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Research paper

Synthesis, anti-varicella-zoster virus and anti-cytomegalovirus activity of quinazoline-2,4-diones containing isoxazolidine and phosphonate substructures

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ABSTRACT

Cycloadditions of *N*-substituted *C*-(diethoxyphosphoryl)nitrones to *N*-allylated quinazoline-2,4-diones functionalized at N3 with substituted benzoyl or benzyl groups proceeded with moderate to good diastereoselectivities (d.e. 28–68%). The synthesized isoxazolidine phosphonates were assessed for the antiviral activity against a broad range of DNA and RNA viruses. Compounds *trans*-**13c**, *cis*-**13c**/*trans*-**13c** (86:14), *cis*-**15b**/*trans*-**15b** (87:13) and *trans*-**15d**/*cis*-**15d** (95:5) exhibited the highest activity toward both TK^+ and TK^- VZV strains (mean EC_{50} values in the range of 3.0–8.7 μM). The EC_{50}'s for isoxazolidines *trans*-**12a**, *cis*-**12a**, *cis*-**13a**, *trans*-**13d**, *cis*-**15a**/*trans*-**15a** (50:50) ranged between 6.9 and 8.5 μM for VZV TK^+ strain and between 10.7 and 13.2 μM for VZV TK^- strain. The isoxazolidine phosphonates *cis*-**15**/*trans*-**15** having benzyl substituents both at N3 of the quinazoline-2,4-dione skeleton and at N2 of the isoxazolidine ring displayed some anti-cytomegalovirus potency but at the same time showed significant cytostatic activity for human embryonic lung fibroblasts (used to carry out the antiviral assays) as well as for other cell lines (i.e. CEM, L1210, HeLa and HMEC-1).

1. Introduction

Herpesviruses are widespread among humans and may cause many diseases. The primary infection is usually followed by a life-long latency of the virus and its reactivation usually occurs during immunosuppression of the host. Infection with varicella-zoster virus (VZV) results in varicella (chickenpox) which usually takes a mild course in children but may be more severe in adults. Later on, after establishing latency in neural tissues, the virus can reactivate causing herpes zoster (shingles) which is often accompanied by neuralgic pain and can lead to post-herpetic neuralgia (PHN) as well as other complications such as loss of vision (zoster ophthalmicus) [1,2].

In most cases immunocompetent patients infected by herpesviruses do not require antiviral therapy. However, reactivation of the virus is of significant concern in immunocompromised individuals, e.g. recipients of solid-organ and hematopoietic stem cell transplant, patients under aggressive chemotherapy or individuals with acquired immunodeficiency syndrome (AIDS). Under these circumstances, efficient antiviral drugs are of crucial importance. Effective treatments of herpesviridae species, including herpes simplex virus (HSV), VZV and human cytomegalovirus (HCMV) [3,4] are available but they are hampered by emergence of drug resistance and significant drug toxicities for some anti-herpesvirus agents (such as ganciclovir, foscavir and cidofovir). Four compounds are currently licensed for the treatment of VZV infections, namely acyclovir, valaciclovir, famciclovir and brivudin [5,6]. Regrettably, AIDS patients often do not respond well to acyclovir therapy or other antiviral drugs due to the emergence of thymidine kinase-deficient or thymidine kinase-altered mutations of VZV [7,8]. Therefore, the extensive search for new anti-VZV agents with superior efficacy compared to currently approved drugs is of high importance.

Numerous structurally diversified compounds have already been synthesized and tested as new potential anti-VZV agents including bicyclic nucleoside analogues, non-nucleoside DNA polymerase inhibitors and *N*-(α-methylbenzyl)-*N*-arylthiourea analogues (Fig. 1) [9–18].

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On the other hand, the antiviral activity of several 1,3-disubstituted quinazoline-2,4-diones (Fig. 2) has been discovered in recent years [19]. A 3-benzylquinazolin-2,4-dione derivative **1** was reported to posses the anti-HIV-1 activity in MT-4 cells and inhibited the recombinant RT in vitro [20]. A quinazolinone-2,4-dione **2** was a potent inhibitor of RSV-induced cytopathic effect ($EC_{50} = 2.14$ μM) [21]. Several other analogues, namely **3**–**5**, proved to be very active toward Respiratory Syncytial Virus (RSV) [21]. Recently, the N3-benzoylquinazolinonedione moiety was successfully incorporated as a nucleobase mimetic into the 1,2,3-triazole analogues of nucleotides **6** [22] and **7** [23]. While the compound **6** showed a moderate activity against both herpes simplex viruses (HSV-1 and HSV-2) ($EC_{50} = 17$ μM) as well as feline herpes virus ($EC_{50} = 24$ μM), its dihydroxylated derivative (1*R*,2*S*)-**7** proved to be even more potent ($EC_{50} = 2.9$, 4 and 4 μM toward HSV-1, HSV-2 and feline herpes virus, respectively), while the enantiomer (1*S*,2*S*)-**16** was inactive [23]. From several functionalized quinazoline-2,4-diones studied as allosteric inhibitors of the NS5B polymerase compounds **8**–**10** exhibited the highest affinity to the enzyme [24]. On the basis of these observations one may conclude that for the antiviral activity of quinazoline-2,4-diones substitution at N3 with aryl, benzyl or benzoyl groups is beneficial.

2. Results and discussion

2.1. Chemistry

Recently, we successfully accomplished the syntheses of homonucleoside analogues **11** which proved inactive against a broad spectrum of DNA and RNA viruses while some of them appeared slightly cytostatic toward several cancerous cell lines [25]. However, later on they were additionally screened for inhibition of VZV and HCMV replication and two compounds **11a** (B = *N*-benzoyluracil) and **12a** (R = benzoyl, R′ = methyl) showed noticeable activity toward VZV (Table 3). Based on this discovery we designed a new series of analogues (Scheme 1) installing at N3 of the quinazoline-2,4-dione skeleton either substituted benzoyl groups (compounds **2** and **3**) or substituted benzyl residues (compounds **14** and **15**).

As previously reported [25], N^1-allyl-N^3-benzoylquinazoline-2,4-dione **18a** was obtained in three steps in 20% overall yield starting from quinazoline-2,4-dione employing bis-N^1,N^3-benzoylation with benzoyl chloride followed by the selective N^1-debenzoylation and subsequent allylation. However, this procedure appeared tedious and the N^1-debenzylation step was the least effective. For this reason another strategy for the syntheses of N^1-allyl-N^3-benzoylquinazoline-2,4-diones **18a-18d** was designed which relied on *N*-allylation of the commercially available isatoic anhydride **20** followed by a subsequent condensation of compound **21** with urea [26,27] and concluded with N^3-benzoylation of the resulted *N*-allylquinazoline-2,4-dione **22** with selected benzoyl chlorides (Scheme 2). Moreover, under these circumstances compounds **19a-d** could be obtained in one step by benzylation of allylquinazoline-2,4-dione **22** (Scheme 2).

1,3-Dipolar cycloadditions of nitrones **16** (R′ = Me) or **7** (R′ = Bn) with the respective N^1-allyl-N^3-benzoylquinazoline-2,4-diones **18a-d** were carried out at 60 °C in toluene or toluene-ethanol mixtures as solvents and afforded mixtures of diastereoisomeric isoxazolidines *trans*-**12** and *cis*-**12** or *trans*-**13** and *cis*-**13** (Scheme 3, Table 1) with the *trans*-isomer predominating. The cis/trans ratios of diastereoisomeric products were determined on the basis of the ^{31}P NMR spectral data. The reactions proceeded with moderate diastereoselectivities (d.e. 28–60%) and with good to excellent overall yields. The isolation of pure isomers was successfully

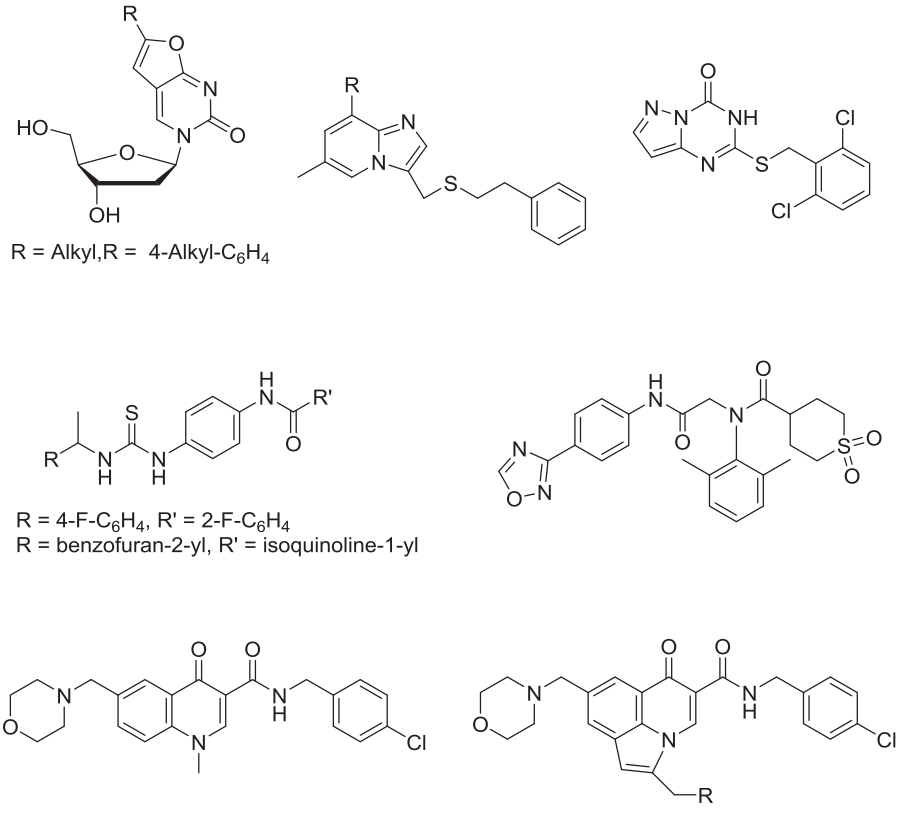


Fig. 1. Examples of anti-VZV active compounds.

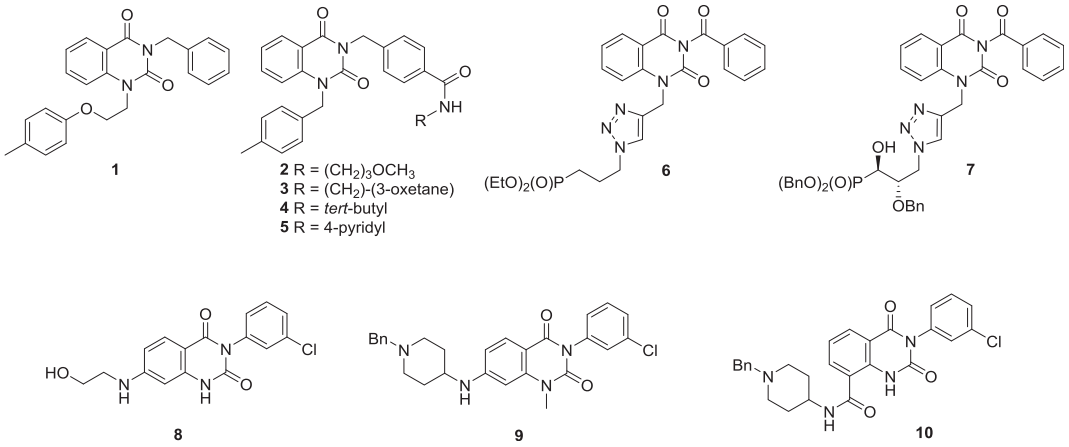
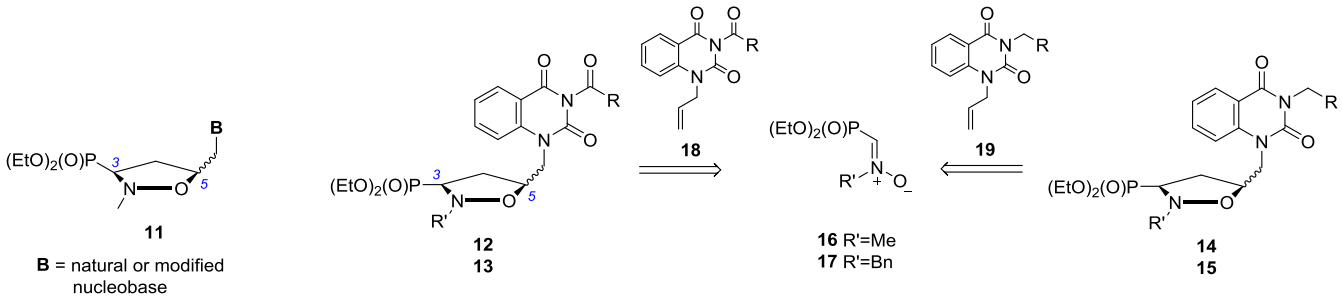
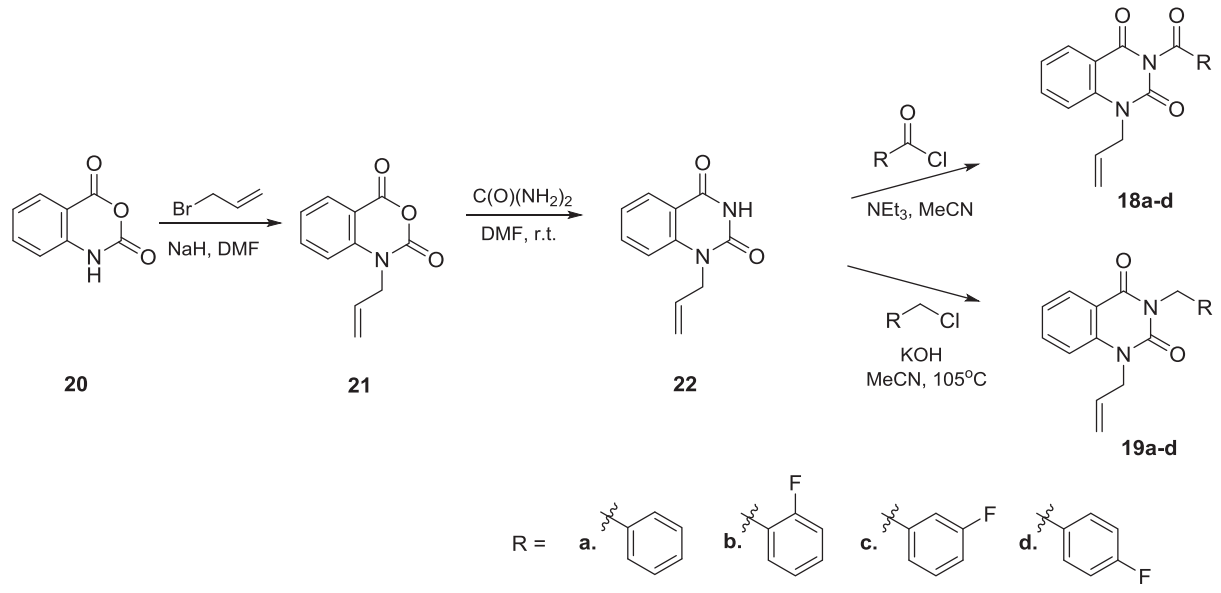


Fig. 2. Examples quinazoline-2,4-dione derivatives exhibiting antiviral activity.



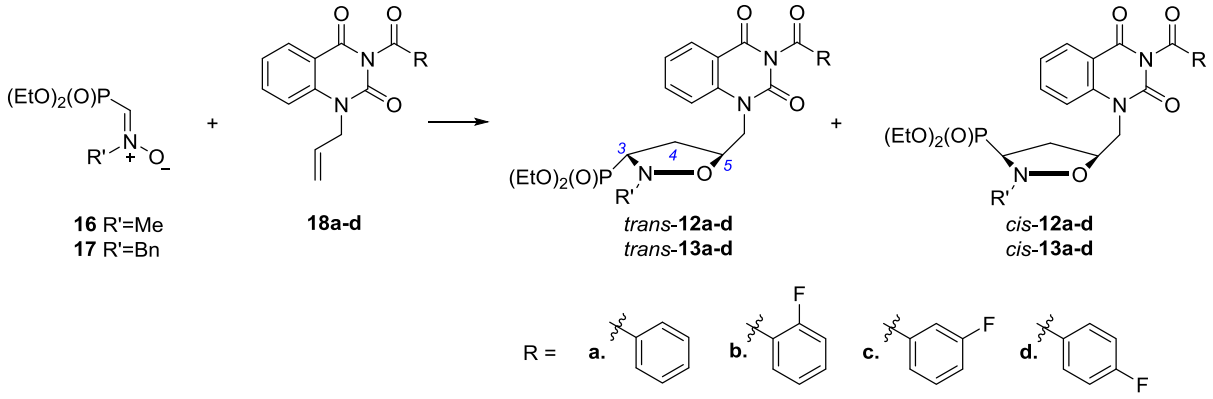
Scheme 1. Retrosynthesis of quinazoline-2,4-diones **12**–**15**.



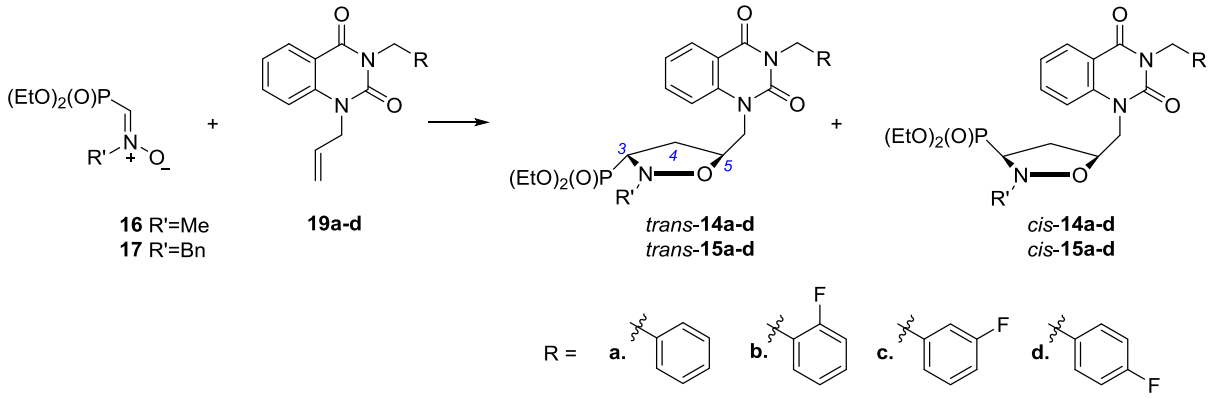
Scheme 2. Synthesis of quinazoline-2,4-diones **18a-d** and **19a-d**.

accomplished chromatographically for major isomers *trans*-**12a**, *trans*-**12b**, *trans*-**12c**, *trans*-**12d**, *trans*-**13c** and *trans*-**13d** but also for minor isomers *cis*-**12a**, *cis*-**12d** and *cis*-**13a**.

To eliminate rigidity within the substituted quinazoline-2,4-dione moiety benzoyl substituents at N3 were replaced by the functionalized benzyl residues. 1,3-Dipolar cycloadditions of nitrones **16** (R′ = Me) or **7** (R′ = Bn) with the respective N^1-allyl-N^3-benzylquinazoline-2,4-diones **19a-d** were carried out under conditions already described for compounds **18**. Diastereoisomeric cycloadducts *trans*-**14** and *cis*-**14** or *trans*-**15** and *cis*-**15** (Scheme 4, Table 2) were formed in good to excellent overall yields and with moderate diastereoselectivities (d.e. 28–60%) which were slightly higher for reactions of the nitrone **7** (R′ = Bn). Chromatographic isolation of pure isomers was achieved for *trans*-**14a**, *cis*-**14b**, *trans*-**14b**, *trans*-**14c** and *trans*-**14d**.



Scheme 3. Reaction and conditions: a) toluene or toluene-ethanol, 60 °C, 72 h.



Scheme 4. Reaction and conditions: a) toluene or toluene-ethanol, 60 °C, 72 h.

Table 1
Cycloadditions of the nitrone **16**/**17** and N^1-allyl-N^3-benzoylquinazoline-2,4-diones **18a-d**.

Nitrone **16**/**17** (R′)	Alkene **18** (R)	*cis*:*trans* ratio	Yield (%)
16 (Me)[17]	**18a** (Ph) [25]	20:80	*cis*-**12a** (11)[a], *trans*-**12a** (43)[a], *cis*-**12a** + *trans*-**12a** (25)[b]
16 (Me)	**18b** (2-F-C_6H_4)	36:64	*trans*-**12b** (43)[a], *cis*-**12b** + *trans*-**12b** (49)[b]
16 (Me)	**18c** (3-F-C_6H_4)	20:80	*trans*-**12c** (47)[a], *cis*-**12c** + *trans*-**12c** (46)[b]
16 (Me)	**18d** (4-F-C_6H_4)	25:75	*cis*-**12d** (4.5)[a], *trans*-**12d** (25)[a], *cis*-**12d** + *trans*-**12d** (53)[b]
17 (Bn)	**18a** (Ph)	27:73	*cis*-**13a** (7.1)[a], *trans*-**13a** (3.6)[a], *cis*-**13a** + *trans*-**13a** (74)[b]
17 (Bn)	**18b** (2-F-C_6H_4)	32:68	*cis*-**13b** + *trans*-**13b** (92)[b]
17 (Bn)	**18c** (3-F-C_6H_4)	28:72	*trans*-**13c** (13)[a], *cis*-**13c** + *trans*-**13c** (81)[b]
17 (Bn)	**18d** (4-F-C_6H_4)	28:72	*trans*-**13d** (27)[a], *cis*-**13d** + *trans*-**13d** (61)[b]

[a] Yield of the pure isomer.
[b] Yield of the pure mixture of *cis*- and *trans*-isomers.

2.2. Antiviral and cytostatic evaluation

The pure isomers of quinazoline-2,4-dione - conjugates [*trans*-**11a**, *cis*-**11a**, *trans*-**12a**, *cis*-**12a**, *trans*-**13a**, *cis*-**13a**, *trans*-**12b**, *trans*-**12c**, *trans*-**13c**, *trans*-**12d**, *cis*-**12d**, *trans*-**13d**, *trans*-**14a**, *trans*-**14b**, *cis*-**14b**, *trans*-**15b**, *trans*-**14c**, *trans*-**14d**] and the respective mixtures of *cis*/*trans* isomers [*cis*-**12b**/*trans*-**12b** (87:13), *trans*-**13b**/*cis*-**13b** (90:10), *cis*-**2c**/*trans*-**2c** (94:6), *cis*-**13c**/*trans*-**13c** (86:14), *cis*-**13d**/*trans*-**13d** (85:15), *cis*-**14a**/*trans*-**14a** (75:25), *trans*-**15a**/*cis*-**15a** (90:10), *cis*-**15a**/*trans*-**15a** (50:50), *cis*-**15b**/*trans*-**15b** (87:13), *cis*-**14c**/*trans*-**14c** (97:3), *trans*-**15c**/*cis*-**15c** (90:10), *cis*-**15c**/*trans*-**15c** (80:20), *cis*-**14d**/*trans*-**14d** (75:25), *trans*-**15d**/*cis*-**15d** (95:5), *cis*-**15d**/*trans*-**15d** (75:52)] were screened as inhibitors of a wide variety of DNA and RNA viruses using the following cell-based assays: (a) human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS strain), herpes simplex virus-2 (G strain), thymidine kinase deficient (acyclovir resistant) herpes simplex virus-1 (TK^- KOS ACV^r strain), vaccinia virus, adenovirus-2, vesicular stomatitis virus, human coronavirus (229E), cytomegalovirus (AD-169 strain and Davis strain), varicella-zoster virus (TK^+ VZV Oka strain and TK^- VZV 07-1 strain); (b) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus; (c) Vero cell cultures: parainfluenza virus 3, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, yellow fever virus; (e) Crandell-Rees feline kidney (CRFK) cell cultures: feline corona virus (FIPV) and feline herpes virus (FHV) and (d) Madin Darby canine kidney (MDCK) cell cultures: influenza A virus (H1N1 and H3N2 subtypes) and influenza B virus. Ganciclovir, cidofovir, acyclovir, brivudin, zalcitabine, zanamivir, alovudine, amantadine, rimantadine, ribavirin, dextran sulfate (molecular weight 10000, DS-10000),

Table 2
Cycloadditions of the nitrones **16** or **17** and N^1-allyl-N^3-benzylquinazoline-2,4-diones **19a-d**.

Nitrone **16**/**17** (R′)	Alkene **19** (R)	*cis*:*trans* ratio	Yield (%)
16 (Me)	**19a** (Ph)	22:78	*trans*-**14a** (37)[a], *cis*-**14a** + *trans*-**14a** (58)[b]
16 (Me)	**19b** (2-F-C_6H_4)	22:78	*cis*-**14b** (6.5)[a], *trans*-**14b** (29)[a], *cis*-**14b** + *trans*-**14b** (56)[b]
16 (Me)	**19c** (3-F-C_6H_4)	16:84	*trans*-**14c** (21)[a], *cis*-**14c** + *trans*-**14c** (75)[b]
16 (Me)	**19d** (4-F-C_6H_4)	23:77	*trans*-**14d** (30)[a], *cis*-**14d** + *trans*-**14d** (56)[b]
17 (Bn)	**19a** (Ph)	34:66	*cis*-**15a** + *trans*-**15a** (92)[b]
17 (Bn)	**19b** (2-F-C_6H_4)	31:69	*cis*-**15b** (3.6)[a], *cis*-**15b** + *trans*-**15b** (86)[b]
17 (Bn)	**19c** (3-F-C_6H_4)	35:65	*cis*-**15c** + *trans*-**15c** (96)[b]
17 (Bn)	**19d** (4-F-C_6H_4)	33:67	*cis*-**15d** + *trans*-**15d** (95)[b]

[a] Yield of the pure isomer.
[b] Yield of the pure mixture of *cis*- and *trans*-isomers.

mycophenolic acid, Hippeastrum hybrid agglutinin (HHA) and Urtica dioica agglutinin (UDA) were used as the reference compounds. The antiviral activity was expressed as the EC_{50}: the compound concentration required to reduce virus plaque formation (VZV) by 50% or to reduce virus-induced cytopathogenicity by 50% (other viruses).

Several synthesized quinazoline-2,4-diones inhibited the replication of both TK^+ and TK^- VZV strains (Table 3). A 95:5 *trans*-**15d**/*cis*-**15d** mixture and a 87:13 *cis*-**15b**/*trans*-**15b** mixture emerged as the most active derivatives with EC_{50}'s of, respectively, 4.7 μM and 3 μM (VZV TK^+ strain) and of 3.6 μM and 5.1 μM (VZV TK^- strain). These two quinazoline-2,4-diones were 4–6-fold less active against the TK^+ virus but proved to be 10–14-fold more active against the TK^- strain when compared to the reference drug acyclovir. These data clearly indicate that these novel derivatives do not require activation by the viral TK. Although these quinazoline-2,4-diones did not significantly altered the morphology of cells in the antiviral assays, they showed considerable cytostatic activity (in the same range as the antiviral activity).

Compounds *trans*-**13c**, a 86:14 *cis*-**13c**/*trans*-**13c** mixture, *trans*-**13d**, and a 85:15 *cis*-**13d**/*trans*-**13d** mixture inhibited both VZV TK^+ and TK^- viruses with EC_{50}'s in the range of 6.0–8.5 μM. Compounds *trans*-**12a**, *cis*-**12a**, *cis*-**13a**, *trans*-**12d** and a 50:50 *cis*-**15a**/*trans*-**15a** mixture also proved active against VZV TK^+ strain (EC_{50}'s of 6.9–7.5 μM) and VZV TK^- strain (EC_{50}'s of 10–14 μM), slightly exceeding in potency against VZV TK^- strains the reference drugs acyclovir and brivudin (EC_{50} = 50.3 μM and 22.7, respectively). However, majority of the studied compounds exhibited significant cytotoxicity and the 95:5 *trans*-**15d**/*cis*-**15d** mixture reduced cell growth (CC_{50}) at concentration as low as 6.6 μM which was almost two orders of magnitude lower than that for acyclovir (CC_{50} = 440 μM).

Among the investigated quinazoline-2,4-diones, the N3-benzoylated compounds (*cis*- and *trans*-**12**/**13**) were found inactive toward both human cytomegalovirus (HCMV) strains. On the other hand, isoxazolidine phosphonates having benzyl substituents both at N3 of the quinazoline-2,4-dione skeleton and at N2 of the isoxazolidine ring (*cis*- and *trans*-**15**) showed weak antiviral activity with EC_{50} in the range of ≥3–≥14.5 μM (Table 4).

Preliminary structure-activity relationship observations revealed a lack of significant differences in activity of *cis vs*. *trans* isoxazolidines and higher potency of isoxazolidines carrying *N*-benzyl substituents in comparison with their *N*-methyl counterparts especially well pronounced for the N^3-benzylquinazoline-2,4-diones **15**. For the active compounds the introduction of a fluorine atom into the benzene ring either in benzyl or benzoyl residues did not improve their efficacy. While the quinazoline-2,4-diones substituted at N3 with benzoyl and benzyl moieties were found effective against VZV, only those carrying substituted benzyl components proved active toward HMCV.

All synthesized isoxazolidine phosphonates were also subjected to antiviral screening with other viruses, but only compound *trans*-**12d** appeared slightly active against other herpesviruses, adenovirus-2 and human Coronavirus (Table 5).

2.3. Cytostatic activity

The 50% cytostatic inhibitory concentration (IC_{50}) causing a 50% decrease in cell proliferation was determined against murine leukemia L1210, human lymphocyte CEM, human cervix carcinoma HeLa and immortalized human dermal microvacsular endothelial cells (HMEC-1) (Table 6). Among all tested compounds only quinazoline-2,4-diones *trans*-**15**/*cis*-**15** having benzyl substituents at N3 in the quinazolinone core and the benzyl group at N2 of the isoxazolidine unit showed significant cytostatic activity toward the tested cell lines. For the CEM cell line, these derivatives were as active as the reference drug 5-fluorouracil. It was noticed that the replacement of the benzyl component within the isoxazolidine moiety for the methyl group (*trans*-**15**/*cis*-**15** vs. the respective *trans*-**14**/*cis*-**14**) resulted in decrease in potency by roughly an order of magnitude.

3. Conclusions

Several series of {5-(2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl-2-methylisoxazolidin-3-yl})phosphonates (*cis*-**12**/*trans*-**12** and *cis*-**14**/*trans*-**14**) and {5-(2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)methyl-2-benzylisoxazolidin-3-yl})phosphonates (*cis*-**13**/*trans*-**13** and *cis*-**15**/*trans*-**15**) modified at N3 in the quinazoline-2,4-dione moiety have been obtained by the 1,3-dipolar cycloaddition of *N*-substituted (*C*-diethoxyphosphoryl)nitrones **16** (R=Me) and **17** (R=Bn) and the respective N^1-allylated quinazoline-2,4-diones substituted at N3 with benzoyl (compounds **18**) or benzyl groups (compounds **19**).

The synthesized isoxazolidine phosphonates were evaluated against a variety of DNA and RNA viruses and several derivatives appeared to be active against varicella-zoster virus and human cytomegalovirus. Among all tested compounds, a 95:5 *trans*-**15d**/*cis*-**15d** (95:5) (EC_{50} = 3.0 μM) and a *cis*-**15b**/*trans*-**15b** (87:13) (EC_{50} = 4.7 μM) showed the highest activity toward TK^+ VZV strain. The potency of these derivatives was 4–6 fold lower than that of acyclovir, used as reference drug.

On the other hand, compounds *trans*-**13c**, mixture *cis*-**13c**/*trans*-**13c** (86:14), *trans*-**13d**, and a 85:15 mixture of *cis*-**13d**/*trans*-**13d** exhibited potency not only against TK^+ VZV strain but also toward TK^- VZV strain and their anti-TK^- VZV activity was significantly higher than that of the reference drugs acyclovir and brivudin (EC_{50} = 50.3 and 22.7 μM, respectively). The isoxazolidine phosphonates *cis*-**15a-d**/*trans*-**15a-d** having benzyl substituents both at N3 of the quinazoline-2,4-dione skeleton and at N2 of the isoxazolidine ring (*cis*- and *trans*-**5**) showed some activity toward human cytomegalovirus (EC_{50} in the range of ≥3 to ≥14.5 μM).

Table 3
Antiviral activity and cytotoxicity against varicella-zoster virus (VZV) in HEL cell cultures.

Compound	R′	R	Antiviral activity EC_{50} (μM)[a]		Cytotoxicity (μM)	
			TK^+ VZV strain	TK^- VZV strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
trans-**11a**	Me		83.6	>100	>100	n.d.
cis-**11a**	Me		65.7	88.4	>100	n.d.
trans-**12a**	Me	C_6H_5	7.5 ± 2.1[d]	13.7 ± 4.7	≥100 ± 0	>100 ± 0
cis-**12a**	Me	C_6H_5	7.7 ± 2.4	10.9 ± 1.6	>100 ± 0	>100 ± 0
trans-**13a**	Bn	C_6H_5	8.5 ± 3.8	>20 ± 0	100 ± 0	28.9 ± 3.1
cis-**13a**	Bn	C_6H_5	8.5 ± 0.3	10.8 ± 1.7	100 ± 0	16.34 ± 0
trans-**12b**	Me	2-F-C_6H_4	36.57	34.2	>100	n.d.
cis-**12b**/*trans*-**12b** (87:13)	Me	2-F-C_6H_4	28.99	25.62	>100	n.d.
trans-**13b**/*cis*-**13b** (90:10)	Bn	2-F-C_6H_4	16.7 ± 4.7	20 ± 0	100 ± 0	21.4 ± 1.0
trans-**12c**	Me	3-F-C_6H_4	16.7 ± 4.7	15.0 ± 3.3	>100 ± 0	16.5 ± 2.5
cis-**12c**/*trans*-**12c** (94:6)	Me	3-F-C_6H_4	7.8 ± 3.6	21.4 ± 13.0	>100 ± 0	30.0 ± 11.2
trans-**13c**	Bn	3-F-C_6H_4	8.7 ± 4.3	8.5 ± 4.6	100 ± 0	9.8 ± 2.3
cis-**13c**/*trans*-**13c** (86:14)	Bn	3-F-C_6H_4	6.0 ± 6.9	8.5 ± 9.6	100 ± 0	19.3 ± 5.3
trans-**12d**	Me	4-F-C_6H_4	6.9 ± 5.3	10.7 ± 0.3	≥100 ± 0	14.7 ± 2.1
cis-**12d**	Me	4-F-C_6H_4	26.15	24.46	>100	n.d.
trans-**13d**	Bn	4-F-C_6H_4	7.5 ± 0.1	8.3 ± 0.2	100 ± 0	12.7 ± 2.7
cis-**13d**/*trans*-**13d** (85:15)	Bn	4-F-C_6H_4	7.4 ± 0.8	7.6 ± 1.1	100 ± 0	12.3 ± 2.0
trans-**14a**	Me	C_6H_5	>20	>20	100	n.d.
cis-**14a**/*trans*-**14a** (75:25)	Me	C_6H_5	>100	>100	>100	n.d.
trans-**15a**/*cis*-**15a** (90:10)	Bn	C_6H_5	>20	>20	100	n.d.
cis-**15a**/*trans*-**15a** (50:50)	Bn	C_6H_5	7.3 ± 1.0	13.2 ± 9.7	100 ± 0	9.0 ± 0.7
trans-**14b**	Me	2-F-C_6H_4	>20	>20	100	n.d.
cis-**14b**	Me	2-F-C_6H_4	58.48	>100	>100	n.d.
trans-**15b**	Bn	2-F-C_6H_4	4	>20	20	n.d.
cis-**15b**/*trans*-**15b** (87:13)	Bn	2-F-C_6H_4	4.7 ± 3.8	5.1 ± 1.6	100 ± 0	11.8 ± 4.6
trans-**14c**	Me	3-F-C_6H_4	55.7	>100	>100	n.d.
cis-**14c**/*trans*-**14c** (97:3)	Me	3-F-C_6H_4	7.0 ± 1.4	27.1 ± 10.0	≥100 ± 0	36.8 ± 3.1
trans-**15c**/*cis*-**15c** (90:10)	Bn	3-F-C_6H_4	>20	20	100	n.d.
cis-**15c**/*trans*-**15c** (80:20)	Bn	3-F-C_6H_4	>20	>20	100	n.d.
trans-**14d**	Me	4-F-C_6H_4	66.87	>20	10	n.d.
cis-**14d**/*trans*-**14d** (75:25)	Me	4-F-C_6H_4	35.54	25.17	100	n.d.
trans-**15d**/*cis*-**15d** (95:5)	Bn	4-F-C_6H_4	3.0 ± 2.3	3.6 ± 2.9	100 ± 0	6.6 ± 0
cis-**15d**/*trans*-**15d** (75:52)	Bn	4-F-C_6H_4	>4	>4	20	n.d.
Acyclovir			0.8 ± 0.1	50.3 ± 14.9	>440 ± 0	440 ± 0
Brivudin			0.005 ± 0.007	22.7 ± 3.1	>300 ± 0	300 ± 0

n.d. – not determined.
[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alternation of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.
[d] Results are mean values ± STDEV of two independent experiments.

The quinazoline-2,4-diones endowed with anti-VZV and anti-HCMV activity did not alter the morphology of cells used in the antiviral assays up to a concentration of 100 μM. However, these derivatives showed considerable cytostatic activity. Cytostatic activity of the obtained compounds was also evaluated on L1210, CEM, HeLa and HMEC-1 cells. Among all tested compounds, only quinazoline-2,4-diones (*trans*-**15**/*cis*-**15**) bearing benzyl substituents at N3 in the quinazolinone core and the benzyl group at N2 of the isoxazolidine unit showed significant (IC_{50} = 10–98 μM) activity toward tested cell lines.

4. Experimental

4.1. General

^1H, ^{13}C and ^{31}P NMR spectra were taken in $CDCl_3$ on the Bruker Avance III spectrometers (600 MHz) with TMS as internal standard at 600, 151 and 243 MHz, respectively.

IR spectra were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on Perkin-Elmer PE 2400 CHNS analyzer.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

N-methyl- and *N*-benzyl-*C*-(diethoxyphosphoryl)nitrones **16** and **17** were obtained according to the literature procedures [28].

4.2. Synthesis of 1-allylquinazoline-2,4-dione (**22**)

To a solution of 1-allyl-1*H*-benzo[*d*] [1,3] oxazine-2,4-dione **21** (0.500 g, 2.46 mmol) in DMF (10 mL) urea (0.221 g, 3.69 mmol) was added. The reaction mixture was stirred for 5 h, the solvent was removed in vacuo and the residue was crystallized from ethanol to give pure **22** as a yellowish amorphous solid, m.p. = 218–219 °C.

IR (KBr, cm^{-1}) ν_{max}: 3165, 3031, 2926, 1673, 1605, 1502, 1398, 1295, 921, 763, 752, 503. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.57 (bs, 1H, N*H*), 8.26–8.24 (m, 1H), 7.71–7.68 (m, 1H), 7.31–7.28 (m, 1H), 7.23–7.22 (m, 1H), 5.95 (ddt, ^3J = 17.3 Hz, ^3J = 10.1 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.31 (ddt, ^3J = 10.1 Hz, ^4J = 3.5 Hz, ^2J = 0.7 Hz, 1H, CH_2–CH=CH*H*), 5.26 (d, ^3J = 17.3 Hz, ^4J = 3.5 Hz, ^2J = 0.7 Hz, 1H, CH_2–CH=C*H*H), 4.79 (dt, ^3J = 5.0 Hz, ^4J = 3.5 Hz, 2H, *CH*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.60 (C=O), 149.97 (C=O), 141.06, 135.45, 131.05, 128.79, 123.21, 117.81, 116.03, 114.68, 45.15. Anal. calcd. For $C_{11}H_{10}N_2O_3$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.11; H, 4.74; N, 13.83.

Table 4
Antiviral activity and cytotoxicity against human cytomegalovirus in HEL cell cultures.

Compound	R′	R	Antiviral activity EC_{50} (μM)[a]		Cytotoxicity (μM)	
			AD-169 strain	Davis strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
trans-**11a**	Me		>100	>100	100	n.d.
cis-**11a**	Me		>100	>100	100	n.d.
trans-**12a**	Me	C_6H_5	>100	>100	100	n.d.
cis-**12a**	Me	C_6H_5	>100	>100	100	n.d
trans-**13a**	Bn	C_6H_5	>20	>20	100	n.d.
cis-**13a**	Bn	C_6H_5	>20	>20	100	n.d.
trans-**12b**	Me	2-F-C_6H_4	>20	66.87	100	n.d.
cis-**12b**/*trans*-**12b** (87:13)	Me	2-F-C_6H_4	>100	63.14	100	n.d.
trans-**13b**/*cis*-**13b** (90:10)	Bn	2-F-C_6H_4	>20	>20	100	n.d.
trans-**12c**	Me	3-F-C_6H_4	>20	>20	100	n.d
cis-**12c**/*trans*-**12c** (94:6)	Me	3-F-C_6H_4	>100	>100	100	n.d.
trans-**13c**	Bn	3-F-C_6H_4	>20	>20	20	n.d.
cis-**13c**/*trans*-**13c** (86:14)	Bn	3-F-C_6H_4	>20	>20	100	n.d.
trans-**12d**	Me	4-F-C_6H_4	>20	>20	100	n.d.
cis-**12d**	Me	4-F-C_6H_4	>20	>20	100	n.d.
trans-**13d**	Bn	4-F-C_6H_4	>20	>20	20	n.d
cis-**13d**/*trans*-**13d** (85:15)	Bn	4-F-C_6H_4	>20	>20	20	n.d.
trans-**14a**	Me	C_6H_5	>100	>100	100	n.d
cis-**14a**/*trans*-**14a** (75:25)	Me	C_6H_5	>100	>100	100	n.d.
trans-**15a**/*cis*-**15a** (90:10)	Bn	C_6H_5	≥14.5 ± 7.8[d]	13.1 ± 3.1	100 ± 0	41.7 ± 10.8
cis-**15a**/*trans*-**15a** (50:50)	Bn	C_6H_5	≥3.0 ± 1.4	6.5 ± 3.5	100 ± 0	9.0 ± 0.7
trans-**14b**	Me	2-F-C_6H_4	>100	100	20	n.d.
cis-**14b**	Me	2-F-C_6H_4	>100	100	100	n.d.
trans-**15b**	Bn	2-F-C_6H_4	>20	>4	20	n.d
cis-**15b**/*trans*-**15b** (87:13)	Bn	2-F-C_6H_4	8.94 ± 0	≥6.5 ± 3.5	100 ± 1	11.8 ± 4.6
trans-**14c**	Me	3-F-C_6H_4	76.47	63.14	>100	n.d.
cis-**14c**/*trans*-**14c** (97:3)	Me	3-F-C_6H_4	>20	44.72	100	n.d.
trans-**15c**/*cis*-**15c** (90:10)	Bn	3-F-C_6H_4	9.9 ± 1.4	8.94 ± 1	100 ± 0	20.8 ± 4.7
cis-**15c**/*trans*-**15c** (80:20)	Bn	3-F-C_6H_4	>20	>20	20	n.d.
trans-**14d**	Me	4-F-C_6H_4	>100	100	100	n.d.
cis-**14d**/*trans*-**14d** (75:25)	Me	4-F-C_6H_4	>20	>20	100	n.d.
trans-**15d**/*cis*-**15d** (95:5)	Bn	4-F-C_6H_4	≥6.5 ± 3.5	8.94 ± 0	100 ± 0	6.6 ± 0
cis-**15d**/*trans*-**15d** (75:52)	Bn	4-F-C_6H_4	>4	>4	20	n.d.
Ganciclovir			14.9 ± 8.1	6.5 ± 2.5	>350 ± 0	>350 ± 0
Cidofovir			1.44 ± 0.56	0.81 ± 0.07	>300 ± 0	>300 ± 0

n.d. – not determined.
[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alternation of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.
[d] Results are mean values ± STDEV of two independent experiments.

Table 5
Antiviral activity and cytotoxicity in HEL cell cultures.

Compound	R′	R	Antiviral activity EC_{50} (μM)[b]					Minimum cytotoxic concentration (μM)[a]
			Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Herpes simplex virus-1 TK^- KOS ACV^r	Adeno virus-2	Human Coronavirus (229E)	
trans-**12d**	Me	4-F-C_6H_4	39.0 ± 15.6[c]	12.0 ± 0	9.0 ± 1.4	17.5 ± 3.5	39.5 ± 7.8	≥100 ± 0
Brivudine			0.11	146	250	–	–	>250
Cidofovir			2	2	3.8	10	–	>250
Acyclovir			0.2	0.4	250	–	–	>250
Ganciclovir			0.032	0.055	4	–	–	>100
Zalcitabine			–	–	–	7.2	–	>250
Alovudine			–	–	–	10	–	>250
UDA			–	–	–	–	0.4	≥100
Ribavirin			–	–	–	–	112	≥250

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.
[c] Results are mean values ± STDEV of two independent experiments.

*4.3. The benzoylation of N-allylquinazoline-2,4-dione **22** – the general procedure*

To a solution of *N*-allylquinazoline-2,4-dione **22** (1.00 mmol) in acetonitrile (10 mL) triethylamine was added (3.00 mmol) followed by the respective benzoyl chloride (2.20 mmol). The mixture was stirred at room temperature for 72 h. The solvent was removed in vacuo, the residue was dissolved in methylene chloride (10 mL) and washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography

Table 6
The inhibitory effect of the tested compounds against the proliferation of murine leukemia (L1210), human T-lymphocyte (CEM), human cervix carcinoma (HeLa) and immortalized human dermal microvascular endothelial cells (HMEC-1).

Compound	R′	R	IC_{50}[a] (μM)			
			L1210	CEM	HeLa	HMEC-1
trans-**11a** [25]	Me		>200	>200	>200	n.d[b]
cis-**11a** [25]	Me		>200	>200	>200	n.d
trans-**12a** [25]	Me	C_6H_5	≥159	70 ± 22[c]	96 ± 11	n.d.
cis-**12a** [25]	Me	C_6H_5	>200	74 ± 33	>200	n.d.
trans-**13a**	Bn	C_6H_5	154 ± 54	≥250	>250	>250
cis-**13a**	Bn	C_6H_5	155 ± 61	≥250	>250	>250
trans-**12d**	Me	4-F-C_6H_4	>250	>250	>250	>250
cis-**12d**	Me	4-F-C_6H_4	>250	>250	>250	>250
trans-**13d**	Bn	4-F-C_6H_4	123 ± 40	170 ± 22	>250	≥250
cis-**13d**/*trans*-**13d** (85:15)	Bn	4-F-C_6H_4	105 ± 46	132 ± 45	>250	≥250
trans-**12b**	Me	2-F-C_6H_4	>250	>250	>250	>250
cis-**12b**/*trans*-**12b** (87:13)	Me	2-F-C_6H_4	>250	>250	>250	>250
trans-**13b**/*cis*-**13b** (90:10)	Bn	2-F-C_6H_4	155 ± 79	158 ± 13	≥250	>250
trans-**12c**	Me	3-F-C_6H_4	228 ± 30	>250	>250	>250
cis-**12c**/*trans*-**12c** (94:6)	Me	3-F-C_6H_4	>250	>250	>250	>250
trans-**13c**	Bn	3-F-C_6H_4	170 ± 105	224 ± 37	>250	>250
cis-**13c**/*trans*-**13c** (86:14)	Bn	3-F-C_6H_4	185 ± 89	166 ± 118	>250	>250
trans-**14a**	Me	C_6H_5	141 ± 28	124 ± 9	119 ± 18	235 ± 22
cis-**14a**/*trans*-**14a** (75:25)	Me	C_6H_5	146 ± 1	104 ± 19	95 ± 41	222 ± 39
trans-**15a**/*cis*-**15a** (90:10)	Bn	C_6H_5	17 ± 7	15 ± 4	73 ± 9	28 ± 3
cis-**15a**/*trans*-**15a** (50:50)	Bn	C_6H_5	18 ± 1	10 ± 6	33 ± 21	28 ± 1
trans-**14b**	Me	2-F-C_6H_4	196 ± 74	99 ± 8	74 ± 28	189 ± 38
cis-**14b**	Me	2-F-C_6H_4	203 ± 8	181 ± 20	128 ± 40	≥250
trans-**15b**	Bn	2-F-C_6H_4	68 ± 4	98 ± 4	79 ± 4	145 ± 1
cis-**15b**/*trans*-**15b** (87:13)	Bn	2-F-C_6H_4	17 ± 1	20 ± 3	17 ± 0	23 ± 9
trans-**14c**	Me	3-F-C_6H_4	132 ± 5	100 ± 16	88 ± 9	152 ± 1
cis-**14c**/*trans*-**14c** (97:3)	Me	3-F-C_6H_4	118 ± 8	77 ± 20	86 ± 13	149 ± 1
trans-**15c**/*cis*-**15c** (90:10)	Bn	3-F-C_6H_4	17 ± 5	17 ± 2	63 ± 18	28 ± 4
cis-**15c**/*trans*-**15c** (80:20)	Bn	3-F-C_6H_4	89 ± 9	49 ± 12	73 ± 11	204 ± 66
trans-**14d**	Me	4-F-C_6H_4	126 ± 6	93 ± 10	82 ± 16	158 ± 8
cis-**14d**/*trans*-**14d** (75:25)	Me	4-F-C_6H_4	≥250	173 ± 51	158 ± 44	≥250
trans-**15d**/*cis*-**15d** (95:5)	Bn	4-F-C_6H_4	17 ± 0	13 ± 1	18 ± 1	26 ± 2
cis-**15d**/*trans*-**15d** (75:52)	Bn	4-F-C_6H_4	19 ± 0	17 ± 3	17 ± 1	27 ± 1
5-Fluorouracil			0.33 ± 0.17	18 ± 5	0.54 ± 0.12	n.d.

[a] 50% Inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%.
[b] n.d. – not determined.
[c] Results are mean values ± STDEV of two independent experiments.

with methylene chloride-hexane mixture (7:3, v/v) and the appropriate fractions were crystallized from a chloroform-hexane mixture.

4.3.1. 1-Allyl-3-(2-fluoro)benzoyl-1H-quinazoline-2,4-dione (**18b**)

An amorphous solid, m.p. = 141–142 °C. IR (KBr, cm^{-1}) ν_{max}: 3253, 2923, 1739, 1693, 1658, 1608, 1478, 1454, 1172, 1013, 944, 755. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 8.15 (dt, *J* = 7,9 Hz, *J* = 1.7 Hz, 1H), 7.73 (ddd, *J* = 8.6 Hz, *J* = 7.3 Hz, *J* = 1.6 Hz, 1H), 7.66–7.62 (m, 1H), 7.35–7.29 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.12 (ddd, *J* = 11.7 Hz, *J* = 8.3 Hz, *J* = 1.0 Hz, 1H), 5.95 (ddt, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^3J = 4.9 Hz, 1H, CH_2–C*H*=CH_2), 5.32 (d, ^3J = 10.2 Hz, 1H, CH_2–CH=CH*H*), 5.28 (d, ^3J = 17.2 Hz, 1H, CH_2–CH=C*H*H), 4.82–4.79 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.80 (C=O), 162.09 (d, $^1J_{(CF)}$ = 259.0 Hz), 160.79 (C=O), 149.07 (C=O), 140.41, 136.84 (d, $^3J_{(CCCF)}$ = 9.8 Hz), 135.85, 133.03, 130.73, 128.92, 125.03 (d, $^4J_{(CCCCF)}$ = 3.3 Hz), 123.43, 120.51 (d, $^2J_{(CCF)}$ = 7.8 Hz), 117.88, 117.21 (d, $^2J_{(CCF)}$ = 23.2 Hz), 114.84, 45.22. Anal. calcd. For $C_{18}H_{13}FN_2O_3$: C, 66.66; H, 4.04; N, 8.64. Found: C, 66.41; H, 3.73; N, 8.59.

4.3.2. 1-Allyl-3-(3-fluoro)benzoyl-1H-quinazoline-2,4-dione (**18c**)

An amorphous solid, m.p. = 125–127 °C. IR (KBr, cm^{-1}) ν_{max}: 3073, 2973, 1743, 1697, 1670, 1481, 1432, 1286, 1048, 779. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.9 Hz), 7.81–7.75 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.50 (dt, *J* = 8.0 Hz, *J* = 5.7 Hz, 1H), 7.38 (dt, *J* = 8.2 Hz, *J* = 2.1 Hz, 1H), 7.35–7.28 (m, 2H), 5.96 (ddt, ^3J = 17.7 Hz, ^3J = 10.9 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.35 (d, ^3J = 10.9 Hz, 1H, CH_2–CH=CH*H*), 5.30 (d, ^3J = 17.7 Hz, 1H, CH_2–CH=C*H*H), 4.80 (d, ^3J = 5.0 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.72 (d, $^4J_{(C(O)CCCF)}$ = 3.2 Hz, C=O), 162.93 (d, $^1J_{(CF)}$ = 248.9 Hz), 161.03 (C=O), 149.13 (C=O), 140.49, 136.03, 133.99 (d, $^3J_{(CCCF)}$ = 7.3 Hz), 130.89 (d, $^3J_{(CCCF)}$ = 7.7 Hz), 130.77, 129.09, 126.14 (d, $^4J_{(CCCCF)}$ = 2.8 Hz), 122.10 (d, $^2J_{(CCF)}$ = 21.8 Hz), 118.39, 117.38 (d, $^2J_{(CCF)}$ = 23.3 Hz), 115.59, 114.83, 45.44. Anal. calcd. For $C_{18}H_{13}FN_2O_3$: C, 66.66; H, 4.04; N, 8.64. Found: C, 66,63; H, 3.64; N, 8.82.

4.3.3. 1-Allyl-3-(4-fluoro)benzoyl-1H-quinazoline-2,4-dione (**18d**)

An amorphous solid, m.p. = 117.0–118.5 °C. IR (KBr, cm^{-1}) ν_{max}: 3084, 2987, 1744, 1700, 1661, 1495, 1411, 1242, 994, 757. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H), 8.04–8.02 (m, 2H), 7.76 (ddd, *J* = 8.7 Hz, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.34 (dd, *J* = 7.7 Hz, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.21–7.18 (m, 2H), 5.97 (ddt, ^3J = 17.0 Hz, ^3J = 10.7 Hz, ^3J = 5.2 Hz, 1H, CH_2–C*H*=CH_2), 5.35 (d, ^3J = 10.7 Hz, 1H, CH_2–CH=CH*H*), 5.30 (d, ^3J = 17.0 Hz, 1H, CH_2–CH=C*H*H), 4.81 (d, ^3J = 5.2 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.45 (C=O), 166.92 (d, $^1J_{(CF)}$ = 258.4 Hz), 161.06 (C=O), 149.17 (C=O), 140.49, 135.98, 133.31 (d, $^3J_{(CCCF)}$ = 9.9 Hz), 130.83, 128.34 (d, $^4J_{(CCCCF)}$ = 2.9 Hz), 123.58, 118.35, 116.54 (d, $^2J_{(CCF)}$ = 22.4 Hz), 115.62, 114.81, 45.43. Anal. calcd. For $C_{18}H_{13}FN_2O_3$: C, 66.66; H, 4.04; N, 8.64. Found: C, 66,75; H, 3.95; N, 8.52.

4.4. The benzylation of N-allylquinazoline-2,4-dione **22** – the general procedure

To a solution of *N*-allylquinazoline-2,4-dione **22** (1.00 mmol) in acetonitrile (15 mL) potassium hydroxide (3.00 mmol) was added followed by the respective benzyl chloride (1.10 mmol). The reaction mixture was stirred at 105 °C for 4 h. The solvent was removed in vacuo, the residue was dissolved in methylene chloride (10 mL) and washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated and the crude product was purified by column chromatography with methylene chloride-hexane mixture (7:3, v/v) and further crystallized from a chloroform-petroleum ether mixture.

4.4.1. 1-Allyl-3-benzyl-1H-quinazoline-2,4-dione (**19a**)

An amorphous solid, m.p. = 85–86 °C. IR (KBr, cm^{-1}) ν_{max}: 3085, 2853, 1699, 1657, 1609, 1484, 1456, 1435, 1269, 946, 759. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28–8.27 (m, 1H), 7.68–7.64 (m, 1H), 7.55–7.74 (m, 2H), 7.34–7.32 (m, 2H), 7.29–7.25 (m, 2H), 7.19–7.18 (m, 1H), 5.95 (ddt, ^3J = 17.0 Hz, ^3J = 10.3 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.32 (s, 2H, C*H*$_2$Ph), 5.29 (d, ^3J = 10.3 Hz, 1H, CH_2–CH=CH*H*), 5.23 (d, ^3J = 17.3 Hz, 1H, CH_2–CH=C*H*H), 4.80 (d, ^3J = 4.9 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.76 (C=O), 150.85 (C=O), 139.90, 137.05, 134.99, 131.30, 129.16, 128.99, 128.42, 122.97, 117.64, 115.75, 114.14, 46.04, 45.05. Anal. calcd. For $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.59; H, 5.52; N, 9.61.

4.4.2. 1-Allyl-3-(2-fluoro)benzyl-1H-quinazoline-2,4-dione (**19b**)

An amorphous solid, m.p. = 105–107 °C. IR (KBr, cm^{-1}) ν_{max}: 3090, 3067, 2975, 1707, 1661, 1608, 1480, 1416, 1290, 975, 917, 752. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.9 Hz, 1H), 7.69–7.66 (m, 1H), 7.31–7.26 (m, 2H), 7.26–7.21 (m, 2H), 7.08–7.06 (m, 2H), 5.95 (ddt, ^3J = 17.3 Hz, ^3J = 10.2 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.42 (s, 2H, C*H*$_2$Ph), 5.29 (d, ^3J = 10.2 Hz, 1H, CH_2–CH=CH*H*), 5.24 (d, ^3J = 17.3 Hz, 1H, CH_2–CH=C*H*H), 4.82 (d, ^3J = 5.0 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.68 (C=O), 160.80 (d, $^1J_{(CF)}$ = 247.6 Hz), 150.70 (C=O), 139.95, 135.10, 131.24, 129.24, 129.23 (d, $^4J_{(CCCCF)}$ = 3.0 Hz), 128.95 (d, $^3J_{(CCCF)}$ = 7.9 Hz), 124.04 (d, $^3J_{(CCCF)}$ = 3.9 Hz), 123.92 (d, $^2J_{(CCF)}$ = 14.3 Hz), 123.05, 117.66, 115.62, 115.48 (d, $^2J_{(CCF)}$ = 21.8 Hz), 114.21, 46.03, 38.93 (d, $^3J_{(CCCF)}$ = 4.7 Hz). Anal. calcd. For $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.75; H, 4.53; N, 9.14.

4.4.3. 1-Allyl-3-(3-fluoro)benzyl-1H-quinazoline-2,4-dione (**19c**)

An amorphous solid, m.p. = 85–86 °C. IR (KBr, cm^{-1}) ν_{max}: 3083, 3017, 1701, 1656, 1483, 1401, 1346, 1209, 978, 943, 760. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28–8.27 (m, 1H), 7.68–7.66 (m, 1H), 7.32–7.27 (m, 3H), 7.24–7.20 (m, 2H), 6.98–6.96 (m, 1H), 5.95 (ddt, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.30–5.29 (m, 3H, C*H*$_2$Ph, CH_2–CH=CH*H*), 5.24 (d, ^3J = 17.2 Hz, 1H, CH_2–CH=C*H*H), 4.81 (d, ^3J = 5.0 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.83 (d, $^1J_{(CF)}$ = 245.8 Hz), 161.69 (C=O), 150.77 (C=O), 139.90, 139.40 (d, $^3J_{(CCCF)}$ = 7.6 Hz), 135.14, 131.20, 129.80 (d, $^3J_{(CCCF)}$ = 7.9 Hz), 129.18, 124.52 (d, $^4J_{(CCCCF)}$ = 3.1 Hz), 123.09, 117.72, 115.78 (d, $^2J_{(CCF)}$ = 21.9 Hz), 115.62, 114.53 (d, $^2J_{(CCF)}$ = 21.0 Hz), 114.21, 46.08, 45.05 (d, $^4J_{(CCCCF)}$ = 1.5 Hz). Anal. calcd. For $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.71; H, 4.48; N, 9.00.

4.4.4. 1-Allyl-3-(4-fluoro)benzyl-1H-quinazoline-2,4-dione (**19d**)

An amorphous solid, m.p. = 94.0–95.5 °C. IR (KBr, cm^{-1}) ν_{max}: 3092, 3021 2964, 1702, 1657, 1603, 1483, 1436, 1216, 1159, 961, 751. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28–8.26 (m, 1H), 7.67–7.64 (m, 1H), 7.57–7.54 (m, 2H), 7.29–7.26 (m, 1H), 7.20–7.18 (m, 1H), 7.02–6.99 (m, 2H), 5.98 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 5.0 Hz, 1H, CH_2–C*H*=CH_2), 5.29 (d, ^3J = 10.2 Hz, 1H, CH_2–CH=CH*H*), 5.27 (s, 2H, C*H*$_2$Ph), 5.23 (d, ^3J = 17.1 Hz, 1H, CH_2–CH=C*H*H), 4.80 (d, ^3J = 5.0 Hz, 2H, C*H*$_2$–CH=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.31 (d, $^1J_{(CF)}$ = 246.8 Hz), 161.71 (C=O), 150.78 (C=O), 139.87, 135.07, 132.87 (d, $^4J_{(CCCCF)}$ = 3.3 Hz), 131.23, 131.05 (d, $^3J_{(CCCF)}$ = 7.6 Hz), 129.12, 123.04, 117.67, 115.67, 115.20 (d, $^2J_{(CCF)}$ = 20.8 Hz), 114.18, 46.03, 44.31. Anal. calcd. For $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.31; H, 4.59; N, 9.18.

4.5. Cycloadditions of C-(diethoxyphosphoryl)nitrones **16** (R = Me) and **17** (R = Bn) and N^1-allylated quinazoline-2,4-diones **18** and **19** – the general procedure

Solutions of nitrones **16** or **17** (1.00 mmol) and the respective N^1-allylated quinazoline-2,4-diones **18** or **19** (1.05 mmol) in toluene or a toluene-ethanol mixture were stirred at 60 °C until the starting nitrone disappeared. Solvents were removed in vacuo and the crude products (the respective mixtures of isoxazolidines *cis*-**12**/*trans*-**12**, *cis*-**13**/*trans*-**13**, *cis*-**14**/*trans*-**14** or *cis*-**15**/*trans*-**15**) were purified on silica gel columns.

4.5.1. Diethyl trans-{5-[(3-(2-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**12b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3451, 2981, 2924, 1748, 1702, 1666, 1609, 1481, 1390, 1234, 1052, 1023, 970, 758. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.7 Hz, 1H), 8.14 (t, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.76–7.73 (m, 1H), 7.66–7.63 (m, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.35–7.31 (m, 2H), 7.12 (dd, *J* = 11.4 Hz, *J* = 8.5 Hz, 1H), 4.51 (dd, ^2J = 15.1 Hz, ^3J = 4.5 Hz, 1H, *H*CHN), 4.45–4.41 (m, 1H, *H*C5), 4.23–4.15 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.02–3.00 (m, 1H, *H*C3), 2.86 (s, 3H, C*H*$_3$N), 2.66 (dddd, $^3J_{(H4\alpha-P)}$ = 19.6 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 13.4 Hz, $^3J_{(H4\alpha-H3)}$ = 7.1 Hz, $^3J_{(H4\beta-H5)}$ = 7.1 Hz, 1H, *H*αC4), 2.45 (dddd, $^2J_{(H4\beta-H4\alpha)}$ = 13.4 Hz, $^3J_{(H4\beta-P)}$ = 13.4 Hz, $^3J_{(H4\beta-H5)}$ = 9.6 Hz, $^3J_{(H4\beta-H3)}$ = 8.1 Hz, 1H, *H*βC4), 1.34 (t, ^3J = 7.1 Hz, 3H, 2 × C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.62 (C=O), 162.07 (d, $^1J_{(CF)}$ = 259.7 Hz), 160.65 (C=O), 149.65 (C=O), 140.71, 136.81 (d, $^3J_{(CCCF)}$ = 9.9 Hz), 135.68, 133.06, 128.89, 125.04 (d, $^4J_{(CCCCF)}$ = 3.4 Hz), 123.65, 120.52 (d, $^2J_{(CCF)}$ = 7.8 Hz), 117.16 (d, $^2J_{(CCF)}$ = 23.2 Hz), 115.76, 115.24, 75.22 (d, $^3J_{(CCCP)}$ = 7.2 Hz, C5), 63.92 (d, $^1J_{(CP)}$ = 168.1 Hz, C3), 63.14 (d, $^2J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.44 (d, $^2J_{(COP)}$ = 7.2 Hz, CH_2OP), 46.27, 45.21, 36.85 (d, $^2J_{(CCP)}$ = 1.3 Hz, C4), 16.49 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH_3CH$_2$OP), 16.43 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH_3CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.67. Anal. calcd. for $C_{24}H_{27}FN_3O_7P$: C, 55.49; H, 5.24; N, 8.09. Found: C, 55.77; H, 5.04; N, 8.01.

4.5.2. Diethyl cis-{5-[(3-(3-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (cis-**12c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3430, 2983, 1751, 1700, 1666, 1605, 1480, 1447, 1395, 1250, 1050, 1025, 970, 790, 757. (^{1}H NMR signals of *cis*-**12c** were extracted from the spectrum of a 94:6 mixture of *cis*-**12c** and *trans*-**12c**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 7.88–7.85 (m, 1H), 7.82–7.73 (m, 1H), 7.70–7.65 (m, 1H), 7.55–7.50 (m, 2H), 7.40–7.30 (m, 2H), 4.65–4.58 (m, 1H, *H*C5), 4.35 (dd, *J* = 14.8 Hz, *J* = 9.8 Hz, 1H, *H*CHN), 4.25–4.15 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 2.99–2.94 (very broad m, 1H, *H*C3), 2.85 (s, 3H, C*H*$_3$N), 2.85–2.77 (m, *H*αC4), 2.48–2.40 (broad m, 1H, *H*βC4), 1.41 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP), 1.40 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *cis*-**12c** were extracted from the spectrum of a 40:60 mixture of *cis*-**12c** and *trans*-**12c**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.83 (d, $^4J_{(C(O)CCCF)}$ = 3.0 Hz, C=O), 162.94 (d, $^1J_{(CF)}$ = 248.5 Hz), 161.23 (C=

O), 149.59 (C=O), 141.75, 135.73, 133.89 (d, $^{3}J_{(CCCF)}$ = 9.6 Hz), 130.85 (d, $^{3}J_{(CCCF)}$ = 4.0 Hz), 128.46, 126.17 (d, $^{4}J_{(CCCCF)}$ = 2.1 Hz), 123.58, 122.08 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 117.11 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 116.24, 115.27, 75.04 (d, $^{3}J_{(CCCP)}$ = 6.9 Hz, C5), 63.62 (d, $^{1}J_{(CP)}$ = 168.0 Hz, C3), 62.88 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 62.65 (d, $^{2}J_{(COP)}$ = 7.2 Hz, CH_2OP), 46.59, 45.17, 35.53 (C4), 16.60 (d, $^{3}J_{(CCOP)}$ = 5.5 Hz, CH_3CH_2OP), 16.52 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.44. Anal. calcd. for $C_{24}H_{27}FN_3O_7P$: C, 55.49; H, 5.24; N, 8.09. Found: C, 55.28; H, 5.27; N, 7.93.

4.5.3. Diethyl trans-{5-[(3-(3-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**12c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3424, 2980, 1752, 1703, 1665, 1608, 1481, 1442, 1389, 1262, 1052, 1024, 968, 794. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H), 7.80–7.75 (m, 2H), 7.70–7.65 (m, 1H), 7.55–7.50 (m, 2H), 7.40–7.32 (m, 2H), 4.54–4.44 (m, 2H, *H*CHN, *H*C5), 4.30–4.15 (m, 5H, 2 × CH_2OP, HC*H*N), 3.10–3.00 (very broad m, 1H, *H*C3), 2.89 (s, 3H, CH_3N), 2.72 (dddd, $^{3}J_{(H4\alpha-P)}$ = 17.0 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.4 Hz, $^{3}J_{(H4\alpha-H3)}$ = 7.4 Hz, $^{3}J_{(H4\beta-H5)}$ = 7.4 Hz, 1H, *H*αC4), 2.48–2.40 (broad m, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.34 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.58 (d, $^{4}J_{(C(O)CCCF)}$ = 3.0 Hz, C=O), 162.94 (d, $^{1}J_{(CF)}$ = 249.1 Hz), 160.91 (C=O), 149.67 (C=O), 140.69, 135.93, 133.89 (d, $^{3}J_{(CCCF)}$ = 9.6 Hz), 130.89 (d, $^{3}J_{(CCCF)}$ = 7.7 Hz), 129.02, 126.19 (d, $^{4}J_{(CCCCF)}$ = 2.4 Hz), 123.86, 122.17 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 117.11 (d, $^{2}J_{(CCF)}$ = 23.2 Hz), 115.56, 115.26, 75.24 (broad s, C5), 63.62 (d, $^{1}J_{(CP)}$ = 168.0 Hz, C3), 63.27 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.59 (d, $^{2}J_{(COP)}$ = 6.9 Hz, CH_2OP), 45.98, 45.57, 35.93 (C4), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.8 Hz, CH_3CH_2OP), 16.44 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.33. Anal. calcd. for $C_{24}H_{27}FN_3O_7P$: C, 55.49; H, 5.24; N, 8.09. Found: C, 55.31; H, 5.41; N, 7.94.

4.5.4. Diethyl cis-{5-[(3-(4-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (cis-**12d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3460, 2923, 1750, 1700, 1699, 1663, 1600, 1485, 1297, 1245, 1025, 970, 760. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22–8.21 (m, 1H), 8.04–8.02 (m, 2H), 7.88–7.86 (m, 1H), 7.76–7.73 (m, 1H), 7.33–7.31 (m, 1H) 7.21–7.18 (m, 2H), 4.63–4.59 (m, 1H, *H*C5), 4.35 (dd, ^{2}J = 14.8 Hz, ^{3}J = 9.8 Hz, 1H, *H*CHN), 4.30–4.22 (m, 4H, 2 × CH_2OP), 4.20 (dd, ^{2}J = 14.8 Hz, ^{3}J = 2.5 Hz, 1H, HC*H*N), 2.95 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.9 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.7 Hz, $^{2}J_{(H3-P)}$ = 2.3 Hz, 1H, *H*C3), 2.85 (s, 3H, CH_3N), 2.84 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.2 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.7 Hz, $^{3}J_{(H4\alpha-H3)}$ = 9.9 Hz, $^{3}J_{(H4\beta-H5)}$ = 8.8 Hz, 1H, *H*αC4), 2.39 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.7 Hz, $^{3}J_{(H4\beta-P)}$ = 11.5 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.7 Hz, $^{3}J_{(H4\beta-H5)}$ = 3.6 Hz, 1H, *H*βC4), 1.42 (t, ^{3}J = 7.2 Hz, 6H, 2 × CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.52 (C=O), 166.92 (d, $^{1}J_{(CF)}$ = 258.5 Hz), 161.25 (C=O), 149.63 (C=O), 141.78, 135.67, 133.34 (d, $^{3}J_{(CCCF)}$ = 9.9 Hz), 128.45, 128.38 (d, $^{4}J_{(CCCCF)}$ = 2.4 Hz), 123.52, 116.51 (d, $^{2}J_{(CCF)}$ = 22.4 Hz), 116.21, 115.32, 75.00 (d, $^{3}J_{(CCCP)}$ = 7.0 Hz, C5), 63.13 (d, $^{1}J_{(CP)}$ = 169.3 Hz, C3), 62.83 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 62.63 (d, $^{2}J_{(COP)}$ = 7.0 Hz, CH_2OP), 46.58, 45.22 (d, ^{3}J = 4.2 Hz, 35.55 (C4), 16.59 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.52 (d, $^{3}J_{(CCOP)}$ = 5.9 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.46. Anal. calcd. for $C_{24}H_{27}FN_3O_7P \times H_2O$: C, 53.63; H, 5.44; N, 7.82. Found: C, 53.68; H, 5.29; N, 7.98.

4.5.5. Diethyl trans-{5-[(3-(4-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**12d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3451, 2963, 1748, 1702, 1664, 1601, 1480, 1390, 1242, 1157, 1100, 1020, 971, 757. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.26–8.24 (m, 1H), 8.04–8.02 (m, 2H), 7.78–7.75 (m, 1H), 7.51–7.50 (m, 1H), 7.36–7.34 (m, 1H), 7.21–7.18 (m, 2H), 4.35 (dd, ^{2}J = 15.0 Hz, ^{3}J = 9.8 Hz, 1H, *H*CHN), 4.46–4.42 (m, 1H, *H*C5), 4.23–4.16 (m, 5H, 2 × CH_2OP, HC*H*N), 3.05–2.99 (m, 1H, *H*C3), 2.88 (s, 3H, CH_3N), 2.72 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.4 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.5 Hz, $^{3}J_{(H4\alpha-H3)}$ = 7.0 Hz, $^{3}J_{(H4\beta-H5)}$ = 7.0 Hz, 1H, *H*αC4), 2.42 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.5 Hz, $^{3}J_{(H4\beta-P)}$ = 12.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 10.1 Hz, $^{3}J_{(H4\beta-H3)}$ = 8.2 Hz, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.34 (t, ^{3}J = 7.2 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.28 (C=O), 166.95 (d, $^{1}J_{(CF)}$ = 258.5 Hz), 160.93 (C=O), 149.69 (C=O), 140.71, 135.81, 133.35 (d, $^{3}J_{(CCCF)}$ = 9.9 Hz), 128.98, 128.25 (d, $^{4}J_{(CCCCF)}$ = 2.7 Hz), 123.77, 116.53 (d, $^{2}J_{(CCF)}$ = 22.7 Hz), 115.60, 115.20, 75.15 (d, $^{3}J_{(CCCP)}$ = 6.7 Hz, C5), 63.91 (d, $^{1}J_{(CP)}$ = 167.9 Hz, C3), 63.14 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.50 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 46.25, 45.54, 36.04 (C4), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.8 Hz, CH_3CH_2OP), 16.43 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.59. Anal. calcd. for $C_{24}H_{27}FN_3O_7P \times H_2O$: C, 53.63; H, 5.44; N, 7.82. Found: C, 53.80; H, 5.32; N, 8.04.

4.5.6. Diethyl cis-{5-[(3-benzoyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-benzylisoxazolidin-3-yl}phosphonate (cis-**13a**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3455, 2960, 1749, 1660, 1642, 1490, 1378, 1296, 1089, 1180, 1050, 1020, 970, 690. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 1H), 7.98–7.97 (m, 2H), 7.67–7.65 (m, 1H), 7.52–7.49 (m, 2H), 7.41–7.39 (m, 1H), 7.35–7.34 (m, 2H), 7.30–7.29 (m, 3H), 7.15–7.12 (m, 2H), 4.64–4.62 (m, 1H, *H*C5), 4.44 (d, ^{2}J = 13.7 Hz, 1H, *H*CHPh), 4.31–4.24 (m, 5H, 2 × CH_2OP, *H*CHN), 4.21 (dd, ^{2}J = 14.9 Hz, ^{3}J = 2.3 Hz, 1H, HC*H*N), 3.92 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.24 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 10.2 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.3 Hz, $^{2}J_{(H3-P)}$ = 3.1 Hz, 1H, *H*C3), 2.81 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.7 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.9 Hz, $^{3}J_{(H4\alpha-H3)}$ = 10.2 Hz, $^{3}J_{(H4\beta-H5)}$ = 10.2 Hz, 1H, *H*αC4), 2.31 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.9 Hz, $^{3}J_{(H4\beta-P)}$ = 12.9 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.3 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.1 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.1 Hz, 6H, 2 × CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.78 (C=O), 161.25 (C=O), 149.75 (C=O), 141.15, 136.61, 135.65, 134.91, 131.89, 130.47, 129.93, 129.13, 128.31, 128.18, 127.59, 123.15, 116.01, 115.08, 75.69 (d, $^{3}J_{(CCCP)}$ = 6.6 Hz, C5), 62.94 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.69 (d, $^{2}J_{(COP)}$ = 7.1 Hz, CH_2OP), 62.36 (d, $^{3}J_{(CNCP)}$ = 5.1 Hz, CH_2Ph), 60.63 (d, $^{1}J_{(CP)}$ = 170.1 Hz, C3), 47.14 (CH_2N), 35.07 (s, C4), 16.61 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.64. Anal. calcd. for $C_{30}H_{32}N_3O_7P$: C, 62.39; H, 5.58; N, 7.28. Found: C, 62.58; H, 5.53; N, 7.18.

4.5.7. Diethyl trans-{5-[(3-benzoyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-benzylisoxazolidin-3-yl} phosphonate (trans-**13a**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3455, 3062, 2982, 1750, 1701, 1665, 1608, 1480, 1390, 1238, 1052, 1023, 968, 757. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 7.98–7.96 (m, 2H), 7.73–7.70 (m, 1H), 7.68–7.66 (m, 1H), 7.52–7.46 (m, 3H), 7.36–7.33 (m, 1H), 7.31–7.28 (m, 5H), 4.47 (d, ^{2}J = 14.8 Hz, ^{3}J = 4.2 Hz, 1H, *H*CHN), 4.46–4.41 (m, 2H, *H*C5, HC*H*N), 4.26–4.17 (m, 5H, 2 × CH_2OP, HC*H*Ph), 3.91 (d, ^{2}J = 13.9 Hz, 1H, HC*H*Ph), 3.30 (ddd, $^{3}J_{(H3-H4\beta)}$ = 10.0 Hz, $^{3}J_{(H3-H4\alpha)}$ = 6.5 Hz, $^{2}J_{(H3-P)}$ = 2.7 Hz, 1H, *H*C3), 2.68 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.0 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.0 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.5 Hz, 1H, *H*αC4), 2.38 (dddd, $^{3}J_{(H4\beta-P)}$ = 14.9 Hz, $^{2}J_{(H4\beta-H4\alpha)}$ = 13.0 Hz, $^{3}J_{(H4\beta-H3)}$ = 10.0 Hz, $^{3}J_{(H4\beta-H5)}$ = 8.12 Hz, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP), 1.34 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.52 (C=O), 160.99 (C=O), 149.80 (C=O), 140.81, 136.46, 135.66, 135.04, 131.68, 130.49, 129.64, 129.19, 128.87, 128.16, 127.52, 123.69, 115.59, 115.52, 75.48 (d, $^{3}J_{(CCCP)}$ = 6.4 Hz, C5), 63.31 (d,

$^{2}J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.71 (d, $^{3}J_{(CNCP)}$ = 3.8 Hz, CH_2Ph), 62.51 (d, $^{2}J_{(COP)}$ = 6.8 Hz, CH_2OP), 60.72 (d, $^{1}J_{(CP)}$ = 170.2 Hz, C3), 45.22 (CH_2N), 35.19 (d, $^{2}J_{(CCP)}$ = 1.8 Hz, C4), 16.57 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP), 16.49 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.67. Anal. calcd. for $C_{30}H_{32}N_3O_7P$: C, 62.39; H, 5.58; N, 7.28. Found: C, 62.18; H, 5.49; N, 7.07.

4.5.8. Diethyl cis-{2-benzyl-5-[(3-(2-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (cis-**13b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3472, 2978, 1744, 1700, 1662, 1607, 1478, 1389, 1240, 1012, 970, 756. (^{1}H NMR signals of *cis*-**13b** were extracted from the spectrum of a 90:10 mixture of *cis*-**13b** and *trans*-**13b**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.20 (m, 1H), 8.16–8.09 (m, 1H), 7.66–7.62 (m, 1H), 7.38–7.34 (m, 4H), 7.32–7.29 (m, 3H), 7.14–7.10 (m, 3H), 4.62 (dddd, $^{3}J_{(H5-H4\alpha)}$ = 9.9 Hz, $^{3}J_{(H5-CH)}$ = 7.4 Hz, $^{3}J_{(H5-H4\beta)}$ = 4.2 Hz, $^{3}J_{(H5-CH)}$ = 4.2 Hz, 1H, *H*C5), 4.43 (d, ^{2}J = 13.9 Hz, 1H, *H*CHPh), 4.31–4.18 (m, 5H, 2 × C*H*$_2$OP, *H*CHN), 4.19 (dd, ^{2}J = 14.8 Hz, $^{3}J_{(HC-H5)}$ = 7.3 Hz, 1H, HC*H*N), 3.92 (d, ^{2}J = 13.9 Hz, 1H, HC*H*Ph), 3.24 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.9 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.6 Hz, $^{2}J_{(H3-P)}$ = 3.1 Hz, 1H, *H*C3), 2.81 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.7 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.7 Hz, $^{3}J_{(H4\alpha-H3)}$ = 9.9 Hz, $^{3}J_{(H4\beta-H5)}$ = 9.9 Hz, 1H, *H*αC4), 2.41 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.7 Hz, $^{3}J_{(H4\beta-P)}$ = 12.7 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.6 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.2 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.1 Hz, 3H, 2 × C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *cis*-**13b** were extracted from the spectrum of a 59:41 mixture of *cis*-**13b** and *trans*-**13b**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.89 (C═O), 162.08 (d, $^{1}J_{(CF)}$ = 259.7 Hz), 160.94 (C═O), 149.57 (C═O), 141.06, 136.66 (d, $^{3}J_{(CCCF)}$ = 9.7 Hz), 136.60, 135.59, 132.96, 129.96, 128.79, 128.28, 127.56, 124.93 (d, $^{4}J_{(CCCCF)}$ = 3.8 Hz), 123.08, 120.55 (d, $^{2}J_{(CCF)}$ = 8.0 Hz), 117.18 (d, $^{2}J_{(CCF)}$ = 23.2 Hz), 115.96, 115.18, 75.67 (d, $^{3}J_{(CCCP)}$ = 7.2 Hz, C5), 62.93 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.65 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.69 (d, $^{3}J_{(CNCP)}$ = 4.0 Hz, CH_2Ph), 60.65 (d, $^{1}J_{(CP)}$ = 170.1 Hz, C3), 47.07 (CH_2N), 35.12 (C4), 16.61 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.61. Anal. calcd. for $C_{30}H_{31}FN_3O_7P$: C, 60.50; H, 5.25; N, 7.06. Found: C, 60.41; H, 5.12; N, 6.82 (obtained on a 59:41 mixture of *cis*-**13b** and *trans*-**13b**).

4.5.9. Diethyl trans-{2-benzyl-5-[(3-(2-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (trans-**13b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3063, 2930, 1749, 1702, 1666, 1609, 1480, 1454, 1391, 1159, 1051, 1022, 967, 775. (NMR signals of *trans*-**13b** were extracted from the spectra of a 10:90 mixture of *cis*-**13b** and *trans*-**13b**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1H), 8.15–8.10 (m, 1H), 7.70–7.67 (m, 1H), 7.66–7.62 (m, 1H), 7.44–7.43 (m, 1H), 7.36–7.27 (m, 7H), 7.13–7.09 (m, 1H), 4.47–4.42 (m, 2H, *H*CHN, *H*C5), 4.43 (d, ^{2}J = 13.8 Hz, 1H, *H*CHPh), 4.26–4.20 (m, 4H, 2 × C*H*$_2$OP), 4.18 (dd, ^{2}J = 14.8 Hz, $^{3}J_{(HC-H5)}$ = 7.1 Hz, 1H, HC*H*N), 3.87 (d, ^{2}J = 13.8 Hz, 1H, HC*H*Ph), 3.28 (ddd, $^{3}J_{(H3-H4\beta)}$ = 9.5 Hz, $^{3}J_{(H3-H4\alpha)}$ = 6.5 Hz, $^{2}J_{(H3-P)}$ = 2.8 Hz, 1H, *H*C3), 2.67 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.2 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.5 Hz, 1H, *H*αC4), 2.37 (dddd, $^{3}J_{(H4\beta-P)}$ = 14.8 Hz, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 9.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 8.0 Hz, 1H, *H*βC4), 1.34 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.33 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.62 (C═O), 162.05 (d, $^{1}J_{(CF)}$ = 259.4 Hz), 160.66 (C═O), 149.70 (C═O), 140.77, 136.80 (d, $^{3}J_{(CCCF)}$ = 9.8 Hz), 136.60, 135.60, 133.06, 129.51, 128.78, 128.14, 127.45, 125.05 (d, $^{4}J_{(CCCCF)}$ = 3.6 Hz), 123.60, 120.51 (d, $^{2}J_{(CCF)}$ = 8.1 Hz), 117.16 (d, $^{2}J_{(CCF)}$ = 23.1 Hz), 115.70, 115.56, 75.50 (d, $^{3}J_{(CCCP)}$ = 6.5 Hz, C5), 63.25 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.76 (d, $^{3}J_{(CNCP)}$ = 4.9 Hz, CH_2Ph), 62.46 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 60.84 (d, $^{1}J_{(CP)}$ = 169.9 Hz, C3), 44.91 (CH_2N), 34.96 (d, $^{2}J_{(CCP)}$ = 1.6 Hz, C4), 16.54 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.47 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.72. Anal. calcd. for $C_{30}H_{31}FN_3O_7P$: C, 60.50; H, 5.25; N, 7.06. Found: C, 60.58.; H, 5.23; N, 6.97 (obtained on a 10:90 mixture of *cis*-**13b** and *trans*-**13b**).

4.5.10. Diethyl cis-{2-benzyl-5-[(3-(3-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (cis-**13c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3063, 3031, 2982, 2930, 1751, 1702, 1665, 1608, 1480, 1389, 1284, 1159, 1051, 1022, 965, 793. (^{1}H NMR signals of *cis*-**13c** were extracted from the spectrum of a 87:13 mixture of *cis*-**13c** and *trans*-**13c**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 1H), 7.76–7.73 (m, 1H), 7.68–7.66 (m, 1H), 7.51–7.46 (m, 4H), 7.33–7.29 (m, 4H), 7.17–7.12 (m, 1H), 4.63 (dddd, $^{3}J_{(H5-H4\alpha)}$ = 10.1 Hz, $^{3}J_{(H5-CH)}$ = 8.5 Hz, $^{3}J_{(H5-H4\beta)}$ = 4.0 Hz, $^{3}J_{(H5-CH)}$ = 2.0 Hz, 1H, *H*C5), 4.44 (d, ^{2}J = 13.4 Hz, 1H, *H*CHPh), 4.32–4.24 (m, 5H, 2 × C*H*$_2$OP, *H*CHN), 4.20 (dd, ^{2}J = 14.6 Hz, ^{3}J = 2.0 Hz, 1H, HC*H*N), 3.92 (d, ^{2}J = 13.4 Hz, 1H, HC*H*Ph), 3.24 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 10.1 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.3 Hz, $^{2}J_{(H3-P)}$ = 3.2 Hz, 1H, *H*C3), 2.82 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.7 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.0 Hz, $^{3}J_{(H4\alpha-H3)}$ = 10.1 Hz, $^{3}J_{(H4\beta-H5)}$ = 10.1 Hz, 1H, *H*αC4), 2.42 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 13.0 Hz, $^{3}J_{(H4\beta-P)}$ = 11.5 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.3 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.0 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.0 Hz, 3H, 2 × C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *cis*-**13c** were extracted from the spectrum of a 59:41 mixture of *cis*-**13c** and *trans*-**13c**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.89 (d, $^{4}J_{(C(O)CCCF)}$ = 3.0 Hz, C═O), 162.93 (d, $^{1}J_{(CF)}$ = 248.8 Hz), 161.21 (C═O), 149.64 (C═O), 141.13, 136.58, 135.79, 134.06 (d, $^{3}J_{(CCCF)}$ = 7.4 Hz), 130.85 (d, $^{3}J_{(CCCF)}$ = 7.1 Hz), 129.95, 128.31, 128.15, 127.59, 126.16 (d, $^{4}J_{(CCCCF)}$ = 2.8 Hz), 123.27, 122.05 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 117.07 (d, $^{2}J_{(CCF)}$ = 23.2 Hz), 116.11, 114.95, 75.63 (d, $^{3}J_{(CCCP)}$ = 6.5 Hz, C5), 62.93 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.69 (d, $^{2}J_{(COP)}$ = 6.3 Hz, CH_2OP), 62.36 (d, $^{3}J_{(CNCP)}$ = 5.0 Hz, CH_2Ph), 60.61 (d, $^{1}J_{(CP)}$ = 170.5 Hz, C3), 47.18 (CH_2N), 35.04 (C4), 16.62 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.2 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.61. Anal. calcd. for $C_{30}H_{31}FN_3O_7P \times H_2O$: C, 58.82; H, 5.27; N, 6.86. Found: C, 58.64; H, 5.17; N, 6.82 (obtained on a 87:13 mixture of *cis*-**13c** and *trans*-**13c**).

4.5.11. Diethyl trans-{2-benzyl-5-[(3-(3-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (trans-**13c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3064, 2983, 2931, 2907, 1752, 1703, 1665, 1608, 1480, 1390, 1285, 1147, 1052, 1023, 965, 756. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.23 (m, 1H), 7.75–7.71 (m, 1H), 7.68–7.66 (m, 1H), 7.49–7.46 (m, 2H), 7.39–7.34 (m, 2H), 7.30–729 (m, 6H), 4.48–4.44 (m, 3H, H_2CN, *H*C5), 4.24–4.17 (m, 5H, 2 × C*H*$_2$OP, *H*'CHPh), 3.92 (d, ^{2}J = 14.0 Hz, 1H, *H*CHPh), 3.32–3.29 (m, 1H, *H*C3), 2.69 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.1 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.5 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.1 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.1 Hz, 1H, *H*αC4), 2.41–2.34 (m, 1H, *H*βC4), 1.35 (t, ^{3}J = 6.1 Hz, 6H, 2 × C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.60 (d, $^{4}J_{(C(O)CCCF)}$ = 2.9 Hz, C═O), 162.94 (d, $^{1}J_{(CF)}$ = 245.1 Hz), 160.92 (C═O), 149.71 (C═O), 140.79, 136.38, 135.79, 139.91 (d, $^{3}J_{(CCCF)}$ = 7.3 Hz), 130.89 (d, $^{3}J_{(CCCF)}$ = 7.8 Hz), 129.64, 128.90, 128.15, 127.53, 126.16 (d, $^{4}J_{(CCCCF)}$ = 2.4 Hz), 123.78, 122.13 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 117.08 (d, $^{2}J_{(CCF)}$ = 23.4 Hz), 115.59, 115.51, 75.48 (d, $^{3}J_{(CCCP)}$ = 6.3 Hz, C5), 63.31 (d, $^{2}J_{(COP)}$ = 6.4 Hz, CH_2OP), 62.67 (br s, CH_2Ph), 62.52 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 60.75 (d, $^{1}J_{(CP)}$ = 170.1 Hz, C3), 45.30 (CH_2N), 35.21 (C4), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.5 Hz, CH_3CH_2OP), 16.47 (d, $^{3}J_{(CCOP)}$ = 5.5 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.58. Anal. calcd. for $C_{30}H_{31}FN_3O_7P \times H_2O$: C, 58.82; H, 5.27; N, 6.86. Found: C, 58.74; H, 5.19; N, 6.92.

*4.5.12. Diethyl cis-{2-benzyl-5-[(3-(4-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (cis-**13d**)*

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3460, 3063, 2990, 1750, 1700, 1669, 1610, 1490, 1391, 1252, 1022, 970, 757, 574. (^{1}H NMR signals of *cis*-**13d** were extracted from the spectrum of a 92:8 mixture of *cis*-**13d** and *trans*-**13d**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 1H), 8.02–7.98 (m, 2H), 7.42–7.40 (m, 1H), 7.35–7.34 (m, 2H), 7.30–7.29 (m, 3H), 7.20–7.12 (m, 4H), 4.65–4.61 (m, 1H, *H*C5), 4.44 (d, ^2J = 13.6 Hz, 1H, *H*CHPh), 4.32–4.23 (m, 5H, 2 × C*H*$_2$OP, *H*CHN), 4.19 (dd, ^2J = 14.9 Hz, $^3J_{(HC-H5)}$ = 2.5 Hz, 1H, HC*H*N), 3.92 (d, ^2J = 13.6 Hz, 1H, HC*H*Ph), 3.24 (ddd, $^3J_{(H3-H4\alpha)}$ = 10.3 Hz, $^3J_{(H3-H4\beta)}$ = 7.3 Hz, $^2J_{(H3-P)}$ = 3.2 Hz, 1H, *H*C3), 2.82 (dddd, $^3J_{(H4\alpha-P)}$ = 18.7 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 13.0 Hz, $^3J_{(H4\alpha-H3)}$ = 10.3 Hz, $^3J_{(H4\beta-H5)}$ = 8.6 Hz, 1H, *H*αC4), 2.39 (dddd, $^2J_{(H4\beta-H4\alpha)}$ = 13.0 Hz, $^3J_{(H4\beta-P)}$ = 11.5 Hz, $^3J_{(H4\beta-H3)}$ = 7.3 Hz, $^3J_{(H4\beta-H5)}$ = 4.1 Hz, 1H, *H*βC4), 1.42 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP), 1.41 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *cis*-**13d** were extracted from the spectrum of a 85:15 mixture of *cis*-**13d** and *trans*-**13d**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.58 (C═O), 166.90 (d, $^1J_{(CF)}$ = 258.7Hz), 161.22 (C═O), 149.70 (C═O), 141.14, 136.60, 135.74, 133.33 (d, $^3J_{(CCCF)}$ = 9.9Hz), 129.91, 128.39 (d, $^4J_{(CCCCF)}$ = 2.5 Hz), 128.32, 128.18, 127.59, 123.22, 116.50 (d, $^2J_{(CCF)}$ = 22.2 Hz), 116.06, 115.01, 75.64 (d, $^3J_{(CCCP)}$ = 6.5 Hz, C5), 62.92 (d, $^2J_{(COP)}$ = 6.7 Hz, CH_2OP), 62.69 (d, $^2J_{(COP)}$ = 6.7 Hz, CH_2OP), 62.38 (d,$^3J_{(CNCP)}$ = 5.0 Hz,CH_2Ph), 60.63 (d, $^1J_{(CP)}$ = 170.2 Hz, C3), 47.15 (CH_2N), 35.04 (d, $^2J_{(CCP)}$ = 1.3 Hz, C4), 16.62 (d, $^3J_{(CCOP)}$ = 5.5 Hz, CH_3CH$_2$OP), 16.51 (d, $^3J_{(CCOP)}$ = 6.5 Hz, CH_3CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.64. Anal. calcd. for $C_{30}H_{31}FN_3O_7P \times H_2O$: C, 58.82; H, 5.27; N, 6.86. Found: C, 58.93; H, 5.29; N, 6.81 (obtained on a 85:15 mixture of *cis*-**13d** and *trans*-**13d**).

*4.5.13. Diethyl trans-{2-benzyl-5-[(3-(4-fluorobenzoyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (trans-**13d**)*

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3458, 2982, 1749, 1701, 1665, 1600, 1479, 1390, 1242, 1022, 969, 756. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.23 (m, 1H), 8.00–7.98 (m, 2H), 7.74–7.71 (m, 1H), 7.47–7.44 (m, 1H), 7.36–7.34 (m, 1H), 7.30–7.27 (m, 5H), 7.19–7.15 (m, 2H), 4.48–4.41 (m, 2H, *H*C5, *H*CHN), 4.45 (d, ^2J = 13.9 Hz, 1H, *H*CHPh), 4.27–4.17 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.91 (d, ^2J = 13.9 Hz, 1H, HC*H*Ph), 3.30 (ddd, $^3J_{(H3-H4\beta)}$ = 9.5 Hz, $^3J_{(H3-H4\alpha)}$ = 6.6 Hz, $^2J_{(H3-P)}$ = 2.8 Hz, 1H, *H*C3), 2.69 (dddd, $^3J_{(H4\alpha-P)}$ = 19.1 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 13.0 Hz, $^3J_{(H4\alpha-H3)}$ = 6.6 Hz, $^3J_{(H4\beta-H5)}$ = 6.6 Hz, 1H, *H*αC4), 2.37 (dddd, $^3J_{(H4\beta-P)}$ = 14.9 Hz, $^2J_{(H4\beta-H4\alpha)}$ = 13.0 Hz, $^3J_{(H4\beta-H3)}$ = 9.5 Hz, $^3J_{(H4\beta-H5)}$ = 8.1 Hz, 1H, *H*βC4), 1.35 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP), 1.34 (t, ^3J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.29 (C═O), 166.93 (d, $^1J_{(CF)}$ = 258.1 Hz), 160.93 (C═O), 149.73 (C═O), 140.79, 136.48, 135.72, 133.33 (d, $^3J_{(CCCF)}$ = 9.9 Hz), 129.61, 128.88, 128.23 (d, $^4J_{(CCCCF)}$ = 2.8 Hz), 128.1, 127.50, 123.73, 116.54 (d, $^2J_{(CCF)}$ = 22.2 Hz), 115.55, 115.53, 75.43 (d, $^3J_{(CCCP)}$ = 6.3 Hz, C5), 63.27 (d, $^2J_{(COP)}$ = 6.3 Hz, CH_2OP), 62.69 (d, $^3J_{(CNCP)}$ = 4.0 Hz, CH_2Ph), 62.50 (d, $^2J_{(COP)}$ = 6.7 Hz, CH_2OP), 60.77 (d, $^1J_{(CP)}$ = 169.8 Hz, C3), 45.30 (CH_2N), 35.24 (d, $^2J_{(CCP)}$ = 1.9 Hz, C4), 16.55 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH_3CH$_2$OP), 16.47 (d, $^3J_{(CCOP)}$ = 5.8 Hz, CH_3CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.64. Anal. calcd. for $C_{30}H_{31}FN_3O_7P \times 1.5\ H_2O$: C, 57.88; H, 5.50; N, 6.75. Found: C, 58.05; H, 5.73; N, 6.81.

*4.5.14. Diethyl cis-{5-[(3-benzyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl}phosphonate (cis-**14a**)*

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3477, 2987, 1750, 1700, 1669, 1610, 1490, 1393, 1256, 1017. (NMR signals of *cis*-**14a** were extracted from the spectrum of a 75:25 mixture of *cis*-**14a** and *trans*-**14a**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1H), 7.76–7.74 (m, 1H), 7.67–7.63 (m, 1H), 7.53–7.52 (m, 2H), 7.33–7.30 (m, 2H), 7.26–7.23 (m, 2H), 5.31 (AB, J_{AB} = 13.9 Hz, 1H, *H*CHN), 5.26 (AB, J_{AB} = 13.9 Hz, 1H, HC*H*N), 4.60 (dddd, $^3J_{(H5-H4\alpha)}$ = 9.6 Hz, $^3J_{(H5-CH)}$ = 7.3 Hz, $^3J_{(H5-H4\beta)}$ = 3.7 Hz, $^3J_{(H5-CH)}$ = 3.7 Hz, 1H, *H*C5), 4.29–4.22 (m, 5H, 2 × C*H*$_2$OP, *H*CHN), 4.18 (dd, ^2J = 14.9 Hz, ^3J = 3.7 Hz, 1H, HC*H*N), 2.93 (ddd, $^3J_{(H3-H4\alpha)}$ = 10.0 Hz, $^3J_{(H3-H4\beta)}$ = 7.8 Hz, $^2J_{(H3-P)}$ = 2.3 Hz, 1H, *H*C3), 2.82 (d, ^4J = 0.6 Hz, CH_3N), 2.84–2.79 (m, 1H, *H*αC4), 2.41 (dddd, $^2J_{(H4\beta-H4\alpha)}$ = 12.8 Hz, $^3J_{(H4\beta-P)}$ = 12.8 Hz, $^3J_{(H4\beta-H3)}$ = 7.8 Hz, $^3J_{(H4\beta-H5)}$ = 3.7 Hz, 1H, *H*βC4), 1.41 (t, ^3J = 7.1 Hz, 6H, 2 × C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.94 (C═O), 151.24 (C═O), 141.15, 137.04, 134.73, 128.97, 128.56, 128.40, 127.54, 128.79, 122.93, 115.55, 115.43, 75.08 (d, $^3J_{(CCCP)}$ = 7.3 Hz, C5), 63.22 (d, $^1J_{(CP)}$ = 168.7 Hz, C3), 62.83 (d, $^2J_{(COP)}$ = 6.7 Hz, CH_2OP), 62.64 (d, $^2J_{(COP)}$ = 6.8 Hz, CH_2OP), 47.19 (s, CH_2N), 45.22 (d, $^3J_{(CNCP)}$ = 3.6 Hz, CH_3N), 44.92 (CH_2Ph), 35.67 (d, $^2J_{(CCP)}$ = 1.7 Hz, C4), 16.59 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH_3CH$_2$OP), 16.51 (d, $^3J_{(CCOP)}$ = 5.5 Hz, CH_3CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.51. Anal. calcd. for $C_{24}H_{30}N_3O_6P$: C, 53.19; H, 6.20; N, 8.62. Found: C, 53.35; H, 5.99; N, 8.36 (obtained on a 75:25 mixture of *cis*-**14a** and *trans*-**14a**).

*4.5.15. Diethyl trans-{5-[(3-benzyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**14a**)*

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3474, 2980, 1703, 1660, 1662, 1609, 1483, 1349, 1238, 1023, 966, 759. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.26–8.24 (m, 1H), 7.66–7.63 (m, 1H), 7.52–7.51 (m, 2H), 7.40–7.38 (m, 1H), 7.32–7.28 (m, 2H), 7.28–7.24 (m, 2H), 5.32 (AB, J_{AB} = 13.9 Hz, 1H, *H*CHN), 5.27 (AB, J_{AB} = 13.9 Hz, 1H, HC*H*N), 4.51 (dd, ^2J = 14.9 Hz, $^3J_{(HC-H5)}$ = 4.1 Hz, 1H, *H*CHN), 4.42–4.37 (m, 1H, *H*C5), 4.21–4.14 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.04–2.98 (m, 1H, *H*C3), 2.86 (s, CH_3N), 2.68 (dddd, $^3J_{(H4\alpha-P)}$ = 19.3 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 12.6 Hz, $^3J_{(H4\alpha-H3)}$ = 7.1 Hz, $^3J_{(H4\beta-H5)}$ = 7.1 Hz, 1H, *H*αC4), 2.41 (dddd, $^2J_{(H4\beta-H4\alpha)}$ = 12.6 Hz, $^3J_{(H4\beta-P)}$ = 12.6 Hz, $^3J_{(H4\beta-H3)}$ = 9.7 Hz, $^3J_{(H4\beta-H5)}$ = 4.4 Hz, 1H, *H*βC4), 1.35 (t, ^3J = 7.3 Hz, 6H, 2 × C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.63 (C═O), 151.29 (C═O), 140.14, 136.93, 134.87, 128.04, 128.9, 128.40, 127.58, 128.79, 123.16, 115.67, 114.57, 75.35 (d, $^3J_{(CCCP)}$ = 7.3 Hz, C5), 63.95 (d, $^1J_{(CP)}$ = 173.5 Hz, C3), 63.14 (d, $^2J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.40 (d, $^2J_{(COP)}$ = 7.1 Hz, CH_2OP), 46.24 (CH_3N), 45.98 (CH_2N), 45.04 (CH_2Ph), 35.99 (C4), 16.50 (d, $^3J_{(CCOP)}$ = 5.9 Hz, CH_3CH$_2$OP), 16.45 (d, $^3J_{(CCOP)}$ = 5.9 Hz, CH_3CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.74. Anal. calcd. for $C_{24}H_{30}N_3O_6P \times H_2O$: C, 57.02; H, 6.38; N, 8.31. Found: C, 57.26; H, 6.09; N, 8.33.

*4.5.16. Diethyl cis-{5-[(3-(2-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (cis-**14b**)*

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2999, 1780, 1720, 1666, 1617, 1450, 1386, 1249, 1032. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.24 (m, 1H), 7.79–7.77 (m, 1H), 7.68–7.66 (m, 1H), 7.32–7.26 (m, 2H), 7.25–7.22 (m, 1H), 7.08–7.05 (m, 2H), 5.41 (AB, J_{AB} = 14.6 Hz, 1H, *H*CHN), 5.37 (AB, J_{AB} = 14.6 Hz, 1H, HC*H*N), 4.62–4.59 (m, 1H, *H*C5), 4.31–4.20 (m, 5H, 2 × C*H*$_2$OP, *H*CHN), 4.20 (dd, ^2J = 15.2 Hz, $^3J_{(HC-H5)}$ = 7.4 Hz, 1H, HC*H*N), 2.95–2.92 (m, 1H, *H*C3), 2.83 (dddd, $^3J_{(H4\alpha-P)}$ = 18.3 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 11.5 Hz, $^3J_{(H4\alpha-H3)}$ = 9.4 Hz, $^3J_{(H4\beta-H5)}$ = 9.4 Hz, 1H, *H*αC4), 2.82 (s, C*H*$_3$N), 2.38 (dddd, $^2J_{(H4\beta-H4\alpha)}$ = 11.5 Hz, $^3J_{(H4\beta-P)}$ = 11.5 Hz, $^3J_{(H4\beta-H3)}$ = 7.9 Hz, $^3J_{(H4\beta-H5)}$ = 3.4 Hz, 1H, *H*βC4), 1.41 (t, ^3J = 7.0 Hz, 6H, 2 × C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *cis*-**14b** were extracted from the spectrum of a 80:20 mixture of *cis*-**14b** and *trans*-**14b**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.91 (s, C═O), 160.77 (d, $^1J_{(CF)}$ = 247.7 Hz), 150.05 (C═O), 141.22, 134.84, 131.24, 129.34 (d, $^3J_{(CCCF)}$ = 3.5 Hz), 128.93 (d, $^3J_{(CCCF)}$ = 7.8 Hz), 124.06 (d, $^4J_{(CCCCF)}$ = 3.2 Hz), 123.95 (d, $^2J_{(CCF)}$ = 14.3 Hz), 123.00, 115.63, 115.43 (d, $^2J_{(CCF)}$ = 21.8 Hz), 114.66,

75.10 (d, $^{3}J_{(CCCP)}$ = 7.1 Hz, C5), 63.21 (d, $^{1}J_{(CP)}$ = 169.2 Hz, C3), 62.82 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.55 (d, $^{2}J_{(COP)}$ = 6.8 Hz, CH_2OP), 47.18 (CH_2N), 45.19 (d, $^{3}J_{(CNCP)}$ = 3.8 Hz, CH_3N), 38.65 (d, $^{3}J_{(CCCF)}$ = 4.7 Hz, CH_2Ph), 35.65 (d, $^{2}J_{(CCP)}$ = 1.6 Hz, C4), 16.58 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.8 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.50. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times 1.5\ H_2O$: C, 54.13; H, 6.06; N, 7.89. Found: C, 54.16; H, 5.96; N, 8.37.

4.5.17. Diethyl trans-{5-[(3-(2-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**14b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3063, 2981, 1707, 1665, 1610, 1483, 1455, 1410, 1347, 1232, 1052, 1023. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27–8.26 (m, 1H), 7.69–7.67 (m, 1H), 7.43–7.42 (m, 1H), 7.30–7.27 (m, 2H), 7.25–7.22 (m, 1H), 7.08–7.05 (m, 2H), 5.40 (AB, J_{AB} = 14.8 Hz, 1H, *H*CHN), 5.38 (AB, J_{AB} = 14.8 Hz, 1H, HC*H*N), 4.53 (dd, ^{2}J = 15.0 Hz, $^{3}J_{(HC-H5)}$ = 4.1 Hz, 1H, *H*CHN), 4.41 (dddd, $^{3}J_{(H5-H4\beta)}$ = 11.9 Hz, $^{3}J_{(H5-CH)}$ = 7.0 Hz, $^{3}J_{(H5-H4\alpha)}$ = 7.0 Hz, $^{3}J_{(H5-CH)}$ = 4.1 Hz, 1H, *H*C5), 4.21–4.15 (m, 5H, 2 × CH_2OP, HC*H*N), 3.04–2.98 (m, 1H, *H*C3), 2.86 (s, CH_3N), 2.68 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.4 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.2 Hz, $^{3}J_{(H4\alpha-H3)}$ = 7.0 Hz, $^{3}J_{(H4\beta-H5)}$ = 7.0 Hz, 1H, *H*αC4), 2.38–2.38 (m, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.34 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.58 (C=O), 160.76 (d, $^{1}J_{(CF)}$ = 247.1 Hz), 150.13 (C=O), 140.19, 134.98, 129.26 (d, $^{4}J_{(CCCCF)}$ = 3.8 Hz), 129.10, 128.96 (d, $^{3}J_{(CCCF)}$ = 8.0 Hz), 124.03 (d, $^{3}J_{(CCCF)}$ = 3.3 Hz), 123.81 (d, $^{2}J_{(CCF)}$ = 14.6 Hz), 123.23, 115.55, 115.44 (d, $^{2}J_{(CCF)}$ = 21.8 Hz), 114.66, 75.32 (d, $^{3}J_{(CCCP)}$ = 7.0 Hz, C5), 63.94 (d, $^{1}J_{(CP)}$ = 169.2 Hz, C3), 63.12 (d, $^{2}J_{(COP)}$ = 6.4 Hz, CH_2OP), 62.40 (d, $^{2}J_{(COP)}$ = 6.8 Hz, CH_2OP), 46.22 (CH_3N), 46.00 (CH_2N), 33.91 (d, $^{3}J_{(CCCF)}$ = 4.5 Hz, CH_2Ph), 35.96 (C4), 16.48 (d, $^{3}J_{(CCOP)}$ = 6.7 Hz, CH_3CH_2OP), 16.43 (d, $^{3}J_{(CCOP)}$ = 6.9 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.72. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times 1.5\ H_2O$: C, 54.13; H, 6.06; N, 7.89. Found: C, 54.22; H, 6.20; N, 5.87.

4.5.18. Diethyl cis-{5-[(3-(3-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (cis-**14c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3065, 2981, 2908, 1704, 1660, 1608, 1481, 1345, 1138, 1050, 1022, 968, 794, 758. (^{1}H NMR signals of *cis*-**14c** were extracted from the spectrum of a 97:3 mixture of *cis*-**14c** and *trans*-**14c**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1H), 7.77–7.76 (m, 1H), 7.67–7.65 (m, 1H), 7.30–7.26 (m, 3H), 7.25–7.22 (m, 1H), 6.98–6.94 (m, 1H), 5.29 (AB, J_{AB} = 14.0 Hz, 1H, *H*CHN), 5.25 (AB, J_{AB} = 14.0 Hz, 1H, HC*H*N), 4.60 (dddd, $^{3}J_{(H5-H4\alpha)}$ = 11.9 Hz, $^{3}J_{(H5-CH)}$ = 6.0 Hz, $^{3}J_{(H5-H4\beta)}$ = 3.0 Hz, $^{3}J_{(H5-CH)}$ = 3.0 Hz, 1H, *H*C5), 4.31–4.29 (m, 5H, 2 × CH_2OP, *H*CHN), 4.21 (dd, ^{2}J = 14.7 Hz, $^{3}J_{(HC-H5)}$ = 3.0 Hz, 1H, HC*H*N), 2.94 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.9 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.7 Hz, $^{2}J_{(H3-P)}$ = 2.2 Hz, 1H, *H*C3), 2.86–2.80 (m, 1H, *H*αC4), 2.82 (s, CH_3N), 2.40 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.5 Hz, $^{3}J_{(H4\beta-P)}$ = 11.6 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.7 Hz, $^{3}J_{(H4\beta-H5)}$ = 3.0 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.1 Hz, 6H, 2 × CH_3CH_2OP); (^{13}C NMR signals of *cis*-**14c** were extracted from the spectrum of a 69:31 mixture of *cis*-**14c** and *trans*-**14c**) ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.79 (d, $^{1}J_{(CF)}$ = 246.2 Hz), 161.87 (C=O), 151.15 (C=O), 141.14, 139.36 (d, $^{3}J_{(CCCF)}$ = 7.5 Hz), 134.88, 129.86 (d, $^{3}J_{(CCCF)}$ = 8.5 Hz), 128.56, 124.52 (d, $^{4}J_{(CCCCF)}$ = 1.7 Hz), 123.05, 115.81 (d, $^{2}J_{(CCF)}$ = 21.9 Hz), 115.62, 114.64, 114.50 (d, $^{2}J_{(CCF)}$ = 21.0 Hz), 75.03 (d, $^{3}J_{(CCCP)}$ = 7.4 Hz, C5), 63.17 (d, $^{1}J_{(CP)}$ = 169.3 Hz, C3), 62.60 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.57 (d, $^{2}J_{(COP)}$ = 7.1 Hz, CH_2OP), 47.20 (CH_2N), 45.17 (d, $^{3}J_{(CNCP)}$ = 4.1 Hz, CH_3N), 44.41 (CH_2Ph), 35.63 (d, $^{2}J_{(CCP)}$ = 1.4 Hz, C4), 16.59 (d, $^{3}J_{(CCOP)}$ = 5.9 Hz, CH_3CH_2OP), 16.51 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.48. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times H_2O$: C, 55.06; H, 5.97; N, 8.03. Found: C, 54.98; H, 5.88; N, 7.91 (obtained on a 69:31 mixture of *cis*-**14c** and *trans*-**14c**).

4.5.19. Diethyl trans-{5-[(3-(3-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**14c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3062, 2981, 1703, 1657, 1610, 1483, 1400, 1346, 1251, 1051, 967, 787. δ = ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, J = 7.7 Hz, 1H), 7.67–7.65 (m, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.30–7.24 (m, 3H), 7.25–7.20 (m, 1H), 6.97–6.93 (m, 1H), 5.28 (AB, J_{AB} = 14.0 Hz, 1H, *H*CHN), 5.25 (AB, J_{AB} = 14.0 Hz, 1H, HC*H*N), 4.51 (dd, ^{2}J = 14.9 Hz, $^{3}J_{(HC-H5)}$ = 4.1 Hz, 1H, *H*CHN), 4.45–4.37 (m, 1H, *H*C5), 4.24–4.15 (m, 5H, 2 × CH_2OP, *H*CHN), 3.05–3.00 (m, 1H, *H*C3), 2.85 (s, CH_3N), 2.76–2.64 (m, 1H, *H*αC4), 2.43–36 (m, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.34 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.80 (d, $^{1}J_{(CF)}$ = 245.8 Hz), 161.58 (C=O), 151.22 (C=O), 140.12, 139.26 (d, $^{3}J_{(CCCF)}$ = 7.5 Hz), 135.04, 129.88 (d, $^{3}J_{(CCCF)}$ = 8.5 Hz), 129.08, 124.52 (d, $^{4}J_{(CCCCF)}$ = 2.4 Hz), 123.29, 115.76 (d, $^{2}J_{(CCF)}$ = 21.8 Hz), 115.56, 114.64 114.56 (d, $^{2}J_{(CCF)}$ = 22.8 Hz), 75.31 (d, $^{3}J_{(CCCP)}$ = 7.1 Hz, C5), 63.93 (d, $^{1}J_{(CP)}$ = 169.9 Hz, C3), 63.18 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.43 (d, $^{2}J_{(COP)}$ = 7.2 Hz, CH_2OP), 46.24 (d, $^{3}J_{(CNCP)}$ = 3.8 Hz, CH_3N), 46.02 (CH_2N), 44.54 (CH_2Ph), 35.06 (C4), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.44 (d, $^{3}J_{(CCOP)}$ = 6.0 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.73. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times H_2O$: C, 55.06; H, 5.97; N, 8.03. Found: C, 55.24; H, 5.55; N, 7.95.

4.5.20. Diethyl cis-{5-[(3-(4-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (cis-**14d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2989, 1711, 1673, 1617, 1483, 1393, 1250, 1020, 970, 770. (NMR signals of *cis*-**14d** were extracted from the spectrum of a 75:25 mixture of *cis*-**14d** and *trans*-**14d**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21–8.20 (m, 1H), 7.75–7.74 (m, 1H), 7.66–7.62 (m, 1H), 7.54–7.51 (m, 2H), 7.29–7.22 (m, 1H), 7.00–6.96 (m, 2H), 5.4125 (AB, J_{AB} = 13.8 Hz, 1H, *H*CHN), 5.21 (AB, J_{AB} = 13.8 Hz, 1H, HC*H*N), 4.58 (dddd, $^{3}J_{(H5-H4\beta)}$ = 11.8 Hz, $^{3}J_{(H5-CH)}$ = 7.0 Hz, $^{3}J_{(H5-H4\alpha)}$ = 3.6 Hz, $^{3}J_{(H5-CH)}$ = 3.6 Hz, 1H, *H*C5), 4.29–4.21 (m, 4H, 2 × CH_2OP), 4.19 (dd, ^{2}J = 14.2 Hz, $^{3}J_{(HC-H5)}$ = 3.6 Hz, 1H, *H*CHN), 4.17 (dd, ^{2}J = 14.2 Hz, $^{3}J_{(HC-H5)}$ = 7.0 Hz, 1H, HC*H*N), 2.93 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.8 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.8 Hz, $^{2}J_{(H3-P)}$ = 2.0 Hz, 1H, *H*C3), 2.85–2.78 (m, 1H, *H*αC4), 2.81 (s, CH_3N), 2.39 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 11.8 Hz, $^{3}J_{(H4\beta-P)}$ = 11.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.8 Hz, $^{3}J_{(H4\beta-H5)}$ = 3.6 Hz, 1H, *H*βC4), 1.40 (t, ^{3}J = 7.0 Hz, 6H, 2 × CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.27 (d, $^{1}J_{(CF)}$ = 246.3 Hz), 161.88 (C=O), 151.16 (C=O), 141.12, 134.79, 132.85 (d, $^{4}J_{(CCCCF)}$ = 3.2 Hz), 131.00 (d, $^{3}J_{(CCCF)}$ = 7.8 Hz), 128.50, 122.98, 115.59, 115.35, 115.17 (d, $^{2}J_{(CCF)}$ = 21.4 Hz), 75.03 (d, $^{3}J_{(CCCP)}$ = 7.3 Hz, C5), 63.20 (d, $^{1}J_{(CP)}$ = 169.0 Hz, C3), 62.82 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.55 (d, $^{2}J_{(COP)}$ = 6.7 Hz, CH_2OP), 47.18 (CH_2N), 45.16 (d, $^{3}J_{(CNCP)}$ = 3.8 Hz, CH_3N), 44.16 (CH_2Ph), 35.65 (C4), 16.57 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.9 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.48. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times H_2O$: C, 55.06; H, 5.97; N, 8.03. Found: C, 54.89; H, 5.92; N, 8.04 (obtained on a 75:25 mixture of *cis*-**14d** and *trans*-**14d**).

4.5.21. Diethyl trans-{5-[(3-(4-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]-2-methylisoxazolidin-3-yl} phosphonate (trans-**14d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3060, 2981, 1704, 1651, 1609, 1607, 1484, 1400, 1223, 1096, 1024, 966, 771, 756. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 7.66–7.64 (m, 1H), 7.54–7.51 (m, 2H), 7.39–7.38 (m, 1H), 7.29–7.25 (m, 1H), 7.00–6.97 (m, 2H), 5.25 (AB, J_{AB} = 13.8 Hz, 1H, *H*CHN), 5.23 (AB, J_{AB} = 13.8 Hz, 1H, HC*H*N), 4.50 (dd, ^{2}J = 15.0 Hz, $^{3}J_{(HC-H5)}$ = 4.3 Hz, 1H, *H*CHN),

4.39 (dddd, $^{3}J_{(H5-H4\beta)}$ = 9.8 Hz, $^{3}J_{(H5-CH)}$ = 7.0 Hz, $^{3}J_{(H5-H4\alpha)}$ = 7.0 Hz, $^{3}J_{(H5-H\delta CHN)}$ = 4.3 Hz, 1H, *H*C5), 4.21–4.15 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.02–2.98 (m, 1H, *H*C3), 2.85 (s, C*H*$_3$N), 2.69 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.4 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.5 Hz, $^{3}J_{(H4\alpha-H3)}$ = 7.0 Hz, $^{3}J_{(H4\beta-H5)}$ = 7.0 Hz, 1H, *H*αC4), 2.41 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.5 Hz, $^{3}J_{(H4\beta-P)}$ = 12.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 9.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 8.0 Hz, 1H, *H*βC4), 1.35 (t, ^{3}J = 7.2 Hz, 3H, C*H*$_3$CH$_2$OP), 1.34 (t, ^{3}J = 7.5 Hz, 3H, C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.30 (d, $^{1}J_{(CF)}$ = 246.3 Hz), 161.60 (C=O), 151.22 (C=O), 140.11, 134.94, 132.76 (d, $^{4}J_{(CCCCF)}$ = 3.2 Hz), 130.85 (d, $^{3}J_{(CCCF)}$ = 8.0 Hz), 129.01, 123.22, 115.62, 115.19 (d, $^{2}J_{(CCF)}$ = 21.4 Hz), 114.61, 75.33 (d, $^{3}J_{(CCCP)}$ = 7.4 Hz, C5), 63.94 (d, $^{1}J_{(CP)}$ = 168.6 Hz, C3), 63.8213 (d, $^{2}J_{(COP)}$ = 6.5 Hz, CH$_2$OP), 62.42 (d, $^{2}J_{(COP)}$ = 7.1 Hz, CH$_2$OP), 46.20 (d, $^{3}J_{(CNCP)}$ = 1.9 Hz, *C*H$_3$N), 45.99 (CH$_2$N), 44.29 (*C*H$_2$Ph), 36.00 (C4), 16.48 (d, $^{3}J_{(CCOP)}$ = 7.2 Hz, *C*H$_3$CH$_2$OP), 16.44 (d, $^{3}J_{(CCOP)}$ = 5.9 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.73. Anal. calcd. for $C_{24}H_{29}FN_3O_6P \times H_2O$: C, 55.06; H, 5.97; N, 8.03. Found: C, 54.82; H, 5.82; N, 7.93.

4.5.22. Diethyl cis-{2-benzyl-5-[(3-benzyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (cis-**15a**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2999, 17123, 1685, 1614, 1599, 1459, 1411, 1260, 1023. (NMR signals of *cis*-**15a** were extracted from the spectrum of a 50:50 mixture of *cis*-**15a** and *trans*-**15a**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.13 (m, 1H), 7.64–7.61 (m, 1H), 7.53–7.50 (m, 2H), 7.37–7.28 (m, 9H), 7.10–7.04 (m, 1H), 5.31 (AB, J_{AB} = 13.9 Hz, 1H, *H*CHN), 5.23 (AB, J_{AB} = 13.9 Hz, 1H, HC*H*N), 4.61 (dddd, $^{3}J_{(H5-H4\alpha)}$ = 9.5 Hz, $^{3}J_{(H5-CH)}$ = 7.7 Hz, $^{3}J_{(H5-H4\beta)}$ = 4.7 Hz, $^{3}J_{(H5-CH)}$ = 3.7 Hz, 1H, *H*C5), 4.43 (dd, ^{2}J = 13.7 Hz, $^{3}J_{(HC-H5)}$ = 4.7 Hz, 1H, *H*CHN), 4.31–4.15 (m, 6H, 2 × C*H*$_2$OP, HC*H*N, *H*CHPh), 3.89 (d, ^{2}J = 13.6 Hz, 1H, HC*H*Ph), 3.23 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.5 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.8 Hz, $^{2}J_{(H3-P)}$ = 2.8 Hz, 1H, *H*C3), 2.84 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.5 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 9.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 9.5 Hz, 1H, *H*αC4), 2.42 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.8 Hz, $^{3}J_{(H4\beta-P)}$ = 12.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.8 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.7 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.0 Hz, 3H, C*H*$_3$CH$_2$OP), 1.40 (t, ^{3}J = 7.0 Hz, 3H, C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.95 (C=O), 151.30 (C=O), 140.51, 137.06, 136.57, 134.82, 129.95, 129.02, 128.96, 128.41, 128.28, 127.55, 127.46, 122.66, 115.38, 115.11, 75.82 (d, $^{3}J_{(CCCP)}$ = 6.8 Hz, C5), 62.96 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH$_2$OP), 62.61 (d, $^{2}J_{(COP)}$ = 6.9 Hz, CH$_2$OP), 62.29 (d, $^{3}J_{(CNCP)}$ = 5.2 Hz, *C*H$_2$Ph), 60.62 (d, $^{1}J_{(CP)}$ = 170.1 Hz, C3), 47.77 (CH$_2$N), 44.91 (*C*H$_2$Ph), 35.15 (C4), 16.62 (d, $^{3}J_{(CCOP)}$ = 6.0 Hz, *C*H$_3$CH$_2$OP), 16.50 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.66. Anal. calcd. for $C_{30}H_{34}N_3O_6P \times 1.5\ H_2O$: C, 61.01; H, 6.31; N, 7.11. Found: C, 60.85; H, 6.53; N, 7.18 (obtained on a 50:50 mixture of *cis*-**15a** and *trans*-**15a**).

4.5.23. Diethyl trans-{2-benzyl-5-[(3-benzyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (trans-**15a**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3087, 2981, 1703, 1658, 1608, 1607, 1453, 1400, 1236, 1022, 963, 757, 701. (NMR signals of *trans*-**15a** were extracted from the spectrum of a 24:76 mixture of *cis*-**15a** and *trans*-**15**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 7.63–7.60 (m, 1H), 7.53–7.50 (m, 2H), 7.35–7.25 (m, 10H), 5.30 (AB, J_{AB} = 13.9 Hz, 1H, *H*CHN), 5.26 (AB, J_{AB} = 13.9 Hz, 1H, HC*H*N), 4.48 (dd, ^{2}J = 14.9 Hz, $^{3}J_{(HC-H5)}$ = 3.4 Hz, 1H, *H*CHN), 4.42 (d, ^{2}J = 13.7 Hz, 1H, *H*CHPh), 4.45–4.40 (m, 1H, *H*C5), 4.29–4.14 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.89 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.29–3.22 (m, 1H, *H*C3), 2.67 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.7 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.4 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.4 Hz, 1H, *H*αC4), 2.46–2.32 (m, 1H, *H*βC4), 1.36 (t, ^{3}J = 6.6 Hz, 3H, C*H*$_3$CH$_2$OP), 1.35 (t, ^{3}J = 6.6 Hz, 3H, C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.65 (s, C(O)), 151.32 (s, C(O)), 140.18, 136.94, 136.51, 134.79, 129.64, 128.92, 128.43, 128.19, 128.12, 127.59, 127.46, 123.13, 115.61, 114.94, 75.64 (d, $^{3}J_{(CCCP)}$ = 6.4 Hz, C5), 62.30 (d, $^{2}J_{(COP)}$ = 6.5 Hz, CH$_2$OP), 62.70 (d, $^{3}J_{(CNCP)}$ = 5.2 Hz, *C*H$_2$Ph), 62.44 (d, $^{2}J_{(COP)}$ = 6.8 Hz, CH$_2$OP), 60.78 (d, $^{1}J_{(CP)}$ = 169.7 Hz, C3), 45.74 (CH$_2$N), 45.05 (*C*H$_2$Ph), 35.15 (C4), 16.57 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.51 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.83. Anal. calcd. for $C_{30}H_{34}N_3O_6P \times 1.5H_2O$: C, 61.01; H, 6.31; N, 7.11. Found: C, 60.81; H, 6.19; N, 7.07 (obtained on a 10:90 mixture of *cis*-**15a** and *trans*-**15a**).

4.5.24. Diethyl cis-{2-benzyl-5-[(3-(2-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (cis-**15b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2978, 1744, 1700, 1662, 1607, 1478, 1389, 1240, 1012, 756. (NMR signals of *cis*-**15b** were extracted from the spectrum of a 85:15 mixture of *cis*-**15b** and *trans*-**15b**) ^{1}H NMR (600 MHz, $CDCl_3$): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17–8.13 (m, 1H), 7.34–7.31 (m, 3H), 7.29–7.26 (m, 5H), 7.11–7.04 (m, 4H), 5.39 (AB, $^{2}J_{AB}$ = 14.8 Hz, 1H, N–C*H*$_{2a}$), 5.34 (AB, $^{2}J_{AB}$ = 14.8 Hz, 1H, N–C*H*$_{2b}$), 4.61 (dddd, $^{3}J_{(H5-H4\alpha)}$ = 10.2 Hz, $^{3}J_{(H5-CH)}$ = 7.9 Hz, $^{3}J_{(H5-H4\beta)}$ = 4.3 Hz, $^{3}J_{(H5-CH)}$ = 4.3 Hz, 1H, *H*C5), 4.43 (d, ^{2}J = 13.7 Hz, 1H, *H*CHPh), 4.32–4.17 (m, 6H, 2 × C*H*$_2$OP, HC*H*N), 3.90 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.23 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 10.2 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.4 Hz, $^{2}J_{(H3-P)}$ = 3.1 Hz, 1H, *H*C3), 2.82 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.3 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 10.2 Hz, $^{3}J_{(H4\beta-H5)}$ = 10.2 Hz, 1H, *H*αC4), 2.41 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.8 Hz, $^{3}J_{(H4\beta-P)}$ = 11.9 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.4 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.3 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP), 1.40 (t, ^{3}J = 7.1 Hz, 3H, C*H*$_3$CH$_2$OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.91 (s, C=O), 160.76 (d, $^{1}J_{(CF)}$ = 247.5 Hz), 151.10 (s, C=O), 140.58, 136.58, 134.95, 129.92, 129.34 (d, $^{3}J_{(CCCF)}$ = 3.8 Hz), 128.93 (d, $^{3}J_{(CCCF)}$ = 7.9 Hz), 128.36, 128.28, 127.55, 124.05 (d, $^{4}J_{(CCCCF)}$ = 3.3 Hz), 123.97 (d, $^{2}J_{(CCF)}$ = 14.3 Hz), 122.74, 115.53, 115.44 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 115.00, 75.84 (d, $^{3}J_{(CCCP)}$ = 6.6 Hz, C5), 62.95 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH$_2$OP), 62.62 (d, $^{2}J_{(COP)}$ = 6.9 Hz, CH$_2$OP), 62.29 (d, $^{3}J_{(CNCP)}$ = 5.2 Hz, *C*H$_2$Ph), 60.64 (d, $^{1}J_{(CP)}$ = 169.9 Hz, C3), 47.77 (CH$_2$N), 38.64 (d, $^{3}J_{(CCCF)}$ = 4.5 Hz, *C*H$_2$Ph), 35.14 (C4), 16.61 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.8 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.62. Anal. calcd. for $C_{30}H_{33}FN_3O_6P$: C, 61.69; H, 5.72; N, 7.23. Found: C, 61.65; H, 5.60; N, 7.35.

4.5.25. Diethyl trans-{2-benzyl-5-[(3-(2-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (trans-**15b**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2981, 1706, 1664, 1609, 1482, 1454, 1400, 1286, 1231, 1097, 1052, 1022, 756. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27–8.26 (m, 1H), 7.67–7.64 (m, 1H), 7.40–7.39 (m, 1H), 7.31–7.26 (m, 7H), 7.25–7.22 (m, 1H), 7.08–7.04 (m, 2H), 5.40 (AB, J_{AB} = 14.8 Hz, 1H, *H*CHN), 5.37 (AB, J_{AB} = 14.8 Hz, 1H, HC*H*N), 4.50 (dd, ^{2}J = 15.1 Hz, $^{3}J_{(HC-H5)}$ = 4.3 Hz, 1H, *H*CHN), 4.43 (d, ^{2}J = 13.7 Hz, 1H, *H*CHPh), 4.40–4.39 (m, 1H, *H*C5), 4.25–4.17 (m, 5H, 2 × C*H*$_2$OP, HC*H*N), 3.89 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.28 (ddd, $^{3}J_{(H3-H4\beta)}$ = 9.4 Hz, $^{3}J_{(H3-H4\alpha)}$ = 6.2 Hz, $^{2}J_{(H3-P)}$ = 2.6 Hz, 1H, *H*C3), 2.67 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.3 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.2 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.2 Hz, 1H, *H*αC4), 2.35 (dddd, $^{3}J_{(H4\beta-P)}$ = 14.8 Hz, $^{2}J_{(H4\beta-H4\alpha)}$ = 13.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 9.4 Hz, $^{3}J_{(H4\beta-H5)}$ = 8.3 Hz, 1H, *H*βC4), 1.36 (t, ^{3}J = 7.4 Hz, 3H, C*H*$_3$CH$_2$OP), 1.35 (t, ^{3}J = 6.8 Hz, 3H, C*H*$_3$CH$_2$OP); (^{13}C NMR signals of *trans*-**15b** were extracted from the spectrum of a 7:93 mixture of *cis*-**15b** and *trans*-**15b**) ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.61 (C=O), 160.77 (d, $^{1}J_{(CF)}$ = 247.1 Hz), 151.17 (C=O), 140.26, 136.50, 134.90, 129.63, 129.26 (d, $^{3}J_{(CCCF)}$ = 3.5 Hz), 129.02, 128.98 (d, $^{3}J_{(CCCF)}$ = 7.9 Hz), 128.10, 127.45, 124.05 (d, $^{4}J_{(CCCCF)}$ = 3.4 Hz), 123.81 (d, $^{2}J_{(CCF)}$ = 14.4 Hz), 123.21, 115.51, 115.46 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 115.01,

75.63 (d, $^{3}J_{(CCCP)}$ = 6.5 Hz, C5), 63.27 (d, $^{2}J_{(COP)}$ = 6.4 Hz, CH_2OP), 62.68 (d, $^{3}J_{(CNCP)}$ = 5.1 Hz, CH_2Ph), 62.43 (d, $^{2}J_{(COP)}$ = 7.0 Hz, CH_2OP), 60.77 (d, $^{1}J_{(CP)}$ = 170.3 Hz, C3), 45.75 (CH_2N), 38.95 (d, $^{3}J_{(CCCF)}$ = 4.9 Hz, CH_2Ph), 35.12 (d, $^{2}J_{(CCP)}$ = 2.3 Hz, C4), 16.54 (d, $^{3}J_{(CCOP)}$ = 5.4 Hz, CH_3CH_2OP), 16.48 (d, $^{3}J_{(CCOP)}$ = 5.4 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.77. Anal. calcd. for $C_{30}H_{33}FN_3O_6P$: C, 61.69; H, 5.72; N, 7.23. Found: C, 61.75; H, 5.83; N, 7.43.

4.5.26. Diethyl cis-{2-benzyl-5-[(3-(3-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (cis-**15c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2986, 1704, 1660, 1609, 1484, 1400, 1250, 1023, 966, 760. (NMR signals of *cis*-**15c** were extracted from the spectrum of a 65:35 mixture of *cis*-**15c** and *trans*-**15c**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.13 (m, 1H), 7.33–7.28 (m, 8H), 7.22–7.21 (m, 1H), 7.11–7.06 (m, 2H), 6.97–6.95 (m, 1H), 5.27 (AB, J_{AB} = 14.1 Hz, 1H, *H*CHN), 5.23 (AB, J_{AB} = 14.1 Hz, 1H, HC*H*N), 4.64–4.58 (m, 1H, *H*C5), 4.43 (dd, ^{2}J = 13.7 Hz, $^{3}J_{(HC-H5)}$ = 4.2 Hz, 1H, *H*CHN), 4.30–4.16 (m, 6H, 2 × CH_2OP, HC*H*N, *H*CHPh), 3.89 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.23 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.6 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.5 Hz, $^{2}J_{(H3-P)}$ = 2.5 Hz, 1H, *H*C3), 2.84 (dddd, $^{3}J_{(H4\alpha-P)}$ = 20.3 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 11.9 Hz, $^{3}J_{(H4\alpha-H3)}$ = 9.6 Hz, $^{3}J_{(H4\beta-H5)}$ = 9.6 Hz, 1H, *H*αC4), 2.43 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 11.9 Hz, $^{3}J_{(H4\beta-P)}$ = 11.9 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 4.4 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.0 Hz, 6H, 2 × CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.81 (d, $^{1}J_{(CF)}$ = 246.1 Hz), 161.85 (C=O), 151.22 (C=O), 140.53, 139.42 (d, $^{3}J_{(CCCF)}$ = 7.5 Hz), 136.58, 134.95, 129.92, 129.84 (d, $^{3}J_{(CCCF)}$ = 8.4 Hz), 128.26, 128.10, 127.53, 124.54 (d, $^{4}J_{(CCCCF)}$ = 2.5 Hz), 122.75, 115.82 (d, $^{2}J_{(CCF)}$ = 21.6 Hz), 115.47, 115.01, 114.49 (d, $^{2}J_{(CCF)}$ = 21.4 Hz), 75.47 (d, $^{3}J_{(CCCP)}$ = 6.7 Hz, C5), 62.94 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.60 (d, $^{2}J_{(COP)}$ = 7.0 Hz, CH_2OP), 62.30 (d, $^{3}J_{(CNCP)}$ = 4.8 Hz, CH_2Ph), 60.66 (d, $^{1}J_{(CP)}$ = 170.2 Hz, C3), 47.81 (CH_2N), 44.41 (CH_2Ph), 35.17 (C4), 16.60 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.54 (d, $^{3}J_{(CCOP)}$ = 5.8 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.60. Anal. calcd. for $C_{30}H_{33}FN_3O_6P$: C, 61.69; H, 5.72; N, 7.23. Found: C, 61.80; H, 5.95; N, 7.25 (obtained on a 65:35 mixture of *cis*-**15c** and *trans*-**15c**).

4.5.27. Diethyl trans-{2-benzyl-5-[(3-(3-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (trans-**15c**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 3457, 3063, 2982, 1705, 1700, 1661, 1610, 1483, 1346, 1250, 1235, 1023, 970, 763. (NMR signals of *trans*-**15c** were extracted from the spectrum of a 13:87 mixture of *cis*-**15c** and *trans*-**15c**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.24 (m, 1H), 7.65–7.62 (m, 1H), 7.38–7.36 (m, 1H), 7.33–7.25 (m, 8H), 7.22–7.20 (m, 1H), 6.97–6.94 (m, 1H), 5.28 (AB, J_{AB} = 14.0 Hz, 1H, *H*CHN), 5.25 (AB, J_{AB} = 14.0 Hz, 1H, HC*H*N), 4.49 (dd, ^{2}J = 15.1 Hz, $^{3}J_{(HC-H5)}$ = 4.3 Hz, 1H, *H*CHN), 4.43 (d, ^{2}J = 13.8 Hz, 1H, *H*CHPh), 4.40 (dddd, $^{3}J_{(H5-H4\beta)}$ = 8.3 Hz, $^{3}J_{(H5-CH)}$ = 6.9 Hz, $^{3}J_{(H5-H4\alpha)}$ = 6.6 Hz, $^{3}J_{(H5-CH)}$ = 4.3 Hz, 1H, *H*C5), 4.25–4.15 (m, 5H, 2 × CH_2OP, HC*H*N), 3.89 (d, ^{2}J = 13.8 Hz, 1H, HC*H*Ph), 3.28 (ddd, $^{3}J_{(H3-H4\beta)}$ = 9.1 Hz, $^{3}J_{(H3-H4\alpha)}$ = 6.6 Hz, $^{2}J_{(H3-P)}$ = 2.6 Hz, 1H, *H*C3), 2.68 (dddd, $^{3}J_{(H4\alpha-P)}$ = 19.0 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 12.9 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.6 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.6 Hz, 1H, *H*αC4), 2.35 (dddd, $^{3}J_{(H4\beta-P)}$ = 14.8 Hz, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.9 Hz, $^{3}J_{(H4\beta-H3)}$ = 9.1 Hz, $^{3}J_{(H4\beta-H5)}$ = 8.3 Hz, 1H, *H*βC4), 1.36 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP), 1.35 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.81 (d, $^{1}J_{(CF)}$ = 246.5 Hz), 161.58 (C=O), 151.26 (C=O), 140.19, 139.28 (d, $^{3}J_{(CCCF)}$ = 7.6 Hz), 136.51, 134.95, 129.90 (d, $^{3}J_{(CCCF)}$ = 9.6 Hz), 129.62, 128.96, 128.10, 127.45, 124.45 (d, $^{4}J_{(CCCCF)}$ = 3.2 Hz), 123.23, 115.77 (d, $^{2}J_{(CCF)}$ = 21.7 Hz), 115.51, 115.00, 114.51 (d, $^{2}J_{(CCF)}$ = 20.9 Hz), 75.61 (d, $^{3}J_{(CCCP)}$ = 6.5 Hz, C5), 63.28 (d, $^{2}J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.70 (d, $^{3}J_{(CNCP)}$ = 4.8 Hz, CH_2Ph), 62.44 (d, $^{2}J_{(COP)}$ = 7.0 Hz, CH_2OP), 60.80 (d, $^{1}J_{(CP)}$ = 170.0 Hz, C3), 45.81 (CH_2N), 44.56 (CH_2Ph), 35.17 (C4), 16.54 (d, $^{3}J_{(CCOP)}$ = 5.5 Hz, CH_3CH_2OP), 16.47 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.76. Anal. calcd. for $C_{30}H_{33}FN_3O_6P \times 1.5H_2O$: C, 59.21; H, 5.96; N, 6.90. Found: C, 59.38; H, 5.98; N, 6.82 (obtained on a 13:87 mixture of *cis*-**15c** and *trans*-**15c**).

4.5.28. Diethyl cis-{2-benzyl-5-[(3-(4-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl}phosphonate (cis-**15d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2989, 1706, 1660, 1510, 1489, 1398, 1348, 1225, 1052, 1024, 965, 754. (NMR signals of *cis*-**15d** were extracted from the spectrum of a 82:18 mixture of *cis*-**15d** and *trans*-**15d**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.12 (m, 1H), 7.54–7.51 (m, 2H), 7.37–7.29 (m, 2H), 7.28–7.26 (m, 5H), 7.10–7.05 (m, 1H), 7.00–6.97 (m, 2H), 5.25 (AB, J_{AB} = 13.9 Hz, 1H, *H*CHN), 5.20 (AB, J_{AB} = 13.9 Hz, 1H, HC*H*N), 4.61 (dddd, $^{3}J_{(H5-H4\beta)}$ = 9.9 Hz, $^{3}J_{(H5-CH)}$ = 7.8 Hz, $^{3}J_{(H5-H4\alpha)}$ = 3.6 Hz, $^{3}J_{(H5-CH)}$ = 3.6 Hz, 1H, *H*C5), 4.43 (d, ^{2}J = 13.7 Hz, 1H, *H*CHPh), 4.32–4.23 (m, 4H, 2 × CH_2OP), 4.21 (dd, ^{2}J = 12.2 Hz, $^{3}J_{(HC-H5)}$ = 7.8 Hz, 1H, *H*CHN), 4.19 (dd, ^{2}J = 12.2 Hz, $^{3}J_{(HC-H5)}$ = 3.6 Hz, 1H, HC*H*N), 3.89 (d, ^{2}J = 13.7 Hz, 1H, HC*H*Ph), 3.23 (ddd, $^{3}J_{(H3-H4\alpha)}$ = 9.9 Hz, $^{3}J_{(H3-H4\beta)}$ = 7.5 Hz, $^{2}J_{(H3-P)}$ = 3.1 Hz, 1H, *H*C3), 2.84 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.2 Hz, $^{3}J_{(H4\alpha-H4\beta)}$ = 12.8 Hz, $^{3}J_{(H4\alpha-H3)}$ = 9.9 Hz, $^{3}J_{(H4\beta-H5)}$ = 9.9 Hz, 1H, *H*αC4), 2.42 (dddd, $^{2}J_{(H4\beta-H4\alpha)}$ = 12.8 Hz, $^{3}J_{(H4\beta-P)}$ = 11.8 Hz, $^{3}J_{(H4\beta-H3)}$ = 7.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 3.6 Hz, 1H, *H*βC4), 1.41 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH_2OP), 1.40 (t, ^{3}J = 7.0 Hz, 3H, CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.29 (d, $^{1}J_{(CF)}$ = 246.4 Hz), 161.90 (C=O), 151.25 (C=O), 140.50, 136.57, 134.89, 132.87 (d, $^{4}J_{(CCCCF)}$ = 3.2 Hz), 131.03 (d, $^{3}J_{(CCCF)}$ = 8.5 Hz), 129.91, 128.27, 128.25, 127.53, 122.72, 115.58, 115.18 (d, $^{2}J_{(CCF)}$ = 21.0 Hz, C3′, C5′), 114.96, 75.78 (d, $^{3}J_{(CCCP)}$ = 6.6 Hz, C5), 62.94 (d, $^{2}J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.61 (d, $^{2}J_{(COP)}$ = 6.6 Hz, CH_2OP), 62.30 (d, $^{3}J_{(CNCP)}$ = 4.8 Hz, CH_2Ph), 60.64 (d, $^{1}J_{(CP)}$ = 170.0 Hz, C3), 47.77 (CH_2N), 44.17 (CH_2Ph), 35.15 (d, $^{2}J_{(CCP)}$ = 1.5 Hz, C4), 16.61 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP), 16.55 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.62. Anal. calcd. for $C_{30}H_{33}FN_3O_6P \times 1.5H_2O$: C, 59.21; H, 5.96; N, 6.90. Found: C, 59.46; H, 5.99; N, 6.92 (obtained on a 82:18 mixture of *cis*-**15d** and *trans*-**15d**).

4.5.29. Diethyl trans-{2-benzyl-5-[(3-(4-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl]isoxazolidin-3-yl} phosphonate (trans-**15d**)

A colorless oil. IR (film, cm^{-1}) ν_{max}: 2983, 1703, 1700, 1658, 1608, 1483, 1400, 1223, 1050, 1024, 966, 754. (NMR signals of *trans*-**15d** were extracted from the spectrum of a 12:88 mixture of *cis*-**15d** and *trans*-**15d**) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 7.64–7.62 (m, 1H), 7.53–7.51 (m, 2H), 7.30–7.25 (m, 7H), 7.00–6.97 (m, 2H), 7.00–6.97 (m, 2H), 5.25 (AB, J_{AB} = 13.8 Hz, 1H, *H*CHN), 5.22 (AB, J_{AB} = 13.8 Hz, 1H, HC*H*N), 4.48 (d, ^{2}J = 13.8 Hz, 1H, *H*CHPh), 4.43–4.39 (m, 2H, *H*C5, *H*CHN), 4.29–4.17 (m, 4H, 2 × CH_2OP), 4.16 (dd, ^{2}J = 15.7 Hz, $^{3}J_{(HC-H5)}$ = 5.7 Hz, 1H, HC*H*N), 3.89 (d, ^{2}J = 13.8 Hz, 1H, HC*H*Ph), 3.29–3.26 (m, 1H, *H*C3), 2.67 (dddd, $^{3}J_{(H4\alpha-P)}$ = 18.5 Hz, $^{2}J_{(H4\alpha-H4\beta)}$ = 13.0 Hz, $^{3}J_{(H4\alpha-H3)}$ = 6.5 Hz, $^{3}J_{(H4\beta-H5)}$ = 6.5 Hz, 1H, *H*αC4), 2.38–2.31 (m, 1H, *H*βC4), 1.37 (t, ^{3}J = 6.0 Hz, 6H, 2 × CH_3CH_2OP); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.30 (d, $^{1}J_{(CF)}$ = 246.2 Hz), 161.67 (C=O), 151.27 (C=O), 140.17, 136.50, 134.85, 132.47 (d, $^{4}J_{(CCCCF)}$ = 3.1 Hz), 130.97 (d, $^{3}J_{(CCCF)}$ = 8.0 Hz), 129.61, 128.92, 128.10, 127.46, 123.19, 115.57, 115.21 (d, $^{2}J_{(CCF)}$ = 21.6 Hz), 114.96, 75.61 (d, $^{3}J_{(CCCP)}$ = 6.2 Hz, C5), 63.27 (d, $^{2}J_{(COP)}$ = 6.5 Hz, CH_2OP), 62.69 (d, $^{3}J_{(CNCP)}$ = 4.5 Hz, CH_2Ph), 62.44 (d, $^{2}J_{(COP)}$ = 7.0 Hz, CH_2OP), 60.80 (d, $^{1}J_{(CP)}$ = 169.8 Hz, C3), 47.78 (CH_2N), 44.31 (CH_2Ph), 35.17 (d, $^{2}J_{(CCP)}$ = 2.0 Hz, C4), 16.54 (d, $^{3}J_{(CCOP)}$ = 5.6 Hz, CH_3CH_2OP), 16.48 (d, $^{3}J_{(CCOP)}$ = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.78. Anal. calcd. for

$C_{30}H_{33}FN_3O_6P$: C, 61.69; H, 5.72; N, 7.23. Found: C, 61.89; H, 5.97; N, 7.28 (obtained on a 12:88 mixture of *cis*-**15d** and *trans*-**15d**).

4.6. Antiviral activity assays

The compounds were evaluated against different herpesviruses, including herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strain G, varicella-zoster virus (VZV) strain Oka, TK^- VZV strain 07-1, human cytomegalovirus (HCMV) strains AD-169 and Davis as well as feline herpes virus (FHV), the poxvirus vaccinia virus (Lederle strain), para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, respiratory syncytial virus (RSV), feline coronovirus (FIPV) and influenza A virus subtypes H1N1 (A/PR/8), H3N2 (A/HK/7/87) and influenza B virus (B/HK/5/72) and human immune deficiency virus (5HVV-1 and HIV-2). The antiviral assays, other than HIV, were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey kidney cells (Vero), human epithelial cervix carcinoma cells (HeLa), Crandell-Rees feline kidney cells (CRFK), or Madin Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 CCID50 of virus (1 CCID50 being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation (VZV) was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathicity or viral plaque formation by 50%. Cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology.

4.7. Cytostatic activity against immortalized cell lines

Murine leukemia (L1210), human T-lymphocyte (CEM), human cervix carcinoma (HeLa) and immortalized human dermal microvascular endothelial cells (HMEC-1) were suspended at 300,000–500,000 cells/mL of culture medium, and 100 μL of a cell suspension was added to 100 μL of an appropriate dilution of the test compounds in 200 μL-wells of 96-well microtiter plates. After incubation at 37 °C for two (L1210), three (CEM) or four (HeLa) days, the cell number was determined using a Coulter counter. The IC50 was defined as the compound concentration required to inhibit cell proliferation by 50%.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.10.002.

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