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Design, synthesis and antifungal activity evaluation of coumarin-3-carboxamide derivatives

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ABSTRACT

A series of coumarin-3-carboxamides/hydrazides have been designed and synthesized, all the target compounds were evaluated in vitro for their antifungal activity against *Botrytis cinerea*, *Alternaria solani*, *Gibberella zeae*, *Rhizoctorzia solani*, *Cucumber anthrax* and *Alternaria* leaf spot, some of the designed compounds **4a**-**4g** exhibited potential activity in the primary assays, this highlighted by the compounds **4a**, **4d**, **4e** and **4f**, EC_{50} values of which against *Rhizoctorzia solani* were as low as 1.80 μg/mL, 2.50 μg/mL, 2.25 μg/mL and 2.10 μg/mL, respectively, exhibiting more effective control with that of the positive control than Boscalid. Furthermore, compounds **4a** and **4e** represented equivalent antifungal activity with Boscalid against *Botrytis cinerea*.

1. Introduction

With readily synthetic methods and excellent chemical/physical characteristics, coumarins have received extensive attention and show great practical values in many fields, such as medicine discovery, dye chemistry, materials chemistry and so on [1–3]. Actually, over 1300 kinds of coumarins have been identified, chiefly as secondary metabolites in green plants [4,5], fungi and bacteria [6–9]. The active ingredient coumarins also can be found in many traditional Chinese herbal medicines, such as the former Hu, founder Ma, Cnidium, pepper, Qin Pekin, etc., and they usually possess a broad scope of pharmacological and biological activities [10].

As the structural core, coumarin is widely used as a scaffold in medicinal and agricultural chemicals (Fig. 1). Such as Warfarin and Acenocoumarol, both are anticoagulant agents that function as vitamin K antagonists, Coumoxystrobin is a strobilurin fungicide bearing a coumarin subunit, it displays a broad spectrum of antifungal activity, and Osthole with a coumarin scaffold has been using as a fungicide for a long history in China. Inspired by these facts, our group designed and synthesized several coumarin derivatives with high antifungal activity [11–13], such as Osthole derivatives, coumarino[8,7-e][1,3]oxazine, furo[3,2-*c*]coumarin, and pyrano[3,2-c] chromene-2,5-dione [8,14–16] (Fig. 1). However, the discovery of coumarin-based fungicides with high activity still has a long way to go.

In the field of fungicide research, the development of carboxylic acid amide (CAA) fungicides has received a lot of attention. Since the early report of amide fungicide carbendazim (carboxin) in 1966, amide fungicides have been used for nearly 50 years [17], and a number of commercial amide fungicides have been launched to the market. During the late 1990s, by the introduction of fluorine atom and active heterocycle to the target molecules, the research on amide fungicides won a big step forward. New structures of amide fungicides were reported with detailed understanding of their mode of action [18]. The newly developed amide fungicides such as Fluopyram, Bixafen, Sedaxane, Isopyrazam, Penthiopyrad and Boscalid [19,20] (Fig. 2) with high activity and broad antifungal spectrum were successfully used to control a variety of plant diseases with very limited cross-resistance to most of the main fungal diseases.

In addition to amide group, molecules with hydrazide scaffolds also displayed a broad scope of pharmacological and biological activities [21,22] and have been widely used as frameworks in drug design. For example, the hydrazide derivative maleic hydrazide [23] has been found a temporary and inhibiting effect on plant growth, and the indole-coumarin [24] exhibited good antiproliferative profile against colon HT-2cell line, and the hydrazide derivative tebufenozide [25] exhibited moderate insecticidal activity as a kind of insect growth regulators (IGRs) (Fig. 3).

Considering these facts, we envisioned that the combination of the coumarin framework with carboxamides/hydrazide units may afford the desired high performance fungicides. Based on our previous work on structural modification and bioscreening of coumarin based fungicides, which exhibited effective control to certain phytopathogenic diseases [8,14,16,26], herein we report the design, synthesis and antifungal activities of novel coumarin carboxamides/hydrazides. It was luckily to discover that a new category of coumarin based fungicides with excellent performance such as high antifungal activities and low

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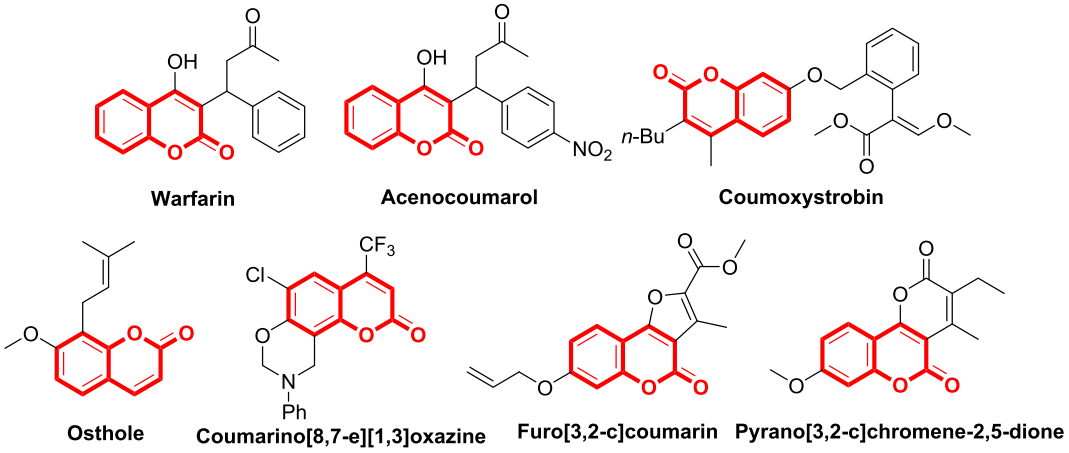

Fig. 1. Sample structures of coumarin-containing drugs and fungicides.

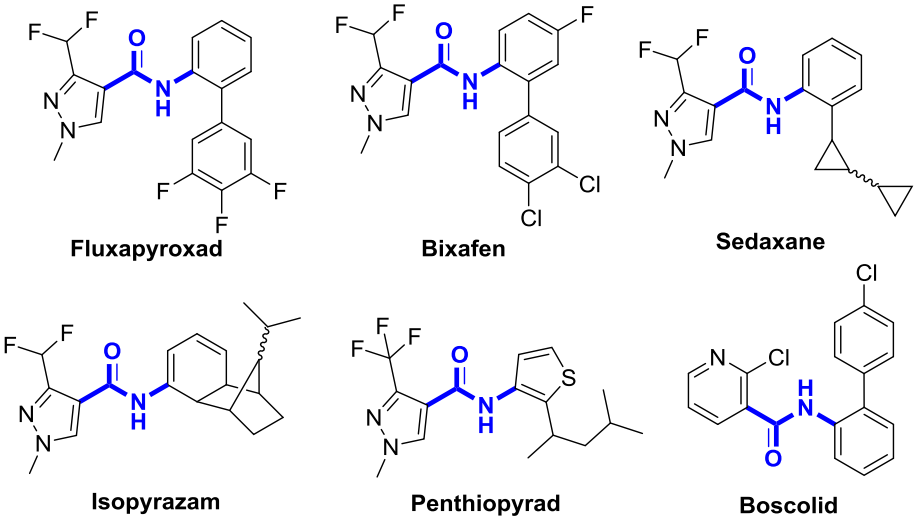

Fig. 2. Representative structures of carboxylic acid amide fungicides.

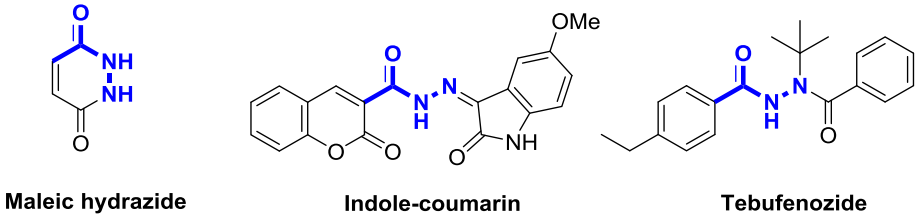

Fig. 3. Representative structures of hydrazide.

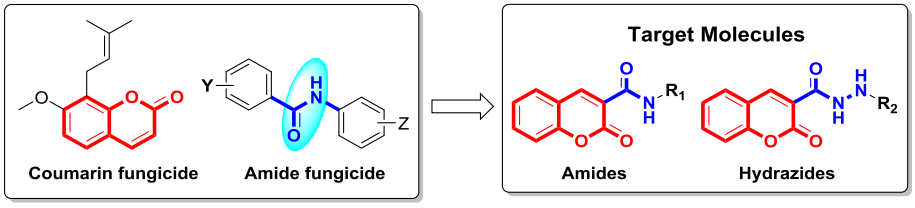

Fig. 4. Design strategy for target molecules.

drug resistance effect was successfully developed (Fig. 4).

2. Materials and methods

2.1. Chemicals and instruments

All commercially available reagents including substituted salicylaldehydes were purchased from Crystal Chemicals and used without