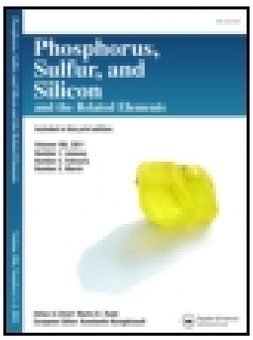

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Synthesis and antiviral activity of novel *a*-aminophosphonates containing a 6-fluorobenzothiazole moiety

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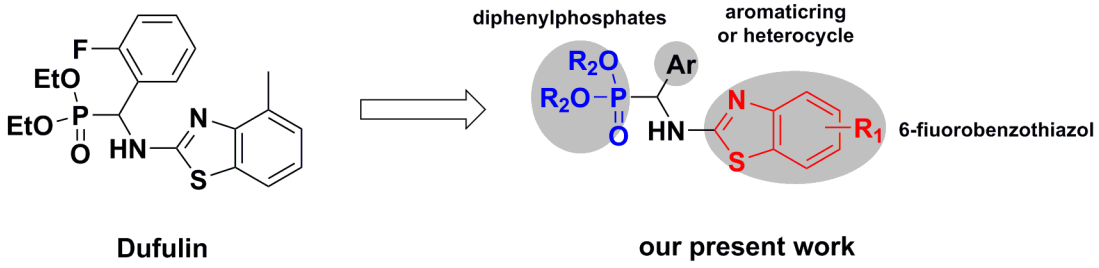
ABSTRACT

A series of novel α-aminophosphonates containing a 6-fluorobenzothiazole moiety derivatives were synthesized by a one-pot reaction under microwave irradiation. The structure of the products was characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis data. Antiviral assays showed that some compounds possess good curative and protective activities against tobacco mosaic virus (TMV) *in vivo* at 500 μg/mL In particular, diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(phenyl)methyl]phosphonate (**4b**), diethyl [(6-methoxybenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (**4j**) and diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (**4q**) exhibited remarkable antiviral activities against TMV and PVY, compared with Ribavirin. Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (**4q**) showed similar curative and protective activity against potato virus Y (PVY) to Dufulin.

Graphical Abstract



Keywords

a-aminophosphonates, 6-fluorobenzothiazole, microwave chemistry, multicomponent reaction, antiviral activity

Introduction

Phosphonic acids are an important class of organophosphorus structures found in many synthetic and natural occurring products with a remarkable spectrum of biological activities [1]. As analogs of phosphonic acids, α-aminophosphonate derivatives have received much attention due to their potential biological activities in agrochemicals, such as antibacterial [2-4], antifungal [5, 6], and antiviral [7, 8]. In our previous work, several series of α-aminophosphonate derivatives were synthesized and exhibited good antiviral activities [9, 10]. Based on these studies we had found that α-aminophosphonates containing the benzo[d]thiazole group (Fig. 1, Dufulin) displayed excellent antiviral activity and have since been commercialized as antiviral agents for controlling plant virus diseases [11]. Then we have made great efforts to optimize the structure of Dufulin and discovered that the skeleton of α-aminophosphonates derivatives containing diphenylphosphates exhibited better antiviral activity than α-aminophosphonates containing dialkylphosphates [12, 13]. Therefore, we believe that introducing diphenylphosphates into the skeleton of Dufulin may enhance the antiviral activity.

On the other hand, since a fluorinated corticosteroid was found to have increased biological activity with the non-fluorinated parent steroid [14, 15] in 1954, organo-fluorine compounds attracted more and more attention due to the special physical and chemical properties of fluoro substituents, such as steric hindrance, strong electronegativity and good permeability [16, 17]. Once fluorine contained groups were introduced into organic compounds, there may be

profound and unexpected improves in biological activity of these compounds [18, 19]. Moreover, the important role of fluorine reflected in the number of fluorine-containing agrochemical has more than tripled in the past few decades [20].

Keeping these considerations in mind, we aim to introduce fluoro substituens into the benzothiazole ring of Dufulin for enhancing the activity and to synthesized a series of novel 6-fluorobenzothiazol or diphenyl phosphate containing *a*-aminophosphonates. The synthetic route is depicted in Fig. 2. The structures of the compounds were confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR spectroscopy and elemental analysis. Preliminary bioassays indicated that some compounds exhibit good antiviral activities against TMV and PVY.

Results and discussion

Chemistry

A typical method for the synthesis of this type of *a*-aminophosphonates consists in the one-pot reaction of aldehydes, 2-amine benzothiazoles, and dialkyl phosphate by Kabachnik-Fields reaction under microwave irradiation.[21-23] Ionic liquids, such as [bmim][BF_4], [bmim][BF_6] and [bmim][SbF_6] are widely used as solvent.[24, 25]. However, ionic liquids have some limitations such as high price and water sensitivity.[26]. Therefore, first of all we have optimized the reaction conditions including solvent, reaction temperature, and reaction time. As shown in Table 1, the choice of solvent proved crucial to the reaction outcome

as no reaction was observed in acetonitrile, DMSO and ethyl alcohol, whereas in toluene an overall yield of 9.4% resulted. It is worth noting that this yield was significantly low. With the increase of reaction temperature, the yield was relatively higher, but no substantial improvement was observed when the reaction system was heated from 150 °C to 160 °C (Table 1, entry 13 and 14). Hence, it seemed better to perform the reaction at 150 °C instead of a lower or higher temperature. When the reaction time was prolonged from 20 to 40 min, the yield increased from 46.8 % to 66.5% (Table 1, entry 13 and 16). When the reaction time was further prolonged to 60 min, there was a further slight improvement of yield (67.9 %, Table 1, entry 17). Therefore, compared with acetonitrile, DMF, DMSO, pyridine, ethyl alcohol and toluene, it turned out that the best solvent was NMP, the best reaction temperature was 150 °C, and the best reaction time was 40 min. Using theses optimized conditions, the compounds **4a**–**4v** were prepared.

The structures of the synthesized compounds were characterized by IR and NMR spectroscopy, and elemental analyses. The IR spectra of products **4m** exhibited bands at ca. 3264.7 cm^{-1}, indicating the presence of NH. The 1207.5 cm^{-1} band was assigned to be due to the P=O stretching mode. Bands at 953.8 cm^{-1} belong to the C-O stretching mode of the P-O-C group. In the ^{1}H NMR spectra, all phenyl proton showed multiplets at 6.89-7.75 ppm. The chemical shift of the PC-H ptoton was 6.41 ppm, and appeared as dd peak due to the coupling of the P atom and N-H. The products showed the N-H proton at 9.44 ppm due to the existence of a hydrogen bridge between P=O of phosphonate and NH of the 6-fluorobenzothiazol group in **4m**

which shifts the N-H signal to lower field. All carbon atoms in the compounds have been identified and the total number of protons calculated from the integration curve agrees with the value expected for the molecular formula. The calculated analytical data for **4m** ($C_{26}H_{19}F_2N_2O_3PS$, Mol. Wt: 508.48, : C, 61.42; H, 3.77; N, 5.51) agree with the experimental values (C, 60.98; H, 3.72; N, 5.60).

Antiviral activity

In this study, the antiviral activities of the target compounds **4a**–**4v** against TMV and PVY were evaluated by using the previous methods.[27] The results are summarized in Table 2 and Table 3, respectively. As show in Table S 1 (Supplemental Materials), some compounds exhibited good antiviral *in vivo* activity against TMV at 500 μg/mL. Compounds **4n** and **4t** exhibited potent curative activities against TMV with values of 48.2% and 47.2%, respectively, at 500 μg/mL, which are better than Ribavirin (38.3%) and similar to Dufulin (47.2%). Compounds **4a**, **4d**, **4e** and **4f** exhibited moderated curative activities, with values of 37.2%, 37.9%, 39.3%, 38.3%, respectively. Moreover, compounds **4b**, **4j**, and **4q** exhibited excellent inactivation activities against TMV with values of 81.1%, 84.2%, and 83.6%, respectively, at 500 μg/mL, which are better than Dufulin (78.6%) and superior to Ribavirin (70.2%). The protective activities of compounds **4c**, **4l** and **4o** at 500 μg/mL were 58.3%, 57.9% and 58.2%, respectively, which is slightly better than Dufulin (56.7%) and superior to Ribavirin (50.6%). As show in Table S 2 (Supplemental Materials), most of title compounds exhibited good antiviral

activity against PVY at 500 μg/mL *in vivo*. Compounds **4o**, **4r**, and **4u** displayed remarkable protection activity against PVY, with value of 49.1%, 47.8%, 48.6%, respectively, which were better than that of Dufulin (46.7%). Compounds **4g**, **4p**, and **4q** showed good curative active with values of 43.4%, 41.6%, and 44.9%, which are similar to Dufulin (43.0%).

Experimental

Materials and Instrumentation

NMR spectra were recorded on a JEOL-ECX 500 NMR spectrometer with TMS as internal standard and DSMO-d_6 as solvent at 500 (^{1}H), 125 (^{13}C), 202 (^{31}P), and 471 (^{19}F) MHz. Elemental analyses were performed on an Elementar Vario-III CHN analyzer. IR spectra (KBr pellets, wavelengths in cm^{-1}) were recorded on a Bruker VECTOR 22 spectrometer. The melting points (mp) of the products were determined on an XT-4 binocular microscope (BeiJing Tech Instrument Co., China). The compounds were synthesized by a monomodal microwave (CEM-Discover), equipped with an infrared pyrometer for controlling the temperature, and operating at a maximum power of 300W. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated, and redistilled before use. The Supplemental Materials file contains sample ^{1}H, ^{13}C and ^{31}P NMR of products 4a – 4v (Figures S 1 – S 84).

General Procedure for the preparation of 4a–4v: 2-Aminobenzothiazole (1.0 mmol), aldehyde (1.0 mmol), dialkyl phosphate (1.2 mmol) were successively added to 1.0 mL of NMP placed in a round bottomed flask. The mixture was heated with stirring in a Discovery^{TM} LabMate instrument at 90 °C and a power of 60 W for 40 min. After the completion, the mixture was diluted with water and extracted with ethyl acetate (20 mL × 3). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and the crude product was purified by column chromatography on silica gel (100–200 mesh, petroleum ether-EtOAc, *V* : *V*=1 : 3) to afford the pure *a*-aminophosphonates **4a**–**4v**.

Characterization of 4a-4v

Diethyl [(4-chlorophenyl)(6-fluorobenzo[d]thiazol-2-ylamino)methyl]phosphonate (4a): White solid, mp 166-168 °C, yield, 70.2 %. ^{1}H NMR: δ_H = 9.09 (dd, *J* = 9.6, 3.8 Hz, 1H, NH), 7.63 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.53 (dd, *J* = 8.6, 2.0 Hz, 2H, ArH), 7.46 (d, *J* = 8.5 Hz, 2H, ArH), 7.37 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.06 (td, *J* = 9.1, 2.8 Hz, 1H, ArH), 5.65 (dd, *J* = 21.8, 9.6 Hz, 1H, CH), 4.11-3.82 (m, 4H, 2CH_2), 1.15 (t, *J* = 7.0 Hz, 3H, CH_3), 1.09 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.8 (d, $^3J_{PC}$ = 10.4 Hz), 158.0 (d, $^1J_{FC}$ = 237.1 Hz), 148.7, 135.5, 133.0, 132.5, 132.4(d, $^3J_{FC}$ = 11.6 Hz), 130.4, 130.3, 128.8, 128.8, 113.5 (d, $^2J_{FC}$ = 24.0 Hz), 108.5 (d, $^2J_{FC}$ = 27.2 Hz), 63.4 (d, $^2J_{PC}$ = 6.8 Hz), 63.1 (d, $^2J_{PC}$ = 7.1 Hz), 54.4 (d, $^1J_{PC}$ = 153.5 Hz), 16.8 (d, $^3J_{PC}$ = 5.0 Hz), 16.6 (d, $^3J_{PC}$ = 5.4 Hz). ^{31}P NMR: 20.9. ^{19}F NMR: –121.3. IR: 3225.1(NH),

1227.2(C=N), 1054.2(P-O-C); Anal. calcd for $C_{18}H_{19}N_2FCl\ O_3PS$ (428.84): C, 50.41; H, 4.47; N, 6.53; found: C, 50.46; H, 4.72; N, 6.67.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(phenyl)methyl]phosphonate (4b): White solid, mp 178-180 °C, yield, 78.6 %. ^{1}H NMR: δ_H = 9.04 (dd, *J* = 9.7, 3.4 Hz, 1H, NH), 7.58 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.51-7.45 (m, 2H, ArH), 7.38-7.31 (m, 3H, ArH), 7.27 (t, *J* = 7.3 Hz, 1H, ArH), 7.01 (td, *J* = 9.1, 2.7 Hz, 1H, NH), 5.60 (dd, *J* = 21.6, 9.7 Hz, 1H, CH), 4.05-3.73 (m, 4H, $2CH_2$), 1.11 (t, *J* = 7.0 Hz, 3H, CH_3), 1.02 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.9 (d, $^3J_{PC}$ = 10.1 Hz), 157.9 (d, $^1J_{FC}$ = 237.0 Hz), 148.8, 136.3, 132.5, 132.4(d, $^3J_{FC}$ = 11.6 Hz), 128.8, 128.8,128.6, 128.6, 119.4, 119.3, 113.5 (d, $^2J_{FC}$ = 23.5 Hz), 108.5 (d, $^2J_{FC}$ = 27.2 Hz), 63.2 (d, $^2J_{PC}$ = 6.9 Hz), 63.0 (d, $^2J_{PC}$ = 6.7 Hz), 55.0 (d, $^1J_{PC}$ = 153.5 Hz), 16.8 (d, $^3J_{PC}$ = 5.1 Hz), 16.6 (d, $^3J_{PC}$ = 5.6 Hz). ^{31}P NMR: 21.4. ^{19}F NMR: –121.5. IR: 3234.1(NH), 1214.2(P=O), 1054.2(P-O-C); Anal. calcd for $C_{18}H_{20}FN_2O_3PS$ (394.40): C, 54.82; H, 5.11; N, 7.10; found: C, 54.66; H, 4.90; N, 7.50.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(2-fluorophenyl)methyl]phosphonate (4c): White solid, mp 143-145 °C, yield, 79.2 %. ^{1}H NMR: δ_H = 9.17 (d, *J* = 9.6 Hz, 1H, NH), 7.64 (dd, *J* = 8.7, 2.7 Hz, 2H, ArH), 7.42 (dd, *J* = 8.8, 4.8 Hz, 2H, ArH), 7.27 (dd, *J* = 13.5, 6.0 Hz, 2H, ArH), 7.10-7.03 (m, 1H, ArH), 5.97 (dd, *J* = 21.5, 9.7 Hz, 1H, CH), 4.13-3.79 (m, 4H, $2CH_2$), 1.19 (t, *J* = 7.0 Hz, 3H, CH_3), 1.06 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.8 (d, $^3J_{PC}$ = 9.6 Hz), 160.1 (dd, $^1J_{FC}$ = 245.9, $^3J_{PC}$ = 6.1 Hz), 158.0 (d, $^1J_{FC}$ = 237.3 Hz), 148.6, 132.4 (d,

$^{3}J_{FC}$ = 11.0 Hz), 130.5 (d, $^{2}J_{PC}$ = 6.8 Hz), 129.9, 125.1, 123.8 (d, $^{3}J_{FC}$ = 15.0 Hz), 119.6 (d, $^{3}J_{FC}$ = 8.8 Hz), 115.8 (d, $^{2}J_{FC}$ = 21.9 Hz), 113.6 (d, $^{2}J_{FC}$ = 23.6 Hz), 108.5 (d, $^{2}J_{FC}$ = 27.3 Hz), 63.5 (d, $^{2}J_{PC}$ = 6.9 Hz), 63.2 (d, $^{2}J_{PC}$ = 7.0 Hz), 47.8 (d, $^{1}J_{PC}$ = 158.3 Hz), 16.8 (d, $^{3}J_{PC}$ = 5.0 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.4 Hz). ^{31}P NMR: 20.6. ^{19}F NMR: –116.8, –121.2. IR: 3244.4(-NH), 1228.7(P=O), 1054.2(P-O-C); Anal. calcd for $C_{18}H_{19}F_2N_2O_3PS$ (412.39): C, 52.43; H, 4.64; N, 6.79; found: C, 52.01; H, 4.39; N, 6.85.

Diethyl [(4-methylbenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (4d): White solid, mp 117-119 °C, yield, 72.6 %. ^{1}H NMR: δ_H = 8.95 (d, *J* = 9.3 Hz, 1H, NH), 7.46 (t, *J* = 5.5 Hz, 2H, ArH), 7.23 (s, 1H, ArH), 7.07-6.98 (m, 2H, 2thiophene-H), 6.92 (t, *J* = 7.6 Hz, 1H, ArH), 5.93 (dd, *J* = 21.3, 9.4 Hz, 1H, CH), 4.02 (tdt, *J* = 37.2, 25.7, 8.8 Hz, 4H, $2CH_2Me$), 2.42 (s, 3H, $ArCH_3$), 1.13 (t, *J* = 7.0 Hz, 3H, CH_3), 1.08 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 164.9 (d, $^{3}J_{PC}$ = 9.0 Hz), 150.8, 138.6, 130.9, 128.2, 127.5, 127.4, 126.8, 126.6, 121.9, 119.0, 63.5 (d, $^{2}J_{PC}$ = 6.7 Hz), 63.3 (d, $^{2}J_{PC}$ = 6.6 Hz), 50.4 (d, $^{1}J_{PC}$ = 160.6 Hz), 18.5, 16.8 (d, $^{3}J_{PC}$ = 5.1 Hz), 16.6 (d, $^{3}J_{PC}$ = 5.4 Hz). ^{31}P NMR: 20.1. IR: 3223.2(NH), 1232.6(P=O), 1049.3(P-O-C); Anal. calcd for $C_{17}H_{21}N_2O_3PS_2$ (396.46): C, 51.50; H, 5.34; N, 7.07; found: C, 51.97; H, 5.09; N, 7.29.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (4e): White solid, mp 147-148 °C, yield, 72.9 %. ^{1}H NMR: δ_H = 9.05 (d, *J* = 9.4 Hz, 1H, NH), 7.64 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.50 (d, *J* = 5.1 Hz, 1H, ArH), 7.42 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.24

(s, 1H, ArH), 7.07 (ddd, J = 15.4, 8.8, 3.8 Hz, 2H, 2thiophene-H), 5.90 (dd, J = 21.4, 9.4 Hz, 1H, CH), 4.15 – 3.91 (m, 4H, $2CH_2$), 1.14 (dt, J = 14.0, 7.1 Hz, 6H, $2CH_3$). ^{13}C NMR: δ_C = 165.8 (d, $^3J_{PC}$ = 8.6 Hz), 158.0 (d, $^1J_{FC}$ = 237.2 Hz), 148.6, 138.5, 132.5 (d, $^3J_{FC}$ = 11.0 Hz), 127.5, 127.4 (d, $^2J_{PC}$ = 6.5 Hz), 126.6, 119.5 (d, $^3J_{FC}$ = 8.8 Hz), 113.6 (d, $^2J_{FC}$ = 23.6 Hz), 108.6 (d, $^2J_{FC}$ = 27.2 Hz), 63.6 (d, $^2J_{PC}$ = 6.9 Hz), 63.3 (d, $^2J_{PC}$ = 6.7 Hz), 50.6 (d, $^1J_{PC}$ = 160.6 Hz), 16.8 (d, $^3J_{PC}$ = 5.2 Hz), 16.6 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR: 19.9. ^{19}F NMR: –121.3. IR: 3213.6(-NH), 1231.6(P=O), 1052.2 (P-O-C); Anal. calcd for $C_{18}H_{19}F_2N_2O_3PS$ (400.42): C, 47.99; H, 4.53; N, 7.00; found: C, 47.86; H, 7.25; N, 7.17.

Diethyl [(2-chlorophenyl)(6-fluorobenzo[d]thiazol-2-ylamino)methyl]phosphonate (4f):

White solid, mp 146-148 °C, yield, 75.4 %. ^{1}H NMR: δ_H = 9.10 (dd, J = 9.5, 3.4 Hz, 1H, NH), 7.66 (d, J = 7.7 Hz, 1H, ArH), 7.58 (dd, J = 8.7, 2.6 Hz, 1H ArH), 7.45 (d, J = 7.9 Hz, 1H ArH), 7.41-7.28 (m, 3H, ArH), 6.10 (dd, J = 21.3, 9.5 Hz, 1H, CH), 3.89 (m, J = 32.7, 25.6, 15.7, 8.1 Hz, 4H, $2CH_2$), 1.15 (t, J = 7.0 Hz, 3H, CH_3), 1.00 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.7 (d, $^3J_{PC}$ = 9.3 Hz), 158.0 (d, $^1J_{FC}$ = 237.0 Hz), 148.6, 134.5, 133.6 (d, $^2J_{PC}$ = 7.3 Hz), 132.5 (d,$^3J_{FC}$ = 11.0 Hz), 130.1, 130.1, 129.8, 127.8, 119.6 (d, $^3J_{FC}$ = 8.6 Hz), 113.5 (d, $^2J_{FC}$ = 23.5 Hz), 108.5 (d, $^2J_{FC}$ = 27.3 Hz), 63.5 (d, $^2J_{PC}$ = 6.6 Hz), 63.2 (d, $^2J_{PC}$ = 6.8 Hz), 51.5 (d, $^1J_{PC}$ = 156.6 Hz), 16.8 (d, $^3J_{PC}$ = 4.9 Hz), 16.5 (d, $^3J_{PC}$ = 5.5 Hz). ^{31}P NMR: 20.7. ^{19}F NMR: –121.3. IR: 3245.5(NH), 1236.4(P=O), 1052.2 (P-O-C); Anal. calcd for $C_{18}H_{19}ClFN_2O_3PS$ (428.84): C, 50.41; H, 4.47; N, 6.53; found: C, 49.97; H, 4.28; N, 6.57.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(p-tolyl)methyl]phosphonate (4g): White solid, mp 149-150 °C, yield, 74.7 %. ^{1}H NMR: δ_H = 9.02 (dd, *J* = 9.7, 3.3 Hz, 1H, NH), 7.62 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.43-7.35 (m, 3H, ArH), 7.19 (d, *J* = 8.0 Hz, 2H, ArH), 7.05 (td, *J* = 9.1, 2.7 Hz, 1H, ArH), 5.58 (dd, *J* = 21.4, 9.7 Hz, 1H, CH), 4.08-3.78 (m, 4H, 2CH_2Me), 2.29 (s, 3H, Ar-CH_3), 1.15 (t, *J* = 7.0 Hz, 3H, CH_3), 1.08 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.9 (d, $^{3}J_{PC}$ = 9.9 Hz), 157.9 (d, $^{1}J_{FC}$ = 237.0 Hz), 148.8, 137.5, 133.3, 132.4(d, $^{3}J_{FC}$ = 11.0 Hz), 129.3, 129.3, 128.5, 128.5, 119.3 (d, $^{3}J_{FC}$ = 8.8 Hz), 113.4 (d, $^{2}J_{FC}$ = 23.7 Hz), 108.5 (d, $^{2}J_{FC}$ = 27.2 Hz), 63.2 (d, $^{2}J_{PC}$ = 6.8 Hz), 63.0 (d, $^{2}J_{PC}$ = 6.8 Hz), 54.8 (d, $^{1}J_{PC}$ = 154.0 Hz), 21.2, 16.8 (d, $^{3}J_{PC}$ = 5.0 Hz), 16.6 (d, $^{3}J_{PC}$ = 5.2 Hz). ^{31}P NMR: 21.6. ^{19}F NMR: −121.5. IR: 3213.6(NH), 1227.7(P=O), 1053.2 (P-O-C); Anal. calcd for $C_{19}H_{22}FN_2O_3PS$ (408.11): C, 55.87; H, 5.43; N, 6.86; found: C, 55.85; H, 5.39; N, 6.90.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (4h): White solid, mp 148-150 °C, yield, 73.6 %. ^{1}H NMR: δ_H = 8.96 (d, *J* = 12.8 Hz, 1H, NH), 7.57 (dd, *J* = 8.7, 2.6 Hz, 1H, ArH), 7.39 (d, *J* = 6.9 Hz, 2H, ArH), 7.34 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.01 (t, *J* = 9.0 Hz, 1H, ArH), 6.90 (d, *J* = 8.7 Hz, 2H, ArH), 5.52 (dd, *J* = 21.0, 9.7 Hz, 1H, CH), 4.04-3.74 (m, 4H, 2CH_2), 3.70 (s, 3H, OCH_3), 1.11 (t, *J* = 7.0 Hz, 3H, CH_3), 1.03 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.9 (d, $^{3}J_{PC}$ = 10.0 Hz), 159.4, 157.9 (d, $^{1}J_{FC}$ = 237.0 Hz), 148.8, 132.4(d,$^{3}J_{FC}$ = 11.3 Hz), 129.9, 129.8, 128.1, 119.3 (d, $^{2}J_{FC}$ = 8.6 Hz), 114.2, 114.2, 113.4 (d, $^{2}J_{FC}$ = 23.8 Hz), 108.5 (d, $^{2}J_{FC}$ = 27.3 Hz), 63.1 (d, $^{2}J_{PC}$ = 6.8 Hz), 62.9 (d, $^{2}J_{PC}$ = 6.8 Hz),

55.6, 54.4 (d, $^{1}J_{PC}$ = 155.1 Hz), 16.8 (d, $^{3}J_{PC}$ = 5.1 Hz), 16.6 (d, $^{3}J_{PC}$ = 5.1 Hz). ^{31}P NMR: 21.8. ^{19}F NMR: –121.5. IR: 3221.3 (NH), 1225.8 (P=O), 1054.2 (P-O-C); Anal. calcd for $C_{19}H_{22}FN_2O_4PS$ (424.43): C, 53.77; H, 5.22; N, 6.60; found: C, 53.80; H, 5.25; N, 6.74.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(4-nitrophenyl)methyl]phosphonate (4i): White solid, mp 124-125 °C, yield, 76.9 %. ^{1}H NMR: δ_H = 9.22 (dd, *J* = 9.3, 4.4 Hz, 1H, NH), 8.28 (d, *J* = 8.7 Hz, 2H, ArH), 7.80 (dd, *J* = 8.8, 1.9 Hz, 2H, ArH), 7.64 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.37 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.06 (td, *J* = 9.1, 2.7 Hz, 1H, ArH), 5.83 (dd, *J* = 22.8, 9.3 Hz, 1H, CH), 4.16-3.86 (m, 4H, $2CH_2$), 1.17 (t, *J* = 7.0 Hz, 3H, CH_3), 1.12 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 165.8 (d, $^{3}J_{PC}$ = 10.4 Hz), 158.0 (d, $^{1}J_{FC}$ = 237.4 Hz), 148.6, 147.6 (d, $^{4}J_{FC}$ = 2.3 Hz), 144.4, 132.5 (d, $^{3}J_{FC}$ = 11.1 Hz), 129.7, 129.6, 124.0, 124.0, 119.6 (d, $^{3}J_{FC}$ = 9.0 Hz), 113.6 (d, $^{2}J_{FC}$ = 23.7 Hz), 108.6 (d, $^{2}J_{FC}$ = 27.3 Hz), 63.7 (d, $^{2}J_{PC}$ = 6.7 Hz), 63.4 (d, $^{2}J_{PC}$ = 6.7 Hz), 54.8 (d, $^{1}J_{PC}$ = 151.2 Hz), 16.8 (d, $^{3}J_{PC}$ = 5.1 Hz), 16.6 (d, $^{3}J_{PC}$ = 5.5 Hz). ^{31}P NMR: 20.0. ^{19}F NMR: –121.1. IR: 3215.5(-NH), 1239.3.6(P=O), 1046.4 (P-O-C); Anal. calcd for $C_{18}H_{19}FN_3O_5PS$ (439.40): C, 49.20; H, 4.36; N, 9.56; found: C, 48.96; H, 4.05; N, 9.69.

Diethyl [(6-methoxybenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (4j): White solid, mp 150-152 °C, yield, 76.7 %. ^{1}H NMR: δ_H = 8.83 (dd, *J* = 9.5, 2.5 Hz, 1H, NH), 7.49 (d, *J* = 4.9 Hz, 1H, ArH), 7.34 (dd, *J* = 5.7, 2.8 Hz, 2H, ArH), 7.23 (s, 1H, thiophene-H), 7.03 (dd, *J* = 5.0, 3.6 Hz, 1H, thiophene-H), 6.84 (dd, *J* = 8.8, 2.6 Hz, 1H, ArH), 5.88 (dd, *J* = 21.5, 9.5 Hz, 1H, CH), 4.15-3.92 (m, 4H, $2CH_2$), 3.74 (s, 3H, OCH_3), 1.16 (t, *J* = 6.5 Hz, 3H,

CH_3), 1.13 (t, J = 6.4 Hz, 3H, CH_3). ^{13}C NMR: δ_C = 164.2 (d, $^3J_{PC}$ = 8.7 Hz), 155.2, 146.0, 138.8, 132.5, 127.5, 127.3 (d, $^2J_{PC}$ = 6.7 Hz), 126.5, 119.4, 113.6, 106.1, 63.5 (d, $^2J_{PC}$ = 6.8 Hz), 63.2 (d, $^2J_{PC}$ = 6.9 Hz), 56.1, 50.6 (d, $^1J_{PC}$ = 160.6 Hz), 16.8 (d, $^3J_{PC}$ = 5.1 Hz), 16.6 (d, $^3J_{PC}$ = 5.5 Hz). ^{31}P NMR: 20.0. IR: 3219.3(-NH), 1229.7(P=O), 1066.1 (P-O-C); Anal. calcd for $C_{17}H_{21}N_2O_4PS_2$ (412.46): C, 49.50; H, 5.13; N, 6.79; found: C, 49.57; H, 4.74; N, 6.88.

Diethyl [(5-bromothiophen-2-yl)(6-fluorobenzo[d]thiazol-2-ylamino)methyl]phosphonate (4k): White solid, mp 128-130 °C, yield, 78.3 %. ^{1}H NMR: δ_H = 9.09 (dd, J = 9.3, 3.2 Hz, 1H, NH), 7.70-7.61 (m, 2H, ArH, NH), 7.43 (dd, J = 8.8, 4.8 Hz, 1H, ArH), 7.22-7.19 (m, 1H, thiophene-H), 7.09 (td, J = 9.1, 2.8 Hz, 1H, thiophene-H), 5.85 (dd, J = 21.6, 9.3Hz, 1H, CH), 4.07 (qdd, J = 19.0, 13.8, 8.7 Hz, 4H, $2CH_2$), 1.19-1.17 (m, 3H, CH_3), 1.17-1.15 (m, 3H, CH_3). ^{13}C NMR: δ_C = 165.7 (d, $^3J_{PC}$ = 9.2 Hz), 158.1 (d, $^1J_{FC}$ = 237.4 Hz), 148.5, 141.0, 132.6 (d, $^3J_{FC}$ = 11.2 Hz), 129.3 (d, $^2J_{PC}$ = 6.7 Hz), 124.3, 119.66 (d, $^3J_{FC}$ = 8.7 Hz), 113.6 (d, $^2J_{FC}$ = 23.8 Hz), 108.7, 108.6 (d, $^2J_{FC}$ = 27.1 Hz), 108.6, 63.8 (d, $^2J_{PC}$ = 6.9 Hz), 63.5 (d, $^2J_{PC}$ = 6.6 Hz), 50.6 (d, $^1J_{PC}$ = 159.7 Hz), 16.8 (d, $^3J_{PC}$ = 5.2 Hz), 16.6 (d, $^3J_{PC}$ = 5.1 Hz). ^{31}P NMR: 19.2. ^{19}F NMR: –121.0. IR: 3211.6(-NH), 1223.9(P=O), 1050.2 (P-O-C); Anal. calcd for $C_{16}H_{17}BrFN_2O_3PS_2$ (479.32): C, 40.09; H, 3.58; N, 5.84; found: C, 40.13; H, 3.51; N, 5.86.

Diethyl [(6-fluorobenzo[d]thiazol-2-ylamino)(thiophen-3-yl)methyl]phosphonate (4l): White solid, mp 147-150 °C, yield, 78.1 %. ^{1}H NMR: δ_H = 8.91 (dd, J = 9.6, 1.5 Hz, 1H, NH), 7.55 (ddd, J = 12.6, 8.3, 2.8 Hz, 3H, ArH), 7.36 (dd, J = 8.8, 4.8 Hz, 1H, ArH), 7.21 (d, J = 4.9 Hz,

1H, ArH), 7.03 (td, *J* = 9.1, 2.7 Hz, 1H, ArH), 5.74 (dd, *J* = 20.4, 9.7 Hz, 1H, CH), 4.05-3.80 (m, 4H, $2CH_2$), 1.08 (dt, *J* = 17.9, 7.0 Hz, 6H, $2CH_3$). ^{13}C NMR: δ_C = 165.8 (d, $^3J_{PC}$ = 8.2 Hz), 157.9 (d, $^1J_{FC}$ = 236.7 Hz), 148.8, 136.5, 132.4 (d, $^3J_{FC}$ = 11.0 Hz), 128.1 (d, $^3J_{PC}$ = 3.1 Hz), 126.9, 124.1 (d, $^2J_{PC}$ = 8.8 Hz), 119.4 (d, $^3J_{FC}$ = 8.7 Hz), 113.5 (d, $^2J_{PC}$ = 23.8 Hz), 108.5 (d, $^2J_{FC}$ = 27.2 Hz), 63.2 (d, $^2J_{PC}$ = 6.7 Hz), 63.0 (d, $^2J_{PC}$ = 6.5 Hz), 51.2 (d, $^1J_{PC}$ = 157.4 Hz), 16.8 (d, $^3J_{PC}$ = 5.2 Hz), 16.6 (d, $^3J_{PC}$ = 5.5 Hz). ^{31}P NMR: 20.9. ^{19}F NMR: –121.5. IR: 3215.5(NH), 1250.9(P=O), 1049.3 (P-O-C); Anal. calcd for $C_{16}H_{18}FN_2O_3PS_2$ (400.42): C, 47.99; H, 4.53; N, 7.00; found: C, 48.04; H, 4.42; N, 7.19.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(2-fluorophenyl)methyl]phosphonate (4m): White solid, mp 114-115 °C, yield, 71.5 %. ^{1}H NMR: δ_H = 9.44 (d, *J* = 8.7 Hz, 1H, NH), 7.74 (s, 1H, ArH), 7.62 (d, *J* = 10.7 Hz, 1H, ArH), 7.46-7.38 (m, 2H, ArH), 7.28 (dd, *J* = 15.1, 7.9 Hz, 6H, ArH), 7.16 (d, *J* = 5.6 Hz, 2H, ArH), 7.05 (t, *J* = 11.3 Hz, 3H, ArH), 6.90 (d, *J* = 7.9 Hz, 2H, ArH), 6.41 (dd, *J* = 22.0, 9.7 Hz, 1H, CH). ^{13}C NMR: δ_C = 165.7 (d, $^3J_{PC}$ = 9.7 Hz), 161.1, 158.2 (d, $^1J_{FC}$ = 237.6 Hz), 150.4 (d, $^2J_{PC}$ = 9.8 Hz), 150.2 (d, $^2J_{PC}$ = 10.0 Hz), 148.4, 132.5 (d, $^3J_{FC}$ = 11.1 Hz), 131.3, 130.5, 130.4, 130.2, 126.1, 126.1, 125.5, 122.4, 122.5, 120.8, 120.8, 120.6, 120.6, 119.9 (d, $^3J_{FC}$ = 8.9 Hz), 116.1 (d, $^2J_{FC}$ = 20.7 Hz), 113.7 (d, $^2J_{FC}$ = 23.9 Hz), 108.6 (d, $^2J_{FC}$ = 27.5 Hz), 48.4 (d, $^1J_{PC}$ = 163.5 Hz). ^{31}P NMR: 13.8. ^{19}F NMR: –116.1, –120.9. IR: 3264.7(NH), 1207.5(P=O), 953.8 (P-OPh); Anal. calcd for $C_{26}H_{19}F_2N_2O_3PS$ (508.48): C, 61.42; H, 3.77; N, 5.51; found: C, 60.98; H, 3.72; N, 5.60.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (4n): White solid, mp 138-139 °C, yield, 78.9 %. ^{1}H NMR: δ_H = 9.37 (d, *J* = 9.5 Hz, 1H, NH), 7.63 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.55 (d, *J* = 5.0 Hz, 1H, ArH), 7.43 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.36 (s, 1H, thiophene-H), 7.34-7.27 (m, 4H, ArH), 7.16 (dd, *J* = 15.9, 7.7 Hz, 2H), 7.05 (ddd, *J* = 27.5, 13.9, 7.9 Hz, 6H, thiophene-H), 6.37 (dd, *J* = 21.9, 9.5 Hz, 1H, CH). ^{13}C NMR: δ_C = 165.6 (d, $^{3}J_{PC}$ = 8.8 Hz), 158.1 (d, $^{1}J_{FC}$ = 237.5 Hz), 150.4 (d, $^{2}J_{PC}$ = 9.7 Hz), 150.2 (d, $^{2}J_{PC}$ = 9.6 Hz), 148.4, 136.8, 132.6 (d, $^{3}J_{FC}$ = 11.0 Hz), 130.5, 130.5, 130.4, 130.4, 128.5, 128.4, 127.8, 127.5, 126.0 (d, $^{2}J_{PC}$ = 7.4 Hz), 120.9, 120.9, 120.9,120.9, 119.8 (d, $^{3}J_{FC}$ = 8.7 Hz), 113.7 (d, $^{2}J_{FC}$ = 23.8 Hz), 108.7 (d, $^{2}J_{FC}$ = 27.3 Hz), 51.0 (d, $^{1}J_{PC}$ = 165.4 Hz). ^{31}P NMR: 13.2. ^{19}F NMR: −120.9. IR: 3240.6 (NH), 1202.7 (P=O), 948.0 (P-OPh); Anal. calcd for $C_{24}H_{18}FN_2O_3PS_2$ (496.51): C, 58.06; H, 3.65; N, 5.64; found: C, 58.10; H, 3.58; N, 5.90.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(phenyl)methyl]phosphonate (4o): White solid, mp 123-124 °C, yield, 76.2 %. ^{1}H NMR: δ_H = 9.44 (dd, *J* = 9.8, 2.7 Hz, 1H, NH), 7.71-7.64 (m, 3H, ArH), 7.48-7.41 (m, 3H, ArH), 7.38 (dd, *J* = 8.9, 7.1 Hz, 1H, ArH), 7.35-7.29 (m, 4H, ArH), 7.18 (t, *J* = 7.4 Hz, 2H, ArH), 7.09 (td, *J* = 9.1, 2.7 Hz, 1H, ArH), 7.03 (d, *J* = 8.6 Hz, 2H, ArH), 6.95 (d, *J* = 8.7 Hz, 2H, ArH), 6.16 (dd, *J* = 22.1, 9.8 Hz, 1H, CH). ^{13}C NMR : δ_C = 165.8 (d, $^{3}J_{PC}$ = 8.1 Hz), 158.1 (d, $^{1}J_{FC}$ = 237.2 Hz), 150.5 (d, $^{2}J_{PC}$ = 10.1 Hz), 150.3 (d, $^{2}J_{PC}$ = 9.8 Hz), 148.6 (d, $^{4}J_{FC}$ = 1.3 Hz), 134.9, 132.5 (d, $^{3}J_{FC}$ = 11.2 Hz), 130.4, 130.4, 130.3, 130.3, 129.1, 129.1, 129.0, 128.9, 125.9, 125.9, 120.9, 120.9, 120.8, 120.8, 119.7 (d, $^{3}J_{FC}$ = 8.7 Hz),

113.6 (d, $^{2}J_{FC}$ = 23.7 Hz), 108.6 (d, $^{2}J_{FC}$ = 27.3 Hz), 55.4 (d, $^{1}J_{PC}$ = 157.2 Hz). ^{31}P NMR: 14.9. ^{19}F NMR: –121.1. IR: 3269.5 (-NH), 1194.0 (P=O), 948.0 (P-OPh); Anal. calcd for $C_{26}H_{20}FN_2O_3PS$ (490.49): C, 63.67; H, 4.11; N, 5.71; found: C, 63.57; H, 3.90; N, 5.97.

Diphenyl [(2-chlorophenyl)(6-fluorobenzo[d]thiazol-2-ylamino)methyl]phosphonate (4p): White solid, mp 109-112 °C, yield, 72.4 %. ^{1}H NMR: δ_H = 9.47 (d, *J* = 9.6 Hz, 1H, NH), 7.81 (d, *J* = 7.6 Hz, 1H, ArH), 7.63 (d, *J* = 8.7 Hz, 1H, ArH), 7.51 (d, *J* = 8.0 Hz, 1H, ArH), 7.41 (ddd, *J* = 30.3, 15.8, 7.4 Hz, 3H, ArH), 7.29 (dt, *J* = 12.1, 8.0 Hz, 4H, ArH), 7.15 (dd, *J* = 16.6, 7.8 Hz, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 3H, ArH), 6.87 (d, *J* = 8.0 Hz, 2H, ArH), 6.63 (dd, *J* = 22.0, 9.6 Hz, 1H, CH). ^{13}C NMR: δ_C = 165.6 (d, $^{3}J_{PC}$ = 9.6 Hz), 158.1 (d, $^{1}J_{FC}$ = 237.6 Hz), 150.4 (d, $^{2}J_{PC}$ = 9.8 Hz), 150.2 (d, $^{2}J_{PC}$ = 9.5 Hz), 148.4, 133.7, 133.2, 132.6 (d, $^{3}J_{FC}$ = 11.2 Hz), 130.8, 130.5, 130.5, 130.4, 130.4, 130.4, 130.1, 128.3, 126.1, 126.0, 120.9, 120.9, 120.5, 120.5, 119.9 (d, $^{3}J_{FC}$ = 8.8 Hz), 113.7 (d, $^{2}J_{FC}$ = 23.6 Hz), 108.7 (d, $^{2}J_{FC}$ = 27.4 Hz), 51.9 (d, $^{1}J_{PC}$ = 160.8 Hz). ^{31}P NMR: 13.9. ^{19}F NMR: –120.8. IR: 3253.1 (-NH), 1205.6 (P=O), 948.0 (P-OPh); Anal. calcd for $C_{26}H_{19}ClFN_2O_3PS$ (524.93): C, 59.49; H, 3.65; N, 5.34; found: C, 59.50; H, 3.63; N, 5.70.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (4q): White solid, mp 133-134 °C, yield, 76.2 %. ^{1}H NMR: δ_H = 9.35 (dd, *J* = 9.8, 2.3 Hz, 1H, NH), 7.65 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.59 (dd, *J* = 8.7, 1.9 Hz, 2H, ArH), 7.44 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.36-7.28 (m, 4H, ArH), 7.18 (dd, *J* = 8.2, 6.6 Hz, 2H, ArH), 7.09 (td, *J* = 9.1, 2.7 Hz, 1H, ArH), 7.05-6.95 (m, 6H, ArH), 6.06 (dd, *J* = 21.5, 9.8 Hz, 1H, CH), 3.76 (s, 3H, OCH_3).

^{13}C NMR: δ_C = 165.8 (d, $^3J_{PC}$ = 9.7 Hz), 159.8, 158.0 (d, $^1J_{FC}$ = 237.4 Hz), 150.6 (d, $^2J_{PC}$ = 9.9 Hz), 150.4 (d, $^2J_{PC}$ = 9.8 Hz), 148.6, 132.5 (d, $^3J_{FC}$ = 11.4 Hz), 130.4, 130.4, 130.3, 130.3, 130.3, 130.2, 126.7, 125.9, 125.9, 120.9, 120.9, 120.9, 120.8, 119.6 (d, $^3J_{FC}$ = 8.9 Hz), 114.6, 114.6, 113.6 (d, $^2J_{FC}$ = 23.7 Hz), 108.6 (d, $^2J_{FC}$ = 27.4 Hz), 55.7, 54.8 (d, $^1J_{PC}$ = 158.6 Hz). ^{31}P NMR: 15.2. ^{19}F NMR: –121.1. IR: 3252.1 (-NH), 1218.1 (P=O), 953.8 (P-OPh); Anal. calcd for $C_{27}H_{22}FN_2O_4PS$ (520.52): C, 62.30; H, 4.26; N, 5.38; found: C, 61.95; H, 4.02; N, 5.55.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(o-tolyl)methyl]phosphonate (4r): White solid, mp 137-138 °C, yield, 79.5 %. ^{1}H NMR: δ_H = 9.45 (dd, *J* = 9.6, 2.9 Hz, 1H, NH), 7.72 (d, *J* = 7.6 Hz, 1H, ArH), 7.65 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.44 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.37-7.25 (m, 7H, ArH), 7.22-7.15 (m, 2H, ArH), 7.1-7.06 (m, 3H, ArH), 6.87 (d, *J* = 8.6 Hz, 2H, ArH), 6.30 (dd, *J* = 22.1, 9.6 Hz, 1H, CH), 2.55 (s, 3H, CH_3). ^{13}C NMR: δ_C = 165.9 (d, $^3J_{PC}$ = 11.1 Hz), 158.1 (d, $^1J_{FC}$ = 237.4 Hz), 150.5 (d, $^2J_{PC}$ = 9.8 Hz), 150.2 (d, $^2J_{PC}$ = 9.6 Hz), 148.5, 137.1 (d, $^3J_{PC}$ = 8.1 Hz), 133.9, 132.5 (d, $^3J_{FC}$ = 11.3 Hz), 130.9, 130.4, 130.4, 130.4, 130.4, 128.9, 128.7, 126.9, 126.0, 121.0 (d, $^3J_{PC}$ = 3.5 Hz), 121.0, 120.9, 120.7, 120.7, 119.7 (d, $^2J_{PC}$ = 9.0 Hz), 113.6 (d, $^2J_{FC}$ = 23.8 Hz), 108.6 (d, $^2J_{FC}$ = 27.2 Hz), 51.4 (d, $^1J_{PC}$ = 158.8 Hz), 20.0. ^{31}P NMR: 15.6. ^{19}F NMR: –121.1. IR: 3246.3 (-NH), 1200.7 (P=O), 941.3 (P-OPh); Anal. calcd for $C_{27}H_{22}FN_2O_3PS$ (504.52): C, 64.28; H, 4.40; N, 5.55; found: C, 64.43; H, 4.07; N, 5.65.

Diphenyl [(6-methoxybenzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl]phosphonate (4s) [23]: White solid, mp 118–120 °C, yield, 74.7 %. ^{1}H NMR: δ_H = 9.20 (d, *J* = 17.6 Hz, 1H, NH),

7.58 (d, *J* = 5.1 Hz, 1H, ArH), 7.42-7.30 (m, 7H, ArH), 7.20 (dd, *J* = 15.8, 7.6 Hz, 2H, ArH), 7.11-7.03 (m, 5H, ArH), 6.87 (dd, *J* = 8.8, 2.6 Hz, 1H, thiophene-H), 6.39 (dd, *J* = 22.0, 9.5 Hz, 1H, CH), 3.75 (s, 3H, OCH_3). ^{13}C NMR: δ_C = 164.1 (d, $^3J_{PC}$ = 9.3 Hz), 155.4, 150.5 (d, $^2J_{PC}$ = 9.7 Hz), 150.3 (d, $^2J_{PC}$ = 9.8 Hz), 145.8, 137.1, 132.6, 130.5, 130.5, 130.4, 130.4, 128.4, 128.3, 127.8, 127.4, 126.0, 126.0, 125.9, 120.9, 120.9, 119.6, 113.8, 106.2, 56.1, 51.0 (d, $^1J_{PC}$ = 165.6 Hz). ^{31}P NMR: 13.5. IR: 3247.3 (NH), 1211.4 (P=O), 949.0 (P-OPh)); Anal. calcd for $C_{25}H_{21}N_2O_4PS_2$ (508.55): C, 59.05; H, 4.16; N, 5.51; found: C, 58.78; H, 3.81; N, 5.67.

Diphenyl [(2-fluorophenyl)(6-methoxybenzo[d]thiazol-2-ylamino)methyl]phosphonate (4t): White solid, mp 116-118 °C, yield, 70.1 %.^1H NMR: δ_H = 9.30 (dd, *J* = 9.8, 2.3 Hz, 1H, NH), 7.80 (t, *J* = 7.6 Hz, 1H, ArH), 7.45 (dd, *J* = 12.7, 6.7 Hz, 1H, ArH), 7.40 (d, *J* = 8.9 Hz, 1H, ArH), 7.38-7.36 (m, 1H, ArH), 7.34 (d, *J* = 8.0 Hz, 4H, ArH), 7.33-7.27 (m, 2H, ArH), 7.20 (dd, *J* = 13.2, 7.2 Hz, 2H, ArH), 7.08 (d, *J* = 8.4 Hz, 2H, ArH), 6.96 (d, *J* = 8.3 Hz, 2H, ArH), 6.87 (dd, *J* = 8.8, 2.6 Hz, 1H, CH), 3.75 (s, 3H, OCH_3). ^{13}C NMR: δ_C = 164.1 (d, $^2J_{PC}$ = 9.7 Hz), 160.1 (dd, $^1J_{FC}$ = 246.5, $^3J_{PC}$ = 6.5 Hz), 155.41, 150.44 (d, $^2J_{PC}$ = 9.7 Hz), 150.2 (d, $^2J_{PC}$ = 9.7 Hz), 145.8, 132.5, 131.2 (d, $^3J_{FC}$ = 8.2 Hz), 130.5, 130.5, 130.4, 130.4, 130.2, 126.0, 126.0, 125.4, 122.7, 122.6, 120.9, 120.9, 120.7, 120.6, 116.1 (d, $^2J_{FC}$ = 22.1 Hz), 113.8, 106.2, 56.1, 48.3 (d, $^1J_{PC}$ = 163.8 Hz). ^{31}P NMR: 14.1. IR: 3259.8 (NH), 1206.5 (P=O), 948.1 (P-OPh); Anal. calcd for $C_{27}H_{22}FN_2O_4PS$ (520.52): C, 62.30; H, 4.26; N, 5.38; found: C, 62.11; H, 3.98; N, 5.44.

Diphenyl [(5-bromothiophen-2-yl)(6-fluorobenzo[d]thiazol-2-ylamino)methyl]phosphon ate (4u): White solid, mp 123-124 °C, yield, 74.7 %. ^{1}H NMR: δ_H = 9.46 (dd, *J* = 9.5, 2.5 Hz, 1H, NH), 7.75-7.67 (m, 2H, ArH), 7.49 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.42-7.32 (m, 5H, ArH), 7.22 (dt, *J* = 11.2, 7.4 Hz, 2H, ArH), 7.17-7.06 (m, 5H, ArH, thiophene-H), 6.47 (dd, *J* = 22.2, 9.4 Hz, 1H, CH). ^{13}C NMR: δ_C = 165.6 (d, $^{2}J_{PC}$ = 9.3 Hz), 158.2 (d, $^{1}J_{FC}$ = 237.7 Hz), 150.4 (d, $^{2}J_{PC}$ = 9.7 Hz), 150.2 (d, $^{2}J_{PC}$ = 9.7 Hz), 148.4, 139.3, 132.7 (d, $^{3}J_{FC}$ = 11.3 Hz), 130.5, 130.5, 130.4, 130.4, 130.3, 126.2, 126.1, 125.2, 120.9, 120.9, 120.8, 120.8, 119.9 (d, $^{3}J_{FC}$ = 8.7 Hz), 113.8 (d, $^{2}J_{FC}$ = 23.7 Hz), 108.9, 108.75 (d, $^{2}J_{FC}$ = 27.4 Hz), 51.0 (d, $^{1}J_{PC}$ = 164.7 Hz). ^{31}P NMR: 12.5. ^{19}F : –120.6. IR: 3238.6 (NH), 1204.6 (P=O), 949.0 (P-OPh); Anal. calcd for $C_{24}H_{17}BrFN_2O_3PS_2$ (575.41): C, 50.10; H, 2.98; N, 4.87; found: C, 50.20; H, 3.01; N, 5.22.

Diphenyl [(6-fluorobenzo[d]thiazol-2-ylamino)(thiophen-3-yl)methyl]phosphonate (4v): White solid, mp 138-140 °C, yield, 75.8 %. ^{1}H NMR: δ_H = 9.34 (d, *J* = 9.7 Hz, 1H, NH), 7.79 (s, 1H, ArH, ArH), 7.68 (dd, *J* = 8.7, 2.7 Hz, 1H, ArH), 7.63 (dd, *J* = 5.0, 3.0 Hz, 1H, ArH), 7.47 (dd, *J* = 8.8, 4.8 Hz, 1H, ArH), 7.40 (d, *J* = 5.0 Hz, 1H, ArH), 7.37-7.30 (m, 4H, ArH), 7.19 (q, *J* = 7.2 Hz, 2H, ArH), 7.11 (td, *J* = 9.1, 2.7 Hz, 1H, thiophene-H), 7.06-6.98 (m, 4H, ArH, thiophene-H), 6.32 (dd, *J* = 20.7, 9.8 Hz, 1H, CH). ^{13}C NMR: δ_C = 165.7 (d, $^{2}J_{PC}$ = 8.0 Hz), 158.1 (d, $^{1}J_{FC}$ = 237.3 Hz), 150.5 (d, $^{2}J_{PC}$ = 10.1 Hz), 150.4 (d, $^{2}J_{PC}$ = 9.8 Hz), 148.6, 134.9, 132.4 (d, $^{3}J_{FC}$ = 11.3 Hz), 130.4, 130.4, 130.3, 130.3, 128.2, 127.5, 125.9, 125.4, 125.3, 120.9, 120.9, 120.9, 120.9, 119.6 (d, $^{3}J_{FC}$ = 8.9 Hz), 113.7 (d, $^{2}J_{FC}$ = 23.6 Hz), 108.7 (d, $^{2}J_{FC}$ = 27.3 Hz),

51.7 (d, $^{1}J_{PC}$ = 161.1 Hz). ^{31}P NMR: 14.4. ^{19}F NMR: –121.0. IR: 3250.2 (-NH), 1209.4 (P=O), 943.2 (P-OPh); Anal. calcd for $C_{24}H_{18}FN_2O_3PS_2$ (496.51): C, 58.06; H, 3.65; N, 5.64; found: C, 57.98; H, 3.48; N, 5.60.

Conclusion

A series of *a*-aminophosphonates were synthesized through multicomponent reaction of 2-aminobenzothiazole, diphenyl phosphate (or dialkyl phosphate) and aldehydes. In general the method is very green, cheap and convenient. The structures of compounds were verified by IR, NMR and elemental analyses and their antiviral activities against TMV and PVY were evaluated. The results showed that **4b**, **4j** and **4q** exhibit higher antiviral activities against TMV and PVY *in vivo* than Ribavirin, and are similar to Dufulin. As far as we know, this was the first indication that this kind of compounds may possess potential anti-PVY activity. Further studies on the structural optimization, design, and development of new antiviral agents are underway.

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Research highlights:

- *a*-aminophosphonates with 6-fluorobenzothiazole unit were synthesized.
- The analogs display good activities against tobacco mosaic virus.
- Compound **4q** showed similar curative and protective activity against potato virus Y (PVY) to Dufulin.

Table 1: Optimization reaction conditions for the synthesis of *a*-aminophosphonates

Entry	solvent	temperature（°C）	Time（min）	Yield(%)
1	acetonitrile	80	20	nr
2	DMF	80	20	4.3
3	DMSO	80	20	nr
4	Pyridine	80	20	4.8
5	ethyl alcohol	80	20	nr
6	toluene	80	20	9.4
7	toluene	90	20	12.8
8	toluene	100	20	20.3
9	NMP	100	20	25.6
10	NMP	120	20	33.1
11	NMP	130	20	37.9
12	NMP	140	20	42.7
13	NMP	150	20	46.8
14	NMP	160	20	47.0
15	NMP	150	30	51.6
16	NMP	150	40	66.5
17	NMP	150	60	67.9

Reaction condition: aldehydes (1.0 mmol), amine (1.0 mmol) and phosphate (1.2 mmol) in organic solvent (1.0 mL) under microwave irradiation at 60 W power.

Table 2: Antiviral activities of the test compounds against tobacco mosaic virus (TMV) *in vivo* at 500 μg/mL

Table 3: Antiviral activities of the test compounds against potato virus Y (PVY) *in vivo* at 500 μg/mL

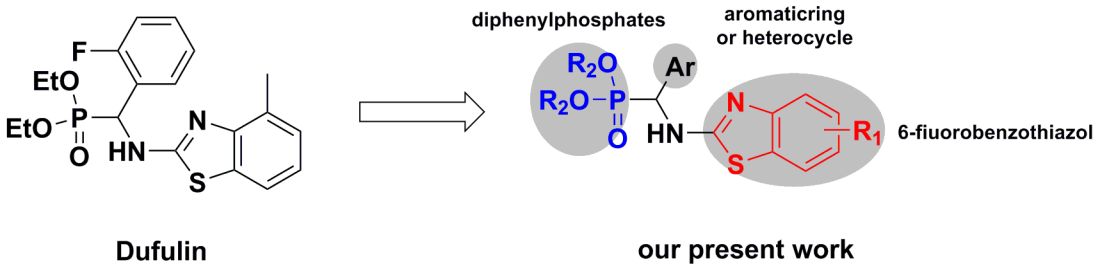

Figure 1: Design of the title compounds **4a**–**4v**

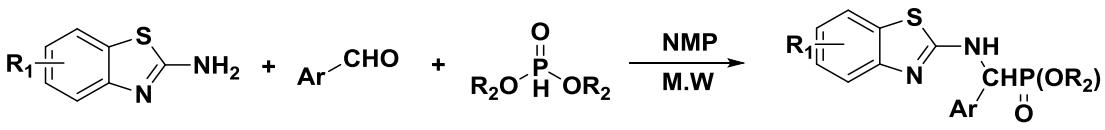

Figure 2: Synthetic route of compounds **4a**–**4v**