Design, Synthesis, Antiviral Activities of Novel Phosphonate Derivatives Containing Quinazoline Based on Chalone Motif

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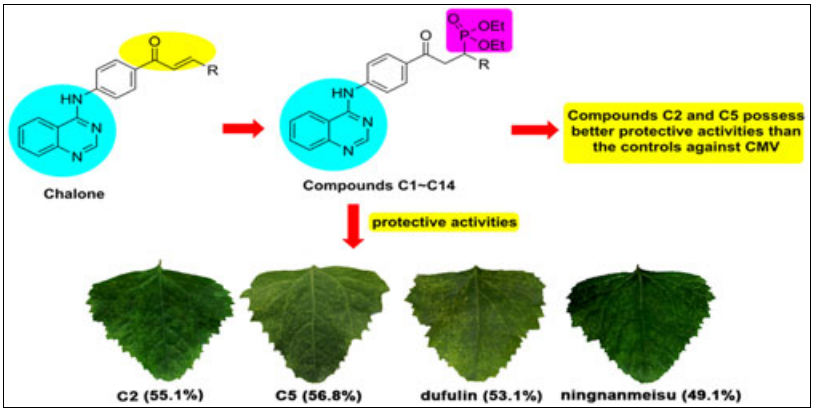


Based on the structure of natural product chalone, a series of novel phosphonate derivatives were designed and synthesized through 1,4-hydrophosphinylation of α,β-unsaturated carbonyl compounds. Their structures were characterized by IR, NMR, MS, and elemental analysis. The antiviral activities against cucumber mosaic virus were evaluated for the first time. The bioassay results indicated that most compounds exhibited good protective activities, low curative activities, and weak inactive activities. The antiviral protective activities of compounds **C2** and **C5** were 55.1% and 56.8%, respectively, which are slightly higher than those of the commercial Ningnanmyin (49.3%) and Dufulin (53.1%). Moreover, compounds **C2 and C9** exhibited moderate curative activities (42.6% and 46.6%). Therefore, the basic motif of **C1** can be used as a new lead structure for developing antivirus agents.

INTRODUCTION

Plant viruses, also named "plant cancer," have caused severe economic losses to agriculture worldwide [1]. Among them, cucumber mosaic virus (CMV), a member of the family *Bromoviridae*, is a major agronomic threat that infects more than 1000 plant species [2]. At present, the commercial antiviral agent such as ningnanmycin and dufulin displayed 30–60% *in vivo* curative effect at 500 μg/mL against CMV [3]. Because of poor field efficacy and huge economic loss, it is still necessary to the development of economically viable antiviral chemicals for application in agriculture.

Natural products have been demonstrated to be used as ideal lead structure to develop agrochemicals, due to its good compatibility, biodegradability and low toxicity [4]. It is well known that chalcone is the precursor of flavonoids and isoflavonoids, which possesses promising biological activities such as antifungal [5], anticancer [6], anti-retroviral [7], anti-inflammatory [8], antioxidant [9], and antimalarial [10]. In our previous study, a series of chalcone derivatives with heterocycle were designed and synthesized, exhibiting moderate to good anti-plant viral activity *in vivo* [11–14]. These findings inspire us to further modify chalcone motif.

In addition, phosphonates and their phosphonic derivatives possess intriguing biological and pharmacological properties, which have been mainly focused on antibiotic activity [15], antibacterial activity [16], enzyme inhibitors [17], and herbicides [18], and can be used as inhibitors of renin [19] or HIV proteases [20]. Moreover, phosphonate derivatives were also found to exhibit good antiviral activities against plant virus [21]. In our previous study, a series of phosphonates with heterocycle [22], thiourea [23], cyanoacrylate [24], and amide [25], respectively, were designed and synthesized, exhibiting moderate to good antiviral activity *in vivo*. Meanwhile, quinazolin-4(3*H*)-one is a heterocycle moiety exhibiting extensive biological activities such as antifungal [26], antibacterial [27], and antitumor [28].

Moreover, we also found that quinazoline derivatives [29,30] possessed excellent antiviral activities *in vivo*.

Herein, a series of novel phosphonate derivatives containing quinazoline were designed and synthesized through 1,4-addition reactions of diethyl phosphite to chalone. Their antiviral activities *in vivo* against CMV were subsequently evaluated, and preliminary structure–activity relationship of these compounds against CMV was discussed.

RESULTS AND DISCUSSION

Synthesis and spectroscopy. The synthesis procedures for intermediates **A**, **B,** and target compound **C** were shown in Scheme 1. Intermediate **A** was synthesized referring to the literature [31] with mainly optimized reaction condition (Scheme 1). The method can efficiently obtain to compound **A** in 96% yield after THF solvent instead of ethanol without adding few drops of conc. HCl. Intermediate **B** can be synthesized classically by Claisene-Schmidt condensation between compound **A** and aromatic aldehyde employing potassium hydroxide as catalyst [31].

Target compound **C** were synthesized through 1,4-hydrophosphinylation of α,β-unsaturated carbonyl compounds. The reaction base had a great influence on the reaction yield in our experiment. As shown in Table 1, the hydrophosphonylation reaction of chalcones derivatives containing quinazoline **B1** with diethyl phosphite was chosen as a model reaction to optimize reaction conditions. In initial studies, different bases were screened in THF as the solvent (5 mL) in room temperature for 12 h (Table 1, entry 1–4), When the reaction was carried out with NaH as the base, it could afford the product **C1** in good yield (Table 1, entry 4). The effects of solvents were then evaluated by using NaH as the base (Table 1, entry 4–7). THF (Table 1, entry 4) was found to be an optimal solvent, giving **C1** in a good yield (up to 55%). With the optimized reaction conditions in hand, the target compounds **C1**–**C14** were synthesized.

Table 1

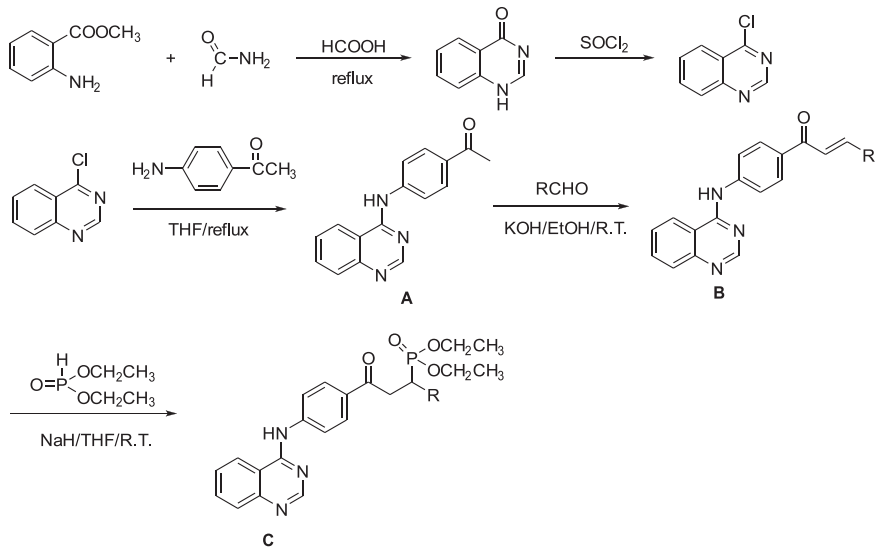
Optimized reaction condition of 1,4-addition.

Entry [a]	Base	Solvent	Time (h)	Yield[b] (%)
1	KOH	THF	12	5
2	NaOEt	THF	12	17
3	$NaNH_2$	THF	12	48
4	NaH	THF	12	55
5	NaH	Toluene	12	10
6	NaH	DMSO	12	25
7	NaH	DMF	12	0

[a]Reaction conditions: **B1** (1 mmol), diethyl phosphite (1.5 mmol), base (1.5 mmol), solvent (5 mL), r.t, 12 h;
[b]Isolated yields.

Compound **C** were identified by melting point, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, elemental analyses, and MS spectra. In ^{1}H NMR, the CH-P proton appeared at δ 3.44–4.96 as m or d, the NH proton appeared at δ 10.02–10.04 as a singlet. In the ^{13}C NMR spectra of compound **C**, the typical carbon resonance at *δ* 195.1–195.7 was indicative of a carbonyl group (C═O). In the ^{31}P NMR spectra of compound **C**, the typical phosphorus resonance at δ 25.80–28.90 was indicative of a phosphorus group. The IR spectra of compound **C** showed bands at 1670–1683 cm^{-1} for C═O stretching.

Scheme 1. The synthetic routes of the title compound **C.**



Antivirus activities. The antiviral activities of the target compounds **C1–C14** against CMV were assayed. The commercial agent ningnanmycin and dufulin were used as controls. Results of the bioassay shown in Table 2 indicated that the title compounds exhibited good protective activities, low curative activities, and weak inactive activities *in vivo* against CMV. Among them, compounds **C2** and **C5** showed good protective activities against CMV at 500 μg/mL, with the inhibition rates of 55.1% and 56.8%, respectively, which were slightly higher than that of ningnanmycin (49.3%) and similar to that of dufulin (53.1%); Meanwhile, compounds **C1**, **C7**, **C9**, **C10**, **C11**, **C12**, **C13,** and **C14** exhibited the similar protective activities against CMV (48.0%, 52.1%, 48.7%, 47.8%, 48.1%, 47.4%, 51.2%, and 51.8%, respectively) to that of ningnanmycin. Moreover, compounds **C3**, **C4**, and **C6** exhibited weak protective activities *in vivo* against CMV (10.7%, 9.3%, and 12.2%, respectively). Among them, compounds **C2** and **C9** showed moderate curative activities. However, other compounds exhibited weak curative activities and inactive activities.

To further investigate the action of introducing phosphonate moiety on title compounds, the title compounds **C1**, **C2,** and **C5** (48.0%, 55.1%, and 56.8%) with typically high protective activities were selected and were compared with those of the accordingly intermediates **B1**, **B2,** and **B5** (17.7%, 12.2%, and 25.6%, respectively). The results indicated that the introduction of phosphonate moiety can effectively improve the antiviral activity of title compounds. Meanwhile, the group at the phenyl ring (R) of the title compounds greatly affects the *in vivo* anti-CMV protective activity. When the group at ortho position is a fluorine moiety, **C2** exhibits good protective activities against CMV. When the group at meta or para positions is a bromine moiety, **C5** and **C7** also exhibited good protective activities against CMV. However, when the group at ortho or para position is a chlorine moiety, **C3**, **C6**, and **C8** showed poor anti-CMV activities. Accidentally, compound **C9** with chlorine moiety exhibited good an-CMV activity mainly for the influence of fluoride group. Meanwhile, **C10–C14** with heterocycle moiety exhibited good activity against CMV. In short, the presence of fluorine, bromine, or heterocycle groups could improve the antiviral activity of the compound more than that of other groups.

In summary, a series of novel phosphonates containing quinazoline based on chalone motif have been synthesized via 1,4-addition reaction in moderate yields and structurally confirmed. Bioassay results showed that the title compounds exhibited good protective activities, low curative activities, and weak inactive activities *in vivo* against CMV. Among them, **C2** and **C9** also exhibited moderate curative activity. Moreover, **C2** and **C5** exhibited slightly high protective activities than that of the controls. Therefore, the basic motif of **C1** can be used as a leading compound for further structural optimization to develop a potential antivirus agent.

EXPERIMENTAL

Materials and methods. Nuclear magnetic resonance spectra were recorded on a JEOL ECX-500 spectrometer (JEOL, Tokyo, Japan). Infrared spectra were recorded on Bruker VECTOR 22 spectrometer (Bruker, Karlsruhe, Germany) using KBr disks. The electron impact (EI) mass

Table 2

In vivo antivirus activity data of title compounds at 500 μg/mL.

Compd.	R	Curative effect (%)[a]	Protective effect (%)[a]	Inactive effect (%)[a]
C1	C_6H_5	33.8 ± 2.3	48.0 ± 2.0	11.5 ± 1.4
C2	2-FC_6H_4	40.5 ± 1.5	55.1 ± 2.3	21.0 ± 0.9
C3	2-ClC_6H_4	15.8 ± 0.5	10.7 ± 1.6	15.9 ± 1.0
C4	2-$CF_3C_6H_4$	15.0 ± 0.8	9.3 ± 2.7	26.2 ± 1.8
C5	3-BrC_6H_4	14.7 ± 0.9	56.8 ± 2.6	35.9 ± 3.5
C6	4-ClC_6H_4	26.0 ± 0.9	12.2 ± 3.0	22.4 ± 2.2
C7	4-BrC_6H_4	10.9 ± 1.2	52.1 ± 1.9	14.3 ± 0.7
C8	2,6-$Cl_2C_6H_3$	29.6 ± 1.8	33.4 ± 2.1	15.7 ± 1.1
C9	2-F-6-ClC_6H_3	46.6 ± 2.0	48.7 ± 1.9	25.9 ± 3.7
C10	2-thiophene	6.1 ± 0.7	47.8 ± 2.5	19.4 ± 0.5
C11	2-furan	17.8 ± 0.6	48.1 ± 1.0	13.3 ± 3.2
C12	2-pyridine	8.8 ± 1.0	47.4 ± 1.4	15.9 ± 0.8
C13	3-pyridine	14.9 ± 1.4	51.2 ± 2.3	21.5 ± 1.2
C14	4-pyridine	11.6 ± 1.7	51.8 ± 3.0	22.5 ± 1.9
Control [b]		51.2 ± 1.8	49.3 ± 2.5	73.2 ± 2.1
Dufulin [c]		52.4 ± 1.2	53.1 ± 1.6	78.4 ± 0.7

[a]Average of three replicates.
[b]Ningnanmycin was used as the control.
[c]Dufulin was also used as the control.

spectra were recorded on a Finnigan Mat SSQ 7000 (70 eV) mass spectrometer (Blue Lion Biotech, LLC, Snoqualmie, WA, USA). Silica gel GF_{254}-coated glass plates (Branch Qingdao Haiyang Chemical Co., Qingdao, China) were used for thin-layer chromatography under detection at 254 nm. Silica gel 200–300 mesh (Branch Qingdao Haiyang Chemical Co., Qingdao, China) was applied to column chromatography. Unless otherwise stated, all reagents were purchased from Aladdin Chemicals Co. (Aladdin, Shanghai, China) and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use.

General synthetic procedure. According to the literature [32], methyl anthranilate was treated with $HCONH_2$ in the presence of HCOOH and then chlorinated to obtain 4-chloroquinazoline.

Preparation of intermediate* N-*(4-acetyl-phenyl)-quinazolin-4-amine (A). Referring to the literature [31] by a modified method, to a solution of 4-chloroquinazoline (3 mmol) in 10 mL THF was added 4-aminoacetophenone (3 mmol) (Scheme 1). The mixture was stirred under reflux for 2 h with TLC monitoring. The reaction mixture was filtered and washed with THF, the filter cake is compound **A** as a pale yellowish solid (0.72 g, yield 91%), mp 256–257°C (lit[32] mp 255–257°C).

Preparation of intermediate substituted chalcones derivatives with quinazoline (B). Referring to the literature [31] with minor improvement, a mixture of **A** (1 mmol) and aromatic aldehydes (1 mmol) was stirred in ethanol (30 mL) and water (1 mL) and then KOH (1 mmol) added to it. The mixture was kept overnight at room temperature and then it was poured onto crushed ice, stirred, and acidified with dilute HCl (pH = 1.0). The solid separated was filtered and recrystallized from ethanol to obtain the intermediates **B**. Among them, characterization data of new compounds are given as follows:

B1: yellow solid, yield 78%; **B2**: yellow solid, yield 81%; **B3**: yellow solid, yield 79%; **B5**: yellow oil, yield 71%; **B6**: yellow solid, yield 81%; **B7**: yellow solid, yield 79%.

B4: The compound was obtained in 88.2% yield as yellowish solid; mp more than 300°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H, NH), 8.71 (s, 1H, quinazoline-2-H), 8.60 (d, J = 8.2 Hz, 1H, quinazoline-8-H), 8.31 (d, J = 7.8 Hz, 1H, Ar-H), 8.20 (dd, J = 25.1, 8.9 Hz, 4H, CH = CH + Ar-H), 8.04 (d, J = 15.3 Hz, 1H, Ar-H), 7.95 (dd, J = 15.4, 2.1 Hz, 1H, Ar-H), 7.88 (t, J = 7.6 Hz, 1H, Ar-H), 7.84–7.74 (m, 3H, Ar-H), 7.70–7.61 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.71 (s), 157.98 (s), 154.72 (s), 150.41 (s), 144.97 (s), 137.70 (s), 133.91 (s), 133.54 (d, J = 4.8 Hz), 132.21 (s), 130.94 (s), 130.31 (s), 129.29 (s), 128.51 (s), 128.12 (s), 127.89 (s), 127.18 (s), 126.81 (s), 126.72 (d, J = 5.0 Hz), 125.85 (s), 123.63 (s), 121.41 (s), 115.91 (s); ^{19}F NMR (471 MHz, DMSO-d_6) δ −57.21 (s). HRMS (ES) m/z for $C_{24}H_{16}F_3N_3O$ $[M + Na]^+$ Calcd. 442.1137. Found: 442.1129.

B8: The compound was obtained in 76.7% yield as yellowish solid; mp 192–194°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H, NH), 8.70 (s, 1H, quinazoline-2-H), 8.59 (d, J = 8.2 Hz, 1H, quinazoline-8-H), 8.14 (dd, J = 36.4, 8.8 Hz, 4H, CH = CH + Ar-H), 7.89–7.78 (m, 3H, Ar-H), 7.70–7.61 (m, 2H, Ar-H), 7.55 (d, J = 8.1 Hz, 2H, Ar-H), 7.38 (t, J = 8.1 Hz,1H, Ar-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.78 (s), 157.94 (s), 154.66 (s), 150.39 (s), 145.05 (s), 136.72 (s), 134.67 (s), 133.86 (s), 132.75 (s), 131.98 (s), 131.45 (s), 131.02 (s), 130.16 (s), 129.64 (s), 128.48 (s), 127.13 (s), 123.64 (s), 121.47 (s), 115.91 (s). HRMS (ES) m/z for $C_{23}H_{15}Cl_2N_3O$ $[M + Na]^+$ Calcd. 442.0485. Found: 442.0481.

B9: The compound was obtained in 85.3% yield as light-brown solid; mp 224–226°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H, NH), 8.69 (s, 1H, quinazoline-2-H), 8.59 (d, J = 8.2 Hz, 1H, quinazoline-8-H), 8.17 (d, J = 8.4 Hz, 2H, CH = CH), 8.08 (d, J = 8.7 Hz, 2H, Ar-H), 7.88–7.73 (m, 4H, Ar-H), 7.64 (t, J = 7.4 Hz, 1H, Ar-H), 7.50–7.38 (m, 2H, Ar-H), 7.34 (t, J = 10.0 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.94 (s), 162.78 (s), 160.76 (s), 157.94 (s), 154.66 (s), 150.37 (s), 144.99 (s), 135.58 (d, J = 4.7 Hz), 133.85 (s), 133.09 (s), 132.47 (d, J = 10.6 Hz), 132.08 (s), 130.05 (s), 129.16 (d, J = 12.0 Hz), 128.46 (s), 127.12 (s), 126.80 (s), 123.65 (s), 122.00 (d, J = 14.4 Hz), 121.47 (s), 115.99 (d, J = 10.0 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ −107.80 (s). HRMS (ES) m/z for $C_{23}H_{15}ClFN_3O$ $[M + Na]^+$ Calcd. 426.0780. Found: 426.0772.

B10: The compound was obtained in 92.2% yield as yellowish solid; mp 253–255°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H, NH), 8.70 (s, 1H, quinazoline-2-H), 8.60 (d, J = 8.3 Hz, 1H, quinazoline-8-H), 8.14 (q, J = 2.3 Hz, 4H, CH = CH + Ar-H), 7.90–7.86 (m, 2H, Ar-H), 7.82 (d, J = 8.1 Hz, 1H, Ar-H), 7.75 (d, J = 5.0 Hz, 1H, Ar-H), 7.68–7.65 (m, 2H, Ar-H), 7.59 (d, J = 15.3 Hz, 1H, thiophene-3-H), 7.17 (dd, J = 5.0, 3.6 Hz, 1H, thiophene-4-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.57 (s), 157.99 (s), 154.74 (s), 150.40 (s), 144.54 (s), 140.43 (s), 136.64 (s), 133.88 (s), 133.17 (s), 132.65 (s), 130.77 (s), 129.90 (s), 129.25 (s), 128.50 (s), 127.14 (s), 123.64 (s), 121.46 (s), 120.91 (s), 115.90 (s). HRMS (ES) m/z for $C_{21}H_{15}N_3OS$ $[M + Na]^+$ Calcd. 380.0829. Found: 380.0821.

B11: The compound was obtained in 87.2% yield as yellowish solid; mp 232–235°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H, NH), 8.71 (s, 1H, quinazoline-2-H), 8.60 (d, J = 8.2 Hz, 1H, quinazoline-8-H), 8.14 (q,

J = 8.9 Hz, 4H, CH = CH + Ar-H), 7.92–7.84 (m, 2H, Ar-H), 7.82 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.67 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.60–7.51 (m, 2H, Ar-H), 7.08 (d, *J* = 3.4 Hz, 1H, furan-3-H), 6.67 (dd, *J* = 3.4, 1.8 Hz, 1H, furan-4-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.54 (s), 157.98 (s), 154.74 (s), 151.81 (s), 150.40 (s), 146.61 (s), 144.54 (s), 133.89 (s), 132.68 (s), 130.45 (s), 129.83 (s), 128.50 (s), 127.16 (s), 123.63 (s), 121.47 (s), 119.29 (s), 117.29 (s), 115.89 (s), 113.65 (s). HRMS (ES) m/z for $C_{21}H_{15}N_3O_2$ $[M + Na]^+$ Calcd. 364.1056. Found: 364.1048.

B12: The compound was obtained in 91.4% yield as yellowish solid; mp 265–267°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H, NH), 8.71 (s, 1H, quinazoline-2-H), 8.66 (d, *J* = 8.3 Hz, 1H, quinazoline-8-H), 8.60 (d, *J* = 8.3 Hz, 1H, pyridine-6-H), 8.24–8.05 (m, 5H, CH = CH + Ar-H), 7.93–7.76 (m, 4H, Ar-H), 7.74–7.61 (m, 2H, Ar-H), 7.45–7.34 (m, 1H, Ar-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.31 (s), 157.97 (s), 154.72 (s), 153.47 (s), 150.56 (s), 150.40 (s), 144.82 (s), 142.96 (s), 137.73 (s), 133.87 (s), 132.47 (s), 130.08 (s), 128.50 (s), 127.14 (s), 125.69 (s), 125.42 (s), 125.26 (s), 123.64 (s), 121.49 (s), 115.90 (s). HRMS (ES) m/z for $C_{22}H_{16}N_4O$ $[M + Na]^+$ Calcd. 375.1217. Found: 375.1221.

B13: The compound was obtained in 93.2% yield as yellowish solid; mp 263–265°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H, NH), 9.01 (d, *J* = 2.1 Hz, 1H, pyridine-2-H), 8.71 (s, 1H, quinazoline-2-H), 8.63–8.51 (m, 2H, quinazoline-8-H+ pyridine-6-H), 8.34 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.20 (dd, *J* = 27.5, 8.9 Hz, 4H, CH = CH+ Ar-H), 8.10 (d, *J* = 15.7 Hz, 1H, Ar-H), 7.88 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.82 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.74 (d, *J* = 15.7 Hz, 1H, Ar-H), 7.67 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.47 (dd, *J* = 7.9, 4.8 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.85 (s), 157.99 (s), 154.74 (s), 151.44 (s), 150.85 (s), 150.41 (s), 144.78 (s), 140.40 (s), 135.61 (s), 133.90 (s), 132.48 (s), 131.20 (s), 130.20 (s), 128.52 (s), 127.17 (s), 124.48 (s), 124.46 (s), 123.63 (s), 121.41 (s), 115.90 (s). HRMS (ES) m/z for $C_{22}H_{16}N_4O$ $[M + Na]^+$ Calcd. 375.1217. Found: 375.1213.

B14: The compound was obtained in 95.1% yield as yellowish solid; mp more than 300°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H, NH), 8.72 (s, 1H, quinazoline-2-H), 8.65 (d, *J* = 6.0 Hz, 2H, pyridine-2,6-2H), 8.60 (d, *J* = 8.2 Hz, 1H, quinazoline-8-H), 8.27–8.13 (m, 5H, CH = CH + Ar-H), 7.89 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.85–7.78 (m, 3H, Ar-H), 7.72–7.60 (m, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.97 (s), 157.99 (s), 154.73 (s), 150.90 (s), 150.41 (s), 144.97 (s), 142.50 (s), 140.92 (s), 133.94 (s), 132.25 (s), 130.32 (s), 128.52 (s), 127.20 (s), 126.96 (s), 123.63 (s), 123.03 (s), 121.42 (s), 115.90 (s). HRMS (ES) m/z for $C_{22}H_{16}N_4O$ $[M + Na]^+$ Calcd. 375.1217. Found: 375.1209.

General procedure for the synthesis of the target compound C. To a solution of compound **B** (1 mmol) and diethyl phosphite (1.5 mmol) in 5 mL THF was added NaH (1 mmol) (Scheme 1). The mixture was stirred at room temperature with TLC monitoring. The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (20 mL × 3). The dichloromethane solution was dried with anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by silica gel column eluted with methanol-ethyl acetate (V : V = 1 : 100) to obtain the target compound **C**. Their characterization data of compound C are given as follows (their spectra data seen in Supporting Information).

C1: The compound was obtained in 56.7% yield as yellowish solid; mp 169–170°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.61–8.51 (m, 1H, quinazoline-8-H), 8.14–8.04 (m, 2 H, Ar-H), 8.03–7.93 (m, 2 H, Ar-H), 7.92–7.59 (m, 3 H, Ar-H), 7.41–7.08 (m, 5 H, Ar-H), 4.02–3.90 (m, 2 H,CH_2CO), 3.88–3.66 (m, 4 H, 2 CH_2O), 3.58–3.45 (m, 1 H, CHP), 1.15 (t, *J* = 7.00 Hz, 3 H, CH_3), 1.01 (t, *J* = 7.10 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.7, 158.0, 154.7, 150.4, 144.7, 136.9, 133.9, 131.5, 129.7, 129.5, 128.7, 128.5, 127.4, 127.1, 123.6, 121.3, 115.8, 62.5, 62.2, 38.6, 38.3, 16.7, 16.2; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 28.90; IR (KBr, cm^{-1}) *v*: 3315, 1673, 1233, 1179, 1051; *Anal.* Calcd. for $C_{27}H_{28}N_3O_4P$: C, 66.25; H, 5.77; N, 8.58; Found: C, 66.45; H, 5.63; N, 8.51; MS (ESI) m/z: 490.2 ($[M + H]^+$), 512.2 ($[M + Na]^+$).

C2: The compound was obtained in 55.6% yield as yellowish solid; mp 143–145°C. ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 10.04 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.58 (d, *J* = 7.9 Hz, 1 H, quinazoline-8-H), 8.23–8.04 (m, 2 H, Ar-H), 8.05–7.93 (m, 2 H, Ar-H), 7.94–7.60 (m, 3 H, Ar-H), 7.55–6.99 (m, 4 H, Ar-H), 4.13 (d, *J* = 10.10 Hz, 1 H, Ar-H, CHP), 4.04–3.92 (m, 2 H, CH_2CO), 3.92–3.71 (m, 4 H, 2 CH_2O), 1.17 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.03 (t, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.3, 158.0, 154.7, 150.4, 144.7, 133.9, 131.3, 130.0, 129.6, 128.5, 127.2, 123.6, 121.3, 115.7, 62.6, 62.4, 37.7, 30.4, 16.7,16.6; ^{31}P NMR (202 MHz, DMSO-d_6) *δ*: 27.80; ^{19}F NMR (471 MHz, DMSO-d_6) δ: −116.4; IR (KBr, cm^{-1}) *v*:3313, 1683, 1238, 1184, 1044; *Anal.* Calcd. for $C_{27}H_{27}FN_3O_4P$: C, 63.90; H, 5.36; N, 8.28; Found: C, 63.76; H, 5.23; N, 8.17; MS (ESI) m/z: 508.2 ($[M + H]^+$), 530.2 ($[M + Na]^+$).

C3: The compound was obtained in 63.5% yield as yellowish solid; mp 175–177°C. ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 10.02 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.57 (d, *J* = 8.20 Hz, 1 H, quinazoline-8-H), 8.07 (t, *J* = 11.61 Hz, 2 H, Ar-H), 7.98 (d,

J = 8.80 Hz, 2 H, Ar-H), 7.91–7.50 (m, 4 H, Ar-H), 7.47–7.07 (m, 3 H, Ar-H), 4.39 (d, *J* = 9.80 Hz, 1 H, CHP), 4.07–3.92 (m, 2 H, CH_2CO), 3.89–3.48 (m, 4 H, 2 CH_2O), 1.18 (t, *J* = 7.01 Hz, 3 H, CH_3), 1.01 (t, *J* = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.4, 158.0, 154.7, 150.4, 144.7, 134.9, 133.9, 131.3, 130.0, 129.8, 129.6, 129.0, 128.5, 127.6, 127.2, 123.6, 121.3, 62.6, 62.5, 35.7, 34.6, 16.8, 16.5; ^{31}P NMR (202 MHz, DMSO-d_6) *δ*: 27.80; IR (KBr, cm^{-1}) *v*: 3285, 1681, 1234, 1177, 1053; *Anal.* Calcd. for $C_{27}H_{27}ClN_3O_4P$: C, 61.89; H, 5.19; N, 8.02; Found: C, 61.95; H, 5.36; N, 8.11; MS (ESI) m/z: 524.2 ($[M + H]^+$), 546.1 ($[M + Na]^+$).

C4: The compound was obtained in 55.6% yield as yellowish solid; mp 179–181°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.58 (d, *J* = 8.21 Hz, 1 H, quinazoline-8-H), 8.09 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.98 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.84 (m, 3 H, Ar-H), 7.74–7.55 (m, 3 H, Ar-H), 7.54–7.30 (m, 1 H, Ar-H), 4.31–4.12 (m, 1 H, CHP), 4.07–3.88 (m, 2 H, CH_2CO), 3.85–3.47 (m, 4 H, 2 CH_2O), 1.14 (t, *J* = 7.00 Hz, 3 H, CH_3), 0.92 (t, *J* = 7.00 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 195.1, 158.0, 154.7, 150.4, 144.7, 136.3, 133.9, 132.9, 131.3, 131.0, 129.6, 128.5, 128.0, 127.1, 123.6, 121.3, 115.9, 62.7, 62.5, 35.4, 34.4, 16.7, 16.39; ^{31}P NMR (202 MHz, DMSO-d_6) *δ*: 27.40; IR (KBr, cm^{-1}) *v*: 3336, 1676, 1235, 1177, 1050; *Anal.* Calcd. for $C_{28}H_{27}F_3N_3O_4P$: C, 60.32; H, 4.88; N, 7.54; Found: C, 60.19; H, 4.95; N, 7.67; MS (ESI) m/z: 558.2 ($[M + H]^+$), 580.2 ($[M + Na]^+$).

C5: The compound was obtained in 49.3% yield as yellowish solid; mp 96–98°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.04 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.58 (d, *J* = 8.20 Hz, 1 H, quinazoline-8-H), 8.09 (d, *J* = 8.90 Hz, 2 H, Ar-H), 8.00 (d, *J* = 8.90 Hz, 2 H, Ar-H), 7.91–7.52 (m, 4 H, Ar-H), 7.49–7.15 (m, 3 H, Ar-H), 4.04–3.92 (m, 2 H, CH_2CO), 3.92–3.73 (m, 4 H, 2 CH_2O), 3.61–3.44 (m, 1 H, CHP), 1.16 (t, *J* = 7.01 Hz, 3 H, CH_3), 1.04 (t, *J* = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) *δ*: 195.5, 158.0, 154.7, 150.4, 144.7, 140.0, 133.9, 132.4, 131.3, 130.7, 130.3, 129.6, 128.8, 128.5, 127.2, 123. 6, 121.9, 121.3, 115.8, 62.6, 62.4, 39.3, 38.2, 16.6,16.7; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 28.10; IR (KBr, cm^{-1}) *v*: 3318, 1676, 1234, 1182, 1042; *Anal.* Calcd. for $C_{27}H_{27}BrN_3O_4P$: C, 57.05; H, 4.79; N, 7.39; Found: C, 57.18; H, 4.87; N, 7.25; MS (ESI) m/z: 570.2 ($[M + H]^+$), 592.1 ($[M + Na]^+$).

C6: The compound was obtained in 51.5% yield as yellowish solid; mp 166–168°C. ^1H NMR (500 MHz, DMSO-d_6) *δ*: 10.03 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.61–8.52 (m, 1 H, quinazoline-8-H), 8.16–8.04 (m, 2 H, Ar-H), 8.03–7.94 (m, 2 H, Ar-H), 7.92–7.58 (m, 3 H, Ar-H), 7.51–7.23 (m, 4 H, Ar-H), 4.02–3.91 (m, 2 H, CH_2CO), 3.91–3.71 (m, 4 H, 2 CH_2O), 3.52–3.54 (m, 1 H, CHP), 1.16 (t, *J* = 7.01 Hz, 3 H, CH_3), 1.04 (t, *J* = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.5, 158.0, 154.7, 150.4, 144.7, 136.1, 133.9, 132.1, 131.5, 131.4, 129.6, 128.6, 128.4, 127.2, 123.6, 121.3, 62.6, 62.3, 39.1, 38.1, 16.8, 16.6; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 28.30; IR (KBr, cm^{-1}) *v*: 3327, 1676, 1235, 1176, 1043; *Anal.* Calcd. for $C_{27}H_{27}ClN_3O_4P$: C, 61.89; H, 5.19; N, 8.02; Found: C, 61.97; H, 5.31; N, 8.17; MS (ESI) m/z: 524.2 ($[M + H]^+$), 546.2 ($[M + Na]^+$).

C7: The compound was obtained in 46.9% yield as yellowish solid; mp 174–176°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1H, NH), 8.68 (s, 1H, quinazoline-2-H), 8.62–8.50 (m, 1H, quinazoline-2-H), 8.16–8.04 (m, 2H, Ar-H), 8.04–7.93 (m, 2H, Ar-H), 7.92–7.58 (m, 3H, Ar-H), 7.54–7.27 (m, 4H, Ar-H), 4.01–3.92 (m, 2H, CH_2CO), 3.91–3.69 (m, 4H, 2 CH_2O), 3.58–3.44 (m, 1H, CHP), 1.16 (t, *J* = 7.01 Hz, 3 H, CH_3), 1.05 (t, *J* = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.5, 158.0, 154.7, 150.4 144.7, 136.6, 133.9, 131.9, 131.5, 129.6, 128.5, 127.2, 123.6, 121.3, 120.6, 62.6, 62.4, 39.7, 38.1, 16.8, 16.6; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 28.10; IR (KBr, cm^{-1}) ν: 3329, 1674, 1234, 1178, 1042; *Anal.* Calcd. for $C_{27}H_{27}BrN_3O_4P$: C, 57.05; H, 4.79; N, 7.39; Found: C, 57.11; H, 4.71; N, 7.36; MS (ESI) m/z: 570.1 ($[M + H]^+$), 592.1 ($[M + Na]^+$).

C8: The compound was obtained in 55.2% yield as yellowish solid; mp 164–166°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1H, NH), 8.68 (s, H, quinazoline-2-H), 8.57 (d, *J* = 8.20 Hz, H, quinazoline-8-H), 8.10 (d, *J* = 8.80 Hz, H, Ar-H), 7.97 (d, *J* = 8.80 Hz, 2 H, Ar-H), 7.90–7.58 (m, 3 H, Ar-H), 7.55–7.16 (m, 3 H, Ar-H), 4.96 (m, 1 H, CHP), 4.10–3.97 (m, 4 H, 2 CH_2O), 3.96–3.83 (m, 2 H, CH_2CO), 1.18 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.05 (t, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.4, 158.0, 154.7, 150.4, 144.7, 137.3, 135.3, 133.9, 133.4, 131.1, 130.6, 129.8, 129.4, 128.5, 127.1, 123.6, 121.4, 115.9, 62.5, 62.4, 37.5, 35.6, 16.8, 16.5; ^{31}P NMR (202 MHz, DMSO-d_6) *δ*: 26.20; IR (KBr, cm^{-1}) *v*: 3311, 1673, 1233, 1179, 1051; *Anal.* Calcd. for $C_{27}H_{26}Cl_2N_3O_4P$: C, 58.08; H, 4.69; N, 7.53; Found: C, 58.17; H, 4.54; N, 7.46; MS (ESI) m/z: 558.2 ($[M + H]^+$), 580.1 ($[M + Na]^+$).

C9: The compound was obtained in 53.7% yield as yellowish solid; mp 167–169°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.04 (s, 1H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.58 (d, *J* = 8.01 Hz, 1 H, quinazoline-8-H), 8.10 (d, *J* = 8.90 Hz, 2 H, Ar-H), 7.96 (d, *J* = 8.84 Hz, 2 H, Ar-H), 7.91–7.59 (m, 3 H, Ar-H), 7.41–6.96 (m, 3 H, Ar-H), 4.51–4.55 (m, 1 H, CHP), 4.07–3.96 (m, 2 H, CH_2CO), 3.95–3.64 (m, 4 H, 2

CH_2O), 1.17 (t, J = 7.00 Hz, 3 H, CH_3), 1.07 (t, J = 7.00 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.5, 158.0, 154.7, 150.4, 144.8, 133.9, 131.1, 130.0, 129.4, 128.5, 127.2, 126.1, 123.6, 121.4, 115.9, 62.7, 62.5, 37.0, 33.7, 16.8, 16.6; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 26.30; IR (KBr, cm^{-1}) v: 3279, 1672, 1245, 1176, 1058; *Anal.* Calcd. for $C_{27}H_{26}ClFN_3O_4P$: C, 59.84; H, 4.84; N, 7.75; Found: C, 59.61; H, 4.75; N, 7.70; MS (ESI) m/z: 542.2 ($[M + H]^+$), 564.2 ($[M + Na]^+$).

C10: The compound was obtained in 55.1% yield as yellowish solid; mp 156–158°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.04 (s, 1H, NH), 8.69 (s, 1 H, quinazoline-2-H), 8.58 (d, J = 8.40 Hz, 1 H, quinazoline-8-H), 8.10 (d, J = 8.80 Hz, 2 H, Ar-H), 8.00 (d, J = 8.90 Hz, 2 H, Ar-H), 7.93–7.58 (m, 3 H, Ar-H), 7.44–6.80 (m, 3 H, thiophene-H), 4.13 (d, J = 9.7 Hz, 1 H, CHP), 4.04–3.79 (m, 4 H, 2 CH_2O), 3.76–3.43 (m, 2 H, CH_2CO), 1.23–1.13 (t, J = 7.01 Hz, 3 H, CH_3), 1.10 (t, J = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.2, 158.0, 154.7, 150.4, 144.8, 138.9, 133.9, 131.3, 129.6, 128.5, 127.2, 127.1, 125.5, 123.6, 121.4, 115.9, 62.8, 62.5, 35.1, 34.0, 16.8, 16.7; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 26.80; IR (KBr, cm^{-1}) ν: 3313, 1678, 1236, 1177, 1046; *Anal.* Calcd. for $C_{25}H_{26}N_3O_4PS$: C, 60.60; H, 5.29; N, 8.48; Found: C, 60.71; H, 5.42; N, 8.41; MS (ESI) m/z: 496.2 ($[M + H]^+$), 518.1 ($[M + Na]^+$).

C11: The compound was obtained in 57.0% yield as yellowish solid; mp 172–174°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.04 (s, 1H, NH), 8.69 (s, 1 H, quinazoline-2-H), 8.58 (d, J = 8.0 Hz, 1 H, quinazoline-8-H), 8.19–8.06 (m, 2 H, Ar-H), 8.05–7.96 (m, 2 H, Ar-H), 7.94–7.62 (m, 3 H, Ar-H), 7.57–7.41 (m, 1 H, furan-H), 6.45–6.20 (m, 2 H, furan-H), 4.05–3.79 (m, 4 H, 2 CH_2O), 3.77–3.64 (m, 2 H, CH_2CO), 3.51–3.38 (m, 1 H, CHP), 1.18 (t, J = 7.01 Hz, 3 H, CH_3), 1.12 (t, J = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.2, 158.0, 154.7, 150.3, 144.8, 142.7, 133.9, 131.2, 129.6, 128.5, 127.2, 123.6, 121.4, 115.8, 111.3, 108.0, 62.7, 62.4, 36.7, 32.7, 16.8; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 25.80; IR (KBr, cm^{-1}) v: 3311, 1680, 1239, 1178, 1043; *Anal.* Calcd. for $C_{25}H_{26}N_3O_5P$: C, 62.63; H, 5.47; N, 8.76; Found: C, 62.79; H, 5.51; N, 8.70; MS (ESI) m/z: 480.2 ($[M + H]^+$), 502.2 ($[M + Na]^+$).

C12: The compound was obtained in 50.0% yield as yellowish solid; mp 187–189°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.62–8.52 (m, 1 H, quinazoline-8-H), 8.46–8.31 (m, 1 H, pyridine-6-H), 8.22–8.05 (m, 2 H, Ar-H), 8.04–7.94 (m, 2 H, Ar-H), 7.93–7.56 (m, 4 H, Ar-H), 7.50–7.11 (m, 2 H, Ar-H), 4.26–4.00 (m, 2 H, CH_2CO), 4.00–3.82 (m, 4 H, 2 CH_2O), 3.54–3.36 (m, 1 H, CHP), 1.15 (t, J = 7.01 Hz, 3 H, CH_3), 1.10 (t, J = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.8, 158.0, 154.7, 150.4, 149.15, 144.6, 136.7, 133.9, 131.5, 129.4, 128.5, 127.1, 125.4, 123.6, 122.5, 121.4, 115.9, 62.4, 42.0, 36.6, 16.7; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 27.70; IR (KBr, cm^{-1})ν: 3316, 1670, 1234, 1181, 1051; *Anal.* Calcd. for $C_{26}H_{27}N_4O_4P$: C, 63.67; H, 5.55; N, 11.42; Found: C, 63.48; H, 5.69; N, 11.51; MS (ESI) m/z: 491.2 ($[M + H]^+$), 513.2 ($[M + Na]^+$).

C13: The compound was obtained in 52.9% yield as yellowish solid; mp 86–88°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.04 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.62–8.32 (m, 3 H, quinazoline-8-H + pyridine-2,6-2H), 8.14–8.04 (m, 2 H, Ar-H), 8.02–7.96 (m, 2 H, Ar-H), 7.91–7.74 (m, 3 H, Ar-H), 7.71–7.18 (m, 2 H, Ar-H), 4.05–3.94 (m, 2 H, CH_2CO), 3.93–3.76 (m, 4 H, 2 CH_2O), 3.66–3.52 (m, 1 H, CHP), 1.16 (t, J = 7.01 Hz, 3 H, CH_3), 1.05 (t, J = 7.01 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.4, 158.0, 154.7, 150.9, 150.4, 148.5, 136.7, 133.9, 133.0, 131.3, 129.6, 128.5, 127.1, 123.8, 123.6, 121.3, 115.9, 62.7, 62.5, 37.8, 36.2, 16.8, 16.6; ^{31}P NMR (202 MHz, DMSO-d_6) δ 27.75; IR (KBr, cm^{-1}) ν: 3305, 1679, 1233, 1179, 1049; *Anal.* Calcd. for $C_{26}H_{27}N_4O_4P$: C, 63.67; H, 5.55; N, 11.42; Found: C, 63.52; H, 5.76; N, 11.47; MS (ESI) m/z: 491.2 ($[M + H]^+$), 513.2 ($[M + Na]^+$).

C14: The compound was obtained in 47.0% yield as yellowish solid; mp 173–175°C. ^1H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1 H, NH), 8.68 (s, 1 H, quinazoline-2-H), 8.57 (d, J = 8.2 Hz, 1 H, quinazoline-8-H), 8.45 (d, J = 5.8 Hz, 2 H, pyridine-2,6–2 H), 8.09 (d, J = 8.91 Hz, 2 H, Ar-H), 8.00 (d, J = 8.82 Hz, 2 H, Ar-H), 7.92–7.58 (m, 3 H, Ar-H), 7.49–7.31 (m, 2 H, Ar-H), 4.05–3.94 (m, 2 H, CH_2CO), 3.94–3.79 (m, 4 H, 2 CH_2O), 3.64–3.51 (m, 1 H, CHP), 1.16 (t, J = 7.01 Hz, 3 H, CH_3), 1.07 (t, J = 7.01 Hz, 3 H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 195.3, 158.0, 154.7, 150.4, 149.8, 146.4, 144.8, 133.9, 131.3, 129.6, 128.5, 127.1, 125.0, 123.6, 121.3, 115.9, 62.8, 62.6, 38.3, 37.5, 16.8, 16.6; ^{31}P NMR (202 MHz, DMSO-d_6) δ: 27.30; IR (KBr, cm^{-1}) v: 3323, 1676, 1239, 1181, 1046; *Anal.* Calcd. for $C_{26}H_{27}N_4O_4P$: C, 63.67; H, 5.55; N, 11.42; Found: C, 63.83; H, 5.47; N, 11.28; MS (ESI) m/z: 491.2 ($[M + H]^+$), 513.2 ($[M + Na]^+$).

The *in vivo antivirus activity assay.* Using the Scott's method [33], cucumber mosaic virus was purified. The biological activity of the title compounds against CMV were evaluated using a half-leaf method according to the previous references [34]. At first, growing *Nicotiana tabacum* L. leaves of the same age were selected. All of the leaves were previously scattered with silicon carbide. General procedure for curative effects of compound **C** is illustrated as follows: purified virus smeared both sides of the leaves after inoculation for 0.5 h, the compound

solution was smeared on the left side of the leaves, and the solvent was smeared on the right side for control. General procedure for protective effects of compound **C** was shown as follows: the compound solution was smeared on the left side of the leaves, and the solvent was smeared on the right side for control. After 12 h, two sides of the leaves were inoculated with purified virus. General procedure for inactive effects of compound **C** was shown as follows: the virus was inhibited after it was mixed with a compound solution of the same volume for 30 min. The compound solution with the virus for 30 min was smeared on the left side of the *N. tabacum* L. leaves; the right side of the *N. tabacum* L. leaves was then inoculated with the virus without the compound **C**. The number of local lesions was recorded 3 to 4 days after the inoculation. Three replications were reproduced for each compound. The inhibitory rate of the compound was calculated according to the references [34].

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