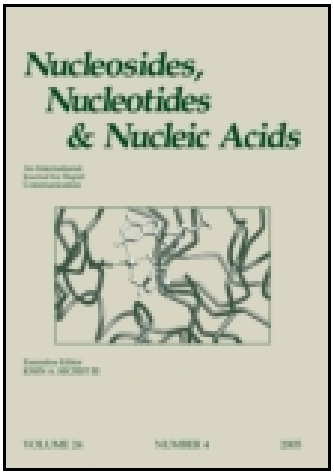


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

Novel 5-Arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates as Nucleotide Analogues

Kamil Kokosza[a], Jan Balzarini[b] & Dorota G. Piotrowska[a]

[a] Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Łódź, Muszyńskiego, Poland

[b] Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat, Leuven, Belgium

Published online: 10 Jul 2014.

To cite this article: Kamil Kokosza, Jan Balzarini & Dorota G. Piotrowska (2014) Novel 5-Arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates as Nucleotide Analogues, Nucleosides, Nucleotides and Nucleic Acids, 33:8, 552-582, DOI: 10.1080/15257770.2014.909046

To link to this article: http://dx.doi.org/10.1080/15257770.2014.909046

Nucleosides, Nucleotides and Nucleic Acids, 33:552–582, 2014

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770.2014.909046

NOVEL 5-ARYLCARBAMOYL-2-METHYLISOXAZOLIDIN-3-YL-3-PHOSPHONATES AS NUCLEOTIDE ANALOGUES

Kamil Kokosza,[1] Jan Balzarini,[2] and Dorota G. Piotrowska[1]
[1]*Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Łódź, Muszyńskiego, Poland*
[2]*Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat, Leuven, Belgium*

□ *A series of 5-substituted 3-phosphonylated isoxazolidines have been obtained via cycloaddition of N-methyl-C-(diethoxyphosphoryl)nitrone with N-heteroaromatic acrylamides. Good trans/cis diastereoselectivities (d.e. 58–76%) of isomeric (3-diethoxyphosphoryl)isoxazolidines were observed. cis- and trans-Isoxazolidine phosphonates were evaluated for their antiviral activity against a broad range of DNA and RNA viruses but were found inactive. Their cytostatic activity toward L1210, CEM, and HeLa cells was also established, and compounds cis-**12r** and trans-**11r** having a 2,2-difluorobenzo[d][1,3]dioxole moiety slightly inhibited proliferation of HeLa cells at IC_{50} values of 186 and 179 μM, respectively.*

Keywords Modified nucleosides; phosphonates; isoxazolidines; 1,3-dipolar cycloaddition

INTRODUCTION

Analogues of nucleosides constitute an important class of compounds in contemporary medicinal chemistry. An extensive body of literature deals with modified nucleosides exhibiting antiviral,[1–3] anticancer,[4–6] antibacterial,[7–9] and antimalarial[10] activities. Structural modifications of naturally occurring nucleosides to design potentially active nucleoside analogues predominantly concern sugar and nucleobase moieties. Moreover, a replacement of the furanoside fragment is not limited to other alicyclic or heterocyclic rings containing one or more heteroatoms, but aliphatic chains can also be incorporated.[11–12] On the other hand, modifications of nucleobase subunits to control a network of hydrogen bonds are not adequately explored. In order to improve the compounds' biological activities, additional

Received 26 November 2013; accepted 21 March 2014.
Address correspondence to Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, 90–151 Łódź, Muszyńskiego 1, Poland. E-mail: dorota.piotrowska@umed.lodz.pl

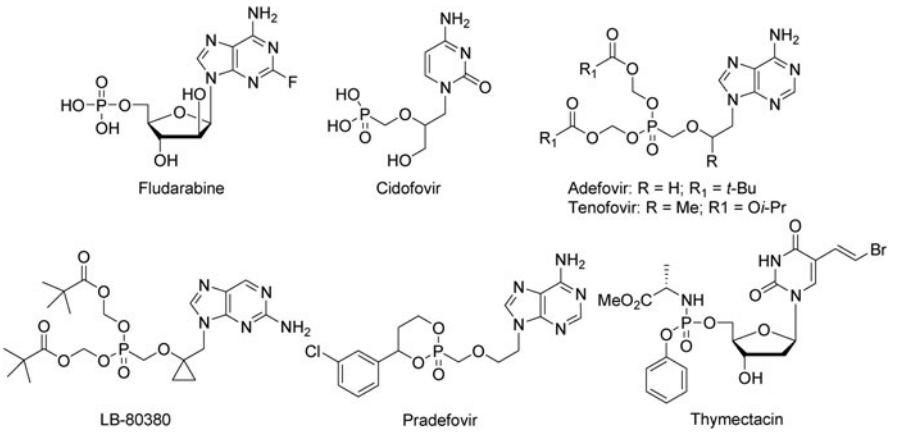


FIGURE 1 Structures of nucleotide analogues approved for clinical use or subject of clinical trials.

linkers can be installed such as an ureidyl,[13] aminyl,[14] carbamoyl,[15–18] or a 1,2,3-triazole group[19–22] to name a few.

In spite of a great number of nucleoside analogues available for treatment of various types of cancers[23] and viral infections,[24] adverse effects, low selectivity, and increasing resistance to currently used medications are the main concerns in pharmacotherapy. The lack of activity of many obtained nucleoside analogues results from their insufficient conversion to their corresponding triphosphates. Recently, more attention has been paid to phosphonate analogues of nucleotides since the rate-limiting step, namely, phosphorylation to the corresponding monophosphate could be omitted and only two phosphorylation steps are required to reach their pharmacologically active form.[25] Extensive search in this field has led to the discovery of many highly-active molecules that are licensed for clinical use, whereas others are currently under clinical or preclinical investigation (Figure 1).[23,24,26–29]

Since 1992 when Tronchet proposed an isoxazolidine ring as an alternative to the furanose subunit,[30] many potent isoxazolidine nucleoside analogues have been synthesized (Figure 2). Among them, compound **1** [(–)-AdFU] substituted at C5 with 5-fluorouracil-induced apoptosis in lymphoid and monocytoid cells and exhibits a low level of cytotoxicity.[31] Bortolini et al. showed antiproliferative properties of 3,5-disubstituted isoxazolidines **2**.[32] Phosphonates of general formula **3**, besides inhibiting reverse transcriptase of HTLV-1 with activity comparable to that of AZT, protect human peripheral blood mononuclear cells against HTLV-1 transmission.[33] Since *N*-methyl-*C*-(diethoxyphosphoryl)nitrone became available in sufficient quantities,[34,35] a great deal of interest was generated due to its possible application in the synthesis of a novel class of nucleotides in which the diethoxyphosphoryl group is directly attached to C3 of the isoxazolidine ring. Biological studies showed that *cis*-configurated analogues containing

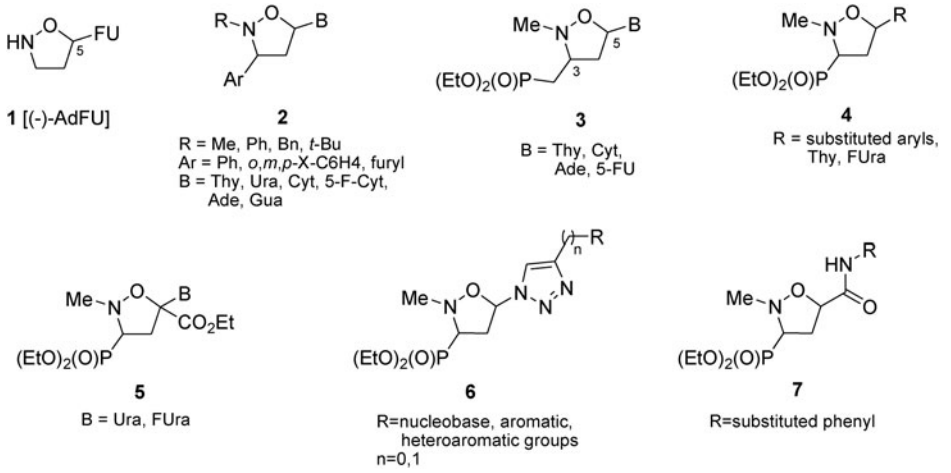


FIGURE 2 Examples of biologically active isoxazolidine nucleosides and nucleotides.

thymine or 5-fluorouracil **4** inhibited the reverse transcriptase activity of two retroviruses, namely, Avian Moloney Virus (AMV), and Human Immunodeficiency Virus (HIV).[36] At the same time, compounds **4** substituted with a 1- and 2-naphthyl proved cytostatic against HeLa and K562 cell lines at concentrations of 0.05 and 0.09 mM (IC_{50}), respectively.[37] Recently, inhibitory activity of derivatives **5** with an additional ethoxycarbonyl substituent against HIV infection has also been reported.[38]

3,5-Disubstituted isoxazolidine analogues containing functionalized 1,2,3-triazoles **6** and a carbamoyl linker **7** have also been obtained. Although none of them showed antiviral activity, cytostatic properties were discovered for derivatives **6** substituted at C4 in the 1,2,3-triazole ring by phenyl, 2-fluoro, 3-fluoro-, and 2,4-difluorophenyl groups.[39] Recently, we have described a convenient synthesis of 5-(arylcarbamoyl)isoxazolidine phosphonates **7**, and again derivatives having 2-fluorophenyl but also 3- and 4-bromophenyl groups proved the most active toward three tested cancer cell lines.[40] In continuation of our search of antiviral and cytostatic properties of (isoxazolidine-3-yl)phosphonates of general formula **8,** it was assumed that the replacement of aryl substituent acting as a nonpolar replacer of natural nucleobase in **7** with various heteroaromatic rings could improve activity of the latter molecules through formation of additional hydrogen bonds (Scheme 1). The general concept of hydrogen-bonding patterns and shape complementarity of various heteroaromatic nucleobase isosters in order to study interactions of nucleoside analogues with enzymes responsible for nucleic acid synthesis were widely explored by several research groups.[41–44] Apart from various nitrogen-containing heteroaromatic groups such as pyrazole, pyridine, pyrimidine, pyrazine, benzo[*d*]imidazole, and indole, applied as nucleobase replacers in the structure of isoxazolidine nucleotide analogues

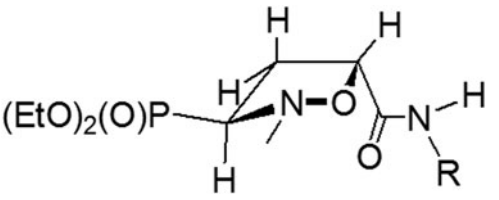
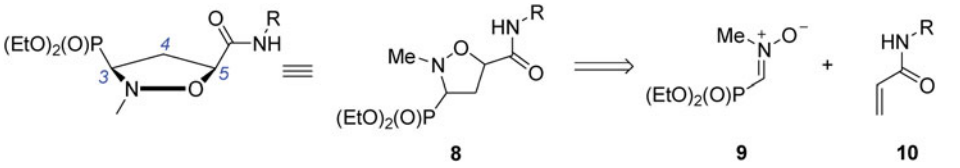


FIGURE 3 The preferred conformations of *trans*-isoxazolidines **11**.

8, substituted benzo[*d*][1,3]dioxole derivatives were also selected, since numerous natural and synthetic compounds containing this structural subunit exhibited antiviral as well as anticancer activities.[45–47]

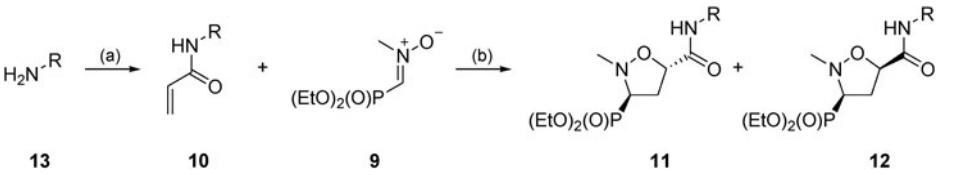


SCHEME 1 Retrosynthesis of (isoxazolidyn-3-yl)phosphonates **8** with a carbamoyl linker. (Color figure available online).

RESULTS AND DISCUSSION

Chemistry

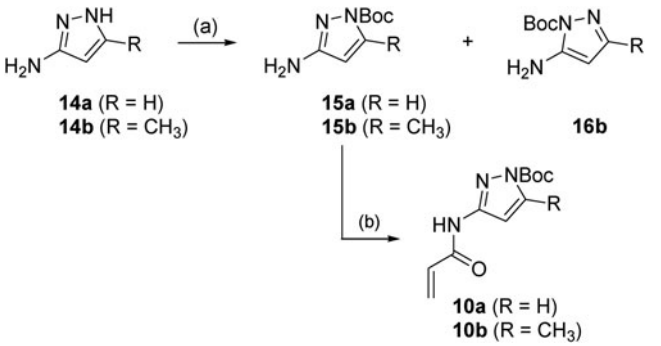
1,3-Dipolar cycloaddition of *N*-methyl-*C*-(diethoxyphosphoryl)nitrone **9**[34,35] with a series of heteroaromatic acrylamides **10** was employed for the synthesis of isoxazolidines *trans*-**11** and *cis*-**12** (Scheme 2).



SCHEME 2 Reagents and conditions: (a) Et_3N, acryloyl chloride, rt, 24 hours; (b) toluene, 70°C, 24 hours, see Table 1.

To the best of our knowledge, all acrylamides, except for **10c-d**, **10f-g**, **10q**, **10t**, **10u,** and **10w**, have not been described in the literature. For the synthesis of all acrylamides **10,** the standard procedure employing acryloyl chloride in the presence of triethylamine was applied.[48] However, under these conditions from 1*H*-3-aminopyrazole **14a** and 1*H*-3-amino-5-methylpyrazole **14b,** complex mixtures of products were formed. To alleviate this problem, compound **14a** and **14b** were reacted with Boc_2O in the presence of

sodium hydride in THF[49] to afford **15a**, whereas in case of **14b** a chromatographically separable mixture (33:67) of two regioisomers **15b** (19%) and **16b** (10%) was obtained (Scheme 3). Even though isomer **16b** was formed predominantly, its isolation from the crude reaction mixture was tedious and less effective. The remaining fractions of less polar **16b** collected after column chromatography were contaminated with unreacted Boc_2O. Subsequent acroylation of **15a** and **15b** gave acrylamides **10a** and **10b** in 45 and 53% yield, respectively.

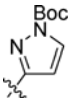
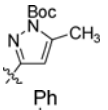
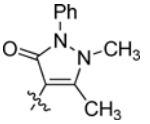
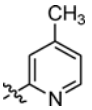
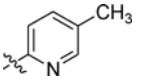
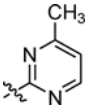
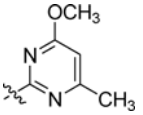
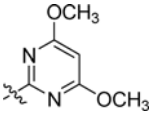
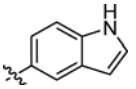
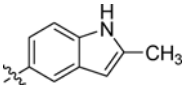
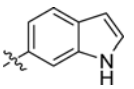


SCHEME 3 Reagents and conditions: (a) NaH, Boc_2O, THF, 2 hours; (b) Et_3N, acryloyl chloride, rt, 24 hours.

The 1,3-dipolar cycloadditions of the nitrone **9** with acrylamides **10a-w** were performed in toluene at 70°C to give mixtures of isomeric (3-diethoxyphosphoryl)isoxazolidines *trans*-**11** and *cis*-**12** with moderate to good *trans*/*cis* diastereoselectivities (d.e. 58–76%) (Scheme 2, Table 1). Crude mixtures of products were subjected to column chromatography to provide almost all major *trans*-isomers (namely **11a-b**, **11d-f**, **11h-j,** and **11l-w)** with moderate yields (Table 1). Attempts to obtain pure minor, *cis*-isomers **12** proved successful for **12f**, **12l-n**, **12r,** and **12u-v** only, but to achieve this goal several separations of mixtures enriched in isoxazolidines **12** on silica gel columns were necessary.

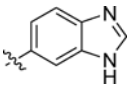
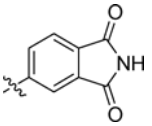
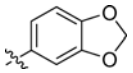
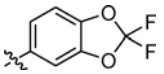
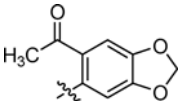
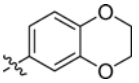
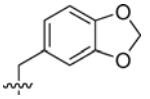
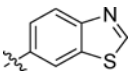
The relative configurations of the isoxazolidines **11a-w** and **12a-w** were established taking advantage of our previous observations made on stereochemistry of cycloaddition of *N*-methyl-*C*-diethoxyphosphorylated nitrone **9** with acrylamides derived from substituted anilines.[40] As expected, incorporation of hetereoaromatic substituents instead of substituted phenyl groups in **10** had no influence on diastereoselectivities observed for the cycloaddition of the nitrone **9** to acrylamides **10** (*trans*:*cis* 8:2). Moreover, similar patterns for the respective isoxazolidine protons (H3, H4α, H4β, and H5) were observed in the ^{1}H NMR spectra in series of isoxazolidines *trans*-**11a-w** and *cis*-**12a-w** as compared to the already described analogous *trans*- and *cis*-cycloadducts obtained from **9** and *N*-arylacrylamides.[40] Indeed, detailed

TABLE 1 Isoxazolidines **11** and **12** produced via Scheme 2.

Entry	Acrylamide **10** Ar	Ratio of **11**: **12**	Yield (%)
a		85:15	**11a** (58)[a] + **11a** and **12a** (16)[b]
b		82:18	**11b** (41)[a] + **11b** and **12b** (40)[b]
c		83:17	**11c** and **12c** (88)[b]
d		88:12	**11d** (56)[a] + **11d** and **12d** (22)[b]
e		87:13	**11e** (60)[a] + **11e** and **12e** (15)[b]
f		84:16	**11f** (56)[a] + **12f** (2)[a] + **11f** and **12f** (20)[b]
g		88:12	**11g** and **12g** (98)[b]
h		87:13	**11h** (7)[a] + **11h** and **12h** (87)[b]
i		86:14	**11i** (30)[a] + **11i** and **12i** (53)[b]
j		86:14	**11j** (61)[a] + **11j** and **1j2** (31)[b]
k		84:16	**11k** and **12k** (96)[b]
l		85:15	**11l** (53)[a] + **12l** (4)[a] + **11l** and **12l** (33)[b]
m		83:17	**11m** (17)[a] + **12m** (4)[a] + **11m** and **12m** (61)[b]
n		87:13	**11n** (40)[a] + **12n** (2)[a] + **11n** and **12n** (49)[b]

(Continued on next page)

TABLE 1 Isoxazolidines **11** and **12** produced via Scheme 2. *(Continued)*

Entry	Acrylamide **10** Ar	Ratio of **11**: **12**	Yield (%)
o		84:16	**11o** (29)[a] + **11o** and **12o** (22)[b]
p		84:16	**11p** (53)[a]
q		85:15	**11q** (29)[a] + **11q** and **12q** (51)[b]
r		78:22	**11r** (60)[a] + **12r** (6)[a] +**11r** and **12r** (31)[b]
s		87:13	**11s** (73)[a] + **11s** and **12s** (21)[b]
t		84:16	**11t** (26)[a] + **11t** and **12t** (73)[b]
u		84:16	**11u** (46)[a] + **12u** (4)[a] + **11u** and **12u** (25)[b]
v		85:15	**11v** (40)[a] + **12v** (4)[a] + **11v** and **12v** (46)[b]
w		80:20	**11w** (39)[a] + **11w** and **12w** (35)[b]

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

conformational analysis of major *trans*-isoxazolidines **11d-w** based on values of vicinal $HCCH$,[50] $HCCP$,[51,52] and $CCCP$[53,54] coupling constants [$J_{CCCP} = 8.8–9.5$ Hz, $J_{H3–H4\alpha} = 7.8–8.4$ Hz, $J_{H3–H4\beta} = 8.4–9.2$ Hz, $J_{H4\alpha–P} = 8.8–10.3$ Hz, $J_{H4\beta–P} = 15.6–16.1$ Hz, $J_{H4\alpha–H5} = 5.2–5.8$ Hz, and $J_{H4\beta–H5} = 8.4–9.2$ Hz] revealed that the isoxazolidine ring in **11** exists in the ${}_3E$ conformation having diethoxyphosphoryl group in the equatorial position and carbamoyl substituents located pseudoequatorially.

Studies on Biological Activity

Antiviral Activity

5-Substituted 2-methylisoxazolidin-3-yl-3-phosphonates *trans*-**11** and *cis*-**12** as well as the respective mixtures of *trans*-**11**/*cis*-**12** enriched with *cis*-**12**

were evaluated for their inhibitory activity against a wide variety of DNA and RNA viruses, using the following cell-based assays: (a) in human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 (TK^- KOS ACV^r), varicella-zoster virus (VZV), and cytomegalovirus (CMV); (b) in HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus; (c) in Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus; (d) in CrFK cell cultures: feline corona virus (FIPV), and feline herpes virus (FHV); (e) in MDCK cell cultures: influenza A virus (H1N1 and H3N2 subtypes) and influenza B virus; and (f) in CEM cell cultures: human immunodeficiency virus type 1 (HIV-1) and HIV-2. Ganciclovir, cidofovir, acyclovir, brivudin, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA], oseltamivir carboxylate, amantadine, rimantadine, ribavirin, dextran sulfate (molecular weight 5000, DS-5000), *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). Unfortunately, no inhibitory activity against any virus was detected for the evaluated compounds at 250 μM.

Cytotoxicity of the Tested Compounds

The cytotoxicity of the tested compounds toward the uninfected host cells was defined as the minimum compound concentration (MCC) that caused a microscopically detectable alteration of normal cell morphology. None of the tested compounds affected cell morphology of HEL, HeLa, Vero, MDCK, and CrFK cells at concentrations up to 100 μM.

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, and human cervix carcinoma HeLa cells. Compounds *trans*-**11r** and *cis*-**12r**, both having a 2,2-difluorobenzo[*d*][1,3]dioxol-6-ylcarbamoyl substituent at C5 in the isoxazolidine ring, were found only to slightly inhibit HeLa cell proliferation by 50% (IC_{50}) at concentrations of 179 ± 59 and 186 ± 49 μM.

CONCLUSIONS

A novel series of 5-arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates has been synthesized in good *trans*/*cis* (d.e. 58–76%) diastereoselectivities *via* 1,3-dipolar cycloaddition of *N*-methyl-*C*-(diethoxyphosphoryl)nitrone and selected heteroaromatic *N*-acrylamides. Evaluation of the antiviral activity of the phosphonates *cis*-**12** and *trans*-**11**

was performed against a wide variety of DNA and RNA viruses. None of the compounds was found active at concentrations up to 250 μM. Several reasons may cause the lack of biological response from the virus-infected cells including bioavailability and subsequent enzymatic hydrolysis followed by phosphorylation of the corresponding phosphonic acids. Cytostatic activity of *cis*- and *trans*-isoxazolidines was conducted on three tumor cell lines (L1210, CEM and HeLa). Compounds *cis*-**12r** and *trans*-**11r** containing a 2,2-difluorobenzo[*d*][1,3]dioxole moiety were cytostatic against human cervix carcinoma HeLa cells at 189 and 179 μM (IC_{50}), respectively.

EXPERIMENTAL

^{1}H NMR spectra were taken in $CDCl_3$ or CD_3OD on the following spectrometers: Varian Mercury-300 and Bruker Avance III (600 MHz) with TMS as internal standard. ^{13}C NMR spectra were recorded for $CDCl_3$ solution on the Varian Mercur-300 machine at 75.5 MHz. ^{31}P NMR spectra were performed in $CDCl_3$ solution on the Varian Mercury-300 at 121.5 MHz. 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 F254.

Starting Materials. All solvents were dried according to the literature methods. The nitrone **9** was previously reported.[17]

*General procedure for the preparation of acrylamides **10***

To a solution of substituted heteroaromatic amine (1.00 mmol) in dichloromethane, DMF or THF (2 mL) triethylamine (1.10 mmol) was added. The mixture was cooled in an ice bath and acryloyl chloride (1.05 mmol) was added dropwise. The reaction mixture was stirred for 24 hours at room temperature and extracted with water (3 × 3 mL). Subsequently, the aqueous layer was extracted with ethyl ether (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. After evaporation of solvents, the residue was purified on a silica column with chloroform:methanol mixtures (100:1, 50:1 v/v) as eluents to afford the respective acrylamides **10**.

tert-***Butyl 3-(acrylamido)-1H-pyrazole-1-carboxylate 10a***

Yield: 45%; white amorphous solid (crystallized from chloroform/hexane) mp 135–136°C; IR (KBr, cm^{-1}) ν_{max}: 3285, 3258, 1763, 1738, 1689, 1578, 1399, 1360, 1308, 1138, 965, 841, 764; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (br s, 1H, N*H*), 8.00 (d, 1H, J = 2.8 Hz), 7.05 (d, 1H, J = 2.8 Hz), 6.45 (dd, 1H, J = 16.9, 1.0 Hz, CH=CH_2), 6.23 (dd, 1H, J = 16.9, 10.3 Hz, C*H*=CH_2), 5.82 (dd, 1H, J = 10.3, 1.0 Hz, CH=CH_2), 1.65 (s, 9H,

3 × CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 163.63 (s, C(O)NH), 151.17 (s, C(O)), 147.25, 131.71, 130.63 (s, *C*H=CH_2), 128.54 (s, CH=*C*H_2), 102.89, 85.80 (s, *C*(CH_3)$_3$), 28.12 (s, 3 × CH_3). Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71; found: C, 55.39; H, 6.26; N, 17.43.

tert-***Butyl 3-(acrylamido)-5-methyl-1H-pyrazole-1-carboxylate 10b***

Yield: 53%; white amorphous solid (crystallized from chloroform/hexane) mp 145–146°C; IR (KBr, cm^{-1}) ν_{max}: 3264, 2989, 1738, 1671, 1600, 1353, 1317, 1160, 1108, 980; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.13 (br s, 1H, N*H*), 6.82 (s, 1H, *H*C4), 6.43 (dd, 1H, J = 17.0, 0.8 Hz, CH=CH_2), 6.21 (dd, 1H, J = 17.0, 10.4 Hz, C*H*=CH_2), 5.81 (dd, 1H, J = 10.4, 0.8 Hz, CH=CH_2), 2.55 (s, 3H, CH_3), 1.67 (s, 9H, 3 × CH_3); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 163.66 (s, C(O)NH), 149.53 (s, C(O)), 148.41, 144.70, 130.87 (s, *C*H = CH_2), 128.01 (s, CH=*C*H_2), 103.81, 85.21 (s, *C*(CH_3), 27.80 (s, 3 × CH_3), 14.88 (s, CH_3). Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72; found: C, 57.10; H, 6.48; N, 16.82.

N-***(4-Methylpyridin-2-yl)acrylamide 10e***

Yield: 22%; white amorphous solid (crystallized from chloroform/hexane) mp 93–93.5°C; IR (KBr, cm^{-1}) ν_{max}: 3185, 3009, 1686, 1614, 1582, 1417, 1210, 956, 834; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (br s, 1H, N*H*), 8.17 (dd, 1H, J = 0.6, 0.6 Hz, *H*C3), 8.14 (dd, 1H, J = 5.2, 0.6 Hz, *H*C6), 6.90 (dd, 1H, J = 5.2, 0.6 Hz, *H*C5), 6.47 (dd, 1H, J = 16.9, 1.4 Hz, CH=CH_2), 6.27 (dd, 1H, J = 16.9, 10.1 Hz, C*H* = CH_2), 5.80 (dd, 1H, J = 10.1, 1.4 Hz, CH = CH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 164.07 (s, C(O)), 152.07, 150.17, 146.90, 130.97 (s, *C*H = CH_2), 128.34 (s, CH = *C*H_2), 121.04, 115.67, 21.58 (s, CH_3). Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27; found: C, 66.62; H, 6.09; N, 17.47.

N-***(4-Methylpyrimidin-2-yl)acrylamide 10h***

Yield: 19%; white amorphous solid (crystallized from chloroform/hexane) mp 133–135°C; IR (KBr, cm^{-1}) ν_{max}: 2924, 1679, 1592, 1572, 1410, 1329, 954, 844; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.47 (d, 1H, J = 5.0 Hz), 8.24 (br s, 1H, N*H*), 6.89 (dd, 1H, J = 16.9, 10.3 Hz, C*H*=CH_2), 6.88 (d, 1H, J = 5.0 Hz), 6.52 (dd, 1H, J = 16.9, 1.4 Hz, CH = CH_2), 5.85 (dd, 1H, J = 10.3, 1.4 Hz, CH=CH_2), 2.49 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.98, 165.24 (s, C(O)), 157.75, 157.51, 130.78 (s, CH=*C*H_2), 129.33 (s, *C*H=CH_2), 116.09, 24.42 (s, CH_3). Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75; found: C, 59.02; H, 5.26; N, 25.91.

N-***(4-Methoxy-6-methylpyrimidin-2-yl)acrylamide 10i***

Yield: 11%; white amorphous solid mp 88–93°C; IR (KBr, cm^{-1}) ν_{max}: 3196, 2990, 1694, 1615, 1542, 1467, 1354, 1186, 1065, 961; ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 8.00 (br s, 1H, N*H*), 7.07 (dd, 1H, J = 17.0, 10.3 Hz, C*H*=CH_2), 6.51 (dd, 1H, J = 17.0, 1.6 Hz, CH=C*H*$_2$), 6.29 (s, 1H, *H*C5), 5.83 (dd, 1H, J = 10.3, 1.6 Hz, CH=C*H*$_2$), 3.95 (s, 3H, C*H*$_3$O), 2.38 (s, C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.67, 168.41, 165.26 (s, C(O)), 156.78, 130.69 (s, CH=*C*H$_2$), 129.01 (s, *C*H=CH_2), 101.78, 54.01 (s, OCH_3), 23.84 (s, CH_3). Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75; found; C, 55.96; H, 5.64; N, 21.71.

N-***(4,6-Dimethoxypyrimidin-2-yl)acrylamide 10j***

Yield: 25%; white amorphous solid (crystallized from chloroform/hexane) mp 108–108.5°C; IR (KBr, cm^{-1}) ν_{max}: 3335, 1674, 1607, 1576, 1420, 1376, 1317, 1224, 1081, 827, 797; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (br s, 1H, N*H*), 7.19 (dd, 1H, J = 17.1, 10.5 Hz, C*H*=CH_2), 6.51 (dd, 1H, J = 17.1, 1.6 Hz, CH=C*H*$_2$), 5.83 (dd, 1H, J = 10.5, 1.6 Hz, CH=C*H*$_2$), 5.77 (s, 1H, *H*C5), 3.92 (s, 6H, 2 × C*H*$_3$O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 171.73, 165.38 (s, C(O)), 156.09, 130.48 (s, CH=*C*H$_2$), 129.34 (s, *C*H=CH_2), 85.12, 54.43 (s, OCH_3). Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09; found: C, 51.66; H, 5.22; N, 20.02.

N-***(Pyrazin-2-yl)acrylamide 10k***

Yield: 21%; white amorphous solid (crystallized from chloroform/hexane) mp 155–157°C; IR (KBr, cm^{-1}) ν_{max}: 3449, 3233, 3097, 1673, 1622, 1546, 1410, 1211, 846; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.64 (d, 1H, J = 1.6 Hz, *H*C3), 8.38 (d, 1H, J = 2.6 Hz, *H*C6), 8.26 (dd, 1H, J = 2.6, 1.6 Hz, *H*C5), 8.11 (br s, 1H, N*H*), 6.53 (dd, 1H, J = 16.9, 1.2 Hz, CH=C*H*$_2$), 6.32 (dd, 1H, J = 16.9, 10.3 Hz, C*H*=CH_2), 5.89 (dd, 1H, J = 10.3, 1.2 Hz, CH=C*H*$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 163.62 (s, C(O)), 148.26, 142.09, 140.42, 137.47, 130.17 (s, CH=*C*H$_2$), 129.84 (s, *C*H=CH_2). Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17; found: C, 56.28; H, 4.93; N, 28.21.

N-***(1*H*-Indol-5-yl)acrylamide 10l***

Yield: 67%; white amorphous solid (crystallized from chloroform/hexane) mp 123–124°C; IR (KBr, cm^{-1}) ν_{max}: 3300, 3235, 1648, 1540, 1477, 1242, 811, 764, 730; ^{1}H NMR (300 MHz, CD_3OD) δ: 7.87–7.86 (m, 1H), 7.35–7.32 (m, 1H), 7.27–7.22 (m, 2H), 6.46 (dd, 1H, J = 16.9, 9.9 Hz, C*H*=CH_2), 6.42–6.41 (m, 1H), 6.34 (dd, 1H, J = 16.9, 2.1 Hz, CH=C*H*$_2$), 5.73 (dd, 1H, J = 9.9, 2.1 Hz, CH=C*H*$_2$); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 165.99 (s, C(O)), 135.15, 132.70 (s, CH=*C*H$_2$), 131.19, 129.32, 126.97 (s, *C*H=CH_2), 126.62, 116.94, 113.70, 112.17, 102.58. Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04; found. C, 70.98; H, 5.56; N, 14.95.

N-***(2-Methyl-1*H*-indol-5-yl)acrylamide 10m***

Yield: 36%; yellowish amorphous solid (crystallized from chloroform/hexane) mp 149–150°C; IR (KBr, cm^{-1}) ν_{max}: 3330, 3260, 1645, 1537, 1406, 1225, 868, 773; ^{1}H NMR (300 MHz, CD_3OD) δ: 7.71–7.70 (m, 1H), 7.22–7.14 (m, 2H), 6.45 (dd, 1H, J = 17.0, 9.9 Hz, C*H*=CH_2), 6.33 (dd, 1H, J = 17.0, 2.1 Hz, CH=C*H*$_2$), 6.09–6.08 (m, 1H), 5.72 (dd, 1H, J = 9.9, 2.1 Hz, CH=C*H*$_2$), 2.40 (s, 3H, C*H*$_3$); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 165.76 (s, C(O)), 137.65, 135.31, 132.59 (s, CH=*C*H$_2$), 130.82, 130.30, 126.73 (s, *C*H=CH_2), 115.62, 112.70, 111.12, 100.45, 13.56 (s, CH_3). Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99; found: C, 71.76; H, 5.78; N, 14.21.

N-***(1*H*-Indol-6-yl)acrylamide 10n***

Yield: 32%; white amorphous solid (crystallized from chloroform/hexane) mp 175–176°C; IR (KBr, cm^{-1}) ν_{max}: 3290, 1649, 1524, 1233, 870, 811, 733; ^{1}H NMR (300 MHz, CD_3OD) δ: 8.00–7.98 (m, 1H), 7.49–7.46 (m, 1H), 7.20–7.19 (m, 1H), 7.06–7.02 (m, 1H), 6.47 (dd, 1H, J = 17.0, 10.0 Hz, C*H*=CH_2), 6.40–6.39 (m, 1H), 6.34 (dd, 1H, J = 17.0, 2.1 Hz, CH=C*H*$_2$), 5.74 (dd, 1H, J = 10.0, 2.1 Hz, CH = C*H*$_2$); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 165.88 (s, C(O)), 137.47, 133.57, 132.69 (s, CH=*C*H$_2$), 127.10 (s, *C*H=CH_2), 126.71, 126.00, 121.18, 114.16, 104.65, 102.34. Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04; found. C, 70.86; H, 5.16; N, 15.34.

N-***(1*H*-Benzo[*d*]imidazol-6-yl)acrylamide 10o***

Yield: 28%; grey solid (crystallized from chloroform) mp > 250°C; IR (KBr, cm^{-1}) ν_{max}: 3407, 3064, 1671, 1603, 1428, 1410, 1236, 806; ^{1}H NMR (300 MHz, CD_3OD) δ: 8.71 (s, 1H), 8.38–8.37 (m, 1H), 7.69–7.66 (m, 1H), 7.50–7.46 (m, 1H), 6.48 (dd, 1H, J = 17.1, 9.3 Hz, C*H* = CH_2), 6.39 (dd, 1H, J = 17.1, 2.6 Hz, CH = C*H*$_2$), 5.81 (dd, 1H, J = 9.3, 2.6 Hz, CH = C*H*$_2$); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 166.18, 142.11, 136.85, 135.65, 132.96, 132.39 (s, CH = *C*H$_2$), 127.96 (s, *C*H = CH_2), 119.08, 116.22, 106.86. Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45; found: C, 63.95; H, 5.05; N, 22.13.

N-***(1,3-Dioxoisoindolin-5-yl)acrylamide 10p***

Yield: 42%; yellow amorphous solid mp 211–212°C; IR (KBr, cm^{-1}) ν_{max}: 3359, 3240, 3062, 1766, 1720, 1614, 1554, 1361, 746; ^{1}H NMR (300 MHz, CD_3OD) δ: 8.26 (d, 1H, J = 1.8 Hz, *H*C4), 7.95 (dd, 1H, J = 8.2, 1.8 Hz, *H*C6), 7.78 (d, 1H, J = 8.2 Hz, *H*C7), 6.52–6.40 (m, 2H), 5.85 (dd, 1H, J = 7.2, 4.6 Hz, CH=C*H*$_2$); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 171.54 (s, C(O)), 170.43 (s, C(O)), 166.26 (s, C(O)), 145.71, 137.04, 131.98 (s, CH = *C*H$_2$), 129.09 (s, *C*H=CH_2), 128.87, 125.84, 125.06, 114.95. Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96; found; C, 60.82; H, 3.71; N, 12.86.

N-*(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)acrylamide 10r*

Yield: 43%; slightly yellowish amorphous solid (crystallized from chloroform) mp 175–176°C; IR (KBr, cm^{-1}) ν_{max}: 3282, 3112, 1665, 1579, 1503, 1225, 1159, 1037, 958, 862, 807; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.70 (br s, 1H), 7.33 (br s, 1H), 7.06 (dd, 1H, J = 8.5, 1.9 Hz, *H*C6), 7.02 (d, 1H, J = 8.5 Hz, *H*C7), 6.47 (dd, 1H, J = 16.8, 1.0 Hz, CH=CH_2), 6.25 (dd, 1H, J = 16.8, 10.3 Hz, C*H*=CH_2), 5.83 (dd, 1H, J = 10.3, 1.0 Hz, CH = CH_2); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 165.96 (s, C(O)), 144.77, 141.10, 136.37, 133.06 (t, J = 250.2 Hz, CF_2), 132.11 (s, *C*H=CH_2), 128.15 (s, CH=*C*H_2), 116.37, 110.49, 103.91. Anal. Calcd. for $C_{10}H_7F_2NO_3$: C, 52.87; H, 3.11; N, 6.17; found; C, 52.73; H, 2.99; N, 5.90.

N-*(5-Acetylbenzo[*d*][1,3]dioxol-6-yl)acrylamide 10s*

Yield: 40%; slightly orange amorphous solid (crystallized from chloroform) mp 137–140°C; IR (KBr, cm^{-1}) ν_{max}: 3075, 2924, 1682, 1611, 1512, 1476, 1365, 1337, 1276, 1249, 1204, 1037, 787; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 7.31 (s, 1H), 6.44 (dd, 1H, J = 17.0, 0.9 Hz, CH = CH_2), 6.32 (dd, 1H, J = 17.0, 10.3 Hz, C*H* = CH_2), 6.07 (s, 2H, OCH_2O), 5.81 (dd, 1H, J = 10.3, 0.9 Hz, CH = CH_2), 2.61 (s, 3H, CH_3C(O)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 200.59 (s, C(O)), 164.45 (s, C(O)NH), 152.88, 142.67, 139.25, 132.52 (s, *C*H = CH_2), 127.40 (s, CH = *C*H_2), 115.40, 109.80, 102.28, 101.66 (s, OCH_2O), 28.92 (s, *C*H_3C(O)). Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01; found; C, 61.84; H, 4.88; N, 5.86.

N-*(Thiazol-2-yl)acrylamide 10v*

Yield: 27%; white (cream) amorphous solid (crystallized from chloroform/hexane) mp 145–146°C; IR (KBr, cm^{-1}) ν_{max}: 3159, 2921, 2863, 1683, 1573, 1399, 1268, 1171, 973, 777; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, 1H, J = 3.6 Hz), 7.07 (d, 1H, J = 3.6 Hz), 6.63 (dd, 1H, J = 16.9, 1.2 Hz, CH=CH_2), 6.45 (dd, 1H, J = 16.9, 10.3 Hz, C*H*=CH_2), 5.96 (dd, 1H, J = 10.3, 1.2 Hz, CH=CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 163.31 (s, C(O)), 160.37, 136.38, 130.21 (s, *C*H=CH_2), 128.90 (s, CH=*C*H_2), 114.17. Anal. Calcd. for $C_6H_6N_2OS$: C, 46.74; H, 3.92; N, 18.17; found: C, 46.57; H, 3.64; N, 18.07.

General Procedure for Preparation of Isoxazolidines 11 and 12

A mixture of the nitrone **9** (1.00 mmol), acrylamide **10** (1.00 mmol), and toluene (2 mL) was stirred at 70°C for 24 hours or until disappearance of the starting nitrone (TLC). After evaporation of the solvent under reduced pressure, the crude products were purified on silica gel columns with chloroform:methanol mixtures as eluents.

Diethyl *trans*-5-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-3-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11a

White amorphous solid (crystallized from ether/hexane) mp 130–131°C; IR (KBr, cm^{-1}) ν_{max}: 3133, 2984, 1763, 1706, 1597, 1468, 1370, 1314, 1208, 1140, 1027, 957; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (br s, 1H, N*H*), 7.99 (d, 1H, $J = 2.8$ Hz), 6.98 (d, 1H, $J = 2.8$ Hz), 4.59 (dd, 1H, $J = 8.6$, 6.0 Hz, *H*C5), 4.25–4.17 (m, 4H, 2 × CH_2OP), 3.08–2.92 (m, 2H, *H*C3 and H_βC4), 3.00 (s, 3H, CH_3N), 2.84–2.70 (m, 1H, H_αC4), 1.67 (s, 9H, C(CH_3)$_3$), 1.38 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$OP), 1.36 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.94 (s, C(O)NH), 149.48 (s, C(O)), 147.29, 131.79, 102.01, 85.90 (s, *C*(CH$_3$)$_3$), 75.99 (d, $J = 9.2$ Hz, C5), 63.66 (d, $J = 166.3$ Hz, C3), 63.60 (d, $J = 6.3$ Hz, CH$_2$OP), 63.18 (d, $J = 6.6$ Hz, CH$_2$OP), 46.85 (s, CH$_3$N), 37.05 (s, C4), 28.19 (s, C(*C*H$_3$)$_3$), 16.81 (d, $J = 4.9$ Hz, *C*H$_3$CH$_2$OP), 16.74 (d, $J = 5.4$ Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.23. Anal. Calcd. for $C_{17}H_{29}N_4O_7P$: C, 47.22; H, 6.76; N, 12.96; found: C, 47.37; H, 6.81; N, 12.90.

Diethyl *trans*-5-(1-(tert-butoxycarbonyl)-5-methyl-1*H*-pyrazol-3-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11b

White amorphous solid (crystallised from ether/hexane) mp 133–134°C; IR (KBr, cm^{-1}) ν_{max}: 2981, 2936, 1765, 1696, 1603, 1479, 1341, 1318, 1233, 1158, 1113, 1027, 978; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.78 (br s, 1H, N*H*), 6.75 (s, 1H, H_{C4}Ar), 4.62–4.55 (m, 1H, *H*C5), 4.26–4.15 (m, 4H, 2 × CH_2OP), 3.08–2.92 (m, 2H, *H*C3 and H_βC4), 3.01 (s, 3H, CH_3N), 2.83–2.69 (m, 1H, H_αC4), 2.53 (s, 3H, CH_3), 1.67 (s, 9H, C(CH_3)$_3$), 1.38 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$OP), 1.36 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.81 (s, C(O)NH), 148.37 (s, C(O)), 147.76, 144.71, 102.94, 85.42 (s, *C*(CH$_3$)$_3$), 75.94 (d, $J = 9.2$ Hz, C5), 63.53 (d, $J = 165.9$ Hz, C3), 63.49 (d, $J = 6.4$ Hz, CH$_2$OP), 62.68 (d, $J = 6.9$ Hz, CH$_2$OP), 46.67 (s, CH$_3$N), 36.98 (s, C4), 28.17 (s, C(*C*H$_3$)$_3$), 16.69 (d, $J = 5.2$ Hz, *C*H$_3$CH$_2$OP), 16.63 (d, $J = 5.4$ Hz, *C*H$_3$CH$_2$OP), 15.14 (s, CH$_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.36. Anal. Calcd. for $C_{18}H_{31}N_4O_7P$: C, 48.43; H, 7.00; N, 12.55; found: C, 48.53; H, 6.92; N, 12.66.

Diethyl *trans*-5-(2,5-dihydro-2,3-dimethyl-5-oxo-1-phenyl-1*H*-pyrazol-4-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11c

Colorless oil. IR (film, cm^{-1}) ν_{max}: 3469, 2984, 1650, 1493, 1454, 1298, 1232, 1022, 968; (signals of *trans*-**11c** were extracted from the spectra of a 89:11 mixture of *trans*-**11c** and *cis*-**12c**); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15

(br s, 1H, N*H*), 7.52–7.34 (m, 5H), 4.66 (dd, 1H, J = 8.9, 5.4 Hz, *H*C5), 4.24–4.16 (m, 4H, 2 × CH_2OP), 3.28–3.16 (m, 1H, *H*C3), 3.17 (s, 3H, CH_3NNPh), 3.07 (s, 3H, CH_3N), 3.04–2.78 (br m, 2H, H_αC4 and H_βC4), 2.31 (s, 3H, CH_3C=C), 1.36 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.95, 161.29, 149.41, 134.37, 129.22, 127.02, 124.15, 107.38, 76.62 (d, J = 9.2 Hz, C5), 63.52 (d, J = 168.6 Hz, C3), 63.33 (d, J = 6.3 Hz, CH$_2$OP), 62.63 (d, J = 6.9 Hz, CH$_2$OP), 46.99 (s, CH$_3$N), 45.93 (s, *C*H$_3$NNPh), 36.18 (s, C4), 16.67 (d, J = 4.2 Hz, *C*H$_3$CH$_2$OP), 16.61 (d, J = 4.6 Hz, *C*H$_3$CH$_2$OP), 12.45 (s, CH$_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.53. Anal. Calcd. for $C_{20}H_{29}N_4O_6P$: C, 53.09; H, 6.46; N, 12.38; found: C, 53.15; H, 6.44; N, 12.49. (obtained on a 89:11 mixture of *trans*-**11c** and *cis*-**12c**).

Diethyl *trans*-5-(pyridin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11d

White amorphous solid (crystallized from ether/hexane) mp 82–83°C; IR (KBr, cm^{-1}) ν_{max}: 3174, 2981, 1693, 1578, 1542, 1434, 1300, 1231, 1025, 787, 554; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75 (br s, 1H, N*H*), 8.32–8.29 (m, 1H), 8.22–8.19 (m, 1H), 7.75–7.70 (m, 1H), 7.11–7.06 (m, 1H), 4.61 (dd, 1H, J= 8.8, 5.7 Hz, *H*C5), 4.27–4.13 (m, 4H, 2 × CH_2OP), 3.11–3.04 (m, 1H, *H*C3), 3.03 (s, 3H, CH_3N), 3.01 (dddd, 1H, J = 15.9, 12.7, 8.8, 8.8 Hz, H_βC4), 2.82 (dddd, 1H, J = 12.7, 9.0, 8.2, 5.7 Hz, H_αC4), 1.36 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.22 (s, C(O)), 150.26, 147.96, 138.38, 120.34, 113.96, 76.21 (d, J = 9.2 Hz, C5), 63.50 (d, J = 169.8 Hz, C3), 63.47 (d, J = 6.3 Hz, CH$_2$OP), 62.64 (d, J = 6.9 Hz, CH$_2$OP), 46.79 (s, CH$_3$N), 36.87 (s, C4), 16.68 (d, J = 5.1 Hz, *C*H$_3$CH$_2$OP), 16.60 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.43. Anal. Calcd. for $C_{14}H_{22}N_3O_5P$: C, 48.98; H, 6.46; N, 12.24; found: C, 48.99; H, 6.40; N, 12.47.

Diethyl *trans*-5-(4-methylpyridin-2-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11e

White amorphous solid (crystallized from ether/hexane) mp 89–91°C; IR (KBr, cm^{-1}) ν_{max}: 3204, 3062, 2987, 1693, 1564, 1418, 1207, 1029, 836, 590; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70 (br s, 1H, N*H*), 8.16–8.15 (m, 1H), 8.05 (s, 1H), 6.91–6.89 (m, 1H), 4.60 (dd, 1H, J= 8.8, 5.4 Hz, *H*C5), 4.26–4.13 (m, 4H, 2 × CH_2OP), 3.08–3.02 (m, 1H, *H*C3), 3.02 (s, 3H, CH_3N), 3.00 (dddd, 1H, J = 15.7, 12.5, 8.8, 8.8 Hz, H_βC4), 2.81 (dddd, 1H, J = 12.5, 8.8, 8.1, 5.4 Hz, H_αC4), 2.38 (s, 3H, CH_3), 1.36 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OP), 1.34 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.03 (s, C(O)), 150.08, 149.80, 147.21, 121.30, 114.34, 76.56 (d, J = 9.2 Hz, C5),

63.28 (d, J = 167.2 Hz, C3), 63.27 (d, J = 6.6 Hz, CH_2OP), 62.46 (d, J = 7.1 Hz, CH_2OP), 36.71 (s, C4), 21.33 (s, CH_3), 16.41 (d, J = 5.7 Hz, CH_3CH_2OP), 16.48 (d, J = 4.9 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.45. Anal. Calcd. for $C_{15}H_{24}N_3O_5P$: C, 50.42; H, 6.77; N, 11.76; found: C, 50.46; H, 6.92; N, 11.93.

Diethyl *trans*-5-(5-methylpyridin-2-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11f

White solid (crystallized from ether/hexane) mp 91–92°C. IR (KBr, cm^{-1}) ν_{max}: 3240, 2987, 1689, 1537, 1300, 1242, 1055, 1026, 575; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.69 (br s, 1H, NH), 8.12–8.08 (m, 2H), 7.55–7.52 (m, 1H), 4.59 (dd, 1H, J = 8.8, 5.8 Hz, HC5), 4.26–4.13 (m, 4H, 2 × CH_2OP), 3.08–3.01 (m, 1H, HC3), 3.03 (s, 3H, CH_3N), 3.00 (dddd, 1H, J = 15.9, 12.5, 8.8, 8.8 Hz, H_βC4), 2.81 (dddd, 1H, J = 12.5, 9.0, 7.8, 5.8 Hz, H_αC4), 2.31 (s, 3H, CH_3), 1.37 (t, 3H, J = 6.9 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 6.9 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.00 (s, C(O)), 148.10, 147.86, 138.88, 129.75, 113.47, 76.22 (d, J = 9.4 Hz, C5), 63.51 (d, J = 168.6 Hz, C3), 63.47 (d, J = 6.6 Hz, CH_2OP), 62.64 (d, J = 6.9 Hz, CH_2OP), 46.84 (s, CH_3N), 36.92 (s, C4), 18.03 (s, CH_3), 16.70 (d, J = 5.1 Hz, CH_3CH_2OP), 16.62 (d, J = 5.4 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.48. Anal. Calcd. for $C_{15}H_{24}N_3O_5P$: C, 50.42; H, 6.77; N, 11.76; found: C, 50.46; H, 6.71; N, 11.88.

Diethyl *cis*-5-(5-methylpyridin-2-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *cis*-12f

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3205, 3063, 2988, 1694, 1613, 1565, 1549, 1419, 1239, 1208, 1056, 1029, 981, 836; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.02 (br s, 1H, NH), 8.10–8.06 (m, 2H), 7.49–7.46 (m, 1H), 4.54 (dd, 1H, J = 8.6, 3.6 Hz, HC5), 4.15–3.98 (m, 4H, 2 × CH_2OP), 3.02–2.79 (m, 3H, HC3, H_αC4 and H_βC4), 2.97 (d, 3H, J = 1.0 Hz, CH_3N), 2.26 (s, 3H, CH_3), 1.24 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.11 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**12f** were extracted from the spectrum of a 64:36 mixture of *trans*-**11f** and *cis*-**12f**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.84 (s, C(O)), 148.56, 147.90, 138.87, 129.39, 113.35, 75.58 (d, J = 8.1 Hz, C5), 63.77 (d, J = 6.4 Hz, CH_2OP), 63.60 (d, J = 167.7 Hz, C3), 62.56 (d, J = 6.9 Hz, CH_2OP), 46.22 (s, CH_3N), 36.95 (s, C4), 18.13 (s, CH_3), 16.62 (d, J = 6.0 Hz, CH_3CH_2OP), 16.47 (d, J = 5.9 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.60. Anal. Calcd. for $C_{15}H_{24}N_3O_5P$: C, 50.42; H, 6.77; N, 11.76; found: C, 50.57; H, 6.90; N, 11.93.

Diethyl *trans*-5-(pyrimidin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11g

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3432, 2984, 1715, 1580, 1513, 1438, 1416, 1229, 1051, 1024; (signals of *trans*-**11g** were extracted from the spectra of a 93:7 mixture of *trans*-**11g** and *cis*-**12g**); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.97 (br s, 1H, N*H*), 8.68 (d, 2H, J = 4.9 Hz, H_{C4}Ar and H_{C6}Ar), 7.10 (t, 1H, J = 4.9 Hz, H_{C5}Ar), 4.69 (dd, 1H, J = 8.9, 5.3 Hz, *H*C5), 4.26–4.15 (m, 4H, 2 × CH_2OP), 3.13–3.08 (m, 1H, *H*C3), 3.05 (s, 3H, CH_3N), 3.04 (dddd, 1H, J = 16.1, 13.1, 8.9, 8.9 Hz, H_βC4), 2.90 (dddd, 1H, J = 13.1, 9.3, 8.0, 5.3 Hz, H_αC4), 1.38 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP), 1.36 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 168.80 (s, C(O)), 158.51, 156.71, 117.29, 76.46 (d, J = 9.3 Hz, C5), 63.45 (d, J = 168.5 Hz, C3), 63.38 (d, J = 6.5 Hz, CH$_2$OP), 62.58 (d, J = 6.8 Hz, CH$_2$OP), 46.72 (s, CH$_3$N), 36.72 (s, C4), 16.49 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.41 (d, J = 6.1 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.19. Anal. Calcd. for $C_{13}H_{21}N_4O_5P$: C, 45.35; H, 6.15; N, 16.27; found: C, 45.19; H, 6.24; N, 16.37 (obtained on a 93:7 mixture of *trans*-**11g** and *cis*-**12g**).

Diethyl *trans*-5-(4-methylpyrimidin-2-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11h

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3401, 2984, 1718, 1594, 1530, 1443, 1402, 1233, 1052, 1025, 971; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.87 (br s, 1H, N*H*), 8.54 (d, 1H, J = 5.0 Hz), 6.96 (d, 1H, J = 5.0 Hz), 4.71–4.65 (br m, 1H, *H*C5), 4.26–4.17 (m, 4H, 2 × CH_2OP), 3.14–3.07 (m, 1H, *H*C3), 3.06 (s, 3H, CH_3N), 3.04 (dddd, 1H, J = 16.0, 13.0, 8.9, 8.9 Hz, H_βC4), 2.90 (dddd, 1H, J = 13.0, 8.9, 8.1, 5.3 Hz, H_αC4), 2.53 (s, 3H, CH_3), 1.38 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.36 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.13, 168.81 (s, C(O)), 157.96, 156.46, 116.93, 76.47 (d, J = 9.3 Hz, C5), 63.45 (d, J = 169.2 Hz, C3), 63.39 (d, J = 6.5 Hz, CH$_2$OP), 62.55 (d, J = 6.8 Hz, CH$_2$OP), 46.73 (s, CH$_3$N), 36.75 (s, C4), 16.48 (d, J = 5.9 Hz, *C*H$_3$CH$_2$OP), 16.42 (d, J = 5.8 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.27. Anal. Calcd. for $C_{14}H_{23}N_4O_5P$: C, 46.93; H, 6.47; N, 15.64; found: C, 46.85; H, 6.71; N, 15.76.

Diethyl *trans*-5-(4-methoxy-6-methylpyrimidin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11i

White amorphous solid (crystallized from ether/hexane) mp 90–91°C; IR (KBr, cm^{-1}) ν_{max}: 3386, 2983, 1717, 1601, 1512, 1422, 1381, 1249, 1055, 1018, 960; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.69 (br s, 1H, N*H*), 6.33 (s, 1H, H_{C5}Ar), 4.74–4.66 (br m, 1H, *H*C5), 4.26–4.12 (m, 4H, 2 × CH_2OP), 3.97

(s, 3H, CH_3O), 3.13–3.09 (m, 1H, *H*C3), 3.03 (s, 3H, CH_3N), 3.03 (dddd, 1H, J = 16.1, 13.0, 8.9, 8.9 Hz, H_βC4), 2.91 (dddd, 1H, J = 13.0, 8.8, 8.3, 5.2 Hz, H_αC4), 2.41 (s, 3H, CH_3), 1.36 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.34 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 170.95, 168.73, 168.73 (s, C(O)), 155.86, 102.61, 76.54 (d, J = 9.1 Hz, C5), 63.45 (d, J = 167.4 Hz, C3), 63.33 (d, J = 6.2 Hz, CH$_2$OP), 62.54 (d, J = 6.7 Hz, CH$_2$OP), 53.88 (s, CH$_3$O), 46.73 (s, CH$_3$N), 36.57 (s, C4), 23.85 (s, CH$_3$), 16.48 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.42 (d, J = 6.2 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 20.80. Anal. Calcd. for $C_{15}H_{25}N_4O_6P$: C, 46.39; H, 6.49; N, 14.43; found: C, 46.45; H, 6.30; N, 14.48.

Diethyl *trans*-5-(4,6-dimethoxypyrimidin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11j

White amorphous solid (crystallized from ether/hexane) mp 98–99°C; IR (KBr, cm^{-1}) ν_{max}: 3399, 1726, 1609, 1569, 1512, 1447, 1412, 1372, 1198, 1171, 1058, 1018, 946; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.61 (br s, 1H, N*H*), 5.84 (s, 1H, H_{C5}Ar), 4.74 (br s, *H*C5), 4.26–4.17 (m, 4H, 2 × CH_2OP), 3.97 (s, 6H, CH_3O), 3.16–3.09 (m, 1H, *H*C3), 3.06 (s, 3H, CH_3N), 3.02 (dddd, 1H, J = 16.0, 13.0, 8.9, 8.9 Hz, H_βC4), 2.91 (dddd, 1H, J = 13.0, 8.9, 8.3, 5.2 Hz, H_αC4), 1.39 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OP), 1.37 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 172.16, 168.76 (s, C(O)), 155.27, 85.66, 76.57 (d, J = 9.0 Hz, C5), 63.45 (d, J = 169.0 Hz, C3), 63.31 (d, J = 6.3 Hz, CH$_2$OP), 62.56 (d, J = 6.7 Hz, CH$_2$OP), 46.73 (s, CH$_3$N), 36.47 (s, C4), 16.48 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.43 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.40. Anal. Calcd. for $C_{15}H_{25}N_4O_7P$: C, 44.55; H, 6.23; N, 13.86; found: C, 44.81; H, 6.05; N, 13.93.

Diethyl *trans*-5-(pyrazin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11k

Colorless oil. IR (film, cm^{-1}) ν_{max}: 3385, 2982, 1703, 1543, 1414, 1296, 1232, 1053, 1023, 969; (signals of *trans*-**11k** were extracted from the spectra of a 96:4 mixture of *trans*-**11k** and *cis*-**12k**); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.56 (d, 1H, J = 1.5 Hz, H_{C3}Ar), 8.77 (br s, 1H, N*H*), 8.41 (d, 1H, J = 2.5 Hz, H_{C6}Ar), 8.30 (dd, 1H, J = 2.5, 1.5 Hz, H_{C5}Ar), 4.67 (dd, 1H, J = 9.0, 5.5 Hz, *H*C5), 4.26–4.17 (m, 4H, 2 × CH_2OP), 3.13–3.07 (m, 1H, *H*C3), 3.05 (s, 3H, CH_3N), 3.04 (dddd, 1H, J = 16.1, 13.0, 8.8, 8.8 Hz, H_βC4), 2.85 (dddd, 1H, J = 13.0, 9.7, 8.3, 5.6 Hz, H_αC4), 1.38 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP), 1.37 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.29 (s, C(O)), 147.14, 142.23, 140.83, 136.89, 76.20 (d, J = 8.9 Hz, C5), 63.55 (d, J = 167.8 Hz, C3), 63.54 (d, J = 6.6 Hz, CH$_2$OP), 62.79 (d, J = 6.9 Hz, CH$_2$OP), 46.80 (s, CH$_3$N), 37.00 (s, C4), 16.72 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP),

16.65 (d, J = 5.1 Hz, CH_3CH_2OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.10. Anal. Calcd. for $C_{13}H_{21}N_4O_5P$: C, 45.35; H, 6.15; N, 16.27; found: C, 45.29; H, 6.29; N, 16.32 (obtained on a 96:4 mixture of *trans*-**11k** and *cis*-**12k**).

Diethyl *cis*-5-(pyrazin-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12k

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3385, 3210, 2983, 1704, 1536, 1414, 1297, 1233, 1027, 971; (signals of *cis*-**12k** were extracted from the spectra of a 14:86 mixture of *trans*-**11k** and *cis*-**12k**); ^1H NMR (600 MHz, $CDCl_3$) δ: 9.57 (d, 1H, J = 1.5 Hz, H_{C3}Ar), 9.24 (brs, 1H, NH), 8.38 (d, 1H, J = 2.5 Hz, H_{C6}Ar), 8.30 (dd, 1H, J = 2.5, 1.5 Hz, H_{C5}Ar), 4.66–4.63 (br m, 1H, HC5), 4.27–4.06 (m, 4H, 2 × CH_2OP), 3.08–2.99 (m, 2H, HC3 and H_βC4), 3.03 (d, 3H, J = 0.7 Hz, CH_3N), 2.93–2.87 (m, 1H, H_αC4), 1.31 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.20 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 171.06 (s, C(O)), 147.68, 142.25, 140.42, 136.81, 75.56 (d, J = 7.7 Hz, C5), 63.51 (d, J = 170.2 Hz, C3), 63.34 (d, J = 6.7 Hz, CH_2OP), 62.59 (d, J = 7.1 Hz, CH_2OP), 45.94 (s, CH_3N), 36.57 (s, C4), 16.36 (d, J = 5.6 Hz, CH_3CH_2OP), 16.23 (d, J = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.43. Anal. Calcd. for $C_{13}H_{21}N_4O_5P$: C, 45.35; H, 6.15; N, 16.27; found: C, 45.29; H, 6.07; N, 16.16 (obtained on a 14:86 mixture of *trans*-**11k** and *cis*-**12k**).

Diethyl *trans*-5-(1*H*-indol-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11l

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3284, 2983, 1669, 1547, 1480, 1231, 1051, 972, 762; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.35 (br s, 1H, NH), 8.21 (br s, 1H, C(O)NH), 7.90–7.89 (m, 1H), 7.36–7.27 (m, 1H), 7.25–7.21 (m, 2H), 6.53–6.51 (m, 1H), 4.64 (dd, 1H, J = 8.9, 5.6 Hz, HC5), 4.27–4.13 (m, 4H, 2 × CH_2OP), 3.15–3.06 (m, 1H, HC3), 3.04 (s, 3H, CH_3N), 3.00 (dddd, 1H, J = 15.8, 13.0, 8.9, 8.9 Hz, H_βC4), 2.88 (dddd, 1H, J = 13.0, 9.1, 8.1, 5.6 Hz, H_αC4), 1.37 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.65 (s, C(O)), 133.61, 129.10, 128.00, 125.65, 115.80, 112.50, 111.47, 102.44, 76.63 (d, J = 9.2 Hz, C5), 63.57 (d, J = 166.3 Hz, C3), 63.56 (d, J = 6.6 Hz, CH_2OP), 62.79 (d, J = 6.9 Hz, CH_2OP), 46.99 (s, CH_3N), 36.74 (s, C4), 16.75 (d, J = 5.2 Hz, CH_3CH_2OP), 16.66 (d, J = 5.4 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.59. Anal. Calcd. for $C_{17}H_{24}N_3O_5P$: C, 53.54; H, 6.34; N, 11.02; found: C, 53.48; H, 6.19; N, 11.18.

Diethyl *cis*-5-(1*H*-indol-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12l

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3281, 2984, 2927, 1668, 1548, 1481, 1232, 1024, 975, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (br s, 1H, C(O)N*H*), 8.22 (br s, 1H, N*H*), 7.93–7.92 (m, 1H), 7.35–7.27 (m, 2H), 7.21–7.19 (m, 1H), 6.52–6.51 (m, 1H), 4.62 (dd, 1H, J = 8.5, 5.2 Hz, *H*C5), 4.21–4.06 (m, 4H, 2 × CH_2OP), 3.11–2.79 (m, 3H, *H*C3, H_αC4 and H_βC4), 2.99 (s, 3H, CH_3N), 1.29 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OP), 1.19 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**12l** were extracted from the spectrum of a 56:44 mixture of *trans*-**11l** and *cis*-**12l**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.68 (s, C(O)), 133.35, 129.83, 128.01, 125.35, 115.83, 112.15, 111.33, 102.65, 75.92 (d, J = 7.8 Hz, C5), 64.02 (d, J = 168.6 Hz, C3), 63.63 (d, J = 6.4 Hz, CH$_2$OP), 62.89 (d, J = 6.1 Hz, CH$_2$OP), 46.35 (s, CH$_3$N), 36.84 (s, C4), 16.71 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.63 (d, J = 5.5 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.06. Anal. Calcd. for $C_{17}H_{24}N_3O_5P$: C, 53.54; H, 6.34; N, 11.02; found: C, 53.66; H, 6.12; N, 10.81.

Diethyl *trans*-5-(2-methyl-1*H*-indol-5-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11m

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3279, 2984, 1669, 1543, 1483, 1231, 1025, 971, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (br s, 1H, C(O)N*H*), 7.99 (br s, 1H, N*H*), 7.74–7.73 (m, 1H), 7.24–7.16 (m, 2H), 6.18–6.19 (m, 1H), 4.59 (dd, 1H, J= 8.8, 5.4 Hz, *H*C5), 4.27–4.13 (m, 4H, 2 × CH_2OP), 3.14–3.01 (m, 1H, *H*C3), 3.04 (s, 3H, CH_3N), 3.00 (dddd, 1H, J = 15.7, 12.8, 8.8, 8.8 Hz, H_βC4), 2.87 (dddd, 1H, J = 12.8, 9.1, 8.2, 5.4 Hz, H_αC4), 2,44 (s, 3H, CH_3), 1.36 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 6.9 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.51 (s, C(O)), 136.63, 133.83, 129.20, 129.03, 114.52, 111.46, 110.52, 100.40, 76.61 (d, J = 9.2 Hz, C5), 63.59 (d, J = 169.8 Hz, C3), 63.56 (d, J = 6.6 Hz, CH$_2$OP), 62.75 (d, J = 6.9 Hz, CH$_2$OP), 46.97 (s, CH$_3$N), 36.79 (s, C4), 16.73 (d, J = 5.1 Hz, *C*H$_3$CH$_2$OP), 16.66 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP), 13.93 (s, CH$_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.60. Anal. Calcd. for $C_{18}H_{26}N_3O_5P$: C, 54.68; H, 6.63; N, 10.63; found: C, 54.86; H, 6.76; N, 10.52.

Diethyl *cis*-5-(2-methyl-1*H*-indol-5-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *cis*-12m

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3281, 2984, 2926, 1668, 1544, 1484, 1452, 1230, 1026, 972, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (br s, 1H, C(O)N*H*), 7.97 (br s, 1H, N*H*), 7.77 (s, 1H), 7.21–7.20 (m, 2H), 6.17 (s, 1H), 4.62 (dd, 1H, J= 8.3, 5.0 Hz, *H*C5), 4.22–4.03 (m, 4H, 2 × CH_2OP), 3.07–2.83 (m, 3H, *H*C3, H_αC4 and H_βC4), 2.99 (s, 3H, CH_3N), 2,42 (s, 3H, CH_3), 1.30 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.19 (t, 3H, J = 7.0 Hz,

CH_3CH_2OP); ^{13}C NMR signals of *cis*-**12m** were extracted from the spectrum of a 34:66 mixture of *trans*-**11m** and *cis*-**12m**, ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.56 (s, C(O)), 136.09, 133.53, 129.95, 129.29, 114.61, 111.16, 110.20, 100.69, 75.82 (d, $J = 7.6$ Hz, C5), 64.03 (d, $J = 168.7$ Hz, C3), 63.37 (d, $J =$ 6.6 Hz, CH_2OP), 62.59 (d, $J = 7.1$ Hz, CH_2OP), 46.15 (s, CH_3N), 36.79 (s, C4), 16.40 (d, $J = 5.5$ Hz, CH_3CH_2OP), 16.34 (d, $J = 5.6$ Hz, CH_3CH_2OP), 13.73 (s, CH_3); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.03. Anal. Calcd. for $C_{18}H_{26}N_3O_5P$: C, 54.68; H, 6.63; N, 10.63; found: C, 54.79; H, 6.64; N, 10.75.

Diethyl *trans*-5-(1*H*-indol-6-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11n

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3291, 2983, 1674, 1536, 1230, 1050, 1024, 969; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.43 (br s, 1H, C(O)N*H*), 8.29 (br s, 1H, N*H*), 8.11–8.10 (m, 1H), 7.58–7.55 (m, 1H), 7.21–7.19 (m, 1H), 6.93–6.89 (m, 1H), 6.52–6.50 (m, 1H), 4.65 (dd, 1H, $J = 8.5, 5.5$ Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × CH_2OP), 3.15–3.02 (m, 1H, *H*C3), 3.05 (dddd, 1H, $J = 15.7, 13.0, 8.5, 8.5$ Hz, H_βC4), 3.04 (s, 3H, CH_3N), 2.87 (dddd, 1H, J = 13.0, 9.8, 8.4, 5.5 Hz, H_αC4), 1.36 (t, 3H, $J = 7.0$ Hz, CH_3CH_2OP), 1.35 (t, 3H, $J = 7.0$ Hz, CH_3CH_2OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.59 (s, C(O)), 136.01, 131.36, 125.30, 125.07, 120.73, 113.01, 103.32, 102.08, 76.75 (d, $J = 8.8$ Hz, C5), 63.58 (d, $J = 167.2$ Hz, C3), 63.52 (d, $J = 6.6$ Hz, CH_2OP), 62.92 (d, $J = 6.9$ Hz, CH_2OP), 47.04 (s, CH_3N), 36.55 (s, C4), 16.74 (d, $J = 5.7$ Hz, CH_3CH_2OP), 16.67 (d, $J = 4.3$ Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.60. Anal. Calcd. for $C_{17}H_{24}N_3O_5P \times 2H_2O$: C, 48.92; H, 6.76; N, 10.07; found: C, 48.91; H, 6.91; N, 9.82.

Diethyl *cis*-5-(1*H*-indol-6-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12n

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3272, 2984, 1675, 1598, 1536, 1456, 1231, 1025, 971, 808; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.77 (br s, 1H, C(O)N*H*), 8.32 (br s, 1H, N*H*), 8.13–8.12 (m, 1H), 7.55–7.53 (m, 1H), 7.19–7.17 (m, 1H), 6.96–6.93 (m, 1H), 6.51–6.49 (m, 1H), 4.63 (dd, 1H, $J = 8.6, 5.1$ Hz, *H*C5), 4.21–4.02 (m, 4H, 2 × CH_2OP), 3.09–2.83 (m, 3H, *H*C3, H_αC4 and H_βC4), 2.99 (d, 3H, $J = 0.8$ Hz, CH_3N), 1.30 (t, 3H, $J = 7.0$ Hz, CH_3CH_2OP), 1.18 (t, 3H, $J = 7.0$ Hz, CH_3CH_2OP); ^{13}C NMR signals of *cis*-**12n** were extracted from the spectrum of a 77:23 mixture of *trans*-**11n** and *cis*-**12n**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.72 (s, C(O)), 136.04, 131.89, 124.98, 124.75, 120.64, 113.06, 102.97, 102.06, 75.95 (d, $J = 7.4$ Hz, C5), 63.58 (d, $J = 168.1$ Hz, C3), 63.58 (d, $J = 6.5$ Hz, CH_2OP), 62.91 (d, J = 6.9 Hz, CH_2OP), 46.37 (s, CH_3N), 36.76 (s, C4), 16.64 (d, $J = 5.2$ Hz, CH_3CH_2OP), 16.57 (d, $J = 5.4$ Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz,

$CDCl_3$) δ: 21.93. Anal. Calcd. for $C_{17}H_{24}N_3O_5P$: C, 53.54; H, 6.34; N, 11.02; found: C, 53.64; H, 6.06; N, 11.01.

Diethyl *trans*-5-(1*H*-benzo[*d*]imidazol-6-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11o

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3192, 2989, 1680, 1604, 1548, 1488, 1449, 1395, 1295, 1230, 1025, 970; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (br s, 1H, C(O)N*H*), 8.14 (d, 1H, J = 1.6 Hz), 8.03 (s, 1H), 7.62 (d, 1H, J = 8.6 Hz), 7.21 (dd, 1H, J = 8.6, 1.6 Hz), 4.68 (dd, 1H, J= 8.6, 5.8 Hz, *H*C5), 4.26–4.15 (m, 4H, 2 × CH_2OP), 3.19–3.09 (m, 1H, *H*C3), 3.03 (dddd, 1H, J = 16.1, 12.6, 8.6, 8.6 Hz, H_βC4), 3.02 (s, 3H, CH_3N), 2.89 (dddd, 1H, J = 12.6, 9.9, 8.3, 5.8 Hz, H_αC4), 1.36 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.96 (s, C(O)), 141.88, 137.10, 136.46, 132.20, 117.12, 116.21, 106.50, 76.85 (d, $J \sim$ 9 Hz, C5), 63.62 (d, J = 167.5 Hz, C3), 63.57 (d, J = 6.6 Hz, CH$_2$OP), 63.11 (d, J = 7.2 Hz, CH$_2$OP), 47.02 (s, CH$_3$N), 36.45 (s, C4), 16.76 (d, J = 5.5 Hz, *C*H$_3$CH$_2$OP), 16.71 (d, J = 5.2 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.92. Anal. Calcd. for $C_{16}H_{23}N_4O_5P$ x $2H_2O$: C, 45.93; H, 6.50; N, 13.39; found: C, 45.95; H, 6.53; N, 13.33.

Diethyl *trans*-5-(1,3-dioxoisoindolin-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11p

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3286, 2984, 1721, 1682, 1614, 1582, 1482, 1435, 1361, 1230, 1023, 973; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (br s, 1H, C(O)N*H*C(O)), 8.31 (br s, 1H, C(O)N*H*), 8.12 (d, 1H, J = 1.7 Hz, H_{C4}Ar), 8.05 (dd, 1H, J = 8.2, 1.7 Hz, H_{C6}Ar), 7.85 (d, 1H, J = 8.2 Hz, H_{C7}Ar), 4.70 (dd, 1H, J= 8.6, 5.6 Hz, *H*C5), 4.29–4.17 (m, 4H, 2 × CH_2OP), 3.25–3.15 (m, 1H, *H*C3), 3.04 (dddd, 1H, J = 15.8, 12.8, 8.4, 8.4 Hz, H_βC4), 2.87 (dddd, 1H, J = 12.8, 10.3, 8.2, 5.4 Hz, H_αC4), 3.04 (s, 3H, CH_3N), 1.39 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.38 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.29 (s, C(O)), 168.08 (s, C(O)), 167.88 (s, C(O)), 142.78, 134.34, 127.99, 124.76, 124.41, 114.47, 76.60 (d, J = 8.8 Hz, C5), 63.48 (d, J = 167.1 Hz, C3), 63.42 (d, J = 6.6 Hz, CH$_2$OP), 63.01 (d, J = 6.7 Hz, CH$_2$OP), 46.48 (s, CH$_3$N), 36.10 (s, C4), 16.49 (d, J = 6.3 Hz, *C*H$_3$CH$_2$OP), 16.44 (d, J = 6.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.60. Anal. Calcd. for $C_{17}H_{22}N_3O_7P \times H_2O$: C, 47.55; H, 5.63; N, 9.79; found: C, 47.46; H, 5.53; N, 9.57.

Diethyl *trans*-5-(benzo[*d*][1,3]dioxol-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11q

Yellow oil; IR (film, cm^{-1}) ν_{max}: 3285, 2985, 2908, 1680, 1537, 1503, 1449, 1229, 1037, 971, 755; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08 (br s, 1H, N*H*), 7.28

(d, 1H, J = 2.1 Hz, H_{C4}Ar), 6.86 (dd, 1H, J = 8.3, 2.1 Hz, H_{C6}Ar), 6.78 (d, 1H, J = 8.3 Hz, H_{C7}Ar), 5.98 (s, 2H, OCH_2O), 4.61 (dd, 1H, J= 8.9, 5.5 Hz, HC5), 4.26–4.18 (m, 4H, 2 × CH_2OP), 3.11–3.06 (m, 1H, HC3), 3.03 (s, 3H, CH_3N), 3.01 (dddd, 1H, J = 16.0, 13.0, 8.9, 8.9 Hz, H_βC4), 2.85 (dddd, 1H, J = 13.0, 8.6, 8.2, 5.5 Hz, H_αC4), 1.39 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP), 1.37 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.53 (s, C(O)), 147.89, 144.69, 131.10, 113.12, 108.19, 102.64, 101.45 (s, OCH$_2$O), 76.45 (d, J = 9.2 Hz, C5), 63.59 (d, J = 169.8 Hz, C3), 63.15 (d, J = 6.6 Hz, CH$_2$OP), 62.75 (d, J = 6.9 Hz, CH$_2$OP), 46.95 (s, CH$_3$N), 36.70 (s, C4), 16.77 (d, J = 5.4 Hz, CH$_3$CH$_2$OP), 16.70 (d, J = 5.4 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.30. Anal. Calcd. for $C_{16}H_{23}N_2O_7P \times 2H_2O$: C, 45.50; H, 6.44; N, 6.63; found: C, 45.48; H, 6.30; N, 6.92.

Diethyl *trans*-5-(2,2-difluorobenzo[*d*][1,3]dioxol-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11r

White amorphous solid (crystallized from ether/hexane) mp 105–106°C; IR (KBr, cm^{-1}) ν_{max}: 3252, 3083, 2986, 1691, 1538, 1501, 1450, 1239, 1156, 964; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.25 (br s, 1H, NH), 7.66 (d, 1H, J = 2.0 Hz, H_{C4}Ar), 7.06 (dd, 1H, J = 8.5, 2.0 Hz, H_{C6}Ar), 7.02 (d, 1H, J = 8.5 Hz, H_{C7}Ar), 4.62 (dd, 1H, J= 8.8, 5.5 Hz, HC5), 4.25–4.17 (m, 4H, 2 × CH_2OP), 3.13–3.06 (m, 1H, HC3), 3.03 (s, 3H, CH_3N), 3.01 (dddd, 1H, J = 16.1, 13.0, 8.8, 8.8 Hz, H_βC4), 2.83 (dddd, 1H, J = 13.0, 9.5, 8.2, 5.5 Hz, H_αC4), 1.38 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP), 1.37 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 168.85 (s, C(O)), 143.84, 140.39, 133.19, 131.74 (t, J = 255.5 Hz, CF_2), 114.76, 109.28, 103.03, 76.36 (d, J = 9.0 Hz, C5), 63.48 (d, J = 167.3 Hz, C3), 63.29 (d, J = 6.5 Hz, CH$_2$OP), 62.64 (d, J = 7.1 Hz, CH$_2$OP), 46.62 (s, CH$_3$N), 36.27 (s, C4), 16.43 (d, J = 5.7 Hz, CH$_3$CH$_2$OP), 16.37 (d, J = 5.8 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.19. Anal. Calcd. for $C_{16}H_{21}F_2N_2O_7P$: C, 45.50; H, 5.01; N, 6.63; found: C, 45.32; H, 5.17; N, 6.38.

Diethyl *cis*-5-(2,2-difluorobenzo[*d*][1,3]dioxol-5-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12r

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3198, 3073, 1698, 1550, 1523, 1508, 1434, 1213, 1161, 1125, 1026; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.99 (br s, 1H, NH), 7.70 (d, 1H, J = 2.0 Hz, H_{C4}Ar), 7.12 (dd, 1H, J = 8.6, 2.0 Hz, H_{C6}Ar), 7.00 (d, 1H, J = 8.6 Hz, H_{C7}Ar), 4.65 (dd, 1H, J= 9.4, 4.4 Hz, HC5), 4.25–4.07 (m, 4H, 2 × CH_2OP), 3.13–3.03 (m, 2H, HC3 and H_βC4), 2.96 (s, 3H, CH_3N), 2.83–2.76 (m, 1H, H_αC4), 1.35 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.26 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.85 (s, C(O)), 143.88, 140.13, 133.86, 131.79 (t, J = 255.1 Hz, CF_2), 114.50, 109.23, 102.75, 76.03 (d, J = 6.5 Hz, C5), 63.68 (d, J = 170.5 Hz,

C3), 63.11 (d, J = 6.4 Hz, CH_2OP), 62.97 (d, J = 6.7 Hz, CH_2OP), 46.01 (s, CH_3N), 36.15 (s, C4), 16.44 (d, J = 5.7 Hz, CH_3CH_2OP), 16.35 (d, J = 5.8 Hz, CH_3CH_2OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 21.16. Anal. Calcd. for $C_{16}H_{21}F_2N_2O_7P$: C, 45.50; H, 5.01; N, 6.63; found: C, 45.75; H, 4.90; N, 6.40.

Diethyl *trans*-5-(5-acetylbenzo[*d*][1,3]dioxol-6-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11s

Yellowish amorphous solid mp 94–95°C; IR (KBr, cm^{-1}) ν_{max}: 3444, 2980, 2914, 1686, 1648, 1611, 1518, 1248, 1049, 1023, 960; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.63 (br s, 1H, N*H*), 8.41 (s, 1H), 7.29 (s, 1H), 6.05 (s, 2H, OCH_2O), 4.59 (dd, 1H, J = 9.1, 5.5 Hz, *H*C5), 4.28–4.15 (m, 4H, 2 × CH_2OP), 3.15 (s, 3H, CH_3N), 3.13–3.05 (m, 1H, *H*C3), 3.02 (dddd, 1H, J = 16.0, 12.8, 9.1, 9.1 Hz, H_βC4), 2.76 (dddd, 1H, J = 12.8, 9.9, 8.0, 5.5 Hz, H_αC4), 2.58 (s, $CH_3C(O)$), 1.37 (t, 3H, J = 7.0 Hz, CH_3CH_2OP), 1.34 (t, 3H, J = 7.0 Hz, CH_3CH_2OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 199.83 (s, C(O)), 170.69 (s, C(O)NH), 152.56, 143.00, 137.58, 116.30, 109.86, 102.33, 101.82 (s, OCH_2O), 76.60 (d, J = 10.0 Hz, C5), 63.41 (d, J = 169.8 Hz, C3), 63.55 (d, J = 6.3 Hz, CH_2OP), 62.64 (d, J = 6.9 Hz, CH_2OP), 46.59 (s, CH_3N), 37.74 (s, C4), 28.90 (s, $CH_3C(O)$), 16.81 (d, J = 4.9 Hz, CH_3CH_2OP), 16.74 (d, J = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.60. Anal. Calcd. for $C_{18}H_{25}N_2O_8P$: C, 50.47; H, 5.88; N, 6.54; found: C, 50.70; H, 5.60; N, 6.47.

Diethyl *cis*-5-(5-acetylbenzo[*d*][1,3]dioxol-6-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12s

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3453, 2980, 2911, 1686, 1645, 1615, 1513, 1240, 1053, 1023, 964; (signals of *cis*-**12s** were extracted from the spectra of a 50:50 mixture of *trans*-**11s** and *cis*-**12s**); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.86 (br s, 1H, N*H*), 8.47 (s, 1H), 7.30 (s, 1H), 6.05 (s, 2H, OCH_2O), 4.56–4.53 (m, 1H, *H*C5), 4.16–4.01 (m, 4H, 2 × CH_2OP), 3.05–2.91 (br m, 2H, *H*C3 and H_βC4), 3.11 (s, 3H, CH_3N), 2.80–2.74 (m, 1H, H_αC4), 2.58 (s, $CH_3C(O)$), 1.29 (t, 3H, J = 7.1 Hz, CH_3CH_2OP), 1.13 (t, 3H, J = 7.1 Hz, CH_3CH_2OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 199.41 (s, C(O)), 172.20 (s, C(O)NH), 152.43, 142.64, 137.86, 116.27, 109.27, 102.08, 101.37 (s, OCH_2O), 75.43 (d, J = 8.6 Hz, C5), 63.33 (d, J = 166.2 Hz, C3), 63.44 (d, J = 6.4 Hz, CH_2OP), 62.15 (d, J = 7.2 Hz, CH_2OP), 46.33 (s, CH_3N), 36.74 (s, C4), 27.84 (s, $CH_3C(O)$), 16.35 (d, J = 6.1 Hz, CH_3CH_2OP), 16.18 (d, J = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.00. Anal. Calcd. for $C_{18}H_{25}N_2O_8P$: C, 50.47; H, 5.88; N, 6.54; found: C, 50.52; H, 5.63; N, 6.30 (obtained on a 50:50 mixture of *trans*-**11s** and *cis*-**12s**).

Diethyl *trans*-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11t

White amorphous solid mp 105–106°C; IR (film, cm^{-1}) ν_{max}: 3273, 2983, 1685, 1509, 1302, 1228, 1053, 1026, 969; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.02 (br s, 1H, N*H*), 7.21 (d, 1H, $J = 2.5$ Hz, H_{C5}Ar), 6.96 (dd, 1H, $J = 8.7, 2.5$ Hz, H_{C7}Ar), 6.84 (d, 1H, $J = 8.7$ Hz, H_{C8}Ar), 4.61 (dd, 1H, $J = 8.9, 5.3$ Hz, *H*C5), 4.28–4.26 (m, 4H, 2 × OCH_2), 4.26–4.17 (m, 4H, 2 × CH_2OP), 3.11–3.05 (m, 1H, *H*C3), 3.03 (s, 3H, CH_3N), 3.00 (dddd, 1H, J = 16.0, 12.9, 8.9, 8.9 Hz, H_βC4), 2.85 (dddd, 1H, J = 12.9, 9.0, 8.1, 5.3 Hz, H_αC4), 1.39 (t, 3H, J = 7.1 Hz, C$H_3$$CH_2$OP), 1.37 (t, 3H, J = 7.1 Hz, C$H_3$$CH_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 168.49 (s, C(O)), 143.59, 140.82, 130.55, 117.28, 113.40, 109.65, 76.36 (d, $J = 9.4$ Hz, C5), 64.42 (s, CH_2O), 64.28 (s, CH_2O), 63.52 (d, J = 169.9 Hz, C3), 63.34 (d, $J = 6.4$ Hz, CH_2OP), 62.53 (d, $J = 6.7$ Hz, CH_2OP), 46.73 (s, CH_3N), 36.55 (s, C4), 16.49 (d, $J = 5.7$ Hz, *C*$H_3$$CH_2$OP), 16.43 (d, J = 5.6 Hz, *C*$H_3$$CH_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.33. Anal. Calcd. for $C_{17}H_{25}N_2O_7P$: C, 51.00; H, 6.29; N, 7.00; found: C, 51.03; H, 6.44; N, 6.97.

Diethyl *trans*-5-((benzo[*d*][1,3]dioxol-5-yl)methylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11u

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3292, 2982, 2911, 1668, 1444, 1239, 1037, 808; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.79–7.74 (m, 3H), 6.71 (br s, 1H, N*H*), 5.96 (s, 2H, OCH_2O), 4.51 (dd, 1H, $J = 8.7, 5.6$ Hz, *H*C5), 4.36 (d, 2H, J = 5.7 Hz, CH_2NH), 4.25–4.12 (m, 4H, 2 × CH_2OP), 3.02–2.93 (m, 1H, *H*C3), 2.94 (dddd, 1H, J = 15.6, 12.6, 8.7, 8.7 Hz, H_βC4), 2.90 (d, 3H, $J = 0.8$ Hz, CH_3N), 2.73 (dddd, 1H, J = 12.6, 9.4, 8.1, 5.6 Hz, H_αC4), 1.35 (t, 3H, J = 7.0 Hz, C$H_3$$CH_2$OP), 1.34 (t, 3H, J = 7.0 Hz, C$H_3$$CH_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.39 (s, C(O)), 147.90, 147.03, 131.56, 121.03, 108.32, 108.29, 101.13, 76.24 (d, J = 9.2 Hz, C5), 63.51 (d, J = 169.8 Hz, C3), 63.44 (d, $J = 6.6$ Hz, CH_2OP), 62.54 (d, $J = 6.9$ Hz, CH_2OP), 46.75 (s, CH_3N), 43.06 (s, CH_2NH), 36.68 (s, C4), 16.65 (d, $J = 5.4$ Hz, *C*$H_3$$CH_2$OP), 16.58 (d, $J = 5.2$ Hz, *C*$H_3$$CH_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.63. Anal. Calcd. for $C_{17}H_{25}N_2O_7P$: C, 51.00; H, 6.29; N, 7.00; found: C, 49.93; H, 6.06; N, 6.91.

Diethyl *cis*-5-((benzo[*d*][1,3]dioxol-5-yl)methylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12u

Yellowish oil; IR (film, cm^{-1}) ν_{max}: 3419, 3318, 2983, 1665, 1531, 1503, 1444, 1238, 1038, 971, 809; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.13 (br s, 1H, N*H*), 6.79–6.74 (m, 3H), 5.93 (s, 2H, OCH_2O), 4.52 (dd, 1H, $J = 8.7, 5.4$ Hz, *H*C5), 4.43 (d_{AB}, 1H, J = 14.7, 5.8 Hz, CH_{2b}NH), 4.30 (d_{AB}, 1H, J = 14.7, 6.4 Hz, CH_{2a}NH), 4.20–4.02 (m, 4H, 2 × CH_2OP), 3.03–2.85 (m, 2H, *H*C3

and H_βC4), 2.89 (d, 3H, J = 1.0 Hz, CH_3N), 2.82–2.63 (m, 1H, H_αC4), 1.32 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.28 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**12u** were extracted from the spectrum of a 45:55 mixture of *trans*-**11u** and *cis*-**12u**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 171.68 (s, (CO)), 147.99, 147.14, 132.01, 121.15, 108.46, 108.32, 101.25, 75.40 (d, J = 8.4 Hz, C5), 64.16 (d, J = 167.9 Hz, C3), 63.27 (d, J = 6.5 Hz, CH$_2$OP), 62.83 (d, J = 6.8 Hz, CH$_2$OP), 46.25 (s, CH$_3$N), 42.85 (s, CH$_2$NH), 36.84 (s, C4), 16.79 (d, J = 4.7 Hz, *C*H$_3$CH$_2$OP), 16.72 (d, J = 5.5 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.12. Anal. Calcd. for $C_{17}H_{25}N_2O_7P$: C, 51.00; H, 6.29; N, 7.00; found: C, 49.70; H, 6.07; N, 7.11.

Diethyl *trans*-5-(thiazol-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *trans*-11v

White amorphous solid (crystallized from ether/hexane) mp 124–125°C; IR (KBr, cm^{-1}) ν_{max}: 2986, 2896, 1700, 1564, 1325, 1286, 1238, 1170, 1020, 973; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, 1H, J = 3.5 Hz), 7.04 (d, 1H, J = 3.5 Hz), 4.71 (dd, 1H, J = 8.6, 5.2 Hz, *H*C5), 4.27–4.13 (m, 4H, 2 × CH_2OP), 3.13–3.04 (m, 1H, *H*C3), 3.02 (dddd, 1H, J = 15.6, 12.7, 8.6, 8.6 Hz, H_βC4), 3.01 (s, 3H, CH_3N), 2.84 (dddd, 1H, J = 12.7, 9.4, 8.3, 5.2 Hz, H_αC4),1.37 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.54 (s, C(O)), 157.99, 137.73, 113.85, 76.05 (d, J = 8.5 Hz, C5), 63.67 (d, J = 167.4 Hz, C3), 63.36 (d, J = 6.4 Hz, CH$_2$OP), 62.80 (d, J = 6.8 Hz, CH$_2$OP), 46.91 (s, CH$_3$N), 36.00 (s, C4), 16.73 (d, J = 5.2 Hz, *C*H$_3$CH$_2$OP), 16.66 (d, J = 5.3 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.22. Anal. Calcd. for $C_{12}H_{20}N_3O_5PS$: C, 41.26; H, 5.77; N, 12.03; found: C, 41.47; H, 5.64; N, 12.17.

Diethyl *cis*-5-(thiazol-2-ylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate *cis*-12v

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3438, 2987, 2927, 1700, 1565, 1286, 1239, 1020, 973; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (d, 1H, J = 3.5 Hz), 7.00 (d, 1H, J = 3.5 Hz), 4.69 (dd, 1H, J = 5.6, 3.5 Hz, *H*C5), 4.19–4.00 (m, 4H, 2 × CH_2OP), 3.10–2.78 (m, 3H, *H*C3, H_αC4 and H_βC4), 2.99 (d, 3H, J = 0.9 Hz, CH_3N), 1.28 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.17 (t, 3H, J = 7.1 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**12v** were extracted from the spectrum of a 58:42 mixture of *trans*-**11v** and *cis*-**12v**, ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 170.24 (s, C(O)), 157.44, 137.75, 113.63, 75.16 (d, J = 7.6 Hz, C5), 63.55 (d, J = 170.8 Hz, C3), 63.30 (d, J = 6.5 Hz, CH$_2$OP), 62.68 (d, J = 6.6 Hz, CH$_2$OP), 45.86 (s, CH$_3$N), 36.15 (s, C4), 16.32 (d, J = 5.9 Hz, *C*H$_3$CH$_2$OP), 16.18 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.50. Anal. Calcd. for $C_{12}H_{20}N_3O_5PS$: C, 41.26; H, 5.77; N, 12.03; found: C, 41.51; H, 5.89; N, 12.21.

Diethyl *trans*-5-(benzo[*d*]thiazol-6-ylcarbamoyl)-2-methylis oxazolidin-3-yl-3-phosphonate *trans*-11w

Colorless oil; IR (film, cm^{-1}) ν_{max}: 3257,3067, 2982, 2910, 1690, 1581, 1530, 1476, 1446, 1401, 1293, 1052, 970; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.96 (s, 1H, $H_{C2}Ar$), 8.59 (d, 1H, $J = 2.1$ Hz, $H_{C7}Ar$), 8.38 (br s, 1H, N*H*), 8.10 (d, 1H, $J = 8.7$ Hz, $H_{C4}Ar$), 7.44 (dd, 1H, $J = 8.7$, 2.1 Hz, $H_{C5}Ar$), 4.68 (dd, 1H, $J = 8.9$, 5.4 Hz, *H*C5), 4.28–4.19 (m, 4H, 2 × CH_2OP), 3.15–3.09 (m, 1H, *H*C3), 3.07 (s, 3H, CH_3N), 3.05 (dddd, 1H, $J = 16.1$, 13.0, 8.9, 8.9 Hz, H_βC4), 2.88 (dddd, 1H, $J = 13.0$, 9.1, 8.0, 5.4 Hz, H_αC4), 1.40 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$OP), 1.38 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 168.98 (s, C(O)), 153.61, 150.31, 134.82, 134.70, 123.69, 119.01, 112.58, 76.43 (d, $J = 9.0$ Hz, C5), 63.54 (d, $J = 169.2$ Hz, C3), 63.34 (d, $J = 6.5$ Hz, CH$_2$OP), 62.61 (d, $J = 6.7$ Hz, CH$_2$OP), 46.71 (s, CH$_3$N), 36.48 (s, C4), 16.49 (d, $J = 5.6$ Hz, *C*H$_3$CH$_2$OP), 16.43 (d, $J = 5.6$ Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.18. Anal. Calcd. for $C_{16}H_{22}N_3O_5PS$: C, 48.11; H, 5.55; N, 10.52; found: C, 48.01; H, 5.37; N, 10.32.

Antiviral Activity Assays

The compounds were evaluated against the following viruses: 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) strains Lyons and G, varicella-zoster virus (VZV) strain Oka, TK^- VZV strain 07−1, human cytomegalovirus (HCMV) strains AD-169 and Davis, vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, Parainfluenza 3, Influenza virus A (subtypes H1N1, H3N2), influenza virus B, Reovirus-1, Sindbis, Reovirus-1, Punta Toro, human immunodeficiency virus type 1 strain III_B, and human immunodeficiency virus type 2 strain ROD. The antiviral, other than anti-HIV, assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa), or Madin-Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque-forming units (PFU) (VZV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation 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 cytopathogenicity or viral plaque formation by 50%.

Anti-HIV Activity Assays

Inhibition of HIV-1(III_B)- and HIV-2(ROD)-induced cytopathicity in CEM cell cultures was measured in microtiter 96-well plates containing ~ 3×10^5 CEM cells/mL infected with 100 $CCID_{50}$ of HIV per milliliter and containing appropriate dilutions of the test compounds. After 4 to 5 days of incubation at 37°C in a CO_2-controlled humidified atmosphere, CEM giant (syncytium) cell formation was examined microscopically. The EC_{50} (50% effective concentration) was defined as the compound concentration required to inhibit HIV-induced giant cell formation by 50%.

Cytostatic Activity Assays

All assays were performed in 96-well microtiter plates. To each well, $(5-7.5) \times 10^4$ tumor cells and a given amount of the test compound were added. The cells were allowed to proliferate for 48 hours (murine leukemia L1210 cells) or 72 hours (human lymphocytic CEM and human cervix carcinoma HeLa cells) at 37°C in a humidified CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a Coulter counter. The IC_{50} (50% inhibitory concentration) was defined as the concentration of the compound that inhibited cell proliferation by 50%.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Mrs. Jolanta Płocka, Mrs. Leentje Persoons, Mrs. Frieda De Meyer, Mrs. Leen Ingels, Mr. Steven Carmans, Mrs. Lies Van den Heurck, Mrs. Anita Camps, and Mrs. Lizette van Berckelaer for excellent technical assistance. The synthetic part of this work was supported by the Medical University of Łódź internal found (503/3-014–1/503-01 and 502-03-/3-014-01/502-34-020). The biological part of this work was supported by the KU Leuven (GOA 10/014).

REFERENCES

1. Williams, J.D; Khan, A.R.; Harden, E.A.; Hartline, C.B.; Jefferson, G.M.; Keith, K.A.; Prichard, M.N.; Zemlicka, J.; Peet, N.P.; Bowlin, T.L. Synthesis and antiviral activity of certain second generation methylenecyclopropane nucleosides. *Bioorg. Med. Chem.* **2012**, 20, 3710–3718.
2. Rios Morales, E.H.; Balzarini, J.; Meier, C. Stereoselective synthesis and antiviral activity of methyl-substituted cyclosal-pronucleotides. *J. Med. Chem.* **2012**, 55, 7245–7252.
3. Agarwal, H.K.; Chhikara, B.S.; Hanley, M. J; Ye, G.; Doncel, G.F.; Parang, K. Synthesis and biological evaluation of fatty acyl ester derivatives of (−)-2′,3′-dideoxy-3′-thiacytidine. *J. Med. Chem.* **2012**, 55, 4861–4871.
4. Ikeuchi, H.; Ahn, Y.-M.; Otokawa, T.; Watanabe, B.; Hegazy, L.; Hiratake, J.; Richards, N.G. J. A sulfoximine-based inhibitor of human asparagine synthetase kills L-asparaginase-resistant leukemia cells. *Bioorg. Med. Chem.* **2012**, 20, 5915–5927.
5. Choi, W.J.; Chung, H.-J.; Chandra, G.; Alexander, V.; Zhao, L.X.; Lee, H.W.; Nayak, A.; Majik, M.S.; Kim, H.O.; Kim, J.-H.; Lee, Y.B.; Ahn, C.H.; Lee, S.K.; Jeong, L.S. Fluorocyclopentenyl-cytosine with broad spectrum and potent antitumor activity. *J. Med. Chem.* **2012**, 55, 4521–4525.

6. Bosc, J.-J.; Latxague, L.; Léger, J.-M.; Balzarini, J.; Forfar, I.; Jarry, C.; Guillon, J. Synthesis and in vitro cytostatic activity of new β-D-arabino-furan[1′,2′:4,5]oxazolo- and arabino-pyrimidinone derivatives. *Eur. J. Med. Chem.* **2010**, 45, 831–839.
7. Krim, J.; Grünewald, C.; Taourirte, M.; Engels, J.W. Efficient microwave-assisted synthesis, antibacterial activity and high fluorescence of 5 benzimidazolyl-2′-deoxyuridines. *Bioorg. Med. Chem.* **2012**, 20, 480–486.
8. Matyugina, E.; Khandazhinskaya, A.; Chernousova, L.; Andreevskaya, S.; Smirnova, T.; Chizhov, A.; Karpenko, I.; Kochetkov, S.; Alexandrova, L. The synthesis and antituberculosis activity of 5′-nor carbocyclic uracil derivatives. *Bioorg. Med. Chem.* **2012**, 20, 6680–6686.
9. Srivastav, N.C.; Shakya, N.; Bhavanam, S.; Agrawal, A.; Tse, C.; Desroches, N.; Kunimoto, D.Y.; Kumar, R. Antimycobacterial activities of 5-alkyl (or halo)-3′-substituted pyrimidine nucleoside analogs. *Bioorg. Med. Chem. Lett.* **2012**, 22, 1091–1094.
10. Hocková, D.; Keough, D.T.; Janeba, Z.; Wang, T.-H.; de Jersey, J.; Guddat, L.W. Synthesis of novel *N*-branched acyclic nucleoside phosphonates as potent and selective inhibitors of human, plasmodium falciparum and plasmodium vivax 6-oxopurine phosphoribosyltransferases. *J. Med. Chem.* **2012**, 55, 6209–6223.
11. Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. Chemical synthesis of heterocyclic-sugar nucleoside analogues. *Chem. Rev.* **2010**, 110, 3337–3370.
12. Ichikawa, E.; Kato, K. Sugar-modified nucleosides in past 10 years, a review. *Curr. Med. Chem.* **2001**, 8, 385–423.
13. Shelton, J.R.; Cutler, C.E.; Oliveira, M.; Balzarini, J.; Peterson, M.A. Synthesis, SAR, and preliminary mechanistic evaluation of novel antiproliferative N^6,5′-bis-ureido- and 5′-carbamoyl-N^6-ureidoadenosine derivatives. *Bioorg. Med. Chem.* **2012**, 20, 1008–1019.
14. Verma, V.A.; Rossman, R.; Bennett, F.; Chen, L.; Gavalas, S.; Girijavallabhan, V.; Huang, Y.; Kim, S.-H.; Kosinski, A.; Pinto, P.; Rizvi, R.; Shankar, B.; Tong, L.; Velazquez, F.; Venkatraman, S.; Kozlowski, J.; MacCoss, M.; Kwong, C.D.; Bansal, N.; Kezar III, H.S.; Reynolds, R.C.; Maddry, J.A.; Ananthan, S.; Secrist III, J.A.; Li, C.; Chase, R.; Curry, S.; Huang, H.-C.; Tong, X.; Njoroge, F.G.; Arasappan, A. Synthesis and SAR of geminal substitutions at the C5′ carbosugar position of pyrimidine-derived HCV inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, 22, 6967–6973.
15. Manfredini, S.; Solaroli, N.; Angusti, A.; Nalin, F.; Durini, E.; Vertuani, S.; Pricl, S.; Ferrone, M.; Spadari, S.; Focher, F.; Verri, A.; De Clercq, E.; Balzarini, J. Design and synthesis of phosphonoacetic acid (PPA) ester and amide bioisosters of ribofuranosylnucleoside diphosphates as potential ribonucleotide reductase inhibitors and evaluation of their enzyme inhibitory, cytostatic and antiviral activity. *Antivir. Chem. Chemother.* **2003**, 14, 183–194.
16. Sargsyan, G.; MacLeod, B.L.; Tohgha, U.; Balaz, M. Sequence and linker dependent chiral dimerization of DNA-porphyrin conjugates. *Tetrahedron* **2012**, 68, 2093–2099.
17. Tosh, D.K.; Phan, K.; Gao, Z.-G.; Gakh, A.A.; Xu, F.; Deflorian, F.; Abagyan, R.; Stevens, R.C.; Jacobson, K.A.; Katritch, V. Optimization of adenosine 5′-carboxamide derivatives as adenosine receptor agonists using structure-based ligand design and fragment screening. *J. Med. Chem.* **2012**, 55, 4297–4308.
18. Hausler, N.E.; Devine, S.M.; McRobb, F.M.; Warfe, L.; Pouton, C.W.; Haynes, J.M.; Bottle, S.E.; White, P.J.; Scammells, P.J. Synthesis and pharmacological evaluation of dual acting antioxidant A_{2A} adenosine receptor agonists. *J. Med. Chem.* **2012**, 55, 3521–3534.
19. Diab, S.A.; De Schutter, C.; Muzard, M.; Plantier-Royon, R.; Pfund, E.; Lequeux, T. Fluorophosphonylated nucleoside derivatives as new series of thymidine phosphorylase multisubstrate inhibitors. *J. Med. Chem.* **2012**, 55, 2758–2768.
20. Chaudhary, P.M.; Chavan, S.R.; Shirazi, F.; Razdan, M.; Nimkar, P.; Maybhate, S.P.; Likhite, A.P.; Gonnade, R.; Hazara, B.G.; Deshpande, M.V.; Deshpande, S.R. Exploration of click reaction for the synthesis of modified nucleosides as chitin synthase inhibitors. *Bioorg. Med. Chem.* **2009**, 17, 2433–2440.
21. Park, S.M.; Yang, H.; Park, S.-K.; Kim, H.M.; Kim, B.H. Design, synthesis, and anticancer activities of novel perfluoroalkyltriazole-appended 2′-deoxyuridines. *Bioorg. Med. Chem. Lett.* **2010**, 20, 5831–5834.
22. Lee, Y.-S.; Park, S.M.; Kim, H.M.; Park, S.-K.; Lee, K.; Lee, C.W.; Kim, B.H. C5-Modified nucleosides exhibiting anticancer activity. *Bioorg. Med. Chem. Lett.* **2009**, 19, 4688–4691.
23. Galmarini, C.M.; Mackey, J.R.; Dumontet, C. Nucleoside analogues and nucleobases in cancer treatment. *Lancet Oncol.* **2002**, 3, 415–4424.

24. De Clercq, E. Highlights in the discovery of antiviral drugs: a personal retrospective. *J. Med. Chem.* **2010**, 53, 1438–1450.
25. Hecker, S.J.; Erion, M.D. Prodrugs of phosphates and phosphonates. *J. Med. Chem.* **2008**, 51, 2328–2345.
26. De Clercq, E. Antiretroviral drugs. *Curr. Opin. Pharmacol.* **2010**, 10, 507–515.
27. Arimilli, M.N.; Kim, C.U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J.P.; Cundy, K.C.; Bischofberger, N. Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. *Antiviral Chem. Chemother.* **1997**, 8, 557–564.
28. Sorbera, L.A.; Serradell, N.; Bolos, J. Pradefovir mesilate treatment of hepatitis B. *Drugs Future* **2007**, 32, 137–143.
29. Harris, S.A.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Synthesis and antiviral evaluation of phosphoramidate derivatives of (E)-5-(2-bromovinyl)-2′-deoxyuridine. *Antiviral Chem. Chemother.* **2001**, 12, 293–300.
30. Tronchet, J.M.J.; Iznaden, M.; Barbalat-Rey, F.; Dhimane, H.; Ricca, A.; Balzarini, J.; De Clercq, E. Isoxazolidine analogs of nucleosides. *Eur. J. Med. Chem.* **1992**, 27, 555–560.
31. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistarà, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. Enantioselective syntheses and cytotoxicity of *N*,*O*-nucleosides. *J. Med. Chem.* **2003**, 46, 3696–3702.
32. Bortolini, O.; De Nino, A.; Eliseo, T.; Gavioli, R.; Maiuolo, L.; Russo, B.; Sforza, F. Synthesis and biological evaluation of diastereoisomerically pure *N*,*O*-nucleosides. *Bioorg. Med. Chem.* **2010**, 19, 6970–6976.
33. Chiacchio, U.; Balestrieri, E.; Macchi, B.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Saglimbeni, M.; Sciortino, M.T.; Valveri, V.; Mastino, A.; Romeo, G. Synthesis of phosphonated carbocyclic 2′-Oxa-3′-aza-nucleosides: novel inhibitors of reverse transcriptase. *J. Med. Chem.* **2005**, 48, 1389–1394.
34. Piotrowska, D.G. N-Substituted C-diethoxyphosphorylated nitrones as useful synthons for the synthesis of α-aminophosphonates. *Tetrahedron Lett.* **2006**, 47, 5363–5366.
35. Piotrowska, D.G. Stereochemistry of substituted isoxazolidines derived from *N*-methyl *C*-diethoxyphosphorylated nitrone. *Tetrahedron* **2006**, 62, 12306–12317.
36. Piperno, A.; Giofrè, S.V.; Iannazzo, D.; Romeo, R.; Romeo, G.; Chiacchio, U.; Rescifina, A.; Piotrowska, D.G. Synthesis of C-4′ Truncated phosphonated carbocyclic 2′-Oxa-3′-azanucleosides as antiviral agents. *J. Org. Chem.* **2010**, 75, 2798–2805.
37. Piotrowska, D.G.; Cieślak, M.; Królewska, K.; Wróblewski, A.E. Design, Synthesis and cytotoxicity of a new series of isoxazolidine based nucleoside analogues. *Arch. Pharm. Chem. Life Sci.* **2011**, 11, 301–310.
38. Romeo, R.; Carnovale, C.; Giofrč, S.V.; Romeo, G.; Macchi, B.; Frezza, C.; Marino-Merlo, F.; Pistarŕ, V.; Chiacchio, U. Truncated phosphonated *C*-1′-branched *N*,*O*-nucleosides: A new class of antiviral agents. *Bioorg. Med. Chem.* **2012**, 20, 3652–3657.
39. Piotrowska, D.G.; Balzarini, J.; Głowacka, I.E. Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a 1,2,3-triazole linker. *Eur. J. Med. Chem.* **2012**, 47, 501–509.
40. Kokosza, K.; Balzarini, J.; Piotrowska, D.G. Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a carbamoyl linker. *Bioorg. Med. Chem.* **2013**, 21, 1097–1108.
41. Francis, A.W.; Helquist, S.A.; Kool, E.T.; David, S.S. Probing the requirements for recognition and catalysis in Fpg and MutY with nonpolar adenine isosteres. *J. Am. Chem. Soc.* **2003**, 125, 16235–16242.
42. Kool, E.T.; Morales, J.C.; Guckian, K.M. Mimicking the structure and function of DNA: insights into DNA stability and replication. *Angew. Chem. Int. Ed.* **2000**, 39, 990–1009.
43. Kool, E.T. Active site tightness and substrate fit in DNA replication. *Annu. Rev. Biochem.* **2002**, 71, 191–219.
44. Štambaský, J.; Hocek, M.; Kočovský, P. *C*-Nucleosides: synthetic strategies and biological applications. *Chem. Rev.* **2009**, 109, 6729–6764.
45. Henwood, J.M.; Brogden, R.N. Etoposide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in combination chemotherapy of cancer. *Drugs* **1990**, 39, 438–490.
46. Stewart, D.J.; Richard, M.T.; Hugenholtz, H.; Dennery, J.; Nundy, D.; Prior, J.; Montpetit, V.; Hopkins, H.S. Penetration of teniposide (VM-26) into human intracerebral tumors. *J. Neurooncol.* **1984**, 2, 315–324.

47. White, P.W.; Titolo, S.; Brault, K.; Thauvette, L.; Pelletier, A.; Welchner, E.; Bourgon, L.; Doyon, L.; Ogilvie, W.W.; Yoakim, C.; Cordingley, M.G.; Archambault, J. Inhibition of human papillomavirus DNA replication by small molecule antagonists of the E1–E2 protein interaction. *J. Biol. Chem.* **2003**, 278, 26765–26772.
48. Fernández, F.; García-Mera, X.; Rodríguez, G.; Urrutia, A. New hexahydrocarbazoles and spiro indoles, and their affinity for D_2 dopamine and 5-HT_{2A} serotonin receptors. *Chem. Pharm. Bull.* **1999**, 47, 1006–1009.
49. Honma, T.; Yoshizumi, T.; Hashimoto, N.; Hayashi, K.; Kawanishi, N.; Fukasawa, K.; Takaki, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Hayama, T.; Nishimura, S.; Morishima, H.A Novel Approach for the development of selective Cdk4 inhibitors: library design based on locations of Cdk4 specific amino acid residues. *J. Med. Chem.* **2001**, 44, 4628–4640.
50. Karplus, M. Vicinal proton coupling in nuclear magnetic resonance *J. Am. Chem. Soc.* **1963**, 85, 2870–2871.
51. Benezra, C., The variation of vicinal $^{31}P–C–C–^{1}H$ couplings with dihedral angle in phosphonates C. *J. Am. Chem. Soc.* **1973**, 95, 6890–6894.
52. Neeser J.-R.; Tronchet, J.M.J.; Charollais, E.J. Structural analysis of 3-*C*-phosphonates, -phosphinates, and -phosphine oxides of branched-chain sugars *Can. J. Chem.* **1983**, 61, 2112–2120.
53. Adiwidjaja, G.; Meyer, B.; Thiem, J. Synthesis and crystal structure of endo-2-dimethylphosphono-exo-2-hydroxy-(−)-camphane for the determination of ^{3}J(CCCP) vicinal coupling constants, *Z. Naturforsch* **1979**, 34b, 1547–1551.
54. Buchanan, G.W.; Bourque, K.; Seeley, A. ^{13}C and ^{31}P NMR spectra of 1-diethylphosphono-1-hydroxycycloalkanes *Magn. Res. Chem.* **1986**, 24, 360–367.