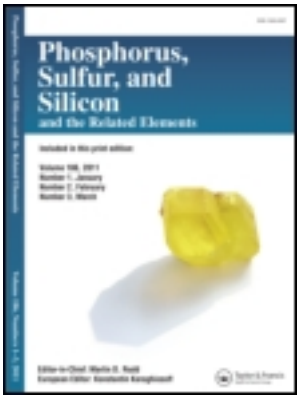

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Bioactivities of α-Aminophosphonate Derivatives Containing Benzothiazole and Thiourea Moieties

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SYNTHESIS AND BIOACTIVITIES OF α-AMINOPHOSPHONATE DERIVATIVES CONTAINING BENZOTHIAZOLE AND THIOUREA MOIETIES

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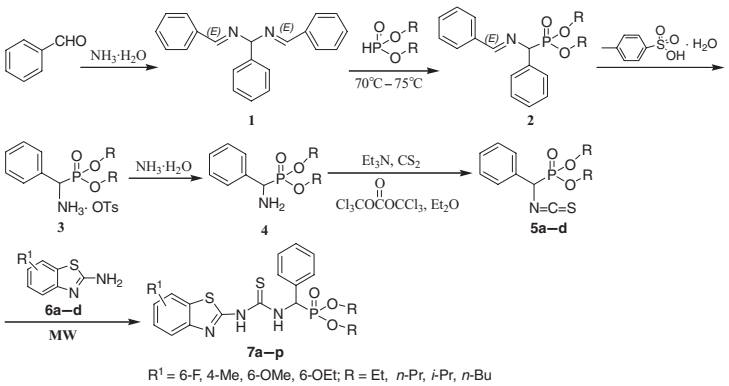
GRAPHICAL ABSTRACT



Abstract *The synthesis of a series of novel α-aminophosphonate derivatives containing benzothiazole and thiourea moieties from substituted 2-aminobenzothiazoles and synthetic intermediates O,O′-dialkylisothiocyanat-(phenyl)methylphosphonates under microwave irradiation has been demonstrated. Several salient features, such as good to excellent yields, shorter reaction times, milder reaction conditions, and simple purification procedures, make the present synthetic protocol highly attractive to access the title compounds. Bioassays indicated that most of the compounds possessed broad-spectrum insecticidal and antiviral activities against*

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Tobacco Mosaic Virus (TMV) in vivo. Interestingly, in comparison with control insecticide Avermectin, two compounds displayed remarkably high in vitro insecticidal activities against Plutella xylostella. Furthermore, according to the results from preliminary bioassay, all were associated with moderate to good anti-TMV activities.

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Tables S1–S4. Figures S1–S52.]*

Keywords α-Aminophosphonate derivatives; thiourea moiety; benzothiazole moiety; synthesis; microwave irradiation; bioactivity

INTRODUCTION

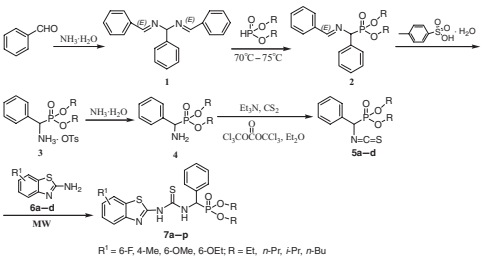
α-Aminophosphonates, structural analogues to natural amino acids, exhibit diverse biological activities such as plant virucides,[1–3] plant growth regulators, herbicides, fungicides, and antitumor agents. Numerous synthetic studies and bioactivities screening of α-aminophosphonates analogues were undertaken in recent years to evaluate their suitability as antiviral agents of plant virus.[4–6]

On the other hand, benzothiazoles belong to an important class of heterocyclic compounds due to their diverse medicinal and pesticidal applications. Some commercial dyes, such as thioflavin, and pharmaceutical drugs, such as riluzole, have benzothiazoles as a structural modifier. They exhibit broad range of biological activities, such as antibacterial, fungicidal, herbicidal, and anti-HIV[7–9] and are often employed as selective antitumor agents against inter alias breast, ovarian, colon, and renal cell lines.[10–12] It is also well documented in the literature[13] that development of suitable synthetic methodologies for their preparation in pure form has been a topic of great interest in the last 20 years.[14–16] In this context, in our previous investigation,[17–19] benzothiazole derivatives bearing an α-aminophosphonate moiety, as demonstrated in the newly designed dufulin(O,O'-diethyl-α-(4-methylbenzothiazole-2-ylamino)-(2-fluorophenyl)phosphonate), was proven to be an effective antiviral agent, which was indeed a breakthrough achieved in this area. The results showed dufulin-induced pathogenesis-related (PR) gene up-regulation in tobacco and increased the activity of the tobacco defense enzyme and chlorophyll content.[18] Plastid–lipid-associated protein and chloroplast cysteine synthase were also related with SA ssalicylic acid (SA) content.[19] In addition, systemic-acquired resistance (SAR) was activated by SA signal molecule. Since thioureas and their derivatives are also associated with significant functional and biological activities and have low toxicity, minimal residues, and impart special biomimetic effects based on hydrogen bonding, we had earlier prepared these compounds containing a phosphonate moiety to demonstrate their utility as potent antiviral and antitumor agents.[20–22] In view of the growing demand for the development of effective and environmentally benign antiviral agents to protect crops from the deadly pests and virus, we envisioned that the introduction of benzothiazole moiety into the parent α-aminophosphonate scaffold through thioureido unit might lead to the generation of novel agents with high bioactivities. Unfortunately, conventional nucleophilic addition reactions designed for this purpose suffer from serious drawbacks such as heating over a long period, low yields, possible thermal decomposition of desired products, and formation of side reaction products thereby making the separation process extremely troublesome. As application of microwave energy can accelerate an organic reaction and offers several other advantages

over conventional techniques,[23] herein we undertook the synthesis of the title compounds under microwave irradiation for shortening reaction times and improving reaction yields. The test result indicated that microwave irradiation could enhance the reaction rate and yield compared to the conventional mode. The structures of compounds **7a–p** were firmly established by IR, ^{1}H, ^{13}C, ^{19}F, and ^{31}P-NMR and elemental analysis. Preliminary bioassay tests showed that the anti-PC3 cells activities of title compounds were low (8.5%–41.5%), but some of the synthesized compounds displayed excellent insecticidal and good antiviral activities against Tobacco Mosaic Virus (TMV) in vivo. To the best of our knowledge, this is the first report on the synthesis, insecticidal, and anti-TMV bioactivities of title compounds.

RESULTS AND DISCUSSION

We synthesized novel α-aminophosphonate derivatives **7a–p** containing benzothiazole and thiourea moieties by reacting substituted aminobenzothiazoles **6a–d** with *O*,*O*′-dialkylisothiocyanato(phenyl)methylphosphonates **5a–d**, which were obtained through multistep synthesis as shown in Scheme 1. The microwave reaction conditions for the final step leading to the synthesis of title compounds were optimized for various reaction parameters, for example, temperature, reaction time, and power input, by taking **7a** as the model. According to the test results, the reaction time was considerably shortened from 24 h to 30 min and the yields were increased from 19.3%–46.6% to 40.2%–81.4% when the reaction was switched to microwave irradiation mode from conventional heating. Under optimized conditions, the products were obtained in dry CH_3CN at a reaction temperature of 90 °C, and a reaction time of 30 min with a power input of 120 W.



R^1 = 6-F, 4-Me, 6-OMe, 6-OEt; R = Et, *n*-Pr, *i*-Pr, *n*-Bu

Compd.	R^1	R	Compd.	R^1	R	Compd.
7a	6-F	Et	**7e**	4-CH_3	Et	**7i**
7b	6-F	*n*-Pr	**7f**	4-CH_3	*n*-Pr	**7j**
7c	6-F	*i*-Pr	**7g**	4-CH_3	*i*-Pr	**7k**
7d	6-F	*n*-Bu	**7h**	4-CH_3	*n*-Bu	**7l**

Scheme 1 Intermediate α-aminophosphonate **4** was prepared according to the procedure in the literature.[28] The screening and optimization of reaction conditions under Microwave assisted and the synthetic results for compounds **7a–p** are provided in the Supporting Materials (available online).

All of the products were unequivocally characterized by Infrared (IR) and nuclear magnetic resonance (NMR) spectral data and elemental analysis. The characteristic IR absorption bands for N-H (3142–3291, s cm^{-1}), C═S (1337–1355 cm^{-1}), P═O (1202–1265 cm^{-1}), and P—O—C (1010–1059 cm^{-1}) confirmed the presence of the respective functional

groups. In ^{1}H NMR spectra, all aromatic protons revealed the expected multiple near $\delta_H =$ 6.95–7.72 ppm. The N–H protons of compounds **7a–p** appeared weak peaks considerably downfield in the region of $\delta_H = 9.42$–12.48 ppm due to the existence of hydrogen bonding with the thioureido moiety. The chemical shift of PCH appeared near δ_H = 6.19–6.28 ppm range as a doublet of doublets due to the presence of CH moiety adjacent to a phosphorus atom. The chemical shifts of OCH_2 generally appeared in the region of $\delta_H = 3.45$–5.02 ppm. The ^{31}P NMR spectral data showed the presence of a phosphorus atom and appeared around $\delta_P = 19.5$–22.3 ppm as singlet or doublets. The fluorine resonance appeared at $\delta_F = 118.2$–118.6 ppm in the corresponding fluorine NMR spectra. All the nonequivalent carbon atoms were identified in ^{13}C NMR, and the typical low intense carbon resonance frequencies at $\delta_C = 178.4$–183.0 ppm in the ^{13}C NMR spectra of **7a–p** also confirmed the presence of C=S double bond.

Antiviral Activity

Antiviral activities of **7a–p** were investigated. The results obtained for anti-TMV activities are given in Table 1. Ningnanmycin was used as the reference antiviral agent. The data provided in Table 1 indicate that the title compounds **7a–p** showed curative rates of 29.5%–52.9%. The compounds **7a**, **7c**, **7e**, **7f**, **7i**, **7j**, and **7n** displayed moderate curative bioactivities of up to 43.8%, 46.6%, 45.7%, 42.8%, 44.9%, 41.4%, and 43.1%, respectively, against TMV at 500 μg/mL. The compound **7b** ($R^1 = F$, R = *n*-Pr) exhibited similar curative activity (52.9%) as that of the standard reference (55.4%), but the rest of the compounds revealed relatively lower curative activities. These data also indicate that these changes as a substituent on the aryl and phosphite moieties can affect the curative activity of **7a–p**. In general, as expected, the aminophosphonate derivatives incorporating benzothiazole and thiourea moieties also provided good antiviral activities.

Insecticidal Activity

The insecticidal activity results of title compounds **7a–p** against *Plutella xylostella* are given in Table 2. Avermectin was used as the reference insecticidal agent. The data in Table 2 indicate that compounds **7a–p** displayed moderate to good insecticidal bioactivities (corrected mortality of 43%–84%) at 100 μg/mL. The corrected mortalities of compounds **7b** ($R^1 = F$, R = *n*-Pr) and **7l** ($R^1 = OMe$, R = *n*-Bu) at 84% and 78%, respectively, at 100 μg/mL have similar effect as the control drug avermectin (corrected mortality 82%).

Table 1 Curative effect of the new compounds **7a–p** against TMV in vivo

Compd.	Concn. (μg/mL)	Curative effect (%)	Compd.	Concn. (μg/mL)	Curative effect (%)
7a	500	43.8	**7i**	500	44.9
7b	500	52.9	**7j**	500	41.4
7c	500	46.6	**7k**	500	32.1
7d	500	33.4	**7l**	500	29.5
7e	500	45.7	**7m**	500	32.8
7f	500	42.8	**7n**	500	43.1
7g	500	31.8	**7o**	500	35.9
7h	500	37.5	**7p**	500	34.6
Ningnamycin	500	55.4			

Table 2 Insecticidal activity of compounds **7a–p** against *Plutella Xylostella* at 100 μg/mL

Compd.	Mortality (%)	Corrected mortality (%)	Compd.	Mortality (%)	Corrected mortality (%)
7a	69	67	**7i**	65	64
7b	85	84	**7j**	70	68
7c	74	71	**7k**	59	57
7d	56	55	**7l**	80	78
7e	52	51	**7m**	58	56
7f	56	53	**7n**	61	60
7g	45	43	**7o**	54	52
7h	49	48	**7p**	68	66
ck	5	–			
Avermectin	83	82			

It was found that most of title compounds possessed broad-spectrum insecticidal and antiviral activities against TMV in vivo. These results are promising, the syntheses are original and well conducted, and biological activities are very interesting. Especially, compound **7b** (R^1 = F, R = *n*-Pr) with both good insecticidal (the corrected mortalities is 84% at 100 μg/mL) and anti-TMV (the curative effect is 52.9% at 500 μg/mL) bioactivities, is valuable for further research and development.

EXPERIMENTAL

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 in KBr disks. ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR (solvent $CDCl_3$) spectra were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as 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.

Preparation of Intermediate 5

According to the procedure given in literature,[21] the key intermediate *O,O′*-dialkylisothio-cyanato(phenyl)methylphosphonate **5** was prepared in 67.4%–78.6% yield by the reaction of **4** bearing different alkyl substituents with bis(trichloromethyl)carbonate (BTC) as shown in Scheme 1.

Preparation of Title Compounds 7a–p Under Conventional Heating Mode

A mixture of substituted 2-aminobenzothiazole **6a–d** (1.0 mmol), tetrabutyl ammonium bromide (1.0 mmol), and *O,O′*-dialkylisothiocyanato(phenyl)methylphos phonate **5a–d** (2 mmol) in dry acetonitrile (10 mL) was refluxed and stirred at 80 °C for 24 h. The progress of the reaction was monitored by TLC, the solvent was removed by evaporation, and the crude product was purified by thin-layer chromatography using a mixture of dichloromethane, acetic ether, and *n*-hexane (V/V/V = 4:1:2) as developing solvent to give the title compounds **7a–p**.

Microwave-Aassisted Preparation of Title Compounds 7a–p

A mixture of substituted 2-aminobenzothiazole **6a–d** (1.0 mmol) and *O,O′*-dialkyl isothiocyanato(phenyl)methylphosphonate **5a–d** (2 mmol) in dry acetonitrile (5 mL) was transferred in a microwave tube, which was then sealed and placed under a pressurized atmosphere inside the Discovery Synthesizer and subjected to microwave irradiation at 120 W for 30 min at a temperature of 90 °C. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by thin-layer chromatography using a mixture of dichloromethane, acetic ether, and *n*-hexane (V/V/V = 4:1:2) as a developing solvent to give the title compounds **7a–p** in 40.2%–81.4% yields.

***O,O′*-Diethyl (3-(6-fluorobenzo[d]thiazol-2-yl)thioureido)(phenyl)methyl phosphonate (7a).** White solid, mp = 215–216 °C; yield 71.3%; IR (ν cm^{-1}): 3279, 3142 (NH), 2974, 1609, 1534, 1458, 1342 (C=S), 1244 (P=O), 1110, 1022(P−O−C), 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.07 (m, 8H, Ar–H), 6.23 (dd, 1H, J = 9.20 Hz, NCH-P), 4.26–3.90 (m, 4H, $2OCH_2$), 1.37, 1.21 (t, 6H, J = 6.8 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2, 172.2, 160.3, 145.2, 134.1, 128.8, 128.3, 128.1, 120.9, 114.1, 107.6, 64.1, 54.3, 16.3; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 22.3; ^{19}F NMR: δ = −118.2 ppm; Anal. Calcd. for $C_{19}H_{21}FN_3O_3PS_2$ (453): C, 50.32; H, 4.67; N, 9.27. Found: C, 50.11; H, 4.76; N, 9.48.

***O,O′*-Dipropyl (3-(6-fluorobenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7b).** White solid, mp = 206–207 °C; yield 53.8%; IR (ν cm^{-1}): 3260, 3150 (NH), 2968, 1611, 1547, 1458, 1355 (C=S), 1217 (P=O), 1013 (P−O−C), 696; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.29 (s, 1H, N-H), 9.49 (s, 1H, N-H), 7.65–7.06 (m, 8H, Ar H), 6.28 (dd, 1H, J = 8.60 Hz, NCH-P), 4.19–3.80 (m, 4H, $2OCH_2$), 1.72–1.58 (m, 4H, $2CH_2$), 0.93, 0.84 (t, 6H, J = 5.75 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.3, 160.4, 158.5, 145.2, 134.3, 132.4, 128.8, 128.5, 121.1, 114.1, 107.4, 69.6, 55.4, 24.1, 9.8; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 22.1; ^{19}F NMR: δ = −118.6 ppm; Anal. Calcd. for $C_{21}H_{25}FN_3O_3PS_2$ (481): C, 52.38; H, 5.23; N, 8.73. Found: C, 52.49; H, 5.51; N, 8.52.

***O,O′*-Diisopropyl (3-(6-fluorobenzo[d]thiazol-2-yl)thioureido)(phenyl) methylphosphonate (7c).** White solid, mp = 232–233 °C; yield = 67.2%; IR (ν cm^{-1}): 3269 (NH), 2976, 1610, 1541, 1456, 1242, 1204 (P=O), 1103, 1011(P−O−C), 851, 696; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.43 (s, 1H, N-H), 9.42 (s, 1H, N-H), 7.72–7.01 (m, 8H, Ar-H), 6.23 (dd, 1H, J = 8.55 Hz, NCH-P), 5.02–4.92 (m, 2H, 2OCH), 1.35, 0.88 (d, 12H, J = 26.35 Hz, $4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.3, 160.3, 158.2, 145.2, 134.4, 128.6, 128.4, 127.6, 121.3, 114.0, 107.5, 73.6, 55.6, 24.3; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 20.7; ^{19}F NMR: δ = −118.4 ppm; Anal. Calcd. for $C_{21}H_{25}FN_3O_3PS_2$ (481): C, 52.38; H, 5.23; N, 8.73. Found: C, 52.55; H, 5.41; N, 8.49.

***O,O′*-Dibutyl (3-(6-fluorobenzo[d]thiazol-2-yl)thioureido)(phenyl)methyl phosphonate (7d).** White solid, mp = 123–125 °C; yield = 48.9%; IR (ν cm^{-1}): 3291 (NH), 2959, 1609, 1528, 1456, 1442, 1346 (C=S), 1192 (P=O), 1028 (P−O−C), 694; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.07 (m, 8H, ArH), 6.24 (dd, 1H, J = 9.15 Hz, NCH-P), 4.21–3.86 (m, 4H, $2OCH_2$), 1.70–1.26 (m, 8H, $2CH_2CH_2$), 0.85 (t, 6H, J = 8.0 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2, 160.4, 158.5, 144.9, 134.3, 129.0, 128.8, 128.5, 128.1, 121.1, 113.7, 107.7, 67.9, 65.9, 32.6, 18.8, 13.6; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 22.4; ^{19}F NMR: δ = −118.4 ppm; Anal. Calcd. for $C_{23}H_{29}FN_3O_3PS_2$ (509): C, 54.21; H, 5.74; N, 8.25. Found: C, 54.53; H, 5.38; N, 8.51.

***O,O′*-Diethyl (3-(4-methylbenzo[d]thiazol-2-yl)thioureido)(phenyl)methyl phosphonate (7e).** White solid, mp = 204–205 °C; yield 55.7%; IR (ν cm^{-1}): 3260

(NH), 2920, 1597, 1541, 1456, 1350 (C=S), 1238, 1207 (P=O), 1015 (P−O−C), 696; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.43 (br, s, 1H, NH), 10.46 (br, s, 1H, NH), 7.58–7.19 (m, 8H, ArH), 6.25 (dd, 1H, J = 8.60 Hz, NCH-P), 4.14–3.93 (m, 4H, $2OCH_2$), 2.73 (br, s, 3H, $ArCH_3$), 1.28, 1.15 (t, 6H, J = 7.15 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 159.6, 146.5, 134.4, 130.6, 128.6, 127.3, 124.4, 118.3, 63.3, 54.0, 18.5, 16.1; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 20.9 ppm; Anal. Calcd. for $C_{20}H_{24}N_3O_3PS_2$ (449): C, 53.44; H, 5.38; N, 9.35. Found: C, 53.49; H, 5.62; N, 9.71.

***O,O′*-Dipropyl (3-(4-methylbenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7f).** White solid, mp = 180–182 °C; yield 46.5%; IR (ν cm^{-1}): 3265 (NH), 2968, 1598, 1543, 1352 (C=S), 1206 (P=O), 1013 (P−O−C), 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.45 (br, s, 1H, N-H), 10.73 (br, s, 1H, N-H), 7.60–7.17 (m, 8H, ArH), 6.28 (dd, 1H, J = 8.05 Hz, NCH-P), 4.02–3.81 (m, 4H, $2OCH_2$), 2.72 (br, s, 3H, $ArCH_3$), 1.65–1.52 (m, 4H, $2CH_2$), 0.87, 0.78 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7, 159.2, 148.1, 134.5, 130.7, 129.8, 128.8, 127.3, 124.3, 118.4, 68.7, 55.9, 24.0, 18.3, 10.2; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 20.7 ppm; Anal. Calcd. for $C_{22}H_{28}N_3O_3PS_2$ (447): C, 55.33; H, 5.91; N, 8.80. Found: C, 55.42; H, 5.63; N, 8.89.

***O,O′*-Diisopropyl (3-(4-methylbenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7g).** White solid, mp = 236–237 °C; yield 52.8%; IR (ν cm^{-1}): 3262 (NH), 2978, 1543, 1356, 1219 (P=O), 1018 (P−O−C), 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.36 (br, s, 1H, N-H), 10.60 (br, s, 1H, N-H), 7.59–7.17 (m, 8H, ArH), 6.22 (s, 1H, NCH-P), 4.77–4.60 (m, 2H, 2OCH), 2.76–2.52 (m, 3H, $ArCH_3$), 1.31, 0.96 (d, 12H, J = 6.35 Hz, $4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6, 171.0, 148.5, 134.6, 130.9, 128.9, 127.2, 126.8, 124.4, 118.5, 72.3, 57.9, 24.2, 18.5; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 19.5 ppm; Anal. Calcd. for $C_{22}H_{28}N_3O_3PS_2$ (477): C, 55.33; H, 5.91; N, 8.80. Found: C, 55.28; H, 5.77; N, 8.65.

***O,O′*-Dibutyl (3-(4-methylbenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7h).** White solid, mp = 134–136 °C; yield 40.2%; IR (ν cm^{-1}): 3267, 3159 (NH), 2959, 1599, 1541, 1458, 1352 (C=S), 1203 (P=O), 1026 (P−O−C), 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.48 (br, s, 1H, N-H), 11.02 (br, s, 1H, N-H), 7.61–7.17 (m, 8H, ArH), 6.28 (dd, 1H, J = 8.60 Hz, NCH-P), 4.08–3.86 (m, 4H, $2OCH_2$), 2.73 (s, 3H, $ArCH_3$), 1.61–1.22 (m, 8H, $2CH_2CH_2$), 0.79 (t, 6H, J = 7.35 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8, 159.7, 148.7, 134.3, 130.8, 128.6, 128.6, 127.3, 124.1, 118.6, 67.4, 56.1, 32.4, 19.0, 18.4, 13.5; ^{31}P NMR (200 MHz, $CDCl_3$) δ = 21.1 ppm; Anal. Calcd. for $C_{24}H_{32}N_3O_3PS_2$ (505): C, 57.01; H, 6.38; N, 8.31. Found: C, 57.34; H, 6.08; N, 8.52.

***O,O′*-Diethyl (3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7i).** White solid, mp = 195–196 °C; yield 74.6%; IR (ν cm^{-1}): 3285 (NH), 2970, 2890, 1610, 1541, 1462, 1337 (C=S), 1265, 1202 (P=O), 1020 (P−O−C), 696; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–6.96 (m, 8H, ArH), 6.21 (dd, 1H, J = 9.15 Hz, NCH-P), 4.21–3.92 (m, 4H, $2OCH_2$), 3.83 (s, 3H, OCH_3), 1.34, 1.19 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0, 173.6, 157.0, 142.1, 134.3, 128.8, 128.4, 124.6, 120.9, 114.9, 104.5, 63.9, 55.9, 54.5, 16.4; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 21.5 ppm; Anal. Calcd. for $C_{20}H_{24}N_3O_4PS_2$ (465): C, 51.60; H, 5.20; N, 9.03. Found: C, 51.24; H, 5.45; N, 9.33.

***O,O′*-Dipropyl (3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7j).** White solid, mp = 202–204 °C; yield 69.1%; IR (ν cm^{-1}): 3161 (NH), 2966, 1602, 1552, 1472, 1354 (C=S), 1226, 1147 (P=O), 1056 (P−O−C), 997, 822, 694; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–6.95 (m, 8H, Ar-H), 6.27 (dd,

1H, J = 9.20 Hz, NCH-P), 4.13–3.85 (m, 4H, $2OCH_2$), 3.83 (s, 3H, OCH_3),1.71–1.58 (m, 4H, $2CH_2$), 0.92, 0.84 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7, 171.3, 156.59, 143.2, 134.3, 129.0, 128.6, 128.4, 128.0, 121.1, 114.9, 104.4, 69.3, 60.3, 55.8, 24.1, 10.0; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 21.9 ppm; Anal. Calcd. for $C_{22}H_{28}N_3O_4PS_2$ (493): C, 53.53; H, 5.72; N, 8.51. Found: C, 53.29; H, 5.56; N, 8.84.

***O,O′*-Diisopropyl (3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)(phenyl) methylphosphonate (7k).** White solid, mp = 216–218 °C; yield 77.2%; IR (ν cm^{-1}): 3163 (NH), 2976, 2830, 1603, 1552, 1472, 1339 (C═S), 1265, 1225, 1148 (P═O), 1059 (P—O—C), 984, 696; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–6.95 (m, 8H, Ar-H), 6.19 (dd, 1H, J = 8.05 Hz, NCH-P), 4.87 (br, s, 2H, 2OCH), 3.83 (s, 3H, OCH_3), 1.37, 0.92 (d, 12H, J = 6.30 Hz, $4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.9, 158.7, 156.5, 143.1, 134.6, 129.0, 128.7, 128.1, 121.1, 114.7, 104.4, 73.4, 60.4, 55.8, 24.1; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 20.5 ppm; Anal. Calcd. for $C_{22}H_{28}N_3O_4PS_2$ (493): C, 53.53; H, 5.72; N, 8.51. Found: C, 53.24; H, 5.85; N, 8.44.

***O,O′*-Dibutyl (3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)(phenyl) methylphosphonate (7l).** White solid, mp = 161–162 °C, yield 62.6%; IR (ν cm^{-1}): 3258 (NH), 2957, 1609, 1551, 1466, 1354 (C═S), 1265, 1213 (P═O), 1028 (P—O—C), 827; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–6.96 (m, 8H, Ar-H), 6.23 (dd, 1H, J = 6.85 Hz, NCH-P), 4.14 (br, s, 3H, OCH_3), 3.88–3.83 (m, 4H, $2OCH_2$), 1.65–1.25 (m, 8H, $2CH_2CH_2$), 0.83 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0, 158.7, 156.8, 143.4, 134.4, 128.8, 128.5, 121.1, 114.7, 104.4, 67.6, 61.0, 55.9, 32.4, 18.8, 13.7; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 21.7 ppm; Anal. Calcd. for $C_{24}H_{32}N_3O_4PS_2$ (521): C, 55.26; H, 6.18; N, 8.06. Found: C, 55.01; H, 6.39; N, 7.95.

***O,O′*-Diethyl (3-(6-ethoxybenzo[d]thiazol-2-yl)thioureido)(phenyl)meth ylphosphonate (7m).** White solid, mp = 189–190 °C; yield 81.4%; IR (ν cm^{-1}): 3265, 3146 (NH), 2978, 1607, 1541, 1458, 1352 (C═S), 1204 (P═O), 1022 (P—O—C), 827, 696; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–6.95 (m, 8H, Ar-H), 6.23 (dd, 1H, J = 9.75 Hz, NCH-P), 4.21–4.04 (m, 6H, $3OCH_2$), 1.43, 1.21 (t, 9H, J = 7.45 Hz, $3CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.0, 170.8, 155.9, 134.3, 128.8, 128.4, 120.9, 115.4, 105.2, 64.2, 60.5, 55.1, 14.9; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 21.5 ppm; Anal. Calcd. for $C_{21}H_{26}N_3O_4PS_2$ (479): C, 52.60; H, 5.46; N, 8.76. Found: C, 52.73; H, 5.11; N, 8.49.

***O,O′*-Dipropyl (3-(6-ethoxybenzo[d]thiazol-2-yl)thioureido)(phenyl)meth ylphosphonate (7n).** White solid, mp = 162–164 °C; yield 70.3%; IR (ν cm^{-1}): 3269 (NH), 2970, 1607, 1545, 1460, 1353 (C═S), 1263, 1207 (P═O), 1061, 1013 (P—O—C), 696; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–6.95 (m, 8H, Ar-H), 6.24 (dd, 1H, J = 8.60 Hz, NCH-P), 4.12–3.45 (m, 6H, $3OCH_2$), 1.71–1.55 (m, 4H, $2CH_2$), 1.44 (t, 3H, J = 6.90 Hz, CH_3), 0.82 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8, 158.5, 156.0, 143.2, 134.3, 128.8, 128.4, 128.0, 121.1, 115.3, 105.1, 69.2, 65.9, 63.9, 55.3, 24.0, 14.7, 9.8; ^{31}P NMR (200 MHz, $CDCl_3$): δ = 21.5 ppm; Anal. Calcd. for $C_{23}H_{30}N_3O_4PS_2$ (507): C, 54.42; H, 5.96; N, 8.28. Found: C, 54.56; H, 5.73; N, 8.45.

***O,O′*-Diisopropyl (3-(6-ethoxybenzo[d]thiazol-2-yl)thioureido)(phenyl) methylphosphonate (7o).** White solid, mp = 220–221 °C; yield 75.9%; IR (ν cm^{-1}): 3275 (NH), 2978, 1611, 1533, 1460, 1342 (C═S), 1265, 1225, 1198 (P═O), 1063, 1010 (P—O—C), 696; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57–6.95 (m, 8H, Ar-H), 6.21 (dd, 1H, J = 6.85 Hz, NCH-P), 4.88 (s, 2H, OCH), 4.05 (q, 2H, J = 6.90 Hz, OCH_2), 1.43 (t, 3H, J = 6.85 Hz, CH_3), 1.37 (d, 12H, J = 5.15 Hz, $4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0, 158.5, 155.9, 142.9, 134.6, 129.0, 128.4, 128.1, 121.0, 115.1, 105.2,

73.1, 64.1, 56.1, 24.4, 14.9; ^{31}P NMR (200 MHz, $CDCl_3$): $\delta = 20.5$ ppm; Anal. Calcd. for $C_{23}H_{30}N_3O_4PS_2$ (507): C, 54.42; H, 5.96; N, 8.28. Found: C, 54.61; H, 5.65; N, 8.57.

***O,O′*-Dibutyl (3-(6-ethoxybenzo[d]thiazol-2-yl)thioureido)(phenyl)methylphosphonate (7p).** White solid, mp = 110–112 °C; yield 65.2%; IR (ν cm^{-1}): 3265 (NH), 2959, 1607, 1545, 1460, 1263, 1211 (P═O), 1061, 1028 (P—O—C), 814, 696; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–6.95 (m, 8H, Ar-H), 6.25 (dd, 1H, J = 9.15 Hz, NCH-P), 4.13–3.45 (m, 6H, $3OCH_2$), 1.64–1.24 (m, 8H, $2CH_2CH_2$), 1.42 (t, 3H, J = 6.85 Hz, CH_3), 0.83 (t, 6H, J = 7.45 Hz, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.9, 173.6, 156.2, 143.1, 134.3, 128.9, 128.7, 128.2, 127.8, 120.7, 115.3, 105.0, 67.6, 64.0, 54.3, 32.6, 18.6, 14.7, 13.2; ^{31}P NMR (200 MHz, $CDCl_3$): $\delta = 21.5$ ppm; Anal. Calcd. for $C_{25}H_{34}N_3O_4PS_2$ (535): C, 56.06; H, 6.40; N, 7.84. Found: C, 56.12; H, 6.54; N, 7.61.

Antiviral Activity Assay

Purification of TMV. Using Gooding's method,[24] the upper leaves of *Nicotiana tabacum* L. inoculated with TMV were selected and grounded in phosphate buffer and then filtered through 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 (UV) spectrophotometer.

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

Curative effect of compounds against TMV in vivo. Growing leaves of *N. tabacum* L. of the same ages were selected. The TMV (with a 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.[25] For each compound, three repetitions were measured. The inhibition rate of the compound was then calculated according to the following formula (average: "av"):

$$\text{Inhibition rate (\%)} = \frac{\text{Av. local lesion numbers of control (not treated with compound)} - \text{av. local lesion numbers smeared with drugs}}{\text{Av. local lesion numbers of control (not treated with compound)}} \times 100. \quad (1)$$

Insecticidal Activity Assay

Insecticidal activities against *Plutella xylostella* of the title compounds **7a–p** and the control drug avermectin were tested by the leaf-dip method using the reported procedure.[26,27] The solution for each test sample was prepared in dimethylformamide at a concentration of 100 μg/mL. Leaf disks (6 cm × 2 cm) were cut from fresh cabbage leaves and dipped into the test solution for 5 s. After air-drying, the treated leaf disks were placed individually into glass tubes. Each dried and treated leaf disk was infested with 10 third-instar *Plutella xylostella* larvae. Percentage mortalities were evaluated 3 days after the treatment. Leaves treated with water and dimethylformamide were provided as controls. Each treatment was performed thrice.

REFERENCES

1. Kafarski, P.; Lejczak, B. *Phosphorus Sulfur* **1991,** 63, 193-215.
2. Song, B. A.; Wu, Y. L.; Yang, S.; Hu, D. Y.; He, X. Q.; Jin, L. H.; Lu, P. *Molecules* **2003,** 8, 186-192.
3. Yang, S.; Gao, X. W.; Diao, C. L.; Song, B. A.; Jin, L. H.; Xu, G. F.; Zhang, G. P.; Wang, W.; Hu, D. Y.; Xue, W.; Zhou, X.; Lu, P. *Chin. J. Chem.* **2006,** 24, 1581-1588.
4. Zhou, J.; Fang, H. T.; Song, B. A.; Jin, L. H.; Bhadury, S. P.; Hu, D. Y.; Yang, S. *Phosphorus Sulfur Silicon Relat. Elem.* **2011,** 186, 81-87.
5. Zhang, Y. P.; Zhang, X. Y.; Zhou, J.; Song, B. A.; Bhadury, S. P.; Hu, D. Y.; Yang, S. *J. Sep. Sci.* **2011,** 34, 402-408.
6. Yang, J. Q.; Song, B. A.; Bhadury, P. S.; Chen, Z.; Yang, S.; Cai, X. J.; Hu, D. Y.; Xue, W. *J. Agric. Food Chem.* **2010,** 58, 2730-2735.
7. Ganzer, M.; Dorfmeister, G.; Frake, W. U.S. Patent 5424443, *Chem. Abstr.* **1995,** 118, 101946.
8. Sidoova, E.; Loos, D.; Bujdakova, H. *Molecules* **1997,** 2, 36-42.
9. Mahran, M. A.; Elnassry, S. M. F.; Allam, S. R. *Pharmazie* **2003,** 58, 527-530.
10. Hutchinson, I.; Chua, M. S.; Browne, H. L.; Stevens, M. F. G. *J. Med. Chem.* **2001,** 44, 1446-1455.
11. Mortimer, C. G.; Wells, G.; Crochard, J. P. *J. Med. Chem.* **2006,** 49, 179-185.
12. Manjula, S. N.; Malleshappa Noolvi, N.; Vipan Parihar, K.; Manohara Reddy, S. A.; Mallikarjuna Rao, C. *Eur. J. Med Chem.* **2009,** 44, 2923-2929.
13. Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity* (John Wiley, Chichester, 2000).
14. Song, B. A.; Wu, Y. L.; Yang, S.; Hu, D. Y.; He, X. Q.; Jin, L. H. *Molecules* **2003,** 8, 186-192.
15. Wang, Q. M.; Chen, Z.; Zeng, Q.; Huang, R. Q. *Heteroatom Chem.* **1999,** 10, 209-212.
16. Wang, Q. M.; Li, H.; Li, Y. H.; Huang, R. Q. *J. Agric. Food Chem.* **2004,** 52, 1918-1922.
17. Song, B. A.; Zhang, G. P.; Hu, D. Y.; Pang, L. L.; Yang, S. CN Patent 1687088, Patent approval certificate No. ZL0200510003041.7, *Chem. Abstr.* **2006,** 145, 145879.
18. Hu, D. Y.; Wan, Q. Q.; Yang, S.; Song, B. A.; Bhadury, P. S.; Jin, L. H. *J. Agric. Food Chem.* **2008,** 56, 998-1001.
19. Song, B. A.; Yang, S.; Jin, L. H.; Bhadury, P. S. *Environment-Friendly Anti-Plant Viral Agent* (Springer, Berlin, Germany, 2009).
20. Chen, M. H.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Cai, X. J.; Hu, D. Y.; Xue, W.; Zheng, S. *J. Agric. Food Chem.* **2009,** 57, 1383-1388.
21. Liu, J. Z.; Yang, S.; Li, X. Y.; Fan, H. T.; Bhadury, P. S.; Xu, W. M.; Wu, J.; Wang, Z. C. *Molecules* **2010,** 15, 5112-5123.
22. Liu, J. Z.; Song, B. A.; Fan, H. T.; Bhadury, P. S.; Wan, W. T.; Yang, S.; Jin, L. H.; Wei, X.; Hu, D. Y.; Zeng, S. *Eur. J. Med. Chem.* **2010,** 45, 5108-5112.
23. Hayes, B. L. *Aldrichimica Acta* **2004,** 37, 66-77.
24. Gooding, G. V., Jr.; Hebert, T. T. *Phytopathology* **1967,** 57, 1285-1290.
25. Song, B. A.; Zhang, H. P.; Wang, H.; Yang, S.; Jin, L. H.; Hu, D. Y.; Pang, L. L.; Xue, W. *J. Agric. Food Chem.* **2005,** 53, 7886-7891.
26. Sayyed, A. H.; Ferre, J.; Wright, D. J. *Pest. Manage. Sci.* **2000,** 56, 743-748.
27. Sun, R. F.; Zhang, Y. L.; Chen, L.; Li, Y. Q.; Li, Q. S.; Song, H. B.; Huang, R. Q.; Bi, F. C.; Wang, Q. M. *J. Agric. Food Chem.* **2009,** 57, 3661-3668.
28. Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005,** 46, 2989-2991.