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Synthesis and Antiviral Activities of Cyanoacrylate Derivatives Containing an α-Aminophosphonate Moiety

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Target compounds **8** were obtained by the reaction of alkyl 2-cyano-3,3-dimethylthioacrylate or cyarylamide (**7a**−**7e**) and α-aminobenzylphosphonate (**5a**−**5e**) under reflux condition using ethanol as solvent. Their structures were clearly verified by spectroscopic data (IR and ^{1}H, ^{13}C, and ^{31}P NMR) and elemental analysis. These compounds were shown to be antivirally active in the bioassay. It was found that title compounds **8d** and **8e** had the same inactivation effect against tobacco mosaic virus (EC_{50} = 55.5 and 55.3 μg/mL) as the commercial product ningnanmycin (EC_{50} = 50.9 μg/mL). To the best of our knowledge, this is the first report on the synthesis and antiviral activity of cyanoacrylate derivatives containing an α-aminophosphonate moiety.

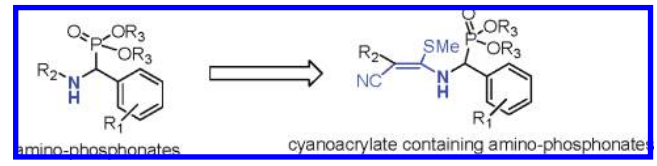
KEYWORDS: Cyanoacrylate; α-aminophosphonate moiety; antiviral activity; synthesis

INTRODUCTION

2-Cyanoacrylates, a class of highly potent herbicial compounds, are known to disrupt photosynthetic electron transportation at a common binding domain on the 32 kDa polypeptide of the photosystem II (PSII) reaction center (*1, 2*). Due to their versatile biological activities and promising application in agrochemistry, a large number of cyanoacrylate derivatives have been reported to show broad spectrum bioactivities, capable of acting as herbicides, insecticides, fungicides, plant virucides, and antitumor agents (*3–8*). In our previous work, we designed and synthesized some chiral cyanoacrylates with antiviral activity by replacing the methylthio moiety of some 2-cyano-3-methyl-thio-3-substituted-phenylacrylates with (*R*)- or (*S*)-1-phenylethylamine groups. The (*E*)-configuration of the reported chiral products was confirmed by X-ray single-crystal structure analysis. The bioassays showed that a chiral compound containing a 4-nitrophenyl moiety [(*E*)-ethyl 3[(*S*)-1-phenylethylamino]-3-(4-nitrophenylamino)-2-cyanoacrylate] exhibited good protection activity against tobacco mosaic virus (TMV) in vivo (*9*). Some alkyl 2-cyano-3-methylthio-3-phosphonylacrylates were found to possess good in vivo curative, protection, and inactivation effects against TMV with inhibitory rates at 500 mg/L (*10*). Recently we reported the synthesis and antiviral activity of (*E*)-ethyl 3-(*R*)- or (*S*)-1-phenylethylamino-3-(substituted-phenylamino)-2-cyanoacrylate. The objective of our study was to show the effects of (*R*)-4p in inducing disease resistance of tobacco leaves in response to virus pathogen attack and on the activity of enzymes or metabolites that might be involved in induced resistance (*11*). On the other hand, α-aminophosphonic acids, bioisosteres of natural amino acids, have been found to exhibit a wide range of bioactivities. Some derivatives of α-aminophosphonic acids find application as plant growth regulators, fungicide, plant virucide, herbicides, and so on (*12–14*). A large volume of research on their synthesis and biological activities has been reported during the last 10 years (*15–20*).

In our previous work, while many substituted aryl aminophosphonate derivatives were shown to have good antiviral activities (*21–26*), and carbonylaminophosphonates possessed better antiviral activities (*27*). As different aminophosphonates and their derivatives display potential bioactivities, screening of cyanoacrylate derivatives bearing various α-amiophosphonate moieties might produce new lead compounds with more potent antiviral activities against TMV. Keeping these considerations in mind, we herein designed and synthesized some novel cyanoacrylate derivatives containing α-aminophosphonates (**Scheme 1**). The synthetic route is shown in **Scheme 2**. The bioassay test showed that the new compounds **8** possessed moderate to good antiviral activities. To the best of our knowledge, this is the first report on the synthesis and antiviral

Scheme 1. Structural Features of Aminophosphonates versus Cyanoacrylate Analogues Containing Aminophosphonates



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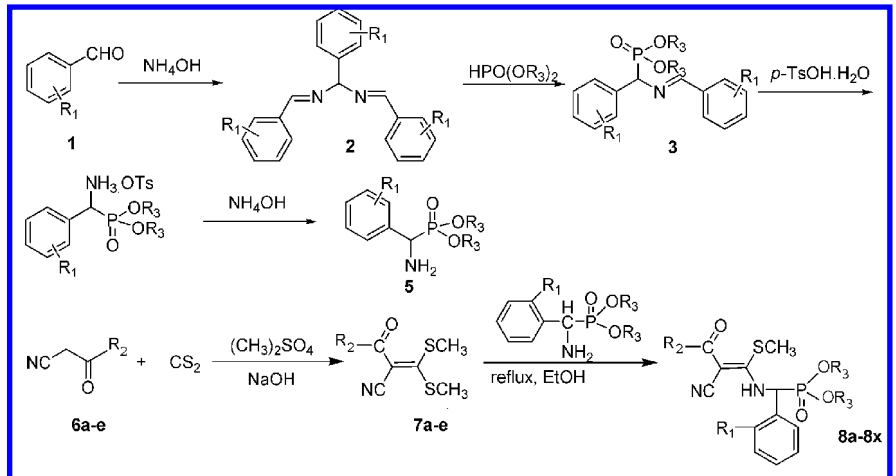
Scheme 2. Synthetic Route to Cyanoacrylate Analogues **8** Containing α-Aminophosphonate



Compd.	R_1	R_2	R_3	Compd.	R_1	R_2	R_3
8a	H	OCH_3	Et	**8b**	H	OCH_3	*n*-Pr
8c	H	OCH_3	*i*-Pr	**8d**	H	OCH_3	*n*-Bu
8e	2-F	OCH_3	Et	**8f**	H	OC_2H_5	*n*-Pr
8g	H	OC_2H_5	*i*-Pr	**8h**	H	OC_2H_5	*n*-Bu
8i	2-F	OC_2H_5	Et	**8j**	H	$OC_2H_5OC_2H_5$	Et
8k	H	$OC_2H_5OC_2H_5$	*n*-Pr	**8l**	H	$OC_2H_5OC_2H_5$	*i*-Pr
8m	H	$OC_2H_5OC_2H_5$	*n*-Bu	**8n**	2-F	$OC_2H_5OC_2H_5$	Et
8o	H	NH_2	Et	**8p**	H	NH_2	*n*-Pr
8q	H	NH_2	*i*-Pr	**8r**	H	NH_2	*n*-Bu
8s	2-F	NH_2	Et	**8t**	H	$PhCH_2NH_2$	Et
8u	H	$PhCH_2NH_2$	*n*-Pr	**8v**	H	$PhCH_2NH_2$	*i*-Pr
8w	H	$PhCH_2NH_2$	*n*-Bu	**8x**	F	$PhCH_2NH_2$	Et

activity of cyanoacrylate derivatives containing an α-aminophosphonate moiety.

MATERIALS AND METHODS

Instruments. The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer with KBr disk. ^{1}H, ^{13}C, and ^{31}P NMR (solvent DMSO-d_6 and $CDCl_3$) spectra were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as AN internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated, and redistilled before use.

Synthetic Procedures. Diethyl phosphite and di-*n*-propyl phosphite were prepared according to literature method as described (*28*). Intermediates **5a**−**f**, **6a**−**e**, and **7a**−**e** were prepared according to the reported methods (*29*) and a detailed procedure can be found in the Supporting Information.

General Procedure for the Preparation of Title Compounds 8a−**8x.** A mixture of alkyl (imido) 2-cyano-3,3-dimethylthioacrylate (**7a**−**e**) (0.1 mmol) and α-aminobenzylphosphonate (**5a**−**e**) (0.1 mmol) in ethanol (10 mL) was refluxed for 4 h. Upon completion of the reaction, the solvent was removed under reduced pressure and the residue was washed with water, filtered off, and purified by silica gel column chromatography (petroleum ether−ethyl acetate, 2:1, v:v) to give the title compounds **8a**−**x** in 25.6−70.0% yields. The reperesentative data for **8a** is shown below, while data for **8b**−**8x** can be found in the Supporting Information.

Data for Methyl 2-Cyano-3-methylthio-3-(diethyl aminobenzylphosphonyl)acrylate (8a). Colorless liquid; 51.3% yield. IR (KBr): ν_{max} 3062.9, 3030.1, 2983.8, 2953.0, 2208.4, 1643.3, 1566.2, 1556.5, 1514.1, 1494.8, 1440.8, 1384.8, 1257.5, 1161.1, 1045.4, 1020.3, 975.9, 840.9, 781.1, 748.3, 698.2, 561.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.28−1.29 (m, 3H, C-CH_3), 1.31−1.32 (m, 3H, C-CH_3), 2.54 (s, 3H, S-CH_3), 3.82 (s, 3H, O-CH_3), 4.05−4.91 (m, 2H, O-CH), 5.59−5.64 (m, 1H, Ar-CH), 7.34−7.40 (m, 5H, Ar−H), 10.94 (s, 1H, C-NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.26, 172.18, 171.18, 168.45, 129.08, 128.76, 127.66, 127.63, 117.93, 63.89, 58.16, 56.94, 52.22, 18.49, 16.47, 16.43, 16.37. ^{31}P NMR ($CDCl_3$, 500 MHz) δ: 19.21. Anal. Calcd for $C_{19}H_{27}N_2O_5SP$ (440.15): C, 51.25; H, 5.82; N, 7.03. Found: C, 51.01; H, 5.90; N, 6.81.

X-ray Diffraction. Colorless blocks of **8v** (0.29 mm × 0.24 mm × 0.21 mm) were counted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 273 K on a Bruker SMART CCD area detector diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å), θ_{max} = 25.00, 19 767 measured reflections, and 3232 independent reflections (R_{int} = 0.1763) of which 4767 had $I > 2\delta(I)$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.7680, T_{max} = 0.8237). The structure was solved by direct methods using SHELXS-97; all other calculations were performed with Bruker SAINT System and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0703P)^2 + 0.0000P]$ gave final values of R = 0.0558, ωR = 0.1610, and GOF(F) = 1.052 for 307 variables and 4767 contributing reflections. The maximum shift/error = 0.001, and max/min residual electron density = 0.400/−0.322 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Antiviral Biological Assay. Purification of Tobacco Mosaic Virus. Using Gooding's method (*30*), the upper leaves of *Nicotiana tabacum L* inoculated with TMV were selected, ground in phosphate buffer, and then filtered through a double-layer pledget. The filtrate was centrifuged at 10 000*g*, treated twice with PEG, and centrifuged again.

The whole experiment was carried out at 4 °C. Absorbance values were estimated at 260 nm using an ultraviolet spectrophotometer.

$$\text{virus concn} = (A_{260} \times \text{dilution ratio}) / E_{1\text{cm}}^{0.1\%,260\text{nm}} \quad (1)$$

Protective Effects of Compounds against TMV in Vivo. The compound solution was smeared on the left side while the solvent served as the control on the right side of growing *N. tabacum* L. leaves of the same ages. The leaves were then inoculated with the virus after 12 h. A brush was dipped in tobacco mosaic virus of 6×10^{-3} mg/mL to inoculate the leaves, which were previously scattered with silicon carbide. The leaves were then washed with water and rubbed softly along the nervature once or twice. The local lesion numbers appearing 3−4 days after inoculation were counted (*9*). Three repetitions were conducted for each compound.

Inactivation Effect of Compounds against TMV in Vivo. The virus was inhibited by mixing with the compound solution at the same volume for 30 min. The mixture was then inoculated on the left side of the leaves of *N. tabacum* L., while the right side of the leaves was inoculated with the mixture of solvent and the virus for control. The local lesion numbers were recorded 3−4 days after inoculation (*9*). Three repetitions were conducted for each compound.

Curative Effect of Compounds against TMV in Vivo. Growing leaves of *N. tabacum. L* of the same ages were selected. The tobacco mosaic virus (concentration of 6×10^{-3} mg/mL) was dipped and inoculated on the whole leaves. Then the leaves were washed with water and dried. The compound solution was smeared on the left side and the solvent was smeared on the right side for control. The local lesion numbers were then counted and recorded 3−4 days after inoculation (*9*). For each compound, three repetitions were measured. The inhibition rate of the compound was then calculated according to the following formula (av means average, and controls were not treated with compound).

$$\text{inhibn rate (\%)} = \frac{\text{av local lesion no. of control} - \text{av local lesion no. of drug-treated}}{\text{av local lesion no. of control}} \times 100\% \quad (2)$$

RESULTS AND DISCUSSION

Synthesis. α-Benzylphosphonates **5a**−**5e** were synthesized from dialkyl phosphites and benzaldehyde in accordance with **Scheme 2**. addition of *p*-toluenesulfonic acid into the imine is highly exothermic and may cause an undesired side reaction. Controlling the reaction temperature near 0 °C during its addition is the most important factor in the synthesis of α-benzylphosphonates.

Esters **6a**−**6c** were prepared conveniently from cyanoacetic acid and primary alcohols in the presence of a catalytic amount of anhydrous H_2SO_4. Amides **6d** and **6e** were synthesized from ethyl cyanoacetate and the corresponding amine in excellent yields. Intermediate 2-cyano-3,3-dimethylthioacrylate **7** was achieved by treating the corresponding ester (amide) **6a**−**6e** with carbon disulfide and 2 mol of dimethyl sulfate in a one-pot reaction using sodium hydroxide as alkali.

The desired products (**8a**−**8x**) were then obtained in moderate yields (**Scheme 2**) by a nucleophilic substitution reaction involving intermediates **7** and α-aminobenzylphosphonate **5a**−**5e** in refluxing ethanol. This reaction is assumed to be initiated by a nucleophilic attack followed by expulsion of SCH_3. The Michael-type attack of the α-aminophosphonate at the α,β-unsaturated center presumably leads to a transition state in which the orientation of α-aminophosphonate and ester carbonyl is cis due to the presence of an intramolecular hydrogen bonding. The (*E*)-configuration of the title compounds was established by X-ray single crystal structure analysis of typical **8v**, as shown in **Figure 1**. All compounds were confirmed by elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectral data.

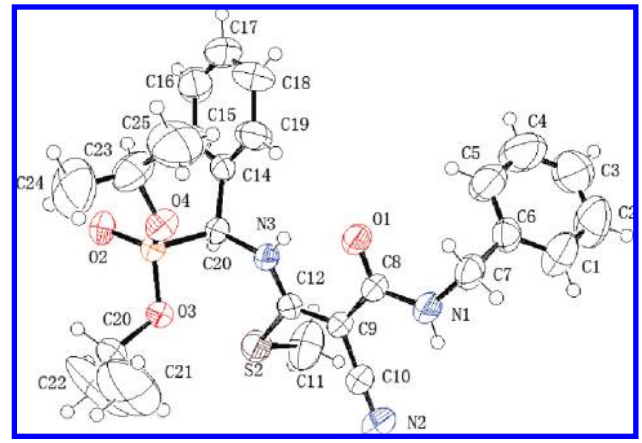


Figure 1. Molecular structure of **8v**.

Antiviral Activity and Structure−Activity Relationship. To make a judgment of the antiviral potency of the synthesized compounds **8a**−**8x**, the commercially available plant virucide Ningnanmycin (*31*), perhaps the most successful registered antiplant viral agent available in China, was used as the control. The antiviral bioassay against TMV is assayed by the reported method (*9, 30*) and the antiviral results of all the compounds against TMV are listed in **Table 1**. The results showed that most of our designed compounds had moderate antiviral activities at 500 mg/L against TMV in vivo.

The title compounds **8a**−**8x** exhibited protection activities of 29.6−56.5% at 500 mg/L. Compounds **8d** (R_1 is H, R_2 is OCH_3, and R_3 is *n*-Bu), **8h** (R_1 is H, R_2 is OC_2H_5, and R_3 is *n*-Bu), **8o** (R_1 is H, R_2 is NH_2, and R_3 is Et), **8q** (R_1 is H, R_2 is NH_2, and R_3 is *i*-Pr), and **8t** (R_1 is H, R_2 is $PhCH_2NH_2$, and R_3 is Et) have the same protection activity (55.9%, 56.5%, 55.6%, 54.4% and 55.1%, respectively) as that of the standard reference (59.9%). In addition, compounds **8b**, **8c**, **8e**, **8f**, **8i**, **8j**, **8k**, **8m**, **8n**, **8p**, **8r**, **8s**, **8u**, **8w**, and **8x** showed 40.8−48.3% protection activities at 500 mg/L. From the data presented in **Table 1**, it can be observed that the title compounds **8a**−**8x** possess potential inactivation bioactivities, with values of 64.1%, 47.1%, 45.7%, 92.8%, 92.1%, 71.0%, 37.8%, 84.0%, 74.1%, 46.8%, 51.5%, 55.9%, 80.6%, 70.0%, 60.8%, 63.0%, 5.7%, 9.6%, 70.7%, 51.9%, 50.0%, 51.5%, 11.0%, and 73.4% at 500 μg/mL, respectively. Among these compounds, **8d** and **8e** are appreciably more active than the rest, with the inactivation rate of 92.8% and 92.1%, respectively, which are similar to that of Ningnanmycin (99.5%) against TMV at 500 μg/mL. The data also indicate that a change in the substituent might also affect the curative activity of title compounds **8a**−**8x**. Compound **8a** (R_1 is H, R_2 is OCH_3, and R_3 is Et), **8d**, **8e** (R_1 is 2-F, R_2 is OCH_3, and R_3 is Et), **8f** (R_1 is H, R_2 is OC_2H_5, and R_3 is *n*-Pr), **8h**, **8i** (R_1 is 2-F, R_2 is OC_2H_5, and R_3 is Et), **8j** (R_1 is H, R_2 is $OC_2H_5OC_2H_5$, and R_3 is Et), **8m** (R_1 is H, R_2 is $OC_2H_5OC_2H_5$, and R_3 is *n*-Bu), **8n** (R_1 is 2-F, R_2 is $OC_2H_5OC_2H_5$, and R_3 is Et), **8o**, **8p** (R_1 is H, R_2 is NH_2, and R_3 is *n*-Pr), **8t**, **8u** (R_1 is H, R_2 is $PhCH_2NH_2$, and R_3 is *n*-Pr), and **8v** (R_1 is H, R_2 is $PhCH_2NH_2$, and R_3 is *i*-Pr) have curative activities against TMV of up to 56.7%, 60.2%, 58.4%, 50.5%, 55.8%, 50.7%, 55.2%, 51.8%, 52.7%, 54.4%, 53.9%, 55.0%, 53.8%, and 52.9%, respectively, at 500 μg/mL. The other compounds have a relatively lower curative activity than those of **8a**, **8d**, **8e**, **8f**, **8h**, **8i**, **8j**, **8m**, **8n**, **8o**, **8p**, **8t**, **8u**, and **8v**. Comparison of biological activities among **8a**−**8x** shows functional groups R_2 = OMe, OEt and R_3 = *n*-Bu to be potentially more active than $R_2 = NH_2$, $PHCH_2NH_2$, $OC_2H_5OC_2H_5$ and R_3 = *n*-Pr, *i*-Pr, Et.

Table 1. Protection Effect, Inactivation Effect, and Curative Effect of the New Compounds against TMV in Vivo[a]

agent	concentration (μg/mL)	protection effect (%)	inactivation effect (%)	curative effect (%)
8a	500	29.6* ± 4.9	64.1* ± 1.6	56.7* ± 2.9
8b	500	44.4* ± 4.0	47.1* ± 2.2	37.7* ± 4.6
8c	500	40.8* ± 4.2	45.7* ± 3.0	43.3* ± 2.7
8d	500	55.9 ± 3.8	92.8** ± 1.9	60.2* ± 2.6
8e	500	44.0* ± 3.3	92.1* ± 1.9	58.4* ± 3.4
8f	500	41.6 ± 5.0	71.0* ± 2.8	50.5 ± 4.3
8g	500	37.6 ± 3.0	37.8* ± 4.1	42.8* ± 3.9
8 h	500	56.5 ± 3.8	84.0** ± 2.1	55.8* ± 4.2
8i	500	48.3* ± 4.0	74.1* ± 2.8	50.7* ± 3.6
8j	500	41.2* ± 3.2	46.8* ± 3.1	55.2* ± 3.1
8k	500	43.1 ± 2.8	51.5* ± 3.5	43.2 ± 2.7
8l	500	38.4 ± 2.8	55.9* ± 4.9	35.1* ± 4.2
8m	500	44.4* ± 2.9	80.6 ± 1.4	51.8* ± 2.8
8n	500	48.3 ± 4.5	70.0* ± 1.6	52.7* ± 3.9
8o	500	55.6* ± 3.2	60.8* ± 3.7	54.4* ± 3.6
8p	500	45.8* ± 5.2	63.0* ± 2.2	53.9 ± 5.4
8q	500	54.4* ± 4.4	5.7 ± 2.1	28.8 ± 4.8
8r	500	40.2* ± 2.6	9.6 ± 2.4	25.4* ± 3.9
8s	500	42.8* ± 3.2	70.7* ± 2.3	25.4* ± 2.1
8t	500	55.1* ± 5.9	51.9* ± 3.0	55.0* ± 2.9
8u	500	42.4* ± 4.1	50.0* ± 2.9	53.8* ± 4.3
8v	500	39.0* ± 3.5	51.5* ± 2.3	52.9 ± 5.9
8w	500	45.0* ± 2.1	11.0 ± 0.9	28.4 ± 2.5
8x	500	47.7* ± 3.7	73.4** ± 2.8	49.9* ± 2.2
Ningnamycin	500	59.9* ± 2.5	99.5** ± 2.9	55.8* ± 1.7

[a] All results are expressed as mean ± SD; $n = 3$ for all groups; *$P < 0.05$, **$P < 0.01$.

Table 2. Antiviral Activities in Vivo (%) of Various Concentrations of Compounds **8d**, **8e**, **8f**, **8h**, **8i**, **8m**, **8n**, **8s**, and **8x** against TMV

	inactivation effect (%)					
compd.	500 μg/mL	250 μg/mL	125 μg/mL	62.5 μg/mL	30.7 μg/mL	EC_{50}(μg/mL)
8d	93.6	70.2	66.9	53.7	37.6	55.5
8e	93.7	69.7	60.6	52.5	40.8	55.3
8f	72.0	50.1	47.9	33.1	20.9	159.0
8 h	85.1	65.7	51.6	48.5	42.6	62.6
8i	75.0	64.1	50.1	39.1	30.7	118.2
8m	80.2	62.0	53.8	42.8	27.8	87.9
8n	70.5	48.8	44.2	34.4	20.8	167.3
8s	71.1	49.0	46.2	35.8	26.9	150.9
8x	74.9	58.9	48.9	41.2	29.0	127.9
Ningnamycin	99.0	80.0	70.0	60.1	42.1	50.9

In addition, as shown in **Table 2**, compounds **8d**, **8e**, **8f**, **8h**, **8i**, **8m**, **8n**, **8s**, and **8x** were found to display good antiviral activities. These compounds were bioassayed further to investigate their inactivation activities at different concentrations with Ningnanmycin serving as the commercial control. As shown in **Table 2**, the inactivation effect against TMV of compounds **8d**, **8e**, **8f**, **8h**, **8i**, **8m**, **8n**, **8s**, and **8x** are significant. The EC_{50} values were 55.5, 55.3, 159.0, 62.6, 118.2, 87.9, 167.3, 150.9, and 127.9 μg/mL, respectively. Among these compounds, **8d** and **8e** had more potent antiviral activity than the others, being similar to that of Ningnanmycin ($EC_{50} = 50.9$ μg/mL) against TMV.

In summary, a series of new cyanoacrylate derivatives containing α-aminophosphonate moieties **8a**−**8x** were designed and synthesized by refluxing a mixture of alkyl 2-cyano-3,3-dimethylthioacrylate or cyarylamide and α-aminobenzylphosphonate in ethanol. The in vivo tests indicated that compounds **8d** and **8 h** exhibited excellent protection effects against TMV and that the curative activity of compound **8d** against TMV is much higher than that of Ningnanmycin, while a very similar inactivation bioactivity level of compounds **8d** and **8e** and Ningnanmycin against TMV was observed. Therefore, the present work demonstrates that the antiviral activity of cyanoacrylate derivatives was significantly improved via the introduction of the α-aminophosphonates moiety. Effects of steric, hydrophobic, electrostatic, and electrostatic parameters on structure−activity relationships and structural modification studies of compounds **8d**, **8e**, and **8h** are currently underway.

Supporting Information Available: Detailed procedure for the synthesis of **5a**−**f**, **6a**−**e**, and **7a**−**e** and analytical data for **8b**−**8x**. This information is available free of charge via the Internet at http://pubs.acs.org.

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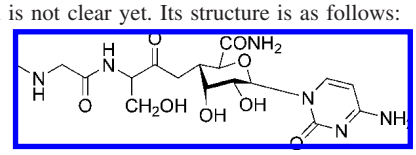
(31) Ningnanmycin is produced by *Strepcomces noursei* var·xichangensisn·var. Ningnanmycin is now commercially available in China as a registered plant virucide. However, its mechanism of action is not clear yet. Its structure is as follows:



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