; PWNs; nematicidal activity; novel nematicide

GRAPHICAL ABSTRACT



Introduction

Phytonematodes are one of the most destructive crop pests and can cause global annual agricultural losses of over 100 billion dollars.[1] Among them, pine-wood nematode (PWN) has been ranked as the eighth most harmful genera of parasitic nematodes.[2] The pine-wood nematode (*Bursaphelenchus xylophilus*)is a notorious invasive species that causes a fatal pine tree disease known as pine wilt disease (PWD).[3] Since the emergence of PWD in Nagasaki in 1905 which caused extensive damage of the pine forest, the PWN has spread all over the world.[4] Today, PWD has been regarded worldwide as a severe threat to pine forests.

Several strategies have been adopted to control the spread of PWD. For example, Metham sodium was used to fumigate dead trees to kill the larvae of PWNs. A trunk injection of nematicides, such as Abamectin or Emamectin benzoate, is another control method to protect pine trees from the nematode infection.[5,6] However, since those nematicides have been widely used for many years, nematodes tend to develop drug resistance due to recurrent exposure and excessive usage. Therefore, the development of nematicides with novel mechanism, high efficacy, low toxicity and environment-friendly is extremely urgent.

Azabicyclo compounds are a group of alkaloids that are ubiquitous in nature. Azabicyclo derivatives are emerging as potent pharmacophores showing distinctive biological activities such as anti-microbial,[7,8] anti-depressant[9,10] and anti-inflammatory.[11] Some azabicyclo derivatives also demonstrated certain pesticidal activities.[12] In 1996, Zeneca reported a series of azabicyclo octane derivatives which had

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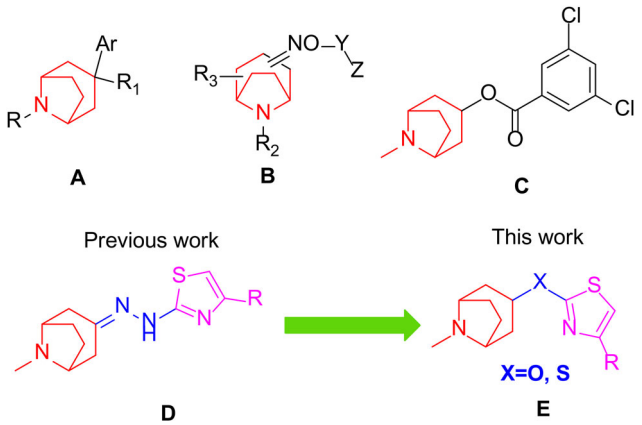


Figure 1. Azabicyclo derivatives with various pesticidal activities.

insecticidal activities against *Myzus persicae* (Figure 1A).[13] Aventis Crop Science found that azabicyclo oxime ether derivatives (Figure 1B) exhibited excellent mortality against *Heliothis virescens* in 2001.[14] Moreover, Trowell and coworkers proved that the human 5-HT_3 receptor antagonist MDL72222 (Figure 1C) had lethal effects on *Caenorhabditis elegans*.[15] In our previous work, azabicyclo thiazole hydrazone derivatives have been found excellent bioactivity against *Bursaphelenchus xylophilus* (Figure 1D).[16] As our continuous efforts on the development of novel nematicides, herein, two categories and 46 unreported compounds with azabicyclo[3.2.1]octane scaffolds were synthesized by introducing an ether or thioether linkage between azabicyclo and thiazole moieties (Figure 1E). The target compounds were synthesized as described in Scheme 1 and the biological activity against *Bursaphelenchus xylophilus in vitro* were tested. The spectra data of synthesized compounds are provided in the supplemental materials.

Results and discussion

Chemistry

The synthetic routes to target compounds 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-thiazole derivatives (**7a–w**) and 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thio)-thiazole derivatives (**10a-w**) were described in Scheme 1. According to the reported literatures,[17,18] the intermediate **4** (*S*-ethyl *O*-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) carbonodithioate) was synthesized by three steps without further purification. The key intermediate **5** (*O*-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) carbamothioate) was prepared by a acylation reaction of the intermediate **4** with ammonia in ethanol.[19] Finally, the intermediate **5** was reacted with substituted ethyl ketone **6a-w** in ethanol under reflux temperature for 3 h to obtain 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-thiazole derivatives (**7a–w**) in moderate to good yields.[20]

According to the reported literatures,[21] the intermediate **8** (8-methyl-8-azabicyclo[3.2.1]octan-3-yl ethanesulfonate) was obtained *via* esterification reaction with 8-methyl-8-azabicyclo[3.2.1]octan-3-olate sodium **2** and ethane sulfonyl chloride. The substituted thiazole-2-thiol **9a–w** were synthesized by ammonium dithiocarbamate and substituted ethyl ketone **6a-w.**[22] Then the 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thio)-thiazole derivatives (**10a-w**) were produced through substitution reaction by using intermediate **8** and **9a-w**.

Two categories of azabicyclo[3.2.1]octane derivatives bearing a thiazole moiety were identified by ^{1}H NMR, ^{13}C NMR and HRMS. For example, in the ^{1}H NMR spectrum of **7a** (Figure S1, Supplemental Materials), the absorption peaks at δ: 7.77–7.29 ppm reveal the existence of phenyl protons. The characteristic singlet at δ: 6.89 ppm is attributed to the absorptions of thiazole. The characteristic triplet at δ: 5.43 ppm is due to OCH of tropane. The characteristic singlets at δ: 3.79 ppm and δ: 2.77 ppm are NH and NCH_3 of tropane respectively. The doublet at δ: 3.04 ppm and multiplet at δ: 2.46–2.23 ppm are CH_2 of tropane. Moreover, in the ^{13}C NMR spectrum of **7a**, the chemical shifts at δ: 171.98–104.86 ppm are attributed to the phenyl and thiazole. The chemical shifts at δ: 72.34–24.55 ppm confirm the existences of tropane fragment (Figure S2, Supplemental Materials). The structure assigned for compound **7a** was fully supported by its mass spectrum, which showed a molecular formula $C_{17}H_{20}N_2OS$ (calcd for $C_{17}H_{20}N_2OS$ $(M)^+$ 300.1296; found, 300.1297) (Figure S3, Supplemental Materials).

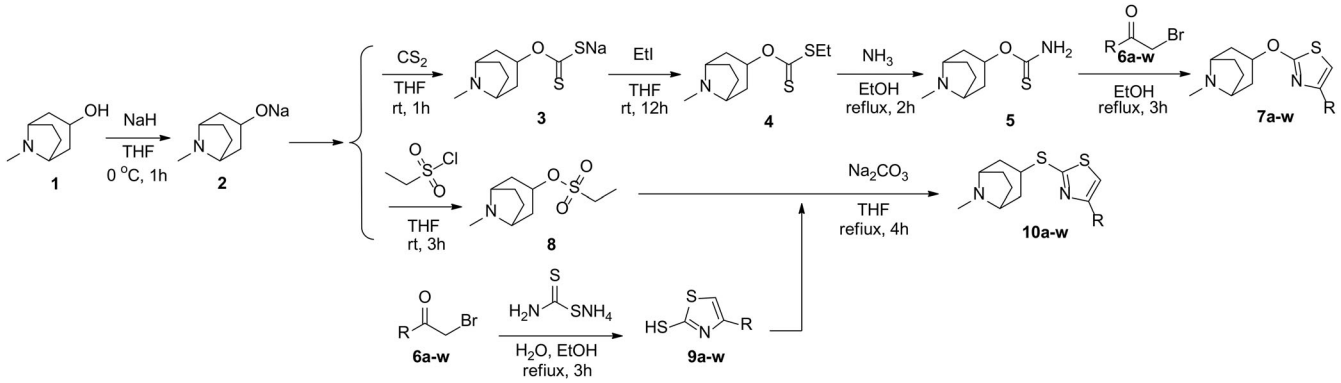
Nematicidal activities

The nematicidal activity of title compounds (**7a-w** and **10a-w**) against *Bursaphelenchus xylophilus* at the concentration of 40 mg/L were listed in Table 1.

As shown in Table 1, the preliminary bioassays indicated that some of the target compounds had good nematicidal activity, for example, compound **7a**, **7e**, **10a**, **10e**, **10f** and **10k** exhibited more than 80% mortality. Especially, compound **7e**, **10a** and **10e** displayed nematicidal activities of 95%, 92% and 94% against *Bursaphelenchus xylophilus* at the concentration of 40 mg/L respectively. In general, the thioether compounds demonstrated higher nematicidal activity than their counterparts with an ether linkage.

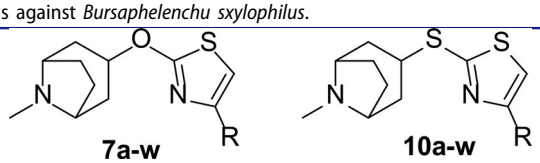
The compounds with substitution at the *para*-position of the benzene ring had higher nematicidal activity than those at the *meta*- or *ortho*-positions, while there were no significant differences between the *meta*- and *ortho*-position. For example, *para*-substituted compounds (**7b-e**) showed higher activity than their *meta*- (**7i-l**) or *ortho*- (**7n-q**) substituted counterparts . When halogen groups were introduced into the phenyl ring, the compounds (**7d-f**) exhibited relatively higher nematicidal activity than other electron-donating groups (**7b** and **7c**) or electron-withdrawing groups (**7f** and **7g**). Furthermore, by changing the phenyl group into a furan group, pyridine group or methyl, the nematicidal activity of the compounds decreased quickly (**7u-w**). When the linkage between azabicyclo and thiazole was changed from O to S, higher nematicidal activity was achieved in most cases (**7a-w***vs***10a-w**).

Due to the high activities of compound **7a**, **7e**, **10a** and **10e**, we further tested the nematicidal activity of these compounds at 40, 20, 10 and 5 mg/L (Table 2) respectively. It was found that even at 10 mg/L,**7e**, **10a** and **10e** still showed good nematicidal activity against *Bursaphelenchus xylophilus* of more than 60%.



Scheme 1. Synthetic routes of the target compounds.

Table 1. Nematicidal activities of title compounds against *Bursaphelenchu sxylophilus*.



Compd.	R	Mortality (%)[a]	Compd.	R	Mortality (%)[a]
7a	C_6H_5	81	**10a**	C_6H_5	92
7b	4-$CH_3C_6H_5$	54	**10b**	4-$CH_3C_6H_5$	72
7c	4-$OMeC_6H_5$	42	**10c**	4-$OMeC_6H_5$	72
7d	4-FC_6H_5	57	**10d**	4-FC_6H_5	77
7e	4-ClC_6H_5	95	**10e**	4-ClC_6H_5	94
7f	4-BrC_6H_5	66	**10f**	4-BrC_6H_5	82
7g	4-$NO_2C_6H_5$	38	**10g**	4-$NO_2C_6H_5$	63
7h	4-$CF_3C_6H_5$	30	**10h**	4-$CF_3C_6H_5$	59
7i	3-$CH_3C_6H_5$	48	**10i**	3-$CH_3C_6H_5$	63
7j	3-$OMeC_6H_5$	37	**10j**	3-$OMeC_6H_5$	63
7k	3-ClC_6H_5	53	**10k**	3-ClC_6H_5	82
7l	3-BrC_6H_5	51	**10l**	3-BrC_6H_5	76
7m	3-$NO_2C_6H_5$	41	**10m**	3-$NO_2C_6H_5$	60
7n	2-$CH_3C_6H_5$	33	**10n**	2-$CH_3C_6H_5$	64
7o	2-$OMeC_6H_5$	27	**10o**	2-$OMeC_6H_5$	61
7p	2-ClC_6H_5	50	**10p**	2-ClC_6H_5	79
7q	2-BrC_6H_5	28	**10q**	2-BrC_6H_5	73
7r	2-$NO_2C_6H_5$	17	**10r**	2-$NO_2C_6H_5$	56
7s	3,4-diClC_6H_5	60	**10s**	3,4-diClC_6H_5	73
7t	3,5-diClC_6H_5	69	**10t**	3,5-diClC_6H_5	76
7u	2-Furan	24	**10u**	2-Furan	39
7v	4-Pyridine	30	**10v**	4-Pyridine	45
7w	Methyl	15	**10w**	Methyl	36
Avermectin[b]		100			100

[a]Mortality at 40 mg/L.
[b]Avermectin at the concentration of 5 mg/L.

Experimental

Synthesis of O-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) carbamothioate (5)

Tropine (**1**) (1 mmol) was dissolved in THF (2 mL) and added dropwise to a suspension of sodium hydride (1.2 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h to give the sodium salt **2**. Then, carbon disulfide *1.5 mmol) in THF (2 mL) was added and the mixture was stirred at room temperature for 1 h to give the xanthate **3**. After that, iodoethane (1.5 mmol) in THF (2 mL) was added into and the mixture was stirred at room temperature for 12 h. Methanol (2 mL) was used to quench the reaction and the solvent was evaporated under reduced pressure to give the xanthate **4**. The residue was dissolved in ethanol (10 mL). Ammonia (600 mg) was bubbled through the reaction mixture continuously at reflux temperature for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, aqueous sodium hydroxide solution (10 mL of a 1.0 M solution) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (DCM/MeOH =8:1, v/v) to afford thiocarbamate **5** (35%) as a brown solid, mp151.3–153.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2 H, $CONH_2$),5.31 (t, J = 4.1 Hz, 1 H, OCH), 3.73 (s, 2 H, NCH), 3.11 (d, J = 15.3 Hz, 2 H, tropaneCH_2), 2.75 (s, 3 H, NCH_3), 2.41 – 2.20 (m, 6 H, tropaneCH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.98(C = O), 82.54(OCH), 60.95(2 NCH), 38.49 (NCH_3), 33.73(2 CH_2), 24.50(2 CH_2).

Table 2. Gradient filtration of target compounds.

	Mortality (%)			
Compd.	40 mg/L	20 mg/L	10 mg/L	5 mg/L
7a	82	67	57	33
7e	95	74	66	36
10a	92	81	67	40
10e	95	79	64	43
Avermectin				100

Synthesis of 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-thiazole 7a-w (general method)

Thiocarbamate **5** (1 mmol) and 2-bromo-1-phenylethanone **6a**-**w** (1.1 mmol) were dissolved in ethanol (10 mL) and refluxed for 3–5 h (monitored by TLC). After cooling to room temperature, the solvent was evaporated under reduced pressure, aqueous sodium hydroxide solution (10 mL of a 1.0 M solution) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (DCM/MeOH =10:1, v/v).

Synthesis of 8-methyl-8-azabicyclo[3.2.1]octan-3-yl ethanesulfonate (8)

Tropine (**1**) (1 mmol) was dissolved in THF (2 mL) and added dropwise to a suspension of sodium hydride (1.2 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1vh to give the sodium salt **2**. Ethane sulfonyl chloride (1.2 mmol) in THF (2 mL) was then added dropwise at 0 °C and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, aqueous sodium hydroxide solution (10 mL of a 1.0 M solution) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the ethyl sulfonate **8** (142 mg, 61%).

Synthesis of thiazole-2-thiol 9a-w (general method)

Ammonium dithiocarbamate (2 mmol) was dissolved in a mixture of ethanol (2 mL) and water (2 mL). 2-bromo-1-phenylethanone **6a**-**w** (1 mmol) in ethanol (2 mL) was added dropwise at 0 °C and the mixture was refluxed for 3–5 h. The organic solvent was evaporated under reduced pressure and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*.

Synthesis of 2-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thio)- thiazole 10a-w (general method)

8-methyl-8-azabicyclo[3.2.1]octan-3-yl ethanesulfonate (**8**) (1 mmol), thiazole-2-thiol **9a**-**w** (1.1 mmol) and sodium carbonate (1.5 mmol) were dissolved in THF (10 mL) and refluxed for 3–5 h (monitored by TLC). After cooling to room temperature, the solvent was evaporated under reduced pressure, aqueous sodium hydroxide solution (10 mL of a 1.0 M solution) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (DCM/MeOH =10:1, v/v).

The Supplemental Materials contains complete characterization data of the products 7a – 7w, 10a-w and sample spectroscopic data of 7a and 10a (Figures S1–S6, Supplemental Materials).

Nematicidal bioassay

Nematicidal activity of the title compounds against *Bursaphelenchus xylophilus* were evaluated. *Bursaphelenchus xylophilus* used in all tests were cultured by Huzhou Modern Agricultural Biotechnology Innovation Center, Chinese Academy of Sciences, China.

Pure compounds (**7a**-**w** and **10a**-**w**) were dissolved in DMSO and diluted with distilled water containing 0.15% Triton X-100.*Bursaphelenchus xylophilus* were inoculated on nematode agar plates at 25 °C for 7 d. The test solution (50 μL) was added to each well of a 96-well plate containing 50 nematodes in 50 μL of distilled water and performed in quadruplicate. The concentration of tested compounds was 40 mg/L. Avermectin (5 mg/L) was used as the positive control and DMSO/H_2O solution as the negative control. All treatments were replicated twice. The plates were covered to prevent the evaporation of solvent and maintained in darkness at 25 °C. After 72 h, the dead nematodes were counted. The nematicidal activity is presented as the percent of dead nematodes corrected according to Schneider-Orelli's formula.

$$\text{Corrected Mortality (\%)} = (\text{M in treat plot} - \text{M in negative control plot}) / (100 - \text{M in negative control plot}) \times 100$$

Conclusions

In conclusion, a series of novel azabicyclo[3.2.1]octan thiazole derivatives with ether or thioether linkage were synthesized and bio-assayed. Some target compounds exhibited good mortality against pine-wood nematode *Bursaphelenchus xylophilus* at 40 mg/L, which implied that it might be a potential nematicidal active structure to be worth studying further.

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