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Synthesis and Anti-TMV Activity of Novel *β*-Amino Acid Ester Derivatives Containing Quinazoline and Benzothiazole Moieties

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ABSTRACT: Here, a series of *β*-amino acid ester derivatives containing quinazoline and benzothiazoles was synthesized and evaluated for anti-tobacco mosaic virus (TMV) activity. The compounds **3n**, **3o**, **3p** and **3q** showed good antiviral activity against TMV at a concentration of 500 μg/mL, with curative rates of 55.55%, 52.32%, 52.77% and 51.2%, respectively, and protection rates of 52.33%, 55.96%, 54.2% and 50.98%, respectively. These values were close to those of the commercially available antiviral agent ningnanmycin (which has curative and protection rates of 55.27% and 52.1%, respectively). To our knowledge, this is the first report of the anti-TMV activity of *β*-amino acid ester derivatives containing quinazoline and benzothiazoles moieties; the results indicate that these novel compounds can potentially be used as protective agents against TMV diseases.

Keywords: *β*-amino acid esters, Benzothiazoles, Quinazoline moiety, Synthesis, Anti-TMV activity.

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Abbreviations used

NMR, nuclear magnetic resonance; TMV, tobacco mosaic virus.

Plant viruses cause diseases often referred to as plant cancers. Tobacco mosaic virus (TMV) is a positive-sense, single-stranded RNA virus with a broad host range and effects that vary according to the host species, which include plants such as tobacco, tomato and many ornamental plants in the Solanaceae family. TMV diseases diminish the quality and yield of crops and undermine global agricultural production, resulting in an estimated loss of one billion U.S. dollars each year.[1,2] The application of traditional agrochemicals has had only limited success, and leaves high levels of residue that have detrimental environmental and ecological effects. Thus, effective and environmentally safe antiviral agents are urgently needed and their development remains an ongoing challenge.

Quinazoline derivatives belonging to the *N*-containing heterocyclic compounds have a variety of proven biological activities,[3] including antitumorigenic,[4] anti-inflammatory,[5] antihypertensive,[6] antimicrobial[7] and sterilization.[8] These properties can be attributed to different active groups linked to the quinazoline rings by synthetic methods;[9–13] applications for these compounds can be found in the areas of biology, pesticide development and medicine.[14] Benzothiazole derivatives likewise have antibacterial, antimicrobial, antihelmintic, antitumorigenic and antiinflammatory activities[15–17] that have many potential applications.[18]

β-amino acid esters and their derivatives also possess diverse biological properties, such as antitumor, immune-stimulating and antiphlogistic activities.[19–21] These esters are found in many natural products and have been widely used as peptidomimetics in the synthesis of enzyme inhibitors, antiviral and antibacterial drugs. These compounds are also used as third-generation pesticides, with potent effects on fungi, insects and weeds; they are also easily broken down, leaving little harmful residue. Various applications for *β*-amino acid esters in drug synthesis and plant protection have been explored.[22–27]

We recently reported a series of amino acid ester derivatives containing benzothiazole moieties (**Fig. 1**) that demonstrated protective effects against TMV.[28] Based on this work, in the present study, a novel family of bioactive molecules were

developed by introducing a quinazoline fragment to the amino acid ester backbone. The synthesis and characterization of 32 *β*-amino acid ester derivatives containing quinazoline and benzothiazoles units have been described. These compounds were screened for potential bioactivity and preliminary structure-activity relationships were examined. The bioassays showed that the compounds have variable inhibitory effects against TMV.

Figure 1

The method used to generate *β*-amino acid ester derivatives containing quinazoline and benzothiazoles units has been previously described[29] and is outlined in **Scheme 1**. Compounds **3a** to **3af** were synthesized from 4-chloroquinethiazole in three steps. The physical characteristics, as well as ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and elemental analysis data for all synthesized compounds, are reported in the Appendix. The results for the representative compound **3n** are shown below.

Scheme 1

*Dimethyl 2-(((6-chlorobenzo[d]thiazol-2-yl)amino)(4-((7-chloroquinazolin -4-yl) oxy)phenyl) methyl)malonate (**3n**):* white solid; m.p., 136–139 °C; yield, 51%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H, ArH), 8.34 (d, 1H, J = 10 Hz, ArH), 8.01 (d, 1H, J = 10 Hz, ArH), 7.94–7.92 (m, 1H, ArH), 7.68–7.65 (m, 1H, ArH), 7.57 (d, 1H, J = 5 Hz, ArH), 7.55 (d, 1H, J = 5 Hz, ArH), 7.28–7.27 (m, 3H, ArH), 7.11–7.08 (m, 1H, ArH), 7.04 (s, 1H, NH), 5.83 (s, 1H, CH), 4.09 (d, 1H, J = 5 Hz, CH), 3.74 (d, 6H, J = 10 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 168.6, 167.3, 166.7, 166.0, 154.2, 152.2, 152.1, 151.8, 136.2, 134.3, 131.0, 130.9, 128.9, 128.1, 128.0, 122.8, 126.0, 123.6, 122.3, 122.1, 120.9, 119.5, 116.5, 57.4, 56.7, 53.3, 53.0. Anal. Calcd for $C_{27}H_{20}Cl_2N_4O_5S$: C, 55.58; H, 3.46; N, 9.60. Found: C, 55.23; H, 3.85; N, 10.02.

The inhibitory effects of the synthesized *β*-amino acid ester derivatives on TMV activities were evaluated *in vivo*. As a positive control, the activity of the commercial antiviral agent ningnanmycin was assessed under the same conditions.[30,31] A

preliminary screen demonstrated that the inhibitory effects of these compounds against TMV was variable (**Table 1**). Compounds **3n**, **3o**, **3p** and **3q** showed high anti-TMV activity at a concentration of 500 μg/mL, with curative rates of 55.55%, 52.32%, 52.77% and 51.2%, respectively, values that were comparable to that of ningnanmycin (55.27%). A strong protective effect was also observed for these four compounds, with rates of 52.33%, 55.96%, 54.21% and 50.98%, respectively, which was similar to the protection rate of ningnanmycin (52.1%).

Table 1

Four conclusions can be drawn from the data presented in **Table 1**. First, when the R-group was -H, regardless of the R^1 and R^2 moieties, compounds showed little variation in anti-TMV activity and only moderate curative effects, with rates not exceeding 48%. Second, when R and R^1 were substituted with -Cl, $-CH_3$, $-C_2H_5$, *n*-C_3H_7 or $-CH_2C_6H_5$ as R^2, the compounds had similar anti-TMV activities, with curative rates of 55.55%, 52.32%, 52.77%, and 51.2%, respectively. Third, compared to compounds that had the same substituents for R^1 and R^2, the activities of -Cl derivatives were superior to those of -H derivatives, such that **3n > 3d**, **3p > 3e** and **3p > 3f**. Last, when R^1 was $-CH_3$, the antiviral activity was consistently lower than those of compounds with -Cl as R^1, irrespective of the functional groups at R and R^2. Thus, introducing an electron-withdrawing group in the quinazoline ring can enhance the inhibition ratio of the compound.

In summary, a series of new *β*-amino acid ester derivatives, compounds **3a** to **3af**, containing quinazoline and benzothiazole moieties, were synthesized via an addition reaction of imines **2a** to **2f** with malonate in CH_2Cl_2. Functional assays indicated that compounds **3n**, **3o**, **3p** and **3q** had strong protective and curative effects against TMV, similar to those of ningnanmycin, with -Cl derivatives being superior to -H derivatives. These novel *β*-amino acid ester derivatives can potentially be used as protective agents against TMV disease in plants.

Acknowledgements

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Appendices

Additional data for this article, including detailed information on the synthesis, characterization, and methods for testing the bioactivity of the compounds can be found in the online version at http://dx.doi.org/10.1016/j.bmcl.

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176 **Figure legend**

177 **Figure 1.** Compounds with putative TMV inhibitory activity.

178

179 **Scheme legend**

180 **Scheme 1.** Synthesis of compounds **3a** to **3af**.

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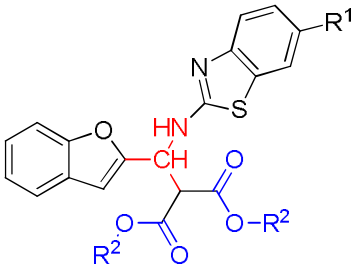
182 **Table legend**

183 **Table 1.** Inhibitory effects of *β*-amino acid ester derivatives against TMV.

184

185 **Figure 1.** Compounds with putative TMV inhibitory activity.



R^1: -H, -Cl, $-OCH_3$, $-CH_3$
R^2: $-CH_3$, $-C_2H_5$, *n*-C_3H_7, $-CH_2C_6H_5$

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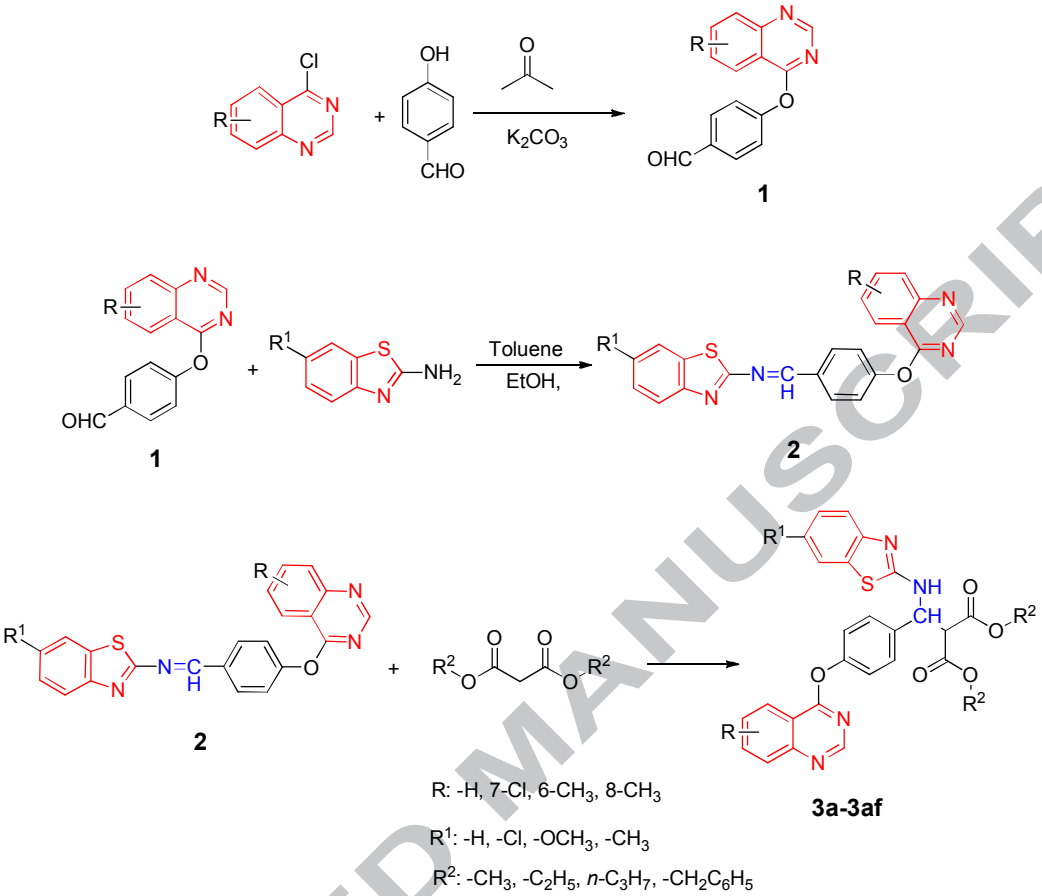
188 **Scheme 1.** Synthesis of compounds **3a** to **3af**.



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191 **Table 1.** Inhibitory effects of *β*-amino acid ester derivatives against TMV.

Comps	R	R^1	R^2	Concentration (μg/mL)	Curative rate (%)	Protection rate (%)
3a	-H	-H	$-CH_3$	500	43.47±3.01	44.21±2.09
3b	-H	-H	*n*-C_3H_7	500	43.02±4.11	39.27±4.78
3c	-H	-H	$-CH_2C_6H_5$	500	40.14±2.46	41.04±3.77
3d	-H	-Cl	$-CH_3$	500	43.68±3.23	29.08±4.32
3e	-H	-Cl	*n*-C_3H_7	500	45.10±2.99	39.70±3.09
3f	-H	-Cl	$-CH_2C_6H_5$	500	46.33±1.97	42.33±3.39
3g	-H	$-OCH_3$	$-CH_3$	500	48.09±4.06	45.96±2.67
3h	-H	$-OCH_3$	$-C_2H_5$	500	44.76±4.89	34.21±4.03
3i	-H	$-OCH_3$	*n*-C_3H_7	500	35.10±4.23	40.98±4.99
3j	-H	$-OCH_3$	$-CH_2C_6H_5$	500	48.30±4.75	49.27±4.06
3k	7-Cl	-H	$-CH_3$	500	32.11±3.81	31.04±4.67
3l	7-Cl	-H	*n*-C_3H_7	500	41.87±4.56	36.88±4.94
3m	7-Cl	-H	$-CH_2C_6H_5$	500	43.66±2.79	49.70±3.18
3n	7-Cl	-Cl	$-CH_3$	500	55.55±4.93	52.33±3.43
3o	7-Cl	-Cl	$-C_2H_5$	500	52.32±3.44	55.96±3.99
3p	7-Cl	-Cl	*n*-C_3H_7	500	52.77±3.90	54.21±4.04
3q	7-Cl	-Cl	$-CH_2C_6H_5$	500	50.91±4.17	50.98±4.75
3r	7-Cl	$-OCH_3$	$-CH_3$	500	41.89±3.02	39.27±4.11
3s	7-Cl	$-OCH_3$	$-C_2H_5$	500	42.96±3.55	44.21±3.86
3t	7-Cl	$-OCH_3$	*n*-C_3H_7	500	46.60±2.23	40.98±4.39
3u	7-Cl	$-OCH_3$	$-CH_2C_6H_5$	500	41.88±4.38	39.27±4.84
3v	7-Cl	$-CH_3$	$-CH_3$	500	46.47±1.90	41.04±4.57
3w	7-Cl	$-CH_3$	*n*-C_3H_7	500	36.56±4.22	46.88±3.02
3x	7-Cl	$-CH_3$	$-CH_2C_6H_5$	500	38.58±4.89	44.21±3.85
3y	6-CH_3	-H	$-CH_3$	500	41.67±4.65	50.98±3.67
3z	6-CH_3	-H	$-C_2H_5$	500	46.57±3.21	49.27±3.35
3aa	6-CH_3	$-OCH_3$	$-CH_3$	500	46.93±4.94	41.04±4.32
3ab	6-CH_3	$-OCH_3$	$-C_2H_5$	500	45.36±4.35	49.08±3.09
3ac	8-CH_3	-H	$-CH_3$	500	44.97±3.78	39.27±4.34
3ad	8-CH_3	-H	$-C_2H_5$	500	38.76±3.09	41.04±4.76
3ae	8-CH_3	-Cl	$-CH_3$	500	31.98±4.88	39.70±2.99
3af	8-CH_3	-Cl	$-C_2H_5$	500	34.85±3.76	42.33±3.45
Ningnanmycin	---			500	55.27±2.36	52.16±3.67

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195 Graphical abstract

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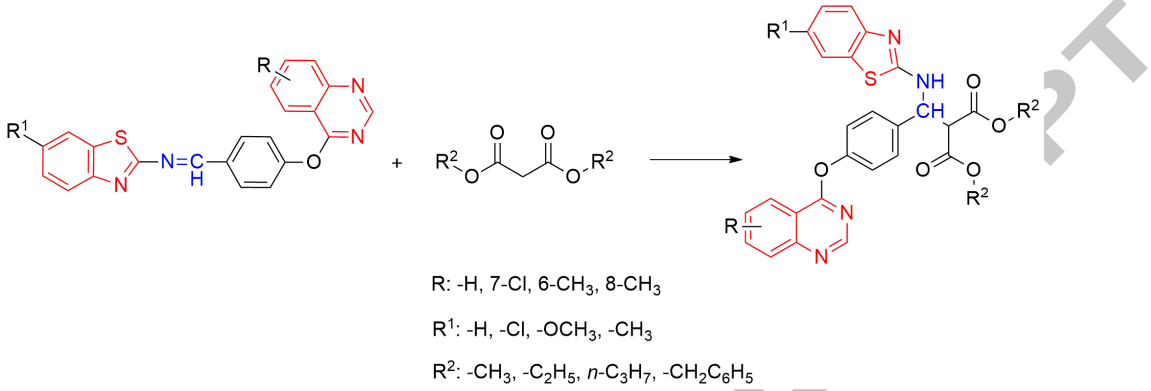

R: -H, 7-Cl, 6-CH_3, 8-CH_3

R^1: -H, -Cl, -OCH_3, -CH_3

R^2: -CH_3, -C_2H_5, *n*-C_3H_7, -$CH_2C_6H_5$

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