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Design, synthesis, anti-TMV, fungicidal, and insecticidal activity evaluation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives based on virus inhibitors of plant sources

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ABSTRACT

By drawing the creation ideas of botanical pesticides, a series of tetrahydro-β-carboline-3-carboxylic acid derivatives were designed and synthesized, and first evaluated for their anti-TMV, fungicidal and insecticidal activities. Most of these derivatives exhibited good antiviral activity against TMV both in vitro and in vivo. Especially, the activities of compounds **8** and **15** in vivo were higher than that of ribavirin. The compound **8** exhibited more than 70% fungicidal activities against *Cercospora arachidicola Hori*, *Alternaria solani*, *Bipolaris maydis*, and *Rhizoctonia solani* at 50 mg/kg, compounds **16** and **20** exhibited more than 60% insecticidal activities against *Mythimna separate* and *Ostrinia nubilalis*.

Plant derived pesticides (such as azadirachtin A, matrine, pyrethrin, nicotine drawn in Fig. 1) offer many advantages over chemical pesticides as follows, be of novel and diverse structures, be difficult to produce resistance due to the unique mode of action, be specific to a target species therefore having low toxicity to humans and non-target organisms, be easily absorbed by plants, and having good environmental compatibility and so on. Therefore, they are potential alternatives to chemical pesticides.[1] However, inevitably botanical pesticides also have some disadvantages such as too complex to synthesize; active ingredients easy to decompose; most botanical pesticides play a pharmacodynamics slowly, need to spray frequently due to very short residual efficient duration, and so on. These shortcomings limit the widespread use of botanical pesticides.[2,3] Therefore, to discover new pesticide based on a precursor from active substances of plant origin is an important and a feasible means to solve the problem above.[4,5]

β-Carboline (such as harmine, Fig. 2), dihydro-β-carboline (such as harmaline), and tetrahydro-β-carboline (such as tetrahydroharmine) alkaloids exist in eight plant families, and there are 64 different kinds of such alkaloids have been separated and found to exhibit a variety of biological activities.[6–11] In our previous study, we found that harmine (antiviral activity against tobacco mosaic virus (TMV) in vitro and inactivation, curative and protection activities in vivo were 44.6%, 40.5%, 38.6%, and 42.4%, respectively, at 500 μg/mL) and tetrahydroharmine (the corresponding activities were 58.2%, 59.8%, 55.5%, and 54.6%, respectively, at 500 μg/mL) exhibited excellent anti-TMV activities. Meanwhile, (1*S*,3*S*)-ethyl 1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (the corresponding activities were 46.5%, 50.4%, 43.9%, and 47.9%, respectively, at 500 μg/mL) maintained high anti-TMV activity, and it exhibited excellent stability and solubility; these advantages made it an ideal lead compound for further derivation.[12] In this Letter, a series of dihydro-β-carbolines and tetrahydro-β-carbolines containing methyl, ethyl, phenyl and pyridine-3-yl on the 1-position and carboxyl, ester, amide and hydrazide on the 3-position were synthesized, and their anti-TMV, fungicidal, and insecticidal activities were evaluated for the first time (Fig. 2).

1-Substituted-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**1**–**6**) were prepared from tryptophan and corresponding aldehydes via Pictet–Spengler reaction (Scheme 1). Different reaction conditions were chosen according to the reactivity difference of the aldehydes. When L/D-tryptophan was reacted with 40% aqueous solution of acetaldehyde or propanal, concentrate sulfuric acid was used as a catalyst and the products **1** or **2** were obtained with moderate yields. However, when 30% formaldehyde was used in the Pictet-Spengler reaction to prepare **4**, this reaction had to be carried out under alkaline conditions. For the less reactive aromatic aldehydes such as benzaldehyde and nicotinaldehyde, glacial acetic acid was chosen as solvent and the mixture were heated at

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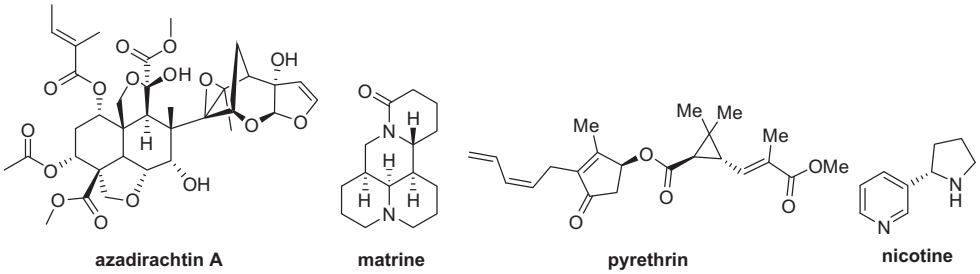


Figure 1. Botanical pesticides.

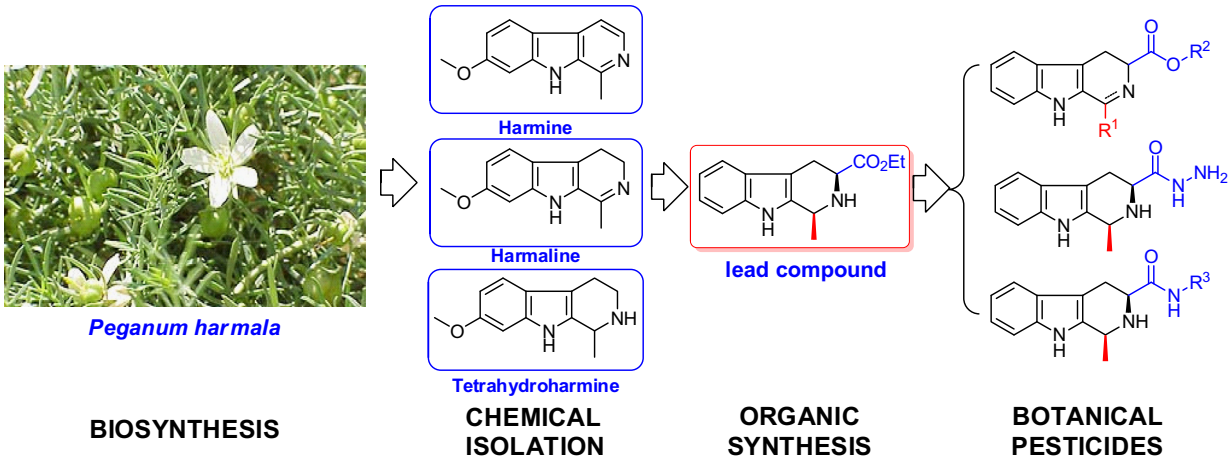
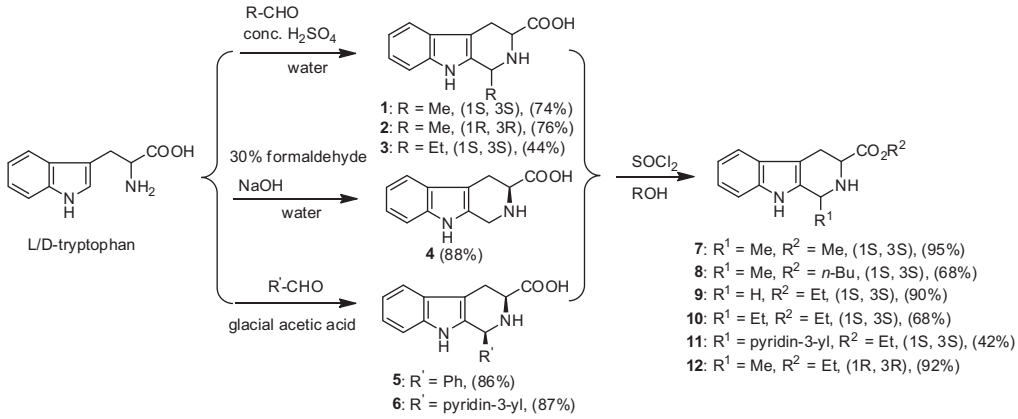


Figure 2. Design of target compounds.



Scheme 1. Synthesis of compounds **1**–**12**.

reflux to prepare the related compounds **5** and **6**, in which the relative configuration was determined by NOE (Nuclear Overhauser effect). Carboxylic acids **1**–**4** and **6** were separately reacted with alcohols (methanol, ethanol and butanol) in $SOCl_2$ to give the corresponding esters **7**–**12**. The lead compound was prepared using same procedure. Ester **14** was obtained via Bischler–Napieralski reaction (Scheme 2): firstly, L-tryptophan was reacted with $SOCl_2$ and ethanol to give ester **13**, and then **13** was reacted with acetyl chloride and treated with $POCl_3$ to give compound **14**.

Hydrazide **15** or amides **16** and **17** were prepared from ester **7**, which was reacted with hydrazine hydrate or corresponding amines (Scheme 3). But for the amines with low reactivity or high boiling point to form compounds **18**–**20**, carboxylic acid **1** was applied to react with amines using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) as a condensation reagent (Scheme 3).

The experimental details and characterization data for compounds **1**–**20** are given in Supplementary materials.[13] After the synthesis of these derivatives, their anti-TMV, fungicidal, and insecticidal activities were evaluated for the first time using our previously reported methods.[14–16]

Antiviral activities: In general, the anti-TMV bioassay in vitro indicated that most of the tested compounds displayed good antiviral activity, of which **8**, **9**, **11**, **14,** and **15** exhibited higher inhibition than ribavirin (40%, 500 μg/mL) (Table 1); especially, compound **8** (48.2%, 500 μg/mL) and **15** (50%, 500 μg/mL) exhibited higher activities than ethyl (1*S*,3*S*)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (the lead compound) (46.5%, 500 μg/mL) and harmine (44.6%, 500 μg/mL). The substituents on 3-position had an important impact on anti-TMV activity of these compounds. The compound containing a hydrazide moiety