Bioorganic & Medicinal Chemistry Letters 27 (2017) 2641–2644

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

# Synthesis and nematicidal activities of 1,2,3-benzotriazin-4-one derivatives containing thiourea and acylthiourea against *Meloidogyne incognita*

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ARTICLE INFO

*Article history:*
Received 29 October 2016
Revised 9 December 2016
Accepted 27 December 2016
Available online 29 December 2016

*Keywords:*
1,2,3-Benzotriazin-4-one
Thiourea
Acylthiourea
*M. incognita*
Nematicidal activity

ABSTRACT

Two series of novel 1,2,3-benzotriazin-4-one derivatives containing thiourea and acylthiourea were designed and synthesized. The bioassay results showed that most of the test compounds showed good nematicidal activity against *M. incognita* at the concentration of 10.0 mg $L^{-1}$ *in vivo*. The compounds **A13**, **A17** and **B3** showed excellent nematicidal activity on the second stage juveniles of the root-knot nematode with the inhibition rate of 51.3%, 58.3% and 51.3% at the concentration of 1.0 mg $L^{-1}$ respectively. It suggested that the structure of 1,2,3-benzotriazin-4-one derivatives containing thiourea and acylthiourea could be optimized further.



Plant-parasitic nematodes (PPNs) cause approximately $157 billion of annual crop losses globally.[1] Among them, root-knot nematodes (RKNs), *Meloidogyne* spp., are considered as the most damaging nematode group in the world as they result in approximately 5% of global crop loss to most cultivated plant species such as tomato, pepper, watermelons and onions.[2–4] Traditional nematocides such as fosthiazate, fenamiphos, oxamyl, dazomet, 1,3-dichloropropene and metham sodium have been applied for many years. However, some of these chemicals are gradually being phased out because of their bad environmental impact. At present, fosthiazate and abamectin are the most commonly used nematocides in the market. Although recently some stars of nematocide industry have entered the pesticide market like fluensulfone[5–7] and tioxazafen[8] (Fig. 1), it is not enough for the increasingly stringent regulatory requirements for protecting the environment and ensuring food safety. Therefore, it is urgent to develop environment-friendly alternatives for PPNs control.

1,2,3-Benzotriazine-4-one is an important class of nitrogen-containing heterocycle and has attracted much attention in both the medicinal and agrochemical fields.[9–11] For example, many pharmacological properties for this class of compounds have been reported, including drugs with sedative, anesthetic, antitumor, antiarthritic, diuretic and antitubercular activities.[12–17] 1,2,3-Benzotriazine-4-one structure has also been applied on organophosphorus insecticide such as azinphos-ethyl and azinphos-methyl, which can be used for crops pests prevention and control. As shown in Fig. 2, the 1,2,3-benzotriazin-4-one derivative also exhibited nematicidal activity. Compound **V1** could inhibit *Anguillula* nematodes.[18] In addition, our research group have reported that 1,2,3-benzotriazin-4-one derivatives **V2** and **V3** exhibited good control efficacy against the cucumber root-knot nematode disease caused by *Meloidogyne incognita* at the concentration of 10.0 mg $L^{-1}$, which implied that 1,2,3-benzotriazin-4-one derivatives might be potential for novel promising nematicides.[19,20] Analyzing the structure characteristic of these lead compounds, we found that the structure includes three parts: 1,2,3-benzotriazin-4-one, linker, heterocycle or aromatic ring. The trial of changing heterocycle and the effect of substituents on 1,2,3-benzotriazin-4-one ring have been investigated before,[19,20] so we focus our attention on the change of linker now. In crop protection and bioactive chemicals, thiourea and acylthiourea have been reported to display a variety of biological activities, such as insecticidal, fungicidal, antimicrobial, antitumor, etc.[21–26] With all this in mind, we introduced thiourea and acylthiourea into 1,2,3-benzotriazin-4-one structure as linker to investigate the effect of the linker type on the nematicidal bioactivity, and designed two series of novel 1,2,3-benzotriazin-4-one derivatives (Fig. 2 A and B). Herein, we described the

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http://dx.doi.org/10.1016/j.bmcl.2016.12.065
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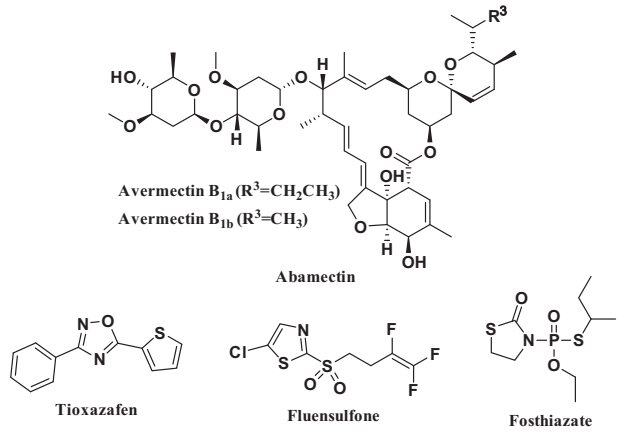
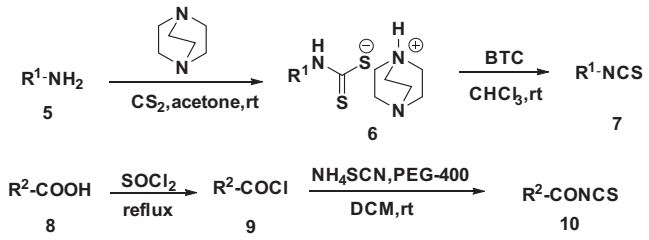



**Fig. 1.** Some representative nematicides.

molecular design, synthesis and preliminarily discussion about the relationship between structure and nematicidal activities against *Meloidogyne incognita in vivo*.




**Scheme 2.** Synthetic route of aryl isothiocyanates and aroyl isothiocyanates.

1,2,3-Benzotriazin-4-one (**2**) was prepared according to the method in reported literature.[27] As depicted in Scheme 1, the compound **3** was readily prepared via N-alkylation of 1,2,3-Benzotriazin-4-one at the 3 position, with 2-(3-bromopropyl) isoindoline-1,3-dione as an alkylation agent. Subsequently, the compound **3** was hydrolysis to 3-(3-aminopropyl)benzo[*d*][1,2,3]-triazin-4(3H)-one (**4**) in the presence of hydrazine through Gabriel's primary amine synthesis.

As shown in Scheme 2, arylamines **5** reacted with $CS_2$ under the organic base (triethylene diamine) condition to afford

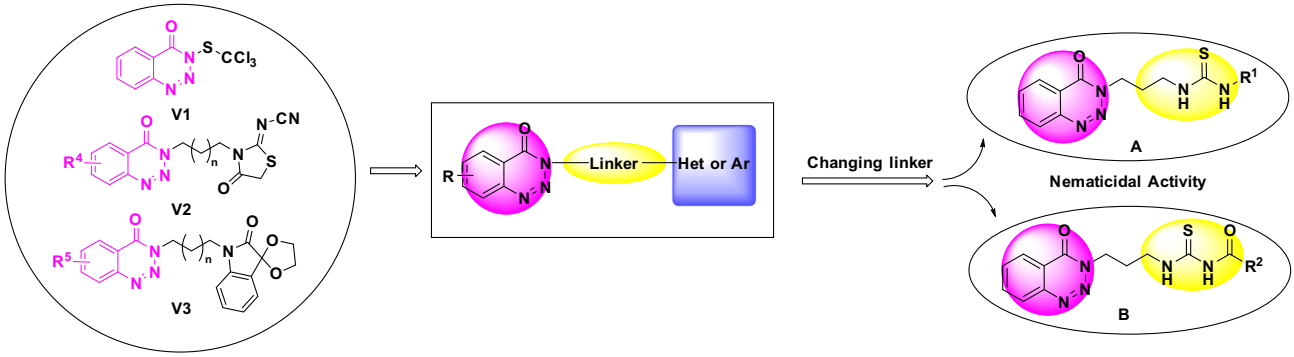
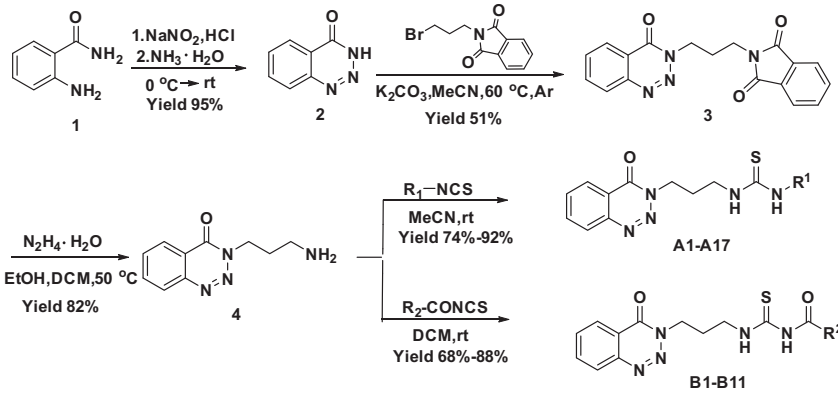



**Fig. 2.** Design strategy for the synthesis of 1,2,3-benzotriazin-4-one derivatives containing thiourea and acylthiourea.




A1. $R^1$=phenyl
A2. $R^1$=2-F-phenyl
A3. $R^1$=2-Br-phenyl
A4. $R^1$=2-$OCH_3$-phenyl
A5. $R^1$=3-F-phenyl
A6. $R^1$=3-$CH_3$-phenyl
A7. $R^1$=4-$NO_2$-phenyl
A8. $R^1$=4-$CF_3$-phenyl
A9. $R^1$=4-CN-phenyl
A10. $R^1$=4-F-phenyl
A11. $R^1$=4-Cl-phenyl
A12. $R^1$=4-I-phenyl
A13. $R^1$=pyridin-3-yl
A14. $R^1$=pyridin-4-yl
A15. $R^1$=5-chloropyridin-2-yl
A16. $R^1$=5-bromopyridin-2-yl
A17. $R^1$=2-chloropyridin-4-yl
B1. $R^2$=phenyl
B2. $R^2$=2-F-phenyl
B3. $R^2$=2-Cl-phenyl
B4. $R^2$=2-$OCF_3$-phenyl
B5. $R^2$=4-$NO_2$-phenyl
B6. $R^2$=4-$CF_3$-phenyl
B7. $R^2$=4-F-phenyl
B8. $R^2$=4-$OCH_3$-phenyl
B9. $R^2$=3-Br-phenyl
B10. $R^2$=2,5-di$OCH_3$-phenyl
B11. $R^2$=2-F,3-Br-phenyl

**Scheme 1.** Synthetic route of title compounds (**A1**–**A17**, **B1**–**B11**).