Synthesis and Antiviral Activity of Novel Pyrazole Amides Containing α-Aminophosphonate Moiety

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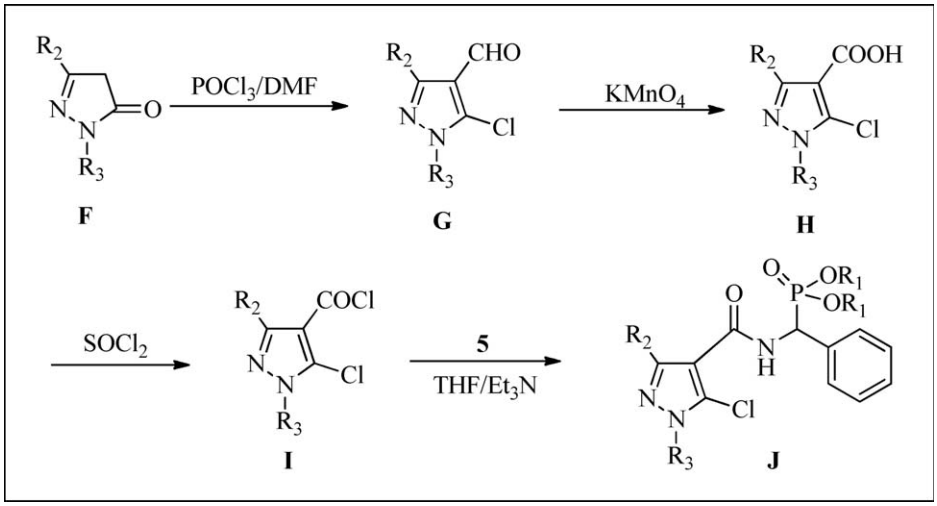

A series of novel pyrazole amides **J1–J15** containing an α-aminophosphonate moiety were synthesized and subsequently characterized by spectral (IR, ^{1}H-, ^{13}C-, ^{31}P-, and ^{19}F-NMR) data and elemental analysis. The racemic sample of **J1** was further separated into its enantiomers under normal-phase condition on two immobilized polysaccharide-based chiral stationary phases (Chiralpak IA and Chiralpak IC). The synthesized compounds revealed certain degree of antiviral activity in the bioassay. The title compounds (**J3**, **J10**, and **J12**) showed some curative activities (39.9%, 41.8%, 50.1%, respectively) against tobacco mosaic virus at 0.5 mg/mL.

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INTRODUCTION

Pyrazole amide derivatives occupy an important position in medicinal and pesticide chemistry due to their diverse bioactivities. Not only they display prominent antagonist, anti-inflammatory, and inhibitory activities as drugs [1–3] but are also used as potent insecticides, fungicides, and herbicides in pesticide science [4–6]. Considerable attention has been paid in recent years to the synthesis of these compounds [7]. Amongst the active compounds, as shown in Figure 1, Furametpyr (Sumitomo Chemical Co., 1997) and Penthiopyrad (Mitsubishi Chemical Co., 2005) are known for their ability to protect certain plants from severe antifungal infection. Another important class of compounds that belongs to α-aminophosphonic acid group has enormous application as growth regulators, fungicides, plant virucides, and herbicides [8–10]. A great deal of research has been directed for the development of suitable synthetic techniques to access biologically active α-aminophosphonates and their derivatives [11–15]. In our continued endeavor to develop environment-friendly antiviral agents, we had earlier prepared a large number of substituted aryl aminophosphonate derivatives containing amide, thiourea, and cyanoacrylate moieties [16–24]. As different aminophosphonates and their derivatives display varying activities, we envisioned that screening of properly substituted pyrazole amide derivatives bearing various α-amiophosphonate moieties might lead to lead structures having superior antiviral activities against tobacco mosaic virus (TMV) (Fig. 2). Keeping these considerations in mind, herein we report preparation of new pyrazole amide derivatives bearing α-aminophosphonate moieties (Scheme 1) and their subsequent evaluation as antiviral agents. To the best of our knowledge, this is the first report on the synthesis and antiviral studies of compounds where aminophosphontes are incorporated into parent pyrazole amide unit.

RESULTS AND DISCUSSION

The title compounds **J** can be synthesized by the reaction of the appropriate amine with carboxylic acid

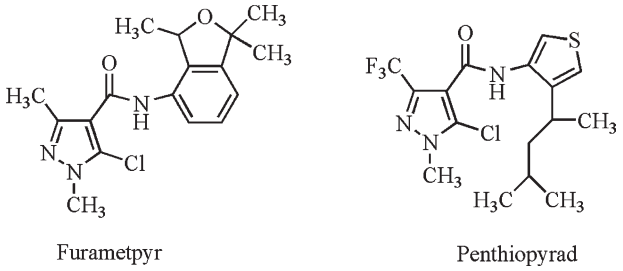


Figure 1. The structures of commercial fungicides.

or by treating the amine with acyl chloride. In the first approach, a controlled addition of 1,3-dicyclohexylcarbodiimide into the mixture of amine and acid is necessary as the reaction is exothermic and tends to get violent. By carefully controlling the reaction temperature at 0°C, the desired product could be prepared but in much lower yield. Using the second method, however, the title compounds **J** could be obtained in 45–80% yield from a reaction of acyl chloride and amine in presence of triethylamine. The base was required as the resulting phosphonates are susceptible to acidolysis by liberated HCl. This later approach was preferred over the former due to the ease of preparation, higher yield and reactivity, and shorter reaction time. The entire synthetic route to access the target compound is shown in Scheme 1. The key intermediate **5** was first synthesized from appropriate dialkyl phosphite and benzaldehyde. The imine **3** was generated in two steps. Addition of *p*-toluenesulfonic acid into **3** 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-aminobenzylphosphonate **5**. The 5-pyrazolones **F** were subjected to Vilsmeier–Haack chloroformylation using *N*,*N*-dimethylformamide (DMF) and an excess of phosphorus oxychloride ($POCl_3$) to yield the corresponding 5-chloro-4-formylpyrazoles **G**, which were further oxidized by potassium permanganate and then chlorinated with thionyl chloride ($SOCl_2$) to provide the intermediate **I**.

To optimize the reaction conditions for the preparation of compound $\mathbf{J_1}$ bearing an asymmetric carbon atom adjacent to the phosphonate moiety, the reaction was carried out in different solvents, such as tetrahydrofuran (THF), dichloromethane (DCM), chloroform, DMF, and acetonitrile. A maximum yield of 70% was achieved when the reaction mixture was stirred in the presence of triethylamine for 0.5 h in THF. The effect of solvent system is summarized in Table 1.

Having established the most suitable condition for the preparation of $\mathbf{J_1}$, we carried out semipreparative enantioseparation of this racemate. This was done to confirm if the individual enantiomers differed in their antiviral bioactivity. The sample was dissolved in a mobile phase consisting of *n*-hexane/isopropyl alcohol (IPA)/DCM (80/15/5, v/v/v) and *n*-hexane/IPA/DCM (80/15/5, v/v/v) at 6.5 mg/mL with an injection volume of 2 mL, flow rate 3.0 mL/min, and detection wavelength 230 nm. The two fractions collected in the order of their elution were assigned as F1 and F2, respectively. After semipreparative separation, the first-eluting enantiomer (F1) and the second-eluting enantiomer (F2) were analyzed by analytical IA column to ascertain their enantiomeric excess (e.e.) values. The analytical samples were dissolved in EtOH at an approximate concentration of 0.5 mg/mL and injection volume of 5 μL. The mobile phase was composed of *n*-hexane/EtOH (90/10, v/v), flow rate was set at 1.0 mL/min and detection wavelength was fixed at 230 nm. Temperature was always kept at 25°C except for those experiments where effect of temperature was studied. The holdup time was determined from the elution of an unretained marker (toluene). The analytical assessment of enantiomeric excess values showed that the collected fractions were practically enantiopure with e.e. exceeding 99% (Fig. 3). Optical rotation values were measured on a WZZ-ZS automatic polarimeter and the data are presented in Table 2.

The main characteristic of the ^{1}H-NMR spectra of $\mathbf{J_1}$–$\mathbf{J_{15}}$ is the appearance of chemical shift in the region 5.38–5.80 ppm as a doublet of a doublet due to the presence of **CH** proton adjacent to phosphorus center and NH group. The typical carbon resonance at 158.3–161.1 ppm in the ^{13}C-NMR spectra was indicative of a carbonyl group, whereas the IR stretching frequencies at 3225–3290 and 1636–1667 cm^{-1} confirmed an amide linkage. The phosphorus resonance at δ_P 20.5–23.1 ppm

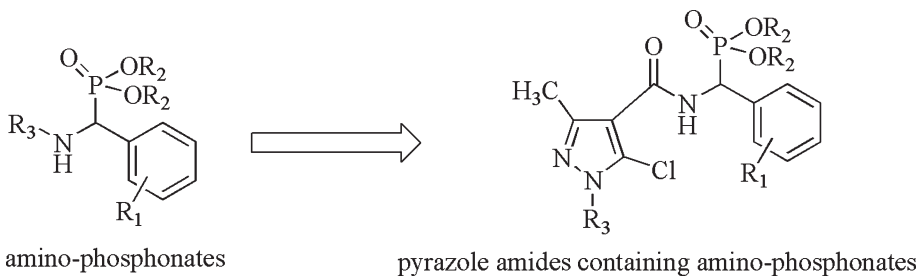
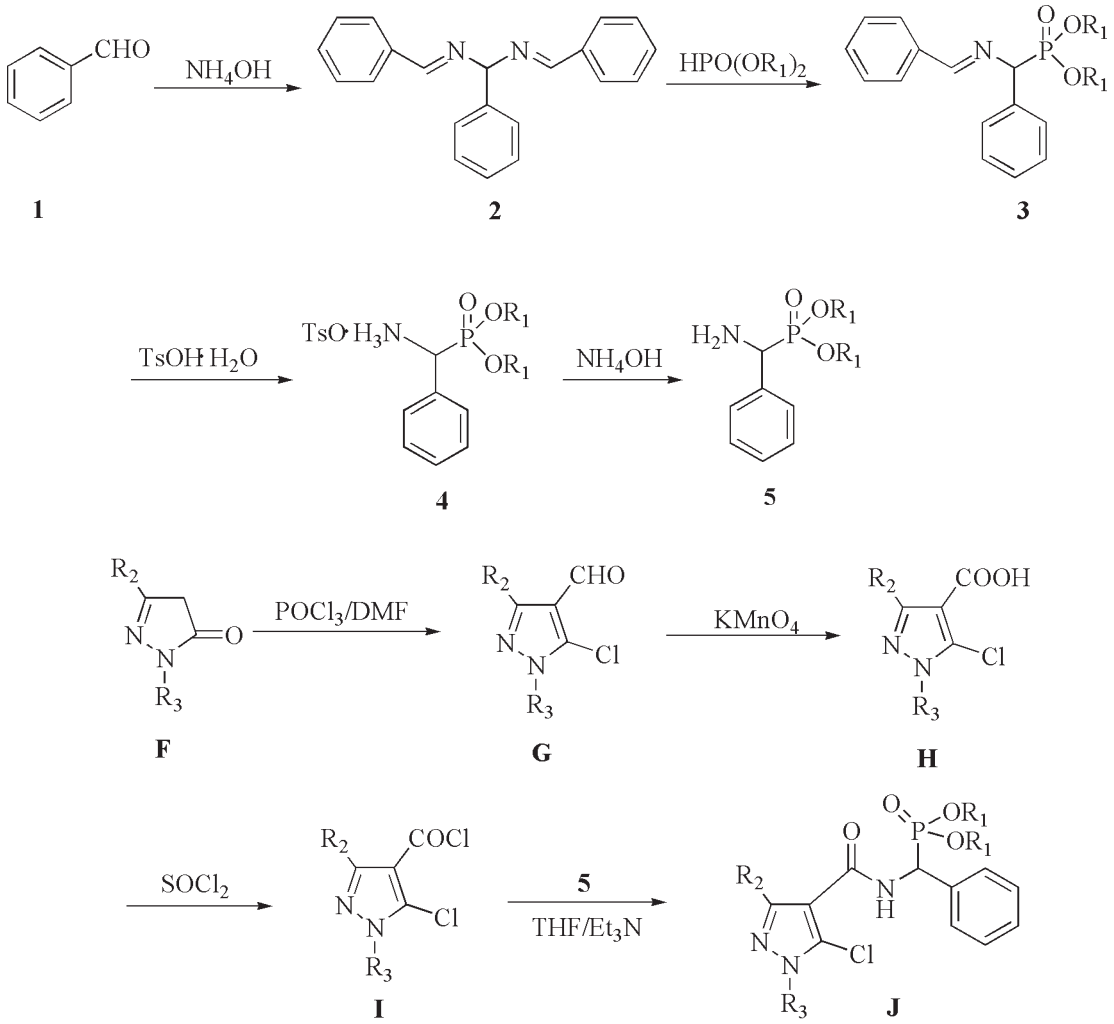


Figure 2. Structural features of aminophosphonates versus pyrazole amides containing aminophosphonates.

Scheme 1. Synthetic route to pyrazole amide analogues $\mathbf{J_1}$–$\mathbf{J_{15}}$ containing α-aminophosphonate.



$\mathbf{J_1}$: R_1=Et, R_2=CH_3, R_3=CH_3; $\mathbf{J_2}$: R_1=*n*-Pr, R_2=CH_3, R_3=CH_3; $\mathbf{J_3}$: R_1=*i*-Pr, R_2=CH_3, R_3=CH_3;
$\mathbf{J_4}$: R_1=*n*-Bu, R_2=CH_3, R_3=CH_3; $\mathbf{J_5}$: R_1=$CH_2CH_2OCH_3$, R_2=CH_3, R_3=CH_3;
$\mathbf{J_6}$: R_1=Et, R_2=CF_3, R_3=CH_3; $\mathbf{J_7}$: R_1=*n*-Pr, R_2=CF_3, R_3=CH_3; $\mathbf{J_8}$: R_1=*n*-Pr, R_2=CF_3, R_3=CH_3;
$\mathbf{J_9}$: R_1=*n*-Bu, R_2=CF_3, R_3=CH_3; $\mathbf{J_{10}}$: R_1=$CH_2CH_2OCH_3$, R_2=CF_3, R_3=CH_3;
$\mathbf{J_{11}}$: R_1=Et, R_2=CF_3, R_3=Ph; $\mathbf{J_{12}}$: R_1=*n*-Pr, R_2=CF_3, R_3=Ph; $\mathbf{J_{13}}$: R_1=*i*-Pr, R_2=CF_3, R_3=Ph;
$\mathbf{J_{14}}$: R_1=*n*-Bu, R_2=CF_3, R_3=Ph; $\mathbf{J_{15}}$: R_1=$CH_2CH_2OCH_3$, R_2=CF_3, R_3=Ph;

in the ^{31}P-NMR spectra of $\mathbf{J_1}$–$\mathbf{J_{15}}$ reveals the presence of phosphorus center coupled to adjacent **CH**. The presence of trifluoromethyl group was confirmed by the appearance of a singlet at −61.4 to −61.6 ppm in the ^{19}F-NMR spectra of the title compounds.

The antiviral activities of compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$ against TMV were assayed by the reported method [25]. The results of bioassay *in vivo* against TMV are given in Table 2. Ningnanmycin, perhaps the most successful registered plant antiviral agent in China, was used as reference antiviral agent. The data provided in Table 3 indicated that the title compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$ had curative rates of 29.4–50.1%, albeit lower than that of the commercial reference (52.8%). Amongst them, the title compounds ($\mathbf{J_3}$, $\mathbf{J_{10}}$, and $\mathbf{J_{12}}$) showed higher curative activities (39.9%, 41.8%, 50.1%, respectively) compared to the rest against TMV at 0.5 mg/mL. From the data in Table 3, it may be observed that the compounds with electron-donating groups in pyrazole ring display higher activity than those with electron-withdrawing ones.

In summary, a series of novel pyrazole amides containing α-aminophosphonate moiety were obtained from the reaction of acyl chloride and amine in THF in the presence of deacidification reagent triethylamine. The

Table 1

Effect of different solvents for synthesis of $\mathbf{J_1}$.

No	Solvent	Yield (%)
1	THF	70
2	CH_2Cl_2	58
3	$CHCl_3$	60
4	DMF	53
5	CH_3CN	57

Volume: 20 mL; reaction time: 0.5 h; temperature: 25°C.

racemic sample of $\mathbf{J_1}$ was separated into its enantiomers under conventional normal phase condition on two immobilized polysaccharide-based chiral stationary phases (Chiralpak IA and Chiralpak IC). Some of the title compounds displayed certain degree of antiviral activity against TMV.

EXPERIMENTAL

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 disk. The ^{1}H-, ^{13}C-, ^{31}P-, and ^{19}F-NMR (solvent $CDCl_3$) spectral analyses 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. The analytical HPLC of the compounds was performed on Agilent 1200 series Apparatus composed of a quarternary pump, an autosampler, a DAD detector, a vacuum degasser, a column oven and Agilent Chemstation software. The two columns used were Chiralpak IA-amylose tris-(3,5-dimethylphenylcarbamate) immobilized on silica-gel and Chiralpak IC-cellullose tris-(3,5-dichlorophenylcarbamate) immobilized on 5-μm silica-gel (both the columns of 250 mm × 4.6 mm i.d., 5 μm, Daicel Chemical Industries). Semipreparative HPLC was carried out by Agilent 1100 series consisting of a preparative pump, a DAD detector, and a manual injector with a 10-mL sample loop. Semipreparative Chiralpak IA column (250 mm × 10 mm i.d., 5 μm) was also purchased from Daicel Chemical Industries. Optical rotation values were measured on a WZZ-ZS automatic polarimeter. Analytical TLC was performed on silica gel GF_{254}. Column chromatographic purification was carried out using silica gel. The solvents *n*-hexane, DCM, IPA, and ethanol (EtOH) were of HPLC grade and purchased from Jiangsu Hanbang Science and Technology Co. (Jiangsu, China). All other reagents were of analytical reagent grade or chemically pure. The solvents were dried, deoxygenated, and redistilled before use.

Table 2

Enantiomeric excess values and some physical constants of the first (F1) and the second (F2) fractions collected after semipreparation.

	First fractions (F1)		Second fractions (F2)	
Compound	e.e. (%)	$[\alpha]_D^{20}$	e.e. (%)	$[\alpha]_D^{20}$
$\mathbf{J_1}$	100	−41.7	100	+37.5

Determination of enantiomeric excess: column: 230 nm; flow rate: 1 mL/min; injection volume: 5 μL; detection: mobile phase: *n*-hexane/EtOH (90/10, v/v), Chiralpak IA column (250 mm × 10 mm i.d., 5 μm); optical rotation measurement: temperature, 25°C; solvent, DCM.

Intermediate **I** was prepared according to the reported methods [26–28], α-aminobenzylphosphonate **5** was made by following the literature procedure [29].

General procedure for the preparation of compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$. A mixture of intermediate **5** (1.5 mmol) and triethylamine (1.5 mmol) in THF (10 mL) was stirred at room temperature and then the system was cooled down to 0°C. The intermediate **I** (1 mmol) in THF (10 mL) was slowly added into the above mixture, heated up to 25°C, and stirred for another 0.5 h. The triethylamine hydrochloride generated was removed by filtration; the solvent was evaporated to afford a crude product which was further purified by column chromatography on silica using a mixture of petroleum ether/ethyl acetate (1/1, v/v) as an eluant to give the target compounds in 45–80% yields. The physical and spectral data for $\mathbf{J_1}$–$\mathbf{J_{15}}$ are provided below.

Diethyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_1). Yellow solid; yield, 70%; mp: 118–120°C; IR (KBr): ν 3248 (NH), 3061, 3030, 2986, 2926, 2909, 1659 (C═O), 1549, 1495, 1474, 1450, 1261, 1234 (P═O), 1150, 1147, 1120 (P─O─C), 976, 762, 721, 700, 561 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.11 (t, J = 7.15 Hz, 3H, CCH_3), 1.31 (t, J = 6.88 Hz, 3H, CCH_3), 2.44 (s, 3H, pyrazole-CH_3), 3.70–3.78 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.92–3.40 (m, 1H, OCH_2), 4.07–4.19 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 23.80 Hz, 1H, NCHP), 7.12–7.15 (br, 1H, NH), 7.27–7.32 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.1, 150.9, 135.3, 128.8, 128.2, 128.0, 126.6, 110.9, 63.6, 63.1,

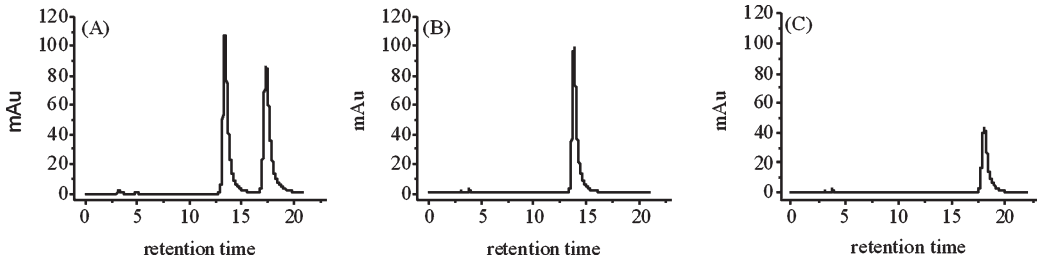


Figure 3. A: Analytical chromatogram of compound $\mathbf{J_1}$. B: Purity determination of the single fraction F1 of compound $\mathbf{J_1}$ collected on a semipreparative scale. C: Purity determination of the single fraction F2 of compound $\mathbf{J_1}$ collected on a semipreparative scale. Column: IA column (250 mm × 4.6 mm i.d., 5 μm); injection volume: 5 μm; detection: 230 nm; flow rate: 1.0 mL/min; mobile phase: *n*-hexane/EtOH (90:10, v/v).

Table 3

The curative effect of the new compounds against TMV *in vivo*.

Compound	Concentration (mg/mL)	Curative effect (%)
J_1	0.500	29.4
J_2	0.500	34. 7
J_3	0.500	39.9
J_4	0.500	36.4
J_5	0.500	36.3
J_6	0.500	24.6
J_7	0.500	34.0
J_8	0.500	38.0
J_9	0.500	31.3
J_{10}	0.500	41.8
J_{11}	0.500	33.5
J_{12}	0.500	50.1
J_{13}	0.500	28.4
J_{14}	0.500	37.4
J_{15}	0.500	35.2
Ningnamycin	0.500	52.8

50.7, 49.5, 36.4, 16.5, 16.2, 14.5; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{17}H_{23}ClN_3O_4P$ (399.11): C, 51.07; H, 5.80; N, 10.51. Found: C, 51.05; H, 6.12; N, 10.35.

Dipropyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)-(phenyl)methyl)phosphonate (J_2). Yellow solid; yield, 63%; mp: 125–127°C; IR (KBr): ν 3240 (NH), 3059, 3030, 2967, 2931, 2911, 1645 (C═O), 1539, 1470, 1456, 1402, 1377, 1246 (P═O), 1228, 1146, 1145, 1107 (P─O─C), 976, 762, 700, 543 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.93 (t, J = 7.42 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.63–1.71 (m, 2H, CCH_2C), 2.44 (s, 3H, pyrazole-CH_3), 3.59–3.65 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.83–3.88 (m, 1H, OCH_2), 3.97–4.07 (m, 2H, OCH_2), 5.61–5.67 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.13–7.15 (br, 1H, NH), 7.27–7.31 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.9, 135.4, 128.7, 128.2, 128.0, 126.6, 110.9, 68.9, 68.5, 50.7, 49.5, 36.4, 24.0, 23.9, 14.5, 11.1, 9.9; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{19}H_{27}ClN_3O_4P$ (427.14): C, 53.34; H, 6.36; N, 9.82. Found: C, 53.70; H, 6.65; N, 9.73.

Diisopropyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_3). Yellow solid; yield, 56%; mp: 98–100°C; IR (KBr): ν 3250 (NH), 3061, 3030, 2978, 2934, 2911, 1651 (C═O), 1523, 1506, 1496, 1456, 1454, 1380, 1375, 1303, 1234 (P═O), 1179, 1144, 1103 (P─O─C), 993, 898, 769, 700, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.75 (d, J = 5.75 Hz, 3H, CCH_3), 1.07 (d, J = 6.30 Hz, 6H, CCH_3), 1.15 (d, J = 6.30 Hz, 6H, CCH_3), 2.25 (s, 3H, pyrazole-CH_3), 3.50 (s, 3H, NCH_3), 4.26–4.32 (m, 1H, OCH), 4.50–4.55 (m, 1H, OCH), 5.38–5.44 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.11–7.13 (br, 2H, ArH and NH), 7.14–7.17 (t, J = 7.18 Hz, 2H, ArH), 7.47 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 160.9, 150.3, 135.6, 128.4, 128.2, 128.0, 127.9, 126.4, 110.9, 72.3, 71.6, 51.2, 49.9, 36.1, 24.1, 24.0, 23.0, 14.2; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 20.5; Anal. Calc. for: $C_{19}H_{27}ClN_3O_4P$ (427.14): C, 53.34; H, 6.36; N, 9.82. Found: C, 53.69; H, 6.74; N, 9.44.

Dibutyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)-(phenyl)methyl)phosphonate (J_4). Yellow solid; yield, 44%; mp: 78–80°C; IR (KBr): ν 3290 (NH), 3061, 3030, 2957, 2932, 2872, 1636 (C═O), 1522, 1506, 1456, 1361, 1450, 1248 (P═O), 1148, 1165, 1130 (P─O─C), 989, 903, 781, 700, 640, 543 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.43 Hz, 3H, CCH_3), 0.89 (t, J = 7.45 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.33–1.45 (m, 4H, CCH_2C), 1.59–1.65 (m, 2H, CCH_2C), 2.44 (s, 3H, pyrazole-CH_3), 3.62–3.68 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.86–3.92 (m, 1H, OCH_2), 4.00–4.11 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.13–7.16 (br, 1H, NH), 7.27–7.31 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 8.00 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.9, 135.4, 128.8, 128.2, 128.0, 126.6, 110.9, 67.1, 66.7, 50.7, 49.4, 36.4, 32.6, 32.3, 18.7, 18.6, 14.5, 13.6; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{21}H_{31}ClN_3O_4P$ (455.17): C, 55.32; H, 6.85; N, 9.22. Found: C, 55.54; H, 7.14; N, 8.86.

Bis(2-methoxyethyl)((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_5). Yellow solid; yield, 46%; mp: 76–78°C; IR (KBr): ν 3254 (NH), 3061, 3030, 2978, 2929, 2889, 2821, 1650 (C═O), 1521, 1456, 1367,1338, 1296, 1253 (P═O), 1200, 1132, 1197, 1155, 1134 (P─O─C), 972, 842, 772, 700, 565 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.44 (s, 3H, pyrazole-CH_3), 3.28 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.36–3.41 (m, 1H, CH_2O), 3.42–3.45 (m, 1H, CH_2O), 3.54–3.55 (m, 2H, CH_2O), 3.81 (s, 3H, NCH_3), 3.87–3.93 (m, 1H, OCH_2), 4.04–4.11 (m, 1H, OCH_2), 4.14–4.21 (m, 2H, OCH_2), 5.69–5.75 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.21–7.24 (br, 1H, NH), 7.28–7.31 (m, 1H, ArH), 7.36 (t, J = 6.90 Hz, 2H, ArH), 7.47 (d, J = 7.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.7, 135.2, 128.7, 128.2, 128.0, 126.8, 111.1, 71.4, 66.1, 65.7, 58.8, 50.9, 49.6, 36.3, 14.4; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 23.1; Anal. Calc. for: $C_{19}H_{27}ClN_3O_6P$ (459.13): C, 49.62; H, 5.92; N, 9.14. Found: C, 49.37; H, 6.28; N, 8.94.

Diethyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_6). Yellow solid; yield, 80%; mp: 132–134°C; IR (KBr): ν 3237 (NH), 3061, 3030, 2986, 2926, 2909, 1645 (C═O), 1553, 1497, 1474, 1452, 1242 (P═O), 1213, 1175, 1163, 1148, 1045, 1026 (P─O─C), 974, 958, 700, 561 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.12 (t, J = 7.15 Hz, 3H, CCH_3), 1.31 (t, J = 6.88 Hz, 3H, CCH_3), 3.70–3.78 (m, 1H, OCH_2), 3.93 (s, 3H, NCH_3), 3.95–4.00 (m, 1H, OCH_2), 4.08–4.19 (m, 2H, OCH_2), 5.59–5.65 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.31–7.33 (m, 1H, ArH), 7.37 (t, J = 7.15 Hz, 2H, ArH), 7.46 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 134.5, 129.9, 128.8, 128.4, 128.0, 123.4, 121.3, 119.2, 112.9, 63.7, 63.1, 51.1, 49.9, 37.4, 16.4, 16.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.6; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{17}H_{20}ClF_3N_3O_4P$ (453.08): C, 45.00; H, 4.44; N, 9.26. Found: C, 45.18; H, 4.71; N, 9.06.

Dipropyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_7). Yellow solid; yield, 62%; mp: 113–115°C; IR (KBr): ν 3230 (NH), 3059, 3020, 2970, 2939, 2987, 1667 (C═O), 1560, 1497, 1456, 1319, 1244 (P═O), 1219, 1180, 1126, 1070, 1022 (P─O─C), 997, 762, 707, 559 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.93 (t, J = 7.18 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.63–1.71 (m, 2H, CCH_2C), 3.59–3.65 (m, 1H, OCH_2), 3.83–3.88 (m, 1H, OCH_2), 3.92 (s, 3H, NCH_3), 3.97–4.07 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.29–

7.33 (m, 1H, ArH), 7.36 (t, J = 7.15 Hz, 2H, ArH), 7.46 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.2, 139.9, 134.8, 129.9, 128.8, 128.4, 128.0, 123.4, 121.3, 119.2, 112.8, 68.9, 68.5, 51.1, 49.9, 37.3, 23.9, 23.7, 14.5, 10.0, 9.8; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{19}H_{24}ClF_3N_3O_4P$ (481.1): C, 47.36; H, 5.02; N, 8.72. Found: C, 47.53; H, 4.82; N, 8.65.

Diisopropyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_8). Yellow solid; yield, 80%; mp: 130–132°C; IR (KBr): ν 3226 (NH), 3061, 3030, 2987, 2934, 1676 (C=O), 1658, 1555, 1506, 1496, 1456, 1379, 1238 (P=O), 1219, 1177, 1140, 1103 (P—O—C), 999, 989, 769, 700, 569 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.90 (d, J = 6.30 Hz, 3H, CCH_3), 1.24 (d, J = 6.30 Hz, 6H, CCH_3), 1.31 (d, J = 6.30 Hz, 3H, CCH_3), 3.90 (s, 3H, NCH_3), 4.43–4.46 (m, 1H, OCH), 4.63–4.69 (m, 1H, OCH), 5.49–5.55 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.01–7.03 (br, 1H, NH), 7.29–7.33 (m, 1H, ArH), 7.33 (t, J = 7.15 Hz, 2H, ArH), 7.44 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.1, 139.9, 135.1, 130.0, 128.6, 128.2, 128.1, 123.4, 121.3, 119.2, 112.9, 72.8, 71.9, 51.9, 50.6, 37.4, 24.3, 24.1, 23.9, 23.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 19.8; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{19}H_{24}ClF_3N_3O_4P$ (481.1): C, 47.36; H, 5.02; N, 8.72. Found: C, 47.48; H, 4.48; N, 8.84.

Dibutyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-arboxamido)(phenyl)methyl)phosphonate (J_9). Yellow solid; yield, 61%; mp: 80–82°C; IR (KBr): ν 3209 (NH), 3040, 3032, 2961, 2935, 1670 (C=O), 1560, 1496, 1456, 1385, 1321, 1248 (P=O), 1219, 1177, 1130, 1026, 1005 (P—O—C), 986, 891, 708, 700, 563 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.15 Hz, 3H, CCH_3), 0.91 (t, J = 7.15 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.33–1.45 (m, 4H, CCH_2C), 1.60–1.65 (m, 2H, CCH_2C) 3.62–3.68 (m, 1H, OCH_2), 3.86–3.91 (m, 1H, OCH_2), 3.92 (s, 3H, NCH_3), 4.00–4.11 (m, 2H, OCH_2), 5.59–5.65 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.30–7.32 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.46 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.2, 139.9, 134.8, 129.8, 128.8, 128.3, 128.0, 123.5, 121.3, 119.2, 112.9, 67.3, 66.7, 51.1, 49.9, 37.3, 32.5, 32.3, 18.7, 18.5, 13.6, 13.5; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.6; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{21}H_{28}ClF_3N_3O_4P$ (509.15): C, 49.47; H, 5.54; N, 8.24. Found: C, 49.63; H, 5.58; N, 8.08.

Bis(2-methoxyethyl)((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{10}). Yellow solid; yield, 56%; mp: 94–96°C; IR (KBr): ν 3238 (NH), 3057, 3032, 2929, 2895, 1666 (C=O), 1551, 1490, 1452, 1317, 1238 (P=O), 1213, 1175, 1132, 1099, 1064, 1041 (P—O—C), 979, 962, 727, 698, 579 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.29 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.36–3.41 (m,1H, CH_2O), 3.42–3.45 (m, 1H, CH_2O), 3.55 (t, J = 4.30 Hz, 2H, CH_2O), 3.93 (s, 3H, NCH_3), 3.94–3.99 (m, 1H, OCH_2), 4.05–4.12 (m, 1H, OCH_2), 4.14–4.25 (m, 2H, OCH_2), 5.69–5.75 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.26–7.29 (br, 1H, NH), 7.30–7.33 (m, 1H, ArH), 7.37 (t, J = 7.43 Hz, 2H, ArH), 7.47 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 140.2, 139.9, 134.6, 129.7, 128.8, 128.3, 128.0, 123.5, 121.3, 119.2, 113.1, 71.4, 66.2, 65.8, 58.8, 51.4, 50.2, 37.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.1; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5; Anal. Calc. for: $C_{19}H_{14}ClF_3N_3O_4P$ (509.15): C, 44.41; H, 4.71; N, 8.18; Found: C, 45.03; H, 4.53; N, 7.81.

Diethyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{11}). Yellow solid; yield, 68.0%; mp: 152–154°C; IR (KBr): ν 3244 (NH), 3068, 3030, 2983, 2931, 2906, 1674 (C=O), 1545, 1490, 1411, 1388, 1315, 1247 (P=O), 1217, 1182, 1024, 1033 (P—O—C), 993, 974, 771, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.12 (t, J = 7.18 Hz, 3H, CCH_3), 1.33 (t, J = 7.15 Hz, 3H, CCH_3), 3.71–3.79 (m, 1H, OCH_2), 3.93–4.00 (m, 1H, OCH_2), 4.09–4.20 (m, 2H, OCH_2), 5.63–5.69 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.18–7.21 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 141.5, 141.2, 136.7, 134.6, 130.1, 129.6, 128.9, 128.5, 128.1, 125.7, 121.3, 119.2, 114.0, 63.8, 63.1, 51.2, 50.0, 16.2, 16.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5; Anal. Calc. for: $C_{22}H_{22}ClF_3N_3O_4P$ (515.10): C, 51.22; H, 4.30; N, 8.15; Found: C, 51.40; H, 3.93; N, 7.86.

Dipropyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{12}). Yellow solid; yield, 79%; mp: 142–144°C; IR (KBr): ν 3244 (NH), 3067, 3030, 2972, 2940, 2899, 2881, 1681 (C=O), 1455, 1385, 1315, 1238 (P=O), 1215, 1174, 1120, 1139, 1012 (P—O—C), 995, 765, 702, 569 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.94 (t, J = 7.45 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.66–1.71 (m, 2H, CCH_2C), 3.58–3.64 (m, 1H, OCH_2), 3.83–3.89 (m, 1H, OCH_2), 3.99–4.09 (m, 2H, OCH_2), 5.64–5.70 (dd, J = 9.15 Hz, J = 20.65 Hz, 1H, NCHP), 7.18–7.20 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 134.7, 130.2, 129.6, 128.8, 128.4, 128.1, 125.7, 121.3, 119.2, 113.9, 69.2, 68.6, 51.2, 50.0, 23.9, 10.1, 9.9; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_4P$ (543.13): C, 53.00; H, 4.82; N, 7.73; Found: C, 53.23; H, 4.54; N, 7.49.

Diisopropyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{13}). Yellow solid; yield, 73%; mp: 126–128°C; IR (KBr): ν 3251 (NH), 3065, 3030, 2980, 2938, 1674 (C=O), 1545, 1489, 1387, 1332, 1315, 1238 (P=O), 1213, 1148, 1099, 1078, 1016 (P—O—C), 991, 770, 694, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.92 (d, J = 6.30 Hz, 3H, CCH_3), 1.27 (t, J = 6.30 Hz, 6H, CCH_3), 1.35 (d, J = 5.70 Hz, 3H, CCH_3), 4.44–4.50 (m, 1H, OCH), 4.67–4.73 (m, 1H, OCH), 5.55–5.61 (dd, J = 9.15 Hz, J = 20.65 Hz, 1H, NCHP), 7.13–7.16 (br, 1H, NH), 7.30–7.54 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 135.1, 130.1, 129.6, 128.8, 128.3, 128.1, 125.8, 121.3, 119.2, 113.9, 72.8, 71.9, 52.0, 50.8, 31.0, 24.4, 21.0, 29.2, 23.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 19.7; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_4P$ (543.13): C, 53.00; H, 4.82; N, 7.73; Found: C, 53.21; H, 4.72; N, 7.58.

Dibutyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{14}). Yellow solid; yield, 78%; mp: 179–181°C; IR (KBr): ν 3225 (NH), 3065, 3032, 2961, 2933, 1674 (C=O), 1558, 1497, 1385, 1332, 1315, 1246, 1224 (P=O), 1186, 1153, 1035, 1006 (P—O—C), 764, 698, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.15 Hz, 3H, CCH_3), 0.91 (t, J = 7.45 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.35–1.46 (m, 4H, CCH_2C), 1.62–1.67 (m, 2H, CCH_2C), 3.61–3.67 (m, 1H, OCH_2), 3.87–3.93 (m, 1H, OCH_2), 4.02–4.14 (m, 2H, OCH_2),

5.63–5.69 (dd, $J = 9.15$ Hz, $J = 20.65$ Hz, 1H, NCHP), 7.16–7.18 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 134.7, 130.2, 129.6, 128.8, 128.4, 128.1, 125.7, 121.3, 119.2, 113.9, 67.4, 66.8, 51.2, 50.0, 32.6, 32.5, 18.7, 18.6, 13.6; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{26}H_{30}ClF_3N_3O_4P$ (571.16): C, 54.60; H, 5.29; N, 7.35; Found: C, 54.37; H, 5.12; N, 7.01.

Bis(2-methoxyethyl)((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carbo-xamido)(phenyl)methyl)phosphonate (J15). Yellow solid; yield, 59%; mp: 112–114°C; IR (KBr): ν 3230 (NH), 3069, 3030, 3001, 2930, 2885, 1670 (C═O), 1557, 1490, 1390, 1339, 1315, 1252, 1219 (P═O), 1184, 1099, 1069, 1037 (P─O─C), 993, 980, 775, 696 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.29 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.37–3.41 (m, 1H, CH_2O), 3.45–3.48 (m, 1H, CH_2O), 3.56 (t, 2H, $J = 4.78$ Hz, CH_2O), 3.96–4.01 (m, 1H, OCH_2), 4.07–4.12 (m, 1H, OCH_2), 4.16–4.26 (m, 2H, OCH_2), 5.74–5.80 (dd, $J = 9.15$ Hz, $J = 21.20$ Hz, 1H, NCHP), 7.31–7.56 (m, 11H, ArH and NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 141.6, 141.2, 136.7, 134.5, 130.2, 129.6, 128.8, 128.3, 128.0, 125.7, 121.3, 119.2, 113.2, 71.4, 66.2, 65.8, 58.3, 50.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.0; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_6P$ (575.12): C, 50.05; H, 4.55; N, 7.30; Found: C, 50.00; H, 4.93; N, 7.40.

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 and were ground in phosphate buffer, 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 spectrophotometer.

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

Curative effect of compounds against TMV *in vivo*. Growing leaves of *Nicotiana tabacum L* of the same ages were selected. The TMV (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 (''av'' means average).

$$\text{Inhibition rate}(\%) = \frac{\text{av local lesion numbers of control(not treated with compound)} - \text{av local lesion numbers smeared with drugs}}{\text{av local lesion numbers of control (not treated with compound)}} \times 100\% \quad (2)$$

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