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Original article

Synthesis and biological activities of novel 2-amino-1,3-thiazole-4-carboxylic acid derivatives

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ABSTRACT

A series of novel 2-amino-1,3-thiazole-4-carboxylic acid derivatives were designed and synthesized. Their structures were confirmed by melting points, IR, ^{1}H NMR, ^{13}C NMR, and HRMS or elemental analysis. Biological activities of all title compounds including fungicidal activity and antivirus activity were evaluated systematically. Preliminary bioassays indicated that these compounds exhibited good fungicidal activity at 50 μg/mL, compounds **4b** and **4i** exhibited over 50% activity against six fungi tested. Most compounds showed good activity against TMV with different models *in vivo* at 100 μg/mL. Compounds **4c** and **4e** stood out with high effects against TMV *in vivo* in all models tested, including protective, inactivative, curative, and inductive activities. These data demonstrate a new strategy for fungi and virus control.

1. Introduction

The application of elicitors is a novel, modern measure for pesticide development and environmental protection because elicitors can induce the immunological system of the plant to provide a broad spectrum of systemic acquired resistance at the physical and physiological level of the host plants [1]. Compound A (Fig. 1) had good systemic acquired resistance activity, which presented a better antimicrobial biology than metsulfovax (Fig. 1) [2]. Both of them belong to the derivatives of 1,3-thiazole. 1,3-Thiazoles are important heterocyclic compounds with low toxicity to mammals and a broad-spectrum of biological activities including insecticidal [3], antifungal [4,5], herbicidal [6,7], regulating plant growth [8,9], and antiviral activities [10]. Many thiazole derivatives such as thiamethoxam [11], imidaclothiz, thiabendazole [12], and benthiavalicarbisopropyl [13] had been commercialized as agrochemicals. In addition, the compounds with an amide or ester group were a versatile class of agrochemicals with wide range of biological activities [14] and have been used as insecticidal [15,16], fungicidal [17,18], herbicidal [19], and antiviral agents [2]. To find novel pesticide candidates with a wide spectrum of biological activities, especially systemic acquired resistance, a series including 20 novel 2-amino-1,3-thiazole-4-carboxylic acid derivatives were designed and synthesized for biological screening according to bioactive substructure coordination strategy.

2. Experimental

Reagents were all analytically or chemically pure. All the solvents and liquid reagents were dried by standard methods in advance and distilled before use. Synthesis of the title compounds was conducted as shown in Scheme 1 and the structure of the title compounds was shown in Fig. 2. The starting material, ethyl 2-aminothiazole-4-carboxylate (compound **1**) was prepared according to the literature [20,21]. Intermediate **2** was obtained through protection of amine group with di-*tert*-butyl dicarbonate (Boc_2O); the hydrolysis of intermediate **2** with NaOH gave acid **3**; the title compounds **4a**–**4k** were obtained by condensation reaction using Et_3N as the base and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI)/1-hydroxybenzotriazole (HOBT) as

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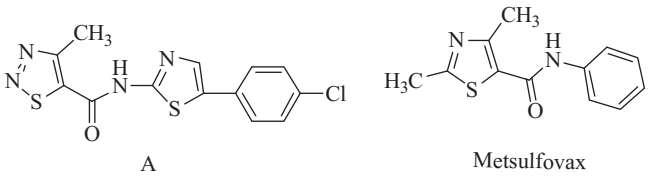

Fig. 1. The structure of compound A and Metsufovax.

condensation agents; compounds **5l**–**5m** were obtained through the same manner of compounds **4a**–**4k**; compounds **6n**–**6o** were synthesized by hydrolysis of ester **5l**–**5m** with NaOH; compounds **7p**–**7t** were obtained by condensation reaction using Et_3N as the base and EDCI/HOBT as condensation agents. The structures of all newly synthesized compounds were characterized by melting points, IR, ^1H NMR, ^{13}C NMR, and HRMS or elemental analysis.

The fungicidal activity determination was conducted by fungi growth inhibition method according to the reference using potato dextrose agar (PDA) as the cultivation medium [22]. Fungi used in this study included *Alternaria solani* (AS), *Botrytis cinerea* (BC), *Cercospora arachidicola* (CA), *Gibberella zeae* (GZ), *Phytophthora infestans* (Mont) de Bary (PI), *Physalospora piricola* (PP), *Pellicularia sasakii* (PS), *Sclerotinia sclerotiorum* (SS), and *Rhizoctonia cerealis* (RC). The antivirus activity against TMV for curative, inactive, inductive, and protective models was also tested according to the literature [23], Tiadinil, Ningnanmycin, and Virazol were used as positive controls. Supplementary materials, including experimental procedures and the physicochemical data of the title compounds, associated with this article can be found in the Supporting Information.

3. Results and discussion

All IR data showed strong carbonyl group absorptions at 1750–1550 cm^{-1}, and absorptions at about 3390–2850 cm^{-1} were observed from the NH group. In the ^1H NMR spectra, the chemical shift of a proton in the thiazole ring of all target compounds was observed at δ 7.49–8.05, nine protons of tert-butyl group were observed at δ 1.56–1.44 as a single peak. In the ^{13}C NMR spectra, the C═O peaks were observed at δ 170–150, the thiazole-C were at δ 165–110, the C of CHF_2 was a triple peak at δ 110–116 and the CH_2 of CH_2CHF_2 also was a triple peak at δ 40–42. The elemental analysis data or HRMS spectral data of all compounds were in good agreement with the calculated value.

The fungicidal activity data in Table 1 indicated that the title compounds had a broad spectrum of fungicidal activity. The majority of them had good fungicidal activity against PP, SS, and RC with growth inhibition over 50%. All compounds except **4j** and **5m** had good fungicidal activity against RC with growth inhibition over 50%. Compounds **4b** and **4i** exhibited over 50% activity against six fungi tested and compound **4d** exhibited over 50% activity against seven fungi tested. Compounds **4a**, **4b**, **4d**, **4e**, **4f**, **4j**, and **4k** stood out with growth inhibition at 100% against PP, SS, SS, SS, CA, SS, and SS, respectively.

Antiviral activities of all title compounds against TMV *in vivo* were evaluated, and the results were shown in Table 2. As can be seen from these data, compounds **4e**, **4g**, **4h**, **4k**, and **7p** had good curative activity against TMV at 100 μg/mL with inhibitions over 50%, which were higher than that of the positive control Ningnanmycin. Compounds **4a**, **4c**, **4e**, **4f**, **4g**, **4h**, **4j**, **5l**, **6n**, **6o**, **7r**, **7s**, and **7t** had good inactivation activity against TMV with inhibition rates over 50%, which were higher than that of the

Compound	R^1	X^1	Compound	R^2	R^3	X^2
4a		NH	**5l**		–	–
4b		NH	**5m**		–	–
4c		NH	**6n**		–	–
4d		NH	**6o**		–	–
4e		NH	**7p**			NH
4f		NH	**7q**			NH
4g		NH	**7r**			NH
4h		NH	**7s**			O
4i		O	**7t**			NH
4j		O				
4k		O				

Fig. 2. The structure of the title compounds.