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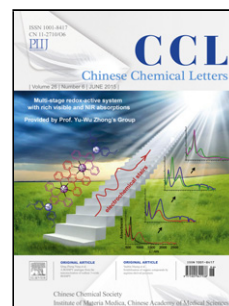
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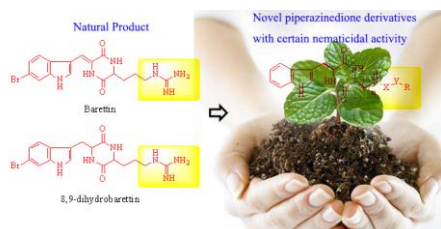
Communication

# Synthesis and nematicidal activity of piperazinedione derivatives based on the natural product Baretin

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## Graphical Abstract



More than 70 diketopiperazine derivatives based on the structure of Baretin have been synthesized and evaluated for the bioactivity against root-knot nematode *M. incognita*. The most active compound showed a nematicidal activity of 75% at 2.4  $\mu\text{mol/L}$ .

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## ABSTRACT

Nematodes are serious constraints of crop production worldwide. However, the traditional nematicides suffer from the side-effects, including environmental and human toxicity. Herein, more than 70 novel piperazinedione derivatives based on the natural product Baretin were synthesized and evaluated against the root-knot nematode *Meloidogyne incognita* (*M. incognita*). While most of synthesized compounds exhibited certain nematicidal activity at high concentration, the best one showed a nematicidal activity of 75% at 2.4  $\mu\text{mol/L}$ .

Phytonematodes are one kind of the major crop pests which can cause significant loss in crop yields worldwide [1]. The most common host plants of phytonematodes include corn, cotton, soybean, peanut, wheat, rice, sugarcane, sorghum, tobacco, numerous vegetable crops, fruit and nut crops, and golf greens [2]. While chemical nematicides such as methyl bromide, carbamates and organophosphates have largely eliminated the damages of nematodes on agriculture, they also exerted detrimental effects on both environment and human health such as groundwater pollution and human poisoning [3-5]. The repeat applications of traditional nematicides have also resulted in serious resistance [6,7]. Hence, the development of potent nematicides with novel mechanism of action, low off-target toxicity and high nematicidal efficiency is extremely urgent.

Natural products can offer powerful leads for the development of valuable pesticide candidates [8-10]. For example, insecticide Cartap was successfully developed based on nereistoxin [11], Resorcinols, the products from *Lithraea molleoides* have shown strong activity against nematodes [12], and the essential oils of *Lantana camara* also revealed certain nematicidal activity [13].

More recently, marine natural products Baretin and 8,9-dihydrobaretin (Fig. 1) produced by the cold water marine sponge *Geodia barretti* were shown to be able to bind specifically to a mammalian serotonin (5-hydroxytryptamine, 5-HT) receptor (5-HT<sub>2</sub>) [14]. 5-HT is a significant monoamine neurotransmitter which plays vital roles in mammalian endocrine function, as well as in the central and peripheral nervous system [15,16]. 5-HT was also found to be an important regulator of various physiological activities in nematodes including feeding, movement and reproduction [17-20].

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