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Heterocyclic pyrrolizinone and indolizinones derived from natural lactam as potential antifungal agents

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ABSTRACT

With the aim to develop highly potential active heterocyclic compounds, two series of multi-substituted pyrrolizinone and indolizinones derived from lactam were designed, synthesized and evaluated for their potential antifungal activities against six species of the plant pathogen fungi (*Fusarium graminearum, Sclerotinia sclerotiorum, Phomopsis adianticola, Gloeosporium theae-sinensis, Alternaria tenuis Nees, Magnaporthe oryzae*). The structure of all the newly molecules were confirmed by analytical spectroscopic data, including ^{1}H NMR, ^{13}C NMR and ESI-MS. According to the preliminary studies on bio-evaluation assay, some of the obtained compounds exhibited moderate and broad-spectrum activities against six fungi compared to the intermediates **6a**, **6f** and the hymexazol. Particularly, the inhibition rate of compounds **7l**, **7m** and **7t** reached 69.25%, 74.76%, 65.38% against *Phomopsis adianticola* and *Magnaporthe oryzae* in vitro activity. Furthermore, compounds **7l** and **7t** displayed obviously inhibition activities against *Phomopsis adianticola* compared to the hymexazol. Consequently, compounds **7l** and **7t** with six-membered alkane ring could be used as new motifs for further investigation.

1. Introduction

In view of the increasing environmental safety issues, the creation of friendly and low toxicity pesticides has become a vital research project in recent years, which is closely related to the development of agricultural production, the stable national economy and the sustainable environment [1–3]. Moreover, leading optimization based on natural products with excellent biological properties has been a useful way to discovery and synthesize better performance agrochemicals more rapidly and effectively [4, 5].

In addition, nitrogen-containing heterocyclic compounds are a very important branch of heterocyclic chemistry in the field of modern pesticide synthesis, and due to the similarity of the chemical structure of alkaloids in organisms, they have some characteristics such as high target specificity and good environmental compatibility [6–8]. Therefore, the molecular design, synthesis and biological activity of nitrogen-containing heterocyclic compounds have been one of the hot fields in the new pesticides creation.

It is well known that lactams [9–11] are natural product fragments that are widely found in terrestrial and marine organisms in nature (including bacteria, fungi, cyanobacteria, sponges, etc.), whose mother nucleus structure is pyrrolidine-2,4-dione [12–16]. According to numerous reports, many lactam fragments-containing natural products have been explored and isolated. What's more, many natural lactam derivatives (Fig. 1) presented extensively remarkable pharmacological and biological activities, including antibacterial [12, 17], antifungal [18, 19], antiviral [20], herbicidal [21], antitumor activities [22], and cytogenetic toxicity [23] etc. Hence, it can be further confirmed that lactam units can be used as a class of important pharmacophores in searching for novel active compounds, which will help us to explore the highly active molecules as soon as possible.

Recently, in the process of studying active compounds, we have synthesized and evaluated a series of novel functionalized multi-substituted heterocyclic compounds containing lactam segments (Fig. 2), and the antifungal activities against plant pathogenic fungi have been estimated. So, in order to explore the potential applications for these heterocyclic compounds, we report herein the synthesis and characterization of twenty pyrrolizinone and indolizinone derivatives via mild cyclization reaction, and their antifungal activities against the phytopathogenic fungi including *Fusarium graminearum, Sclerotinia sclerotiorum, Phomopsis adianticola, Gloeosporium theae-sinensis, Alternaria tenuis Nees, Magnaporthe oryzae* have also been fully investigated. It is hoped that these pyrrolizinone and indolizinone derivatives containing lactam unit will provide a certain theoretical basis and useful information for the creation and innovation of novel antifungal agents.

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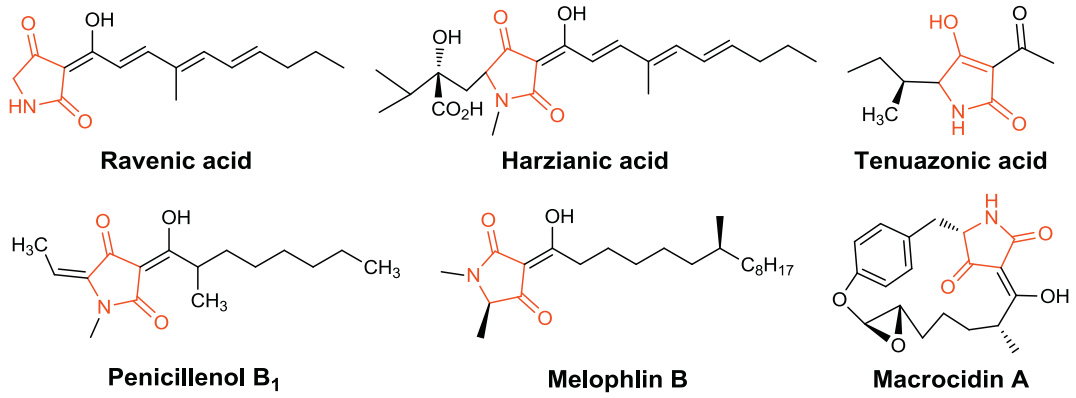

Fig. 1. Representative structure of naturally occurring lactam derivatives.

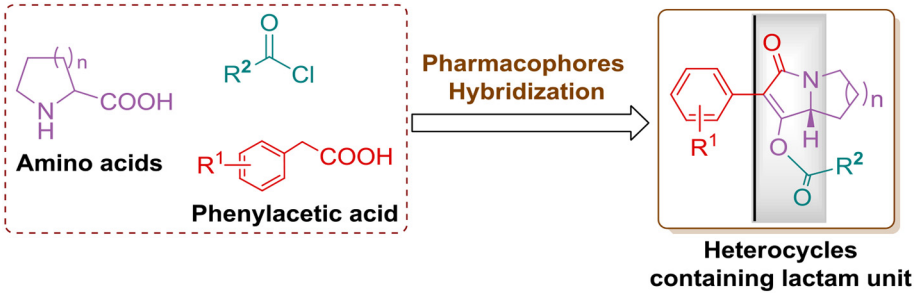

Fig. 2. Design strategy of pyrrolizinone and indolizinone derivatives containing lactam unit.

2. Materials and methods

2.1. Instrumentation and chemicals

All chemicals or reagents used for syntheses were of AR grand, were commercially available and used directly without purification. Anhydrous CH_2Cl_2 and MeOH were obtained under standard methods. ^{1}H NMR spectra were recorded on a Brucker spectrometer at 600 MHz with the $CDCl_3$ as the solvent and TMS as the internal standard. ^{13}C NMR spectra were recorded on a Brucker spectrometer at 150 MHz with $CDCl_3$ as the solvent. Chemical shifts were reported in δ (parts per million) values. Coupling constants ^nJ was reported in Hz. Mass spectra were performed on a Waters ACQUITY UPLC® H-CLASS PDA (Waters®) instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates, and spots were visualized with ultraviolet light. Column chromatography was carried out on silica gel (Qingdao Haiyang Chemical, Qingdao, China).

2.2. General synthetic procedures for intermediates 2

To a solution of α-amino acid **1** (0.134 mmol) in methanol (50 ml) was slowly added dropwise thionyl chloride (0.200 mmol), which was stired at ice bath (0 °C) for 30 min, and then the mixture was heated to 80 °C for 12 h reaction,and monitored by TLC. After the completion of reaction, the reaction solution was concentrated, filtered and washed twice with CH_2Cl_2 to obtain the crude amino-acid ester hydrochlorides **2**, which were used for the next reaction without further purification.

2.3. General synthetic procedures for intermediates 4

The substituted phenylacetic acid (3 mmol) and thionyl chloride (10 ml) were placed in a dry round-bottomed flask, and the mixture was heated to reflux at 65–70 °C for 12 h, which was detected by TLC. After the completion of reaction, the solvent was removed in vacuo and the residue was washed with CH_2Cl_2. The above procedure was repeated twice to obtain the crude intermediates **4**, which were used for the next reaction without further purification.

2.4. General synthetic procedures for intermediates 5

To a solution of methyl piperidinecarboxylate hydrochloride **2** (0.02 mol) in methylene chloride (20 ml) was added in a dried round-bottom flask, to which triethylamine (0.05 mol) and solution of phenylacetyl chloride in methylene chloride (0.024 mol) was added dropwise separately in an ice bath for over 20 min, next the cold bath was removed. The reaction was stirred at room temperature for 12 h, and TLC traced the reaction to completion. After the completion of the reaction, the solution was dissolved in water (20 ml), and the aqueous solution was extracted with methylene chloride (30 ml × 2) twice. The combined organic phases were washed with 5% Na_2CO_3 solution (30 ml × 2) and water to neutrality and dried over anhydrous Na_2SO_4. After filtration and concentration, the corresponding compound **5** were received through the above methods.

2.5. General synthetic procedures for intermediates 6a-j

A freshly prepared intermediates **5** (17.5 mmol) and the tetrahydrofuran solution (30 ml) were dissolved under stirring and then potassium tert-butoxide (30 mmol) was added. A 12 h reflux reaction under heating in a 70 °C oil bath, and TLC monitored the reaction to completion. Then added water to the system and stirred for 10 min, adjusted the pH to 2–3 with 10% dilute hydrochloric acid. The aqueous phase was extracted twice with ethyl acetate (30 ml × 2). The organic phases were combined and washed by water once, and dried over