Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Bioorganic & Medicinal Chemistry 21 (2013) 1097–1108

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a carbamoyl linker

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

[a] Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Muszyńskiego 1, 90-151 Łódź, Poland
[b] Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 15 November 2012
Revised 27 December 2012
Accepted 2 January 2013
Available online 16 January 2013

Keywords:
1,3-Dipolar cycloaddition
Isoxazolidines
Phosphonates
Antiviral
Cytostatic

ABSTRACT

5-Arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates have been synthesised from *N*-methyl-*C*-diethoxyphosphorylnitrone and *N*-arylacrylamides in good yields. *cis*- and *trans*-isoxazolidine phosphonates obtained herein were evaluated for activity against a broad range of DNA and RNA viruses. None of the compounds were endowed with antiviral activity at subtoxic concentrations. Isoxazolidines having phenyl substituted with halogen (Ar = 2-F-C_6H_4; 3-Br-C_6H_4; and 4-Br-C_6H_4) have been found to inhibit proliferation of L1210, CEM as well as HeLa cells with IC_{50} in the 100–170 μM range.

1. Introduction

Nucleoside analogues are of great interest in medicinal chemistry due to their broad spectrum of biological activities. Extensive search for modified nucleosides has led to the discovery of many potent drugs for treatment of various viral infections[1] and diverse types of neoplasms (Fig. 1).[2] The adverse effects of the available therapies, low selectivity and the observed drug resistance have become a driving force in a search for new analogues with improved pharmacokinetic and pharmacodynamic properties. Numerous modifications of naturally occurring nucleosides have provided analogues with altered sugar and/or nucleobase subunits. Heterocycles containing one or more heteroatoms and carbocycles of various sizes as well as straight or branched chains also with heteroatoms have been applied as an alternative to the furanose ring.[3,4] So far less attention has been paid to the synthesis of analogues having modified nucleobase residues in comparison to sugar-modified analogues due to ensuring base pairing, but recently it has been proven that other aromatic rings are able to base-pair as well.[5] A long list of nucleoside analogues continues to expand by incorporation of several linkers such as a 1,2,3-triazole group,[6–9] a carbamoyl[10–17] or an ureidyl function[18] among others.

The isoxazolidine framework has successfully been applied as a surrogate for a furanose ring in the synthesis of nucleoside analogues with anticancer or antiviral activity (Fig. 2). Nucleoside analogue **1** [(−)-AdFU] having a fluorouracil residue attached to the isoxazolidine ring induces apoptosis on lymphoid and monocytoid cells and exhibits low level of cytotoxicity.[19] Phosphonylated isoxazolidines **2** inhibit reverse transcriptase of HTLV-1 with activity comparable to that of AZT and protect human peripheral blood mononuclear cells against HTLV-1 transmission.[20] Furthermore, compounds of general formula **3** show high cytotoxic activity against several cancer cell lines comparable to the known anticancer drugs, namely, Mitomycin C, Paclitaxel and 5-Fluorouracil, used as positive controls.[21] Synthesis and promising antiproliferative properties of isoxazolidines **4** have been reported by Bortolini et al.[22]

Recently, a series of 3,5-disubstituted isoxazolidine nucleosides **5**[23,24] as well as their further modifications **6** with an 1,2,3-triazole spacer[25] have been obtained and their antiviral and cytotoxic properties were evaluated. Isoxazolidines **5** substituted with 1- and 2-naphthyl at C5 were found cytotoxic against HeLa and K562 cell lines (R = 1-naphthyl and 2-naphthyl; IC_{50} 0.05 and 0.09 mM, respectively),[23] while *cis*-configured 5-fluorouracil and 5-thymine derivatives **5** completely inhibited the reverse transcriptase activity of Avian Moloney Virus (AMV) and Human Immunodeficiency Virus (HIV).[24] Although (1,2,3-triazolyl)isoxazolidinephosponates **6** did not show antiviral activity at subtoxic concentrations, derivatives of **6** having the unsubstituted and fluorosubstituted phenyl at C4 in the 1,2,3-triazole ring proved slightly cytostatic.[25] Encouraged by these results a new series of 5-substituted (3-diethoxyphosphoryl)isoxazolidines **7** was designed (Scheme 1).

* Corresponding author. Tel.: +48 42 677 9235; fax: +48 42 678 8398.
E-mail address: dorota.piotrowska@umed.lodz.pl (D.G. Piotrowska).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.01.007

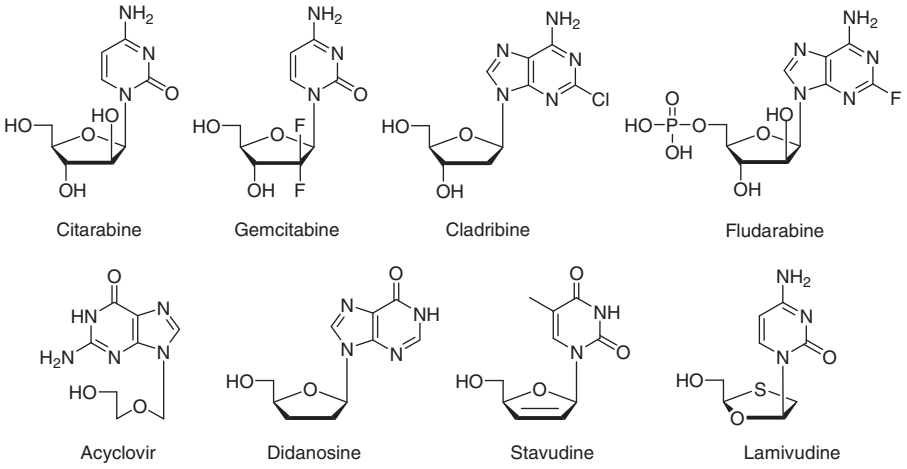


Figure 1. Examples of clinically applied nucleoside analogues with anticancer or antiviral activity.

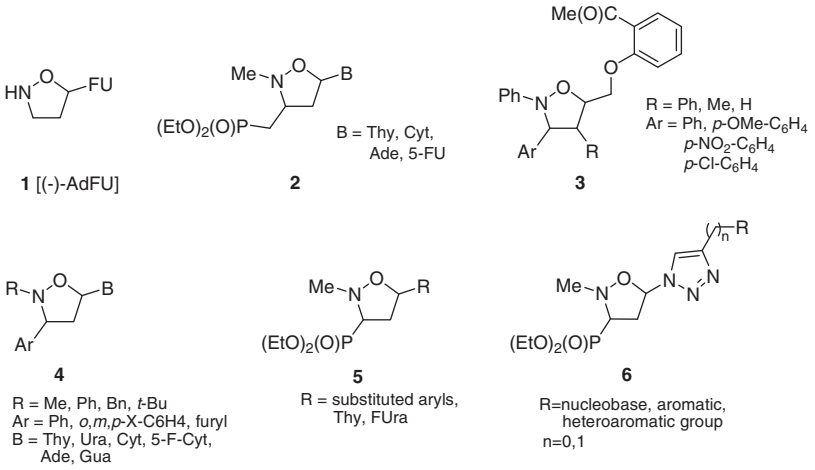


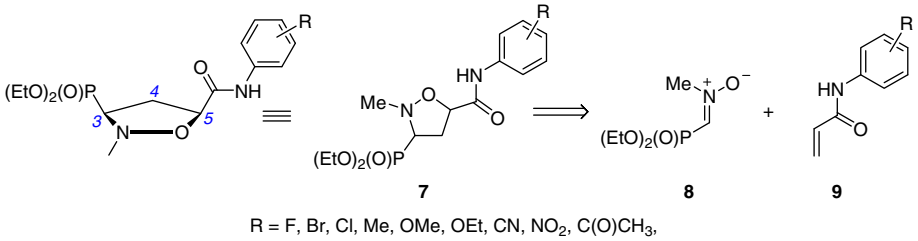
Figure 2. Examples of isoxazolidine nucleosides with cytotoxic and antiviral properties.

Compounds **7** could be regarded as nucleotide prodrugs due to incorporation of a bioisosteric diethoxyphosphoryl function at C3 of the isoxazolidine ring which mimics nucleoside monophosphate.[26] Moreover, it was anticipated that insertion of a carbamoyl linker between the isoxazolidine moiety and careful selection of mono-, di- or trisubstituted phenyl groups as nucleobase replacer would improve their interaction within DNA/RNA strands by forming stronger hydrogen bonds.

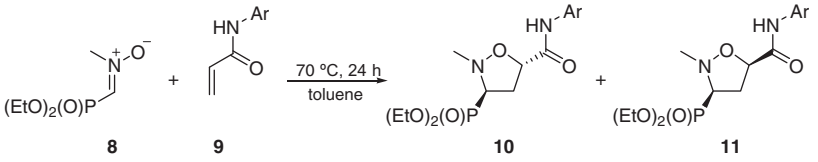
2. Results and discussion

2.1. Chemistry

To synthesise the desired isoxazolidines **10** and **11** 1,3-dipolar cycloaddition of *N*-methyl *C*-phosphorylnitrone **8**[27,28] with a series of acrylamides **9** was employed (Scheme 2). Most of substituted acrylamides **9** used in this paper have already been described in the literature. However, compounds **9ab**, **9ad**, **9an**, **9az** and **9ba** were prepared according to the standard procedure from commercially available substituted anilines and acryloyl chloride in the presence of triethylamine.[29] Cycloadditions of nitrone **8** with acrylamides **9aa**–**9ba** were carried out in toluene at 70 °C and afforded mixtures of diastereoisomeric (3-diethoxyphosphoryl)isoxazolidines *trans*-**10aa**–**10ba** and *cis*-**11aa**–**11ba** (Scheme 2, Table 1). In all cases moderate to good *trans*/*cis* diastereoselectivities (de 50–80%) were observed. The crude mixtures of the respective cycloadducts were subjected to column chromatography and in almost all cases (except for **10ae**, **10ah** and **10aq**) pure major *trans*-isomers **10** were separated in moderate to good yields (Table 1). Isolation of pure minor *cis*-isomers **11**, which are very cru-



Scheme 1. Retrosynthesis of isoxazolidynylphosphonates **7** with a carbamoyl linker.



Scheme 2. Synthesis of compounds **10** and **11**.

Table 1
Isoxazolidines **10** and **11** obtained according to Scheme 2

Entry	Acrylamide **9** Ar	**10**:**11** ratio	Yield (%)
aa	2-F-C_6H_4	88:12	**10aa** (43)[a] + **11aa** (6)[a] + **10aa** and **11aa** (24)[b]
ab	3-F-C_6H_4	78:22	**10ab** (55)[a] + **11ab** (6)[a] + **10ab** and **11ab** (25)[b]
ac	4-F-C_6H_4	80:20	**10ac** (48)[a] + **11ac** (6)[a] + **10ac** and **11ac** (34)[b]
ad	2,4-diF-C_6H_3	85:15	**10ad** (56)[a] + **10ad** and **11ad** (38)[b]
ae	2-Br-C_6H_4	90:10	**10ae** and **11ae** (94)[b]
af	3-Br-C_6H_4	77:23	**10af** (37)[a] + **10af** and **11af** (51)[b]
ag	4-Br-C_6H_4	78:22	**10ag** (68)[a] + **10ag** and **11ag** (16)[b]
ah	2-Cl-C_6H_4	86:14	**10ah** and **11ah** (91)[b]
ai	3-Cl-C_6H_4	75:25	**10ai** (48)[a] + **11ai** (3)[a] + **10ai** and **11ai** (39)[b]
aj	4-Cl-C_6H_4	86:14	**10aj** (60)[a] + **11aj** (8)[a] + **10aj** and **11aj** (20)[b]
ak	2-NO_2-C_6H_4	83:17	**10ak** (18)[a] + **10ak** and **11ak** (69)[b]
al	3-NO_2-C_6H_4	80:20	**10al** (26)[a] + **11al** (8)[a] + **10al** and **11al** (57)[b]
am	4-NO_2-C_6H_4	80:20	**10am** (60)[a] + **11am** (14)[a]
an	3-CN-C_6H_4	78:22	**10an** (17)[a] **+11an** (6)[a] + **10an** and **11an** (67)[b]
ao	4-CN-C_6H_4	80:20	**10ao** (10)[a] + **10ao** and **11ao** (85)[b]
ap	2-$CH_3C(O)$-C_6H_4	80:20	**10ap** (22)[a] + **11ap** (7)[a] + **10ap** and **11ap** (55)[b]
aq	3-$CH_3C(O)$-C_6H_4	81:19	**10aq** (53)[a] **+11aq** (5)[a] + **10aq** and **11aq** (31)[b]
ar	4-$CH_3C(O)$-C_6H_4	83:17	**10ar** (51)[a] + **11ar** (11)[a]
as	3-CH_3-C_6H_4	78:22	**10as** (40)[a] + **11as** (7)[a]
at	4-CH_3-C_6H_4	77:23	**10at** (70)[a] + **11at** (10)[a]
au	3-CH_3O-C_6H_4	76:24	**10au** (42)[a] + **10au** and **11au** (48)[b]
av	4-C_2H_5O-C_6H_4	79:21	**10av** (38)[a] + **11av** (4)[a] + **10av** and **11av** (47)[b]
aw	3,4-diCH_3O-C_6H_3	84:16	**10aw** (17)[a] **+11aw** (4)[a] + **10aw** and **11aw** (44)[b]
ax	3,5-diCH_3O-C_6H_3	80:20	**10ax** (25)[a] + **10ax** and **11ax** (70)[b]
ay	3,4,5-triCH_3O-C_6H_2	81:19	**10ay** (39)[a] **+11ay** (9)[a] + **10ay** and **11ay** (40)[b]
az	4,5-diCH_3O-2-CN-C_6H_2	80:20	**10az** (26)[a] + **10az** and **11az** (40)[b]
ba	4,5-diCH_3O-2-$CH_3C(O)$-C_6H_2	80:20	**10ba** (10)[a] **+ 10ba** and **11ba** (74)[b]

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

cial for biological evaluation, was not a trivial task. However, several purifications of the enriched diastereoisomeric mixtures of the respective isoxazolidines **10**/**11** on silica gel columns proved fruitful for isoxazolidines **11aa**, **11ab**, **11ac**, **11ai**, **11aj**, **11al**, **11am**, **11an**, **11ap**, **11aq**, **11ar**, **11as**, **11at**, **11av**, **11aw** and **11ba** (Table 1) making minute quantities of *cis*-**11** available.

Stereochemistry of the cycloaddition of N-substituted C-phosphorylated nitrones to various alkenes has already been described and the relative configurations of *trans*- and *cis*-isoxazolidine cycloadducts were established based on detailed conformational analyses.[23–25,27,28] Indeed, the assignment of relative configurations in isoxazolidines has often been difficult due to conformational flexibility of substituted five-membered ring, but in the case of isoxazolidines containing the diethoxyphosphoryl group at C3 stereochemically valuable data are extended over *PCCH*[30,31] and *PCCC*[31–34] vicinal couplings, which appeared to be extremely useful in establishing the stereochemistries of phosphorus-labelled heterocycles.[35,36] For the major isomers of all obtained isoxazolidines **10aa**–**10ba** *trans*-configuration was assigned taking advantage of our previous observations regarding stereochemistry of cycloaddition of *N*-methyl-*C*-phosphorylated nitrone **8** with terminal alkenes.[27,28] In this series a similar approach to configurational assignment was applied. Thus, based on the values of vicinal coupling constants [J_{CCCP} = 8.6–9.5 Hz, $J_{H3-H4\alpha}$ = 7.7–8.3 Hz, $J_{H3-H4\beta}$ = 8.5–9.2 Hz, $J_{H4\alpha-P}$ = 8.0–9.8 Hz, $J_{H4\beta-P}$ = 15.4–16.1 Hz, $J_{H4\alpha-H5}$ = 5.0–5.7 Hz and $J_{H4\beta-H5}$ = 8.5–9.2 Hz] extracted from the ^1H and ^{13}C NMR spectra of compounds **10al**–**10ao**, **10aq**, **10at** and **10aw**–**10ba** preferred $_3E$ conformation of the isoxazolidine ring (Fig. 3) was established. In this conformation the diethoxyphosphoryl group resides in the equatorial position of the isoxazolidine ring while carbamoyl substituents are located pseudoequatorially. Furthermore, a similar spectral pattern was previously observed for structurally related methyl *trans*-3-(diethoxyphosphoryl)-2-methylisoxazolidin-5-yl-5-carboxylate.[27,28]

To provide an additional piece of evidence for the already established relative configuration at C3 and C5 in isoxazolidines *trans*-**10** and *cis*-**11** 2D NOE experiments were performed for *trans*-**10ay** and *cis*-**11ay** (Fig. 4). The occurrence of NOE signal between *H*C5 and *H*C3 was noticed for *cis*-**11ay**, while the spectrum of *trans*-**10ay** lacks such correlation.

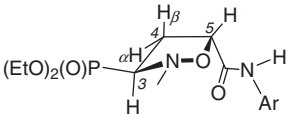


Figure 3. The preferred conformations of *trans*-isoxazolidines **10**.

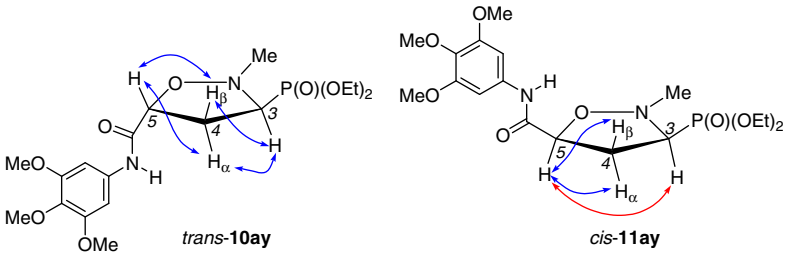


Figure 4. Observed NOEs for *trans*-**10ay** and *cis*-**11ay.**

2.2. Antiviral and cytostatic evaluation

5-Arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates *trans*-**10** and *cis*-**11** were evaluated for inhibitory activity against 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), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus and herpes simplex virus-1 (TK^- KOS ACV^r); (b) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus; (c) Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus; (d) MDCK cell cultures: influenza A virus (H1N1 and H3N2 subtypes) and influenza B virus; (e) CrFK cell cultures: feline herpes virus (FHV) and feline corona virus (FIPV) and (f) 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.

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. 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. None of the tested compounds affected cell morphology of HEL, HeLa, Vero, MDCK and CrFK cells at concentrations up to 100 μM. However, several compounds, having phenyl residue substituted with F, Br, Cl, NO_2 and $CH_3C(O)$ groups, were able to inhibit cell proliferation by 50% (CC_{50}) at concentrations ranging from 116 to 228 μM for L1210 cells, and from 102 to 227 μM for CEM and HeLa cells (Table 2).

Structure–activity relationship studies for a series of 5-arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates *trans*-**10** and *cis*-**11** described in this paper revealed that, in general, *cis*-isomers **11** are more cytostatic toward tested tumour cell lines than the respective *trans*-**10** (**11aa** vs **10aa**, **11ab** vs **10ab**, **11af** vs **10af**, **11ag** vs **10ag**, **11aj** vs **10aj** and **11ar** vs **10ar**). Isoxazolidines **11ab** (Ar = 3-F-C_6H_4), **10ag** (Ar = 4-Br-C_6H_4), **11aj** (Ar = 4-Cl-C_6H_4), **10ak** (Ar = 2-NO_2-C_6H_4) and **11ar** (Ar = 4-$CH_3C(O)$-C_6H_4) slightly inhibit cell proliferation of murine leukemia (L1210), while they are less active or inactive toward human T-lymphocyte (CEM) and human cervix cells (HeLa) at 250 μM. Compounds containing phenyl substituted with halogen, namely, *cis*-**11aa** (Ar = 2-F-C_6H_4), *cis*-**11af** (Ar = 3-Br-C_6H_4), and *cis*-**11ag** (Ar = 4-Br-C_6H_4) appeared to be the most active toward L1210, CEM as well as HeLa cells at IC_{50}'s consistently ranging between 100 and 200 μM against all three tumor cell lines. 5-Arylcarbamoyl derivatives **10** and **11** substituted with CN, Me, MeO or EtO did not show any appreciable cytostatic activity on the tested tumour cell lines. Among 5-arylcarbamoyl derivatives substituted with fluorine atom, compound **11aa** (Ar = 2-F-C_6H_4) is the most cytostatic. According to Kool, a 2,4-fluorophenyl group could be regarded as an uracil non-polar isoster due to the steric and electrostatic similarities.[37–40] To our surprise introduction of additional fluorine atoms into the aromatic ring resulted in loss of cytostatic activity (**10ad**/**11ad**; Ar = 2,4-diF-C_6H_3).

Table 2
Inhibitory effect of several 5-arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates against the proliferation of murine leukemia (L1210), human T-lymphocyte (CEM) and human cervix carcinoma cells (HeLa)

Compound	Ar	IC_{50}[a] (μM)		
		L1210	CEM	HeLa
10aa	2-F-C_6H_4	>250	>250	⩾250
11aa	2-F-C_6H_4	130 ± 24	145 ± 30	177 ± 42
10ab	3-F-C_6H_4	>250	>250	>250
11ab	3-F-C_6H_4	228 ± 12	⩾250	⩾250
10af	3-Br-C_6H_4	>250	⩾250	180 ± 35
11af/10af (77:23)	3-Br-C_6H_4	156 ± 1	140 ± 16	136 ± 11
10ag	4-Br-C_6H_4	177 ± 20	227 ± 32	⩾250
11ag/10ag (87:13)	4-Br-C_6H_4	116 ± 2	102 ± 9	136 ± 11
10aj	4-Cl-C_6H_4	>250	>250	⩾250
11aj	4-Cl-C_6H_4	170 ± 27	⩾250	>250
10ak	2-NO_2-C_6H_4	168 ± 24	⩾250	>250
11ak	2-NO_2-C_6H_4	Not available		
10ar	4-$CH_3C(O)$-C_6H_4	>250	>250	>250
11ar	4-$CH_3C(O)$-C_6H_4	150 ± 9	227 ± 18	211 ± 55

[a] 50% Inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%.

3. Conclusions

A new series of 5-arylcarbamoyl-2-methylisoxazolidin-3-yl-3-phosphonates have been efficiently obtained from *N*-methyl-*C*-diethoxyphoshporylnitrone and the respective *N*-arylacrylamides via the 1,3-dipolar cycloaddition. All synthesised isoxazolidineposphonates *trans*-**10** and *cis*-**11** were evaluated against a variety of DNA and RNA viruses but were not active at 250 μM.

Cytostatic activity of *trans*-**10** and *cis*-**11** compounds were performed on three tumor cell lines (L1210, CEM and HeLa) and showed that *cis*-configurated isoxazolidines containing phenyl substituted with halogen [*cis*-**11aa** (Ar = 2-F-C_6H_4), *cis*-**11af** (Ar = 3-Br-C_6H_4), and *cis*-**11ag** (Ar = 4-Br-C_6H_4)] are the most active toward all tested cancerous cell lines (IC_{50} 100–180 μM).

Further studies on isoxazolidinephosphonates of general formula **7** containing natural or modified nucleobases instead of aryl groups are in progress and will be published in due course.

4. Experimental section

^1H 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 F_{254}.

Starting materials: All solvents were dried according to the literature methods. Nitrone **8** was previously reported.[27]

4.1. General procedure for the preparation of acrylamides 9

To a solution of substituted aniline (1.00 mmol) in dichloromethane (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 h at room temperature and extracted with water (3 × 3 mL). Subsequently, the inorganic 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 **9**.

4.1.1. *N*-(3-Fluorophenyl)acrylamide (9ab)

Yield: 46%; white amorphous solid (crystallised from chloroform/hexane) mp 125–126 °C; IR (KBr, cm^{-1}) ν_{max}: 3277, 1666, 1611, 1549, 1491, 1443, 1223, 774, 677; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.52–7.48 (m, 1H), 7.34 (br s, 1H, N*H*), 7.24–7.11 (m, 2H), 6.79–6.73 (m, 1H), 6.38 (dd, 1H, *J* = 16.9, 1.2 Hz, CH=C*H*$_2$), 6.17 (dd, 1H, *J* = 16.9, 10.1 Hz, C*H*=CH$_2$), 5.73 (dd, 1H, *J* = 10.1, 1.2 Hz, CH=C*H*$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 164.68 (s, C(O)), 162.73 (d, *J* = 243.3 Hz, C3), 139.62 (d, *J* = 10.9 Hz, C1), 130.89 (s, *C*H=CH$_2$), 129.89 (d, *J* = 9.2 Hz, C5), 127.85 (s, CH=CH$_2$), 115.52 (s, C6), 110.96 (d, *J* = 21.2 Hz, C4), 107.53 (d, *J* = 26.1 Hz, C2). Anal. Calcd for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48; found: C, 65.24; H, 4.63; N, 8.56.

4.1.2. *N*-(2,4-Difluorophenyl)acrylamide (9ad)

Yield: 56%; white plates (crystallised from chloroform/hexane) mp 105–106 °C; IR (KBr, cm^{-1}) ν_{max}: 3277, 1668, 1549, 1503, 1214, 1142, 1099, 847, 808, 699; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.41–8.33 (m, 1H), 7.36 (br s, 1H, N*H*), 6.94–6.85 (m, 2H), 6.47 (dd, 1H, *J* = 16.9, 1.2 Hz, CH=C*H*$_2$), 6.28 (dd, 1H, *J* = 16.9, 10.2 Hz, C*H*=CH$_2$), 5.83 (dd, 1H, *J* = 10.2, 1.2 Hz, CH=C*H*$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 163.87 (s, C(O)), 158.84 (dd, *J* = 246.3, 11.7 Hz, C4), 153.02 (dd, *J* = 245.4, 10.6 Hz, C2), 130.66 (s, *C*H=CH$_2$), 128.41 (s, CH=CH$_2$), 123.65 (d, *J* = 9.8 Hz, C6), 122.36 (dd, *J* = 10.7, 3.8 Hz, C5), 111.21 (dd, *J* = 21.8, 3.7 Hz, C1), 103.69 (dd, *J* = 26.6, 23.5 Hz, C3). Anal. Calcd for $C_9H_7F_2NO$: C, 59.02; H, 3.85; N, 7.65; found: C, 58.83; H, 3.94; N, 7.68.

4.1.3. *N*-(3-Cyanophenyl)acrylamide (9an)

Yield: 86%; yellow amorphous solid; mp 125–126 °C; IR (KBr, cm^{-1}) ν_{max}: 3253, 3077, 2230, 1665, 1606, 1556, 1484, 1415, 1328, 1212; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 7.84–7.83 (m, 1H), 7.58 (br s, 1H, N*H*), 7.48–7.42 (m, 2H), 6.50 (dd, 1H, *J* = 16.9, 0.8 Hz, CH=C*H*$_2$), 6.29 (dd, 1H, *J* = 16.9, 10.3 Hz, C*H*=CH$_2$), 5.87 (dd, 1H, *J* = 10.3, 0.8 Hz, CH=C*H*$_2$); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 164.40, 139.13, 130.77 (s, *C*H=CH$_2$), 129.87, 128.64 (s, CH=*C*H$_2$), 127.68, 124.38, 123.26, 118.65 (s, CN), 112.66. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27; found: C, 69.83; H, 4.85; N, 16.31.

4.1.4. *N*-(2-Cyano-4,5-dimethoxyphenyl)acrylamide (9az)

Yield: 91%; yellow amorphous solid mp 158–162 °C; IR (KBr, cm^{-1}) ν_{max}: 3247, 2225, 1663, 1610, 1514, 1450, 1356, 1283, 1226, 1109; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 7.65 (br s, 1H, N*H*), 6.99 (s, 1H), 6.51 (dd, 1H, *J* = 16.8, 0.9 Hz, CH=C*H*$_2$), 6.34 (dd, 1H, *J* = 16.8, 10.3 Hz, C*H*=CH$_2$), 5.90 (dd, 1H, *J* = 10.3, 0.9 Hz, CH=C*H*$_2$), 3.99 (s, 3H, C*H*$_3$O), 3.91 (s, 3H, C*H*$_3$O); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 163.65 (s, C(O)), 153.71, 145.68, 136.33, 130.59 (s, *C*H=CH$_2$), 129.07 (s, CH=*C*H$_2$), 116.80 (s, CN), 112.91, 104.97, 92.54, 56.32 (s, CH_3O), 56.17 (s, CH_3O). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 62.07; H, 5.28; N, 11.97.

4.1.5. *N*-(2-Acethyl-4,5-dimethoxyphenyl)acrylamide (9ba)

Yield: 88%; yellow amorphous solid; mp 89–90 °C; IR (KBr, cm^{-1}) ν_{max}: 3447, 3120, 2938, 1683, 1615, 1522, 1366, 1253, 1207, 1153; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.67 (s, 1H), 7.32 (s, 1H), 6.45 (dd, 1H, *J* = 16.9, 1.0 Hz, CH=C*H*$_2$), 6.34 (dd, 1H, *J* = 16.9, 10.2 Hz, C*H*=CH$_2$), 5.81 (dd, 1H, *J* = 10.2, 1.0 Hz, CH=C*H*$_2$), 4.02 (s, 3H, C*H*$_3$O), 3.94 (s, 3H, C*H*$_3$O), 2.65 (s, 3H, C*H*$_3$–C(O)); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 200.82 (s, C(O)), 164.63 (s, C(O)NH), 154.74, 143.76, 137.88, 132.53 (s, *C*H=CH$_2$), 127.22 (s, CH=*C*H$_2$), 114.50, 113.86, 103.65, 56.43 (s, CH_3O), 56.21 (s, CH_3O), 28.37 (s, *C*H$_3$C(O)). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; found: C, 62.69; H, 6.16; N, 5.74.

4.2. General procedure for preparation of isoxazolidines 10 and 11

A mixture of nitrone **8** (1.00 mmol), acrylamide **9** (1.00 mmol) and toluene (2 mL) was stirred at 70 °C for 24 h or until disappearance of the starting nitrone. After evaporation of the solvent under reduced pressure the crude products were purified by silica gel chromatography with chloroform/methanol mixtures as eluents.

4.2.1. Diethyl (*3RS,5SR*)-5-(2-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10aa)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3396, 2983, 1700, 1531, 1456, 1238, 1053, 1025, 757; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.56 (br s, 1H, N*H*), 8.34–8.29 (m, 1H), 7.18–7.08 (m, 3H), 4.65 (dd, 1H, *J* = 8.8, 4.9 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 3.15–2.93 (m, 2H, H_βC4 and *H*C3), 3.05 (s, 3H, C*H*$_3$N), 2.90–2.80 (m, 1H, H_αC4), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.13 (s, C(O)), 152.61 (d, *J* = 243.6 Hz, *C*2′), 125.37 (d, *J* = 10.0 Hz, *C*1′), 125.04 (d, *J* = 7.7 Hz, *C*4′), 124.67 (d, *J* = 3.7 Hz, *C*6′), 121.51 (s, *C*5′), 115.03 (d, *J* = 18.9 Hz, *C*3′), 76.51 (d, *J* = 9.4 Hz, C5), 63.59 (d, *J* = 6.6 Hz, CH_2OP), 63.51 (d, *J* = 168.6 Hz, C3), 62.78 (d, *J* = 6.9 Hz, CH_2OP), 47.08 (s, CH_3N), 36.90 (s, C4), 16.76 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.69 (d, *J* = 5.2 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.20. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 49.83; H, 6.04; N, 7.96.

4.2.2. Diethyl (*3RS,5RS*)-5-(2-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11aa)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3397, 2983, 1699, 1619, 1531, 1457, 1236, 1053, 1024, 970; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.95 (br s, 1H, N*H*), 8.37–8.28 (m, 1H), 7.15–7.06 (m, 3H), 4.63–4.58 (m, 1H, *H*C5), 4.16–4.05 (m, 4H, 2 × C*H*$_2$OP), 3.02 (s, 3H, C*H*$_3$N), 3.10–2.82 (m, 3H, H_2C4 and *H*C3), 1.28 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.17 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR signals of *cis*-**11aa** were extracted from the spectrum of a 65:35 mixture of *trans*-**10aa** and *cis*-**11aa**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.50

(s, C(O)), 152.58 (d, J = 243.7 Hz, *C*2′), 125.89 (d, J = 10.1 Hz, *C*1′), 124.54 (d, J = 3.8 Hz, *C*6′), 124.46 (d, J = 8.3 Hz, *C*4′), 121.26 (s, *C*2′), 114.89 (d, J = 19.1 Hz, *C*3′), 75.70 (d, J = 8.0 Hz, C5), 63.80 (d, J = 169.3 Hz, C3), 63.58 (d, J = 6.0 Hz, CH_2OP), 62.75 (d, J = 6.8 Hz, CH_2OP), 45.99 (s, CH_3N), 36.97 (s, C4), 16.56 (d, J = 6.1 Hz, CH_3CH_2OP), 16.41 (d, J = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.51. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 49.97; H, 6.01; N, 7.94.

4.2.3. Diethyl (*3RS,5SR*)-5-(3-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ab)

White amorphous solid (crystallised from ether/hexane); mp 85–87 °C. IR (KBr, cm^{-1}) ν_{max}: 3267, 3084, 3051, 2995, 1698, 1623, 1562, 1445, 1215, 1021, 877, 583; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.24 (br s, 1H, N*H*), 7.56–7.51 (m, 1H), 7.33–7.25 (m, 1H), 7.20–7.17 (m, 1H), 6.88–6.82 (m, 1H), 4.62 (dd, 1H, J = 8.8, 5.2 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × CH_2OP), 3.10–2.90 (m, 2H, H_βC4 and *H*C3), 3.02 (s, 3H, CH_3N), 2.89–2.77 (m, 1H, H_αC4), 1.37 (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: 168.88 (s, C(O)), 162.87 (d, J = 244.5 Hz, *C*3′), 138.39 (d, J = 10.9 Hz, *C*1′), 130.18 (d, J = 9.2 Hz, *C*5′), 115.14 (d, J = 2.9 Hz, *C*6′), 111.53 (d, J = 21.5 Hz, *C*4′), 107.37 (d, J = 26.3 Hz, *C*2′), 76.45 (d, J = 8.9 Hz, C5), 63.52 (d, J = 167.8 Hz, C3), 63.51 (d, J = 6.3 Hz, CH_2OP), 62.78 (d, J = 6.9 Hz, CH_2OP), 46.83 (s, CH_3N), 36.51 (s, C4), 16.72 (d, J = 5.4 Hz, CH_3CH_2OP), 16.65 (d, J = 5.2 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.16. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 49.99; H, 5.92; N, 7.98.

4.2.4. Diethyl (*3RS,5RS*)-5-(3-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11ab)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3276, 2984, 2931, 1690, 1613, 1536, 1445, 1230, 1052, 1026, 966; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.92 (br s, 1H, N*H*), 7.59–7.55 (m, 1H), 7.29–7.20 (m, 2H), 6.84–6.78 (m, 1H), 4.61 (dd, 1H, J = 8.7, 5.7 Hz, *H*C5), 4.23–4.02 (m, 4H, 2 × CH_2OP), 3.17–2.99 (m, 2H, *H*C3 and H_βC4), 3.02 (s, 3H, CH_3N), 2.90–2.74 (m, 1H, H_αC4), 1.31 (t, 3H, J = 7.0 Hz, CH_3CH_2OP), 1.21 (t, 3H, J = 7.0 Hz, CH_3CH_2OP); ^{13}C NMR signals of *cis*-**11ab** were extracted from the spectrum of a 68:32 mixture of *trans*-**10ab** and *cis*-**11ab**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.09 (s, C(O)), 162.96 (d, J = 245.0 Hz, *C*3′), 139.04 (d, J = 10.9 Hz, *C*1′), 130.09 (d, J = 9.5 Hz, *C*5′), 115.08 (d, J = 3.1 Hz, *C*6′), 111.08 (d, J = 21.2 Hz, *C*4′), 107.18 (d, J = 26.3 Hz, *C*2′), 76.06 (d, J = 6.7 Hz, C5), 63.78 (d, J = 169.8 Hz, C3), 63.31 (d, J = 6.8 Hz, CH_2OP), 63.14 (d, J = 6.8 Hz, CH_2OP), 46.21 (s, CH_3N), 36.48 (s, C4), 16.70 (d, J = 5.9 Hz, CH_3CH_2OP), 16.57 (d, J = 5.8 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.08. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 50.03; H, 6.24; N, 7.82.

4.2.5. Diethyl (*3RS,5SR*)-5-(4-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ac)

White amorphous solid (crystallised from ether/hexane) mp 59–62 °C. IR (KBr, cm^{-1}) ν_{max}: 3278, 3084, 2999, 1701, 1512, 1211, 1021, 834, 582; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.17 (br s, 1H, N*H*), 7.54–7.48 (m, 2H), 7.07–7.00 (m, 2H), 4.60 (dd, 1H, J = 8.7, 5.4 Hz, *H*C5), 4.26–4.13 (m, 4H, 2 × CH_2OP), 3.15–2.90 (m, 2H, *H*C3 and H_βC4), 3.01 (s, 3H, CH_3N), 2.87–2.76 (m, 1H, H_αC4), 1.36 (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: 168.65 (s, C(O)), 159.43 (d, J = 243.6 Hz, *C*4′), 132.92 (d, J = 2.8 Hz, *C*1′), 121.67 (d, J = 7.7 Hz, *C*2′ and *C*6′), 115.66 (d, J = 22.6 Hz, *C*3′ and *C*5′), 76.40 (d, J = 9.2 Hz, C5), 63.45 (d, J = 168.9 Hz, C3), 63.42 (d, J = 6.3 Hz, CH_2OP), 62.71 (d, J = 6.9 Hz, CH_2OP), 46.86 (s, CH_3N), 36.48 (s, C4), 16.66 (d, J = 5.4 Hz, CH_3CH_2OP), 16.59 (d, J = 5.4 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.38. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 50.04; H, 5.94; N, 8.00.

4.2.6. Diethyl (*3RS,5RS*)-5-(4-fluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (cis-11ac)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3279, 2983, 1688, 1532, 1510, 1227, 1052, 1025, 971; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.81 (br s, 1H, N*H*), 7.58–7.54 (m, 2H), 7.05–6.98 (m, 2H), 4.64–4.60 (m, 1H, *H*C5), 4.21–4.06 (m, 4H, 2 × CH_2OP), 3.12–2.97 (m, 2H, *H*C3 and H_βC4), 2.96 (s, 3H, CH_3N), 2.88–2.73 (m, 1H, H_αC4), 1.31 (t, 3H, J = 7.0 Hz, CH_3CH_2OP), 1.21 (t, 3H, J = 7.0 Hz, CH_3CH_2OP); ^{13}C NMR signals of *cis*-**11ac** were extracted from the spectrum of a 48:52 mixture of *trans*-**10ac** and *cis*-**11ac**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.77 (s, C(O)), 159.28 (d, J = 242.9 Hz, *C*4′), 133.56 (d, J = 2.8 Hz, *C*1′), 121.38 (d, J = 7.9 Hz, *C*2′ and *C*6′), 115.82 (d, J = 22.5 Hz, *C*3′ and *C*5′), 75.99 (d, J = 6.8 Hz, *C*5), 63.78 (d, J = 169.7 Hz, C3), 63.56 (d, J = 6.5 Hz, CH_2OP), 63.09 (d, J = 6.8 Hz, CH_2OP), 46.28 (s, CH_3N), 36.69 (s, C4), 16.69 (d, J = 5.9 Hz, CH_3CH_2OP), 16.57 (d, J = 5.7 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.14. Anal. Calcd for $C_{15}H_{22}FN_2O_5P$: C, 50.00; H, 6.15; N, 7.77; found: C, 49.98; H, 6.16; N, 7.82.

4.2.7. Diethyl (*3RS,5SR*)-5-(2,4-difluorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ad)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3397, 2984, 1698, 1534, 1432, 1236, 1054, 1025, 964, 848; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H, N*H*), 8.31–8.23 (m, 1H), 6.93–6.87 (m, 2H), 4.63 (dd, 1H, J = 8.5, 4.6 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × CH_2OP), 3.20–2.95 (m, 2H, *H*C3 and H_βC4), 3.04 (s, 3H, CH_3N), 2.95–2.78 (m, 1H, H_αC4), 1.37 (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: 169.06 (s, C(O)), 158.82 (dd, J = 246.5, 11.5 Hz, *C*4′), 152.69 (dd, J = 246.6, 11.8 Hz, *C*2′), 122.57 (dd, J = 9.1, 2.2 Hz, *C*6′), 121.70 (dd, J = 10.3, 3.7 Hz, *C*5′), 111.34 (dd, J = 21.7, 3.8 Hz, *C*1′), 103.79 (dd, J = 26.6, 23.2 Hz, *C*3′), 76.36 (d, J = 9.4 Hz, C5), 63.54 (d, J = 6.6 Hz, CH_2OP), 63.48 (d, J = 167.8 Hz, C3), 62.72 (d, J = 6.9 Hz, CH_2OP), 46.98 (s, CH_3N), 36.85 (s, C4), 16.73 (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: 21.25. Anal. Calcd for $C_{15}H_{21}F_2N_2O_5P$: C, 47.62; H, 5.60; N, 7.40; found: C, 47.38; H, 5.66; N, 7.31.

4.2.8. Diethyl (*3RS,5SR*)-5-(2-bromophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ae)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3354, 2980, 1698, 1524, 1439, 1245, 1052, 1025, 755; (signals of *trans*-**10ae** were extracted from the spectra of a 86:14 mixture of *trans*-**10ae** and *cis*-**11ae**); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.94 (br s, 1H, N*H*), 8.42–8.38 (m, 1H), 7.58–7.55 (m, 1H), 7.36–7.31 (m, 1H), 7.04–6.99 (m, 1H), 4.64 (dd, 1H, J = 8.8, 4.6 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × CH_2OP), 3.14–2.90 (m, 2H, *H*C3 and H_βC4), 3.09 (s, 3H, CH_3N), 2.90–2.77 (m, 1H, H_αC4), 1.37 (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: 169.24 (s, C(O)), 134.84, 132.36, 128.41, 125.61, 121.34, 113.59, 76.39 (d, J = 9.7 Hz, C5), 63.52 (d, J = 6.6 Hz, CH_2OP), 63.44 (d, J = 168.6 Hz, C3), 62.67 (d, J = 7.2 Hz, CH_2OP), 47.07 (s, CH_3N), 37.09 (s, C4), 16.71 (d, J = 5.2 Hz, CH_3CH_2OP), 16.64 (d, J = 5.4 Hz, CH_3CH_2OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.15. Anal. Calcd for $C_{15}H_{22}BrN_2O_5P$: C, 42.77; H, 5.26; N, 6.65; found: C, 42.52; H, 5.07; N, 6.71 (obtained on a 86:14 mixture of *trans*-**10ae** and *cis*-**11ae**).

4.2.9. Diethyl (*3RS,5SR*)-5-(3-bromophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10af)

White amorphous solid (crystallised from ether/hexane); mp 111–112 °C. IR (KBr, cm^{-1}) ν_{max}: 3254, 3107, 3070, 2995, 1699, 1612, 1546, 1422, 1215, 1022, 582; ^1H NMR (300 MHz, $CDCl_3$) δ:

8.16 (br s, 1H, N*H*), 8.20–7.81 (m, 1H), 7.49–7.45 (m, 1H), 7.29–7.18 (m, 2H), 4.61 (dd, 1H, *J* = 8.5, 5.2 Hz, *H*C5), 4.27–4.13 (m, 4H, 2 × C*H*$_2$OP), 3.10–2.92 (m, 2H, *H*C3 and H_βC4), 3.02 (s, 3H, C*H*$_3$N), 2.89–2.76 (m, 1H, H_αC4), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.86 (s, C(O)), 138.20, 130.35, 127.71, 122.74, 122.63, 118.33, 76.45 (d, *J* = 8.9 Hz, C5), 63.51 (d, *J* = 167.5 Hz, C3), 63.47 (d, *J* = 6.9 Hz, CH_2OP), 62.78 (d, *J* = 7.2 Hz, CH_2OP), 46.94 (s, CH_3N), 36.50 (s, C4), 16.73 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.66 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.27. Anal. Calcd for $C_{15}H_{22}BrN_2O_5P$: C, 42.77; H, 5.26; N, 6.65; found: C, 42.88; H, 4.99; N, 6.90.

4.2.10. Diethyl (*3RS,5SR*)-5-(4-bromophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ag)

White amorphous solid (crystallised from ether/hexane); mp 81–82 °C. IR (KBr, cm^{-1}) ν_{max}: 3260, 3057, 2988, 1705, 1547, 1489, 1219, 1025, 827, 577; ^{1}H NMR (300 MHz, CDCl3) δ: 8.22 (br s, 1H, N*H*), 7.52–7.38 (m, 4H), 4.59 (dd, 1H, *J* = 8.8, 5.5 Hz, *H*C5), 4.25–4.12 (m, 4H, 2 × C*H*$_2$OP), 3.15–2.90 (m, 2H, *H*-C3 and H_β-C4), 3.00 (s, 3H, C*H*$_3$N), 2.89–2.75 (m, 1H, H_α-C4), 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: 168.77 (s, C(O)), 135.99, 132.06, 121.44, 117.47, 76.48 (d, *J* = 9.2 Hz, C5), 63.67 (d, *J* = 161.4 Hz, C3), 63.54 (d, *J* = 6.6 Hz, CH_2OP), 62.79 (d, *J* = 6.9 Hz, CH_2OP), 46.91 (s, CH_3N), 36.57 (s, C4), 16.76 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.69 (d, *J* = 5.2 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 20.63. Anal. Calcd for $C_{15}H_{22}BrN_2O_5P$: C, 42.77; H, 5.26; N, 6.65; found: C, 42.95; H, 5.06, N, 6.86.

4.2.11. Diethyl (*3RS,5SR*)-5-(2-chlorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ah)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3477, 3368, 2982, 1699, 1593, 1528, 1442, 1242, 1055, 1027, 756; (signals of *trans*-**10ah** were extracted from the spectra of a 81:19 mixture of *trans*-**10ah** and *cis*-**11ah**); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.95 (br s, 1H, N*H*), 8.43–8.40 (m, 1H), 7.41–7.38 (m, 1H), 7.32–7.27 (m, 1H), 7.11–7.05 (m, 1H), 4.65 (dd, 1H, *J* = 8.8, 4.6 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 3.07 (s, 3H, C*H*$_3$N), 3.15–2.78 (m, 3H, H_2C4 and *H*C3), 1.37 (t, 3H, *J* = 6.9 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.27 (s, C(O)), 133.75, 129.18, 127.82, 125.19, 123.19, 121.15, 76.51 (d, *J* = 9.7 Hz, C5), 63.59 (d, *J* = 6.6 Hz, CH_2OP), 63.52 (d, *J* = 165.8 Hz, C3), 62.76 (d, *J* = 6.9 Hz, CH_2OP), 47.13 (s, CH_3N), 37.07 (s, C4), 16.76 (d, *J* = 5.2 Hz, *C*H$_3$CH$_2$OP), 16.68 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.17. Anal. Calcd for $C_{15}H_{22}ClN_2O_5P$: C, 47.82; H, 5.89; N, 7.44; found: C, 47.52; H, 5.60; N, 7.53 (obtained on a 81:19 mixture of *trans*-**10ah** and *cis*-**11ah**).

4.2.12. Diethyl (*3RS,5SR*)-5-(3-chlorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ai)

White amorphous solid (crystallised from ether/hexane); mp 106–109 °C. IR (KBr, cm^{-1}) ν_{max}: 3256, 3071, 2963, 1699, 1597, 1548, 1425, 1258, 1216, 1022, 583; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (br s, 1H, N*H*), 7.70–7.68 (m, 1H), 7.42–7.40 (m, 1H), 7.27–7.23(m, 1H), 7.14–7.11 (m, 1H), 4.63 (dd, 1H, *J* = 8.8, 4.6 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 2.95–3.20 (m, 2H, *H*C3 and H_βC4), 3.03 (s, 3H, C*H*$_3$N), 2.90–2.75 (m, 1H, H_αC4), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.87 (s, C(O)), 138.07, 134.62, 130.04, 124.75, 119.92, 117.84, 76.45 (d, *J* = 8.9 Hz, C5), 63.52 (d, *J* = 167.8 Hz, C3), 63.45 (d, *J* = 6.6 Hz, CH_2OP), 62.56 (d, *J* = 6.9 Hz, CH_2OP), 46.89 (s, CH_3N), 36.49 (s, C4), 16.71 (d, *J* = 5.2 Hz, *C*H$_3$CH$_2$OP), 16.64 (d, *J* = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.17. Anal. Calcd for $C_{15}H_{22}ClN_2O_5P$: C, 47.82; H, 5.89; N, 7.44; found: C, 47.92; H, 5.75; N, 7.63.

4.2.13. Diethyl (*3RS,5RS*)-5-(3-chlorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11ai)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3256, 3071, 2908, 1698, 1596, 1547, 1426, 1258, 1217, 1050, 1022, 973; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (br s, 1H, N*H*), 7.72–7.71 (m, 1H), 7.44–7.40 (m, 1H), 7.26–7.21 (m, 1H), 7.09–7.06 (m, 1H), 4.61 (dd, 1H, *J* = 9.0, 5.4 Hz, *H*C5), 4.23–4.01 (m, 4H, 2 × C*H*$_2$OP), 3.12–2.94 (m, 2H, *H*C3 and H_βC4), 2.96 (s, 3H, C*H*$_3$N), 2.88–2.72 (m, 1H, H_αC4), 1.31 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.21 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR signals of *cis*-**11ai** were extracted from the spectrum of a 70:30 mixture of *trans*-**10ai** and *cis*-**11ai**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.05 (s, C(O)), 138.52, 134.44, 129.85, 124.25, 119.62, 117.63, 75.88 (d, *J* = 6.9 Hz, C5), 63.50 (d, *J* = 167.2 Hz, C3), 63.17 (d, *J* = 6.9 Hz, CH_2OP), 63.01 (d, *J* = 6.9 Hz, CH_2OP), 46.12 (s, CH_3N), 36.31 (s, C4), 16.62 (d, *J* = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.51 (d, *J* = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.97. Anal. Calcd for $C_{15}H_{22}ClN_2O_5P$: C, 47.82; H, 5.89; N, 7.44; found: C, 47.84; H, 5.61; N, 7.56.

4.2.14. Diethyl (*3RS,5SR*)-5-(4-chlorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10aj)

White amorphous solid (crystallised from ether/hexane); mp 75–76 °C. IR (KBr, cm^{-1}) ν_{max}: 3259, 3059, 1705, 1549, 1493, 1302, 1219, 1027, 832, 577; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (br s, 1H, N*H*), 7.55–7.49 (m, 2H), 7.33–7.25 (m, 2H), 4.60 (dd, 1H, *J* = 8.7, 5.1 Hz, *H*C5), 4.26–4.13 (m, 4H, 2 × C*H*$_2$OP), 3.15–2.89 (m, 2H, *H*C3 and H_βC4), 3.01 (s, 3H, C*H*$_3$N), 2.88–2.76 (m, 1H, H_αC4), 1.36 (t, 3H, *J* = 7.2 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.50 (s, C(O)), 135.31, 129.39, 128.75, 120.88, 76.20 (d, *J* = 9.2 Hz, C5), 63.28 (d, *J* = 167.2 Hz, C3), 63.18 (d, *J* = 6.6 Hz, CH_2OP), 62.48 (d, *J* = 6.9 Hz, CH_2OP), 46.58 (s, CH_3N), 36.21 (s, C4), 16.45 (d, *J* = 5.1 Hz, *C*H$_3$CH$_2$OP), 16.38 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.31. Anal. Calcd for $C_{15}H_{22}ClN_2O_5P$: C, 47.82; H, 5.89; N, 7.44; found: C, 47.93; H, 5.82; N, 7.58.

4.2.15. Diethyl (*3RS,5RS*)-5-(4-chlorophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11aj)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3286, 3264, 2983, 2924, 1691, 1537, 1494, 1234, 1051, 1025, 971; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (br s, 1H, N*H*), 7.58–7.53 (m, 2H), 7.31–7.26 (m, 2H), 4.61 (dd, 1H, *J* = 9.0, 4.8 Hz, *H*C5), 4.23–4.01 (m, 4H, 2 × C*H*$_2$OP), 3.12–2.99 (m, 2H, *H*C3 and H_βC4), 2.95 (s, 3H, C*H*$_3$N), 2.88–2.72 (m, 1H, H_αC4), 1.31 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.20 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR signals of *cis*-**11aj** were extracted from the spectrum of a 51:49 mixture of *trans*-**10aj** and *cis*-**11aj**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.91 (s, C(O)), 136.12, 129.21, 128.9, 120.93, 76.04 (d, *J* = 6.9 Hz, C5), 63.56 (d, *J* = 168.4 Hz, C3), 63.25 (d, *J* = 6.9 Hz, CH_2OP), 63.13 (d, *J* = 6.0 Hz, CH_2OP), 46.89 (s, CH_3N), 36.40 (s, C4), 16.67 (d, *J* = 6.8 Hz, *C*H$_3$CH$_2$OP), 16.58 (d, *J* = 7.1 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.16. Anal. Calcd for $C_{15}H_{22}ClN_2O_5P$: C, 47.82; H, 5.89; N, 7.44; found: C, 47.84; H, 5.81; N, 7.40.

4.2.16. Diethyl (*3RS,5SR*)-5-(2-nitrophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ak)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3320, 2982, 1704, 1503, 1278, 1238, 1051, 1023, 969, 745; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84–8.80 (m, 1H), 8.28–8.25 (m, 1H), 7.71–7.66 (m, 1H), 7.28–7.22 (m, 1H), 4.66 (dd, 1H, *J* = 8.9, 5.6 Hz, *H*C5), 4.28–4.15 (m, 4H, 2 × C*H*$_2$OP), 3.14–2.98 (m, 2H, *H*C3 and H_βC4), 3.12 (s, 3H, C*H*$_3$N), 2.89–2.75 (m, 1H, H_αC4), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.36 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 170.43 (s, C(O)), 136.77, 135.86, 133.74, 125.85, 123.86, 122.00, 76.30 (d, *J* = 9.7 Hz, C5), 63.43 (d, *J* = 166.8 Hz, C3), 63.37 (d, *J* = 6.4 Hz, CH_2OP), 62.63 (d, *J* = 6.9 Hz, CH_2OP), 46.57 (s, CH_3N),

37.27 (s, C4), 16.49 (d, J = 6.1 Hz, CH$_3$CH$_2$OP), 16.41 (d, J = 5.7 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, CDCl$_3$) δ: 21.06. Anal. Calcd for $C_{15}H_{22}N_3O_7P$: C, 46.51; H, 5.73; N, 10.85; found: C, 46.32; H, 5.82; N, 10.95.

4.2.17. Diethyl (*3RS,5SR*)-5-(3-nitrophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10al)

Yellowish amorphous solid (crystallised from ether/hexane); mp 139–142 °C; IR (KBr, cm^{-1}) ν_{max}: 3271, 3103, 2982, 1704, 1608, 1530, 1353, 1227, 1050, 1040, 977, 738; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.54 (s, 1H, N*H*), 8.47–8.45 (m, 1H), 8.03–7.98 (m, 2H), 7.56–7.50 (m, 1H), 4.68 (dd, 1H, J = 8.5, 5.7 Hz, *H*C5), 4.28–4.15 (m, 4H, 2 × C*H*$_2$OP), 3.10–3.08 (br m, 1H, *H*C3), 3.05 (s, 3H, C*H*$_3$N), 3.00 (dddd, 1H, J = 15.9, 13.0, 8.5, 8.5 Hz, H_βC4), 2.86 (dddd, 1H, J = 13.0, 9.5, 8.3, 5.7 Hz, H_αC4), 1.38 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.36 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 169.29 (s, C(O)), 148.41, 138.36, 129.86, 125.60, 119.16, 114.71, 76.61 (d, J = 8.6 Hz, C5), 63.52 (d, J = 168.6 Hz, C3), 63.43 (d, J = 6.6 Hz, CH$_2$OP), 62.94 (d, J = 6.9 Hz, CH$_2$OP), 46.79 (s, CH$_3$N), 36.20 (s, C4), 16.70 (d, J = 5.4 Hz, CH$_3$CH$_2$OP), 16.63 (d, J = 5.2 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, CDCl$_3$) δ: 20.93. Anal. Calcd for $C_{15}H_{22}N_3O_7P$: C, 46.51; H, 5.73; N, 10.85; found: C, 46.51; H, 5.73; N, 10.87.

4.2.18. Diethyl (3*RS*,5*RS*)-5-(3-nitrophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11al)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3222, 3095, 2988, 1708, 1570, 1509, 1330, 1231, 1024, 974; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 9.28 (s, 1H, N*H*), 8.52–8.51 (m, 1H), 8.01–7.98 (m, 2H), 7.53–7.50 (m, 1H), 4.69 (dd, 1H, J = 9.2, 4.5 Hz, *H*C5), 4.27–4.08 (m, 4H, 2 × C*H*$_2$OP), 3.15–3.06 (m, 2H, H_βC4 and *H*C3), 2.98 (s, 3H, C*H*$_3$N), 2.87–2.79 (m, 1H, H_αC4), 1.35 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.25 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, CDCl$_3$) δ: 170.39 (s, C(O)), 148.63, 138.85, 129.70, 125.39, 118.79, 114.49, 76.09 (d, J = 6.4 Hz, C5), 63.56 (d, J = 170.8 Hz, C3), 63.23 (d, J = 7.1 Hz, CH$_2$OP), 62.92 (d, J = 7.1 Hz, CH$_2$OP), 45.94 (s, CH$_3$N), 36.02 (s, C4), 16.42 (d, J = 5.7 Hz, CH$_3$CH$_2$OP), 16.31 (d, J = 5.7 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, CDCl$_3$) δ: 21.14. Anal. Calcd for $C_{15}H_{22}N_3O_7P$: C, 46.51; H, 5.73; N, 10.85; found: C, 46.58; H, 5.66; N, 10.89.

4.2.19. Diethyl (*3RS,5SR*)-5-(4-nitrophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10am)

Yellowish amorphous solid (crystallised from ether/hexane); mp 98–99 °C; IR (KBr, cm^{-1}) ν_{max}: 3221, 3095, 2990, 2910, 1710, 1600, 1570, 1510, 1332, 1300, 1270, 1230, 1050, 1025, 974; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.56 (s, 1H, N*H*), 8.25–8.21 (m, 2H), 7.79–7.76 (m, 2H), 4.67 (dd, 1H, J = 8.8, 5.5 Hz, *H*C5), 4.28–4.15 (m, 4H, 2 × C*H*$_2$OP), 3.10–3.08 (m, 1H, *H*C3), 3.04 (s, 3H, C*H*$_3$N), 3.01 (dddd, 1H, J = 15.7, 12.7, 8.8, 8.8 Hz, H_βC4), 2.84 (dddd, 1H, J = 12.7, 8.8, 8.3, 5.5 Hz, H_αC4), 1.37 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.36 (t, 3H, J = 6.9 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 169.30 (s, C(O)), 143.78, 142.85, 125.04, 119.41, 76.57 (d, J = 8.6 Hz, C5), 63.52 (d, J = 166.3 Hz, C3), 63.49 (d, J = 6.3 Hz, CH$_2$OP), 62.93 (d, J = 7.2 Hz, CH$_2$OP), 46.79 (s, CH$_3$N), 36.30 (s, C4), 16.73 (d, J = 5.2 Hz, CH$_3$CH$_2$OP), 16.66 (d, J = 5.4 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, CDCl$_3$) δ: 20.97. Anal. Calcd for $C_{15}H_{22}N_3O_7P$: C, 46.51; H, 5.73; N, 10.85; found: C, 46.60; H, 5.66; N, 10.94.

4.2.20. Diethyl (3*RS*,5*RS*)-5-(4-nitrophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11am)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3215, 3085, 2920, 1715, 1607, 1580, 1500, 1260, 1250, 1057, 1020; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 9.49 (s, 1H, N*H*), 8.24–8.19 (m, 2H), 7.83–7.78 (m, 2H), 4.68 (dd, 1H, J = 9.2, 4.7 Hz, *H*C5), 4.28–4.03 (m, 4H, 2 × C*H*$_2$OP), 3.20–3.00 (m, 2H, H_βC4 and *H*C3), 2.95 (s, 3H, C*H*$_3$N), 2.87–2.71 (m, 1H, H_αC4), 1.26 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.23 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 170.35 (s, C(O)), 142.85, 142.85, 125.14, 119.33, 76.58 (br s, C5), 63.69 (d, J = 6.9 Hz, CH$_2$OP), 63.65 (d, J = 171.2 Hz, C3), 63.16 (d, J = 6.9 Hz, CH$_2$OP), 46.11 (s, CH$_3$N), 36.14 (s, C4), 16.73 (d, J = 5.2 Hz, CH$_3$CH$_2$OP), 16.66 (d, J = 5.4 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, CDCl$_3$) δ: 22.20. Anal. Calcd for $C_{15}H_{22}N_3O_7P$: C, 46.51; H, 5.73; N, 10.85; found: C, 46.59; H, 5.73; N, 10.96.

4.2.21. Diethyl (*3RS,5SR*)-5-(3-cyanophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10an)

White amorphous solid (crystallised from ether/hexane); mp 85–86 °C; IR (KBr, cm^{-1}) ν_{max}: 3268, 3081, 2984, 2231, 1695, 1590, 1537, 1485, 1432, 1305, 1231, 1050, 1026, 971, 796; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 8.36 (br s, 1H, N*H*), 8.02–8.01 (m, 1H), 7.79–7.77 (m, 1H), 7.48–7.43 (m, 2H), 4.64 (dd, 1H, J = 8.8, 5.6 Hz, *H*-C5), 4.26–4.18 (m, 4H, 2 × C*H*$_2$OP), 3.13–3.08 (m, 1H, *H*C3), 3.04 (s, 3H, C*H*$_3$N), 3.02 (dddd, 1H, J = 16.0, 12.7, 8.8, 8.8 Hz, H_βC4), 2.84 (dddd, 1H, J = 12.7, 9.8, 8.3, 5.6 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: 169.19 (s, C(O)), 137.88, 129.94, 128.12, 123.89, 122.99, 118.26 (s, CN), 113.19, 76.35 (d, J = 8.8 Hz, C5), 63.55 (d, J = 165.5 Hz, C3), 63.33 (d, J = 6.5 Hz, CH$_2$OP), 62.63 (d, J = 7.2 Hz, CH$_2$OP), 46.62 (s, CH$_3$N), 36.28 (s, C4), 16.54 (d, J = 2.0 Hz, CH$_3$CH$_2$OP), 16.52 (d, J = 4.8 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, CDCl$_3$) δ: 20.11. Anal. Calcd for $C_{16}H_{22}N_3O_5P$: C, 52.31; H, 6.04; N, 11.44; found: C, 52.52; H, 6.07; N, 11.44.

4.2.22. Diethyl (3*RS*,5*RS*)-5-(3-cyanophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11an)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3212, 3079, 2980, 2228, 1703, 1594, 1432, 1211, 1048, 1015, 961; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 9.20 (s, 1H, N*H*), 8.07–8.06 (m, 1H), 7.82–7.80 (m, 1H), 7.45–7.40 (m, 2H), 4.67 (dd, 1H, J = 9.4, 4.4 Hz, *H*C5), 4.26–4.08 (m, 4H, 2 × C*H*$_2$OP), 3.15–3.05 (m, 2H, H_βC4 and *H*C3), 2.96 (s, 3H, C*H*$_3$N), 2.83–2.76 (m, 1H, H_αC4), 1.35 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.25 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, CDCl$_3$) δ: 170.23 (s, C(O)), 138.59, 129.78, 127.64, 123.79, 122.78, 118.49 (s, CN), 113.03, 76.14 (d, J = 5.8 Hz, C5), 63.58 (d, J = 171.3 Hz, C3), 63.29 (d, J = 7.0 Hz, CH$_2$OP), 62.90 (d, J = 6.8 Hz, CH$_2$OP), 45.96 (s, CH$_3$N), 35.98 (s, C4), 16.43 (d, J = 5.8 Hz, CH$_3$CH$_2$OP), 16.32 (d, J = 5.7 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, CDCl$_3$) δ: 21.22. Anal. Calcd for $C_{16}H_{22}N_3O_5P$: C, 52.31; H, 6.04; N, 11.44; found: C, 52.50; H, 6.18; N, 11.46.

4.2.23. Diethyl (*3RS,5SR*)-5-(4-cyanophenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ao)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3261, 2985, 2224, 1701, 1600, 1521, 1410, 1311, 1233, 1025, 970, 842; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.36 (s, 1H, N*H*), 7.73–7.71 (m, 2H), 7.67–7.65 (m, 2H), 4.64 (dd, 1H, J = 8.8, 5.6 Hz, *H*C5), 4.27–4.18 (m, 4H, 2 × C*H*$_2$OP), 3.13–3.08 (m, 1H, *H*C3), 3.04 (s, 3H, C*H*$_3$N), 3.03 (dddd, 1H, J = 16.1, 13.0, 8.8, 8.8 Hz, H_βC4), 2.84 (dddd, 1H, J = 13.0, 9.8, 8.3, 5.6 Hz, H_αC4), 1.39 (t, 3H, J = 6.9 Hz, C*H*$_3$CH$_2$OP), 1.38 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, CDCl$_3$) δ: 169.28 (s, C(O)), 141.11, 133.22, 119.60, 118.64 (s, CN), 107.62, 76.46 (d, J = 8.6 Hz, C5), 63.42 (d, J = 167.6 Hz, C3), 63.29 (d, J = 6.5 Hz, CH$_2$OP), 62.75 (d, J = 6.8 Hz, CH$_2$OP), 46.61 (s, CH$_3$N), 36.04 (s, C4), 16.46 (d, J = 5.8 Hz, CH$_3$CH$_2$OP), 16.40 (d, J = 6.1 Hz, CH$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, CDCl$_3$) δ: 20.00. Anal. Calcd for $C_{16}H_{22}N_3O_5P$: C, 52.31; H, 6.04; N, 11.44; found: C, 52.39; H, 6.11; N, 11.67.

4.2.24. Diethyl (3*RS*,5*SR*)-5-(2-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ap)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3472, 3217, 2981, 2912, 1691, 1660, 1580, 1518, 1451, 1251, 1050, 1023, 964; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.78–8.74 (m, 1H), 7.93–7.90 (m, 1H), 7.59–7.54 (m, 1H), 7.19–7.14 (m, 1H), 4.60 (dd, 1H, J = 9.1, 5.0 Hz, *H*C5), 4.27–4.12 (m, 4H, 2 × C*H*$_2$OP), 3.16 (s, 3H, C*H*$_3$N), 3.12–2.95 (m, 2H, H_βC4 and *H*C3), 2.80–2.68 (m, 1H, H_αC4), 2.67 (s, 3H, C*H*$_3$C(O)), 1.36 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.34 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 201.92 (s, C(O)), 170.60 (s, C(O)NH), 139.52, 134.75, 131.54, 122.98, 122.66, 120.76, 76.51 (d, J = 9.7 Hz, C5), 63.28 (d, J = 6.5 Hz, CH_2OP), 63.27 (d, J = 167.2 Hz, C3), 62.49 (d, J = 6.9 Hz, CH_2OP), 46.42 (s, CH_3N), 37.26 (s, C4), 28.36 (s, *C*H$_3$C(O)), 16.40 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.33 (d, J = 5.8 Hz, CH$_3$*C*H$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.55. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 52.86; H, 6.80; N, 7.35.

4.2.25. Diethyl (3*RS*,5*RS*)-5-(2-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11ap)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3482, 2980, 2915, 1690, 1670, 1585, 1520, 1450, 1250, 1050, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.82–8.79 (m, 1H), 7.91–7.87 (m, 1H), 7.56–7.51 (m, 1H), 7.15–7.10 (m, 1H), 4.54 (dd, 1H, J = 8.5, 5.2 Hz, *H*C5), 4.15–3.92 (m, 4H, 2 × C*H*$_2$OP), 3.10 (s, 3H, C*H*$_3$N), 2.96–2.88 (m, 3H, H_2C4 and *H*C3), 2.65 (s, 3H, C*H*$_3$C(O)), 1.27 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.08 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 201.49 (s, C(O)), 172.25 (s, C(O)NH), 139.94, 134.68, 131.45, 122.83, 122.62, 120.57, 75.51 (d, J = 8.5 Hz, C5), 63.83 (d, J = 166.3 Hz, C3), 63.44 (d, J = 6.0 Hz, CH_2OP), 62.15 (d, J = 7.1 Hz, CH_2OP), 45.36 (s, CH_3N), 36.79 (s, C4), 28.44 (s, *C*H$_3$C(O)), 16.33 (d, J = 6.2 Hz, *C*H$_3$CH$_2$OP), 16.11 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.95. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 53.38; H, 6.68; N, 7.37.

4.2.26. Diethyl (3*RS*,5*SR*)-5-(3-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10aq)

Yellowish amorphous solid (crystallised from ether/hexane); mp 99–103 °C; IR (KBr, cm^{-1}) ν_{max}: 3244, 3084, 2974, 1701, 1596, 1433, 1212, 1047, 1016, 953; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.32 (s, 1H, N*H*), 8.05–8.04 (m, 1H), 7.94–7.91 (m, 1H), 7.75–7.72 (m, 1H), 7.49–7.44 (m, 1H), 4.62 (dd, 1H, J = 8.8, 5.3 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 3.13–3.08 (m, 1H, *H*C3), 3.04 (s, 3H, C*H*$_3$N), 3.04 (dddd, 1H, J = 16.0, 12.7, 8.8, 8.8 Hz, H_βC4), 2.86 (dddd, 1H, J = 12.7, 8.9, 8.3, 5.3 Hz, H_αC4), 2.62 (s, 3H, C*H*$_3$C(O)), 1.37 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 197.64 (s, C(O)), 169.08 (s, C(O)NH), 137.85, 137.40, 129.53, 124.75, 124.44, 119.33, 76.42 (d, J = 9.2 Hz, C5), 63.42 (d, J = 167.6 Hz, C3), 63.58 (d, J = 6.6 Hz, CH_2OP), 62.81 (d, J = 6.9 Hz, CH_2OP), 47.00 (s, CH_3N), 36.72 (s, C4), 26.99 (s, *C*H$_3$C(O)), 16.80 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.73 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.30. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 52.97; H, 6.52; N, 7.23.

4.2.27. Diethyl (3*RS*,5*RS*)-5-(3-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11aq)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3274, 2981, 1700, 1680, 1617, 1564, 1237, 1046, 1016, 972; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.93 (s, 1H, N*H*), 8.11 (s, 1H), 7.93–7.90 (m, 1H), 7.72–7.69 (m, 1H), 7.46–7.41 (m, 1H), 4.63 (dd, 1H, J = 8.9, 4.9 Hz, *H*-C5), 4.20–4.06 (m, 4H, 2 × C*H*$_2$OP), 2.98 (s, 3H, C*H*$_3$N), 3.15–2.92 (m, 2H, H_βC4 and *H*C3), 2.90–2.76 (m, 1H, H_αC4), 2.62 (s, 3H, C*H*$_3$C(O)), 1.30 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.22 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR signals of *cis*-**11aq** were extracted from the spectrum of a 65:35 mixture of *trans*-**10aq** and *cis*-**11aq**, ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 197.77 (s, C(O)), 170.34 (s, C(O)NH), 137.99, 137.87, 129.27, 124.23, 124.12, 119.28, 75.88 (d, J = 7.4 Hz, C5), 63.49 (d, J = 169.1 Hz, C3), 63.16 (d, J = 5.9 Hz, CH_2OP), 62.88 (d, J = 7.2 Hz, CH_2OP), 46.70 (s, CH_3N), 36.50 (s, C4), 26.63 (s, *C*H$_3$C(O)), 16.39 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.29 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.01. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 52.90; H, 6.54; N, 7.22.

4.2.28. Diethyl (3*RS*,5*SR*)-5-(4-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ar)

White amorphous solid (crystallised from ether/hexane); mp 66–67 °C; IR (KBr, cm^{-1}) ν_{max}: 3258, 3188, 3103, 1707, 1678, 1600, 1642, 1269, 1226, 1050, 1017, 957; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.39 (s, 1H, N*H*), 7.95–7.92 (m, 2H), 7.67–7.64 (m, 2H), 4.44 (dd, 1H, J = 8.5, 5.5 Hz, *H*C5), 4.24–4.11 (m, 4H, 2 × C*H*$_2$OP), 3.06–2.91 (m, 2H, H_βC4 and *H*C3), 3.01 (s, 3H, C*H*$_3$N), 2.87–2.78 (m, 1H, H_αC4), 2.56 (s, 3H, C*H*$_3$C(O)), 1.34 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.33 (t, 3H, J = 6.9 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 196.77 (s, C(O)), 169.05 (s, C(O)NH), 141.16, 133.33, 129.29, 119.64, 76.42 (d, J = 9.2 Hz, C5), 63.40 (d, J = 167.5 Hz, C3), 63.52 (d, J = 6.3 Hz, CH_2OP), 62.81 (d, J = 6.9 Hz, CH_2OP), 47.00 (s, CH_3N), 36.54 (s, C4), 26.99 (s, *C*H$_3$C(O)), 16.80 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.73 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.16. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 53.37; H, 6.47; N, 7.10.

4.2.29. Diethyl (3*RS*,5*RS*)-5-(4-acetylphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11ar)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3258, 3188, 3060, 3001, 1710, 1679, 1599, 1542, 1270, 1230, 1051, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.11 (s, 1H, N*H*), 7.96–7.92 (m, 2H), 7.72–7.69 (m, 2H), 4.64 (dd, 1H, J = 8.4, 5.4 Hz, *H*C5), 4.23–4.05 (m, 4H, 2 × C*H*$_2$OP), 3.11–3.02 (m, 2H, H_βC4 and *H*C3), 2.97 (s, 3H, C*H*$_3$N), 2.85–2.79 (m, 1H, H_αC4), 2.58 (s, 3H, C*H*$_3$C(O)), 1.31 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.19 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 196.87 (s, C(O)), 170.32 (s, C(O)NH), 141.88, 133.04, 129.68, 118.97, 76.07 (d, J = 6.6 Hz, C5), 63.64 (d, J = 170.3 Hz, C3), 63.07 (d, J = 6.7 Hz, CH_2OP), 63.03 (d, J = 7.4 Hz, CH_2OP), 45.99 (s, CH_3N), 36.24 (s, C4), 26.38 (s, *C*H$_3$C(O)), 16.41 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.30 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.94. Anal. Calcd for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29; found: C, 52.91; H, 6.43; N, 7.18.

4.2.30. Diethyl (3*RS*,5*SR*)-5-(m-tolylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10as)

White amorphous solid (crystallised from ether/hexane); mp 96–97 °C; IR (KBr, cm^{-1}) ν_{max}: 3273, 3104, 2899, 1698, 1621, 1600, 1566, 1293, 1262, 1214, 1055, 1020, 959; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (s, 1H, N*H*), 7.33–7.26 (m, 2H), 7.18–7.13 (m, 1H), 6.91–6.88 (m, 1H), 4.55 (dd, 1H, J = 8.7, 5.4 Hz, *H*C5), 4.20–4.06 (m, 4H, 2 × C*H*$_2$OP), 3.00–2.88 (m, 2H, H_βC4 and *H*C3), 2.96 (s, 3H, C*H*$_3$N), 2.85–2.76 (m, 1H, H_αC4), 2.28 (s, 3H, C*H*$_3$), 1.30 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.28 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.62 (s, C(O)), 138.89, 136.73, 128.80, 125.51, 120.38, 116.88, 76.45 (d, J = 9.4 Hz, C5), 63.47 (d, J = 167.5 Hz, C3), 63.38 (d, J = 6.6 Hz, CH_2OP), 62.61 (d, J = 6.9 Hz, CH_2OP), 46.84 (s, CH_3N), 36.58 (s, C4), 21.56 (s, CH_3), 16.65 (d, J = 5.2 Hz, *C*H$_3$CH$_2$OP), 16.58 (d, J = 5.4 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.22. Anal. Calcd for $C_{16}H_{25}N_2O_5P$: C, 53.93; H, 7.07; N, 7.86; found: C, 54.16; H, 7.30; N, 7.99.

4.2.31. Diethyl (3*RS*,5*RS*)-5-(m-tolylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11as)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3216, 2971, 2900, 1700, 1600, 1565, 1453, 1290, 1210, 1050, 1020; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.66 (s, 1H, N*H*), 7.44 (s, 1H), 7.39–7.38 (m, 1H), 7.24–7.22 (m, 1H), 6.96–6.94 (m, 1H), 4.61 (dd, 1H, *J* = 8.6, 5.1 Hz, *H*C5), 4.22–4.06 (m, 4H, 2 × C*H*$_2$OP), 3.08–2.99 (m, 2H, H_βC4 and *H*C3), 3.00 (s, 3H, C*H*$_3$N), 2.90–2.81 (m, 1H, H_αC4), 2.37 (s, 3H, C*H*$_3$), 1.33 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$OP), 1.23 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.91 (s, C(O)), 138.84, 137.36, 128.77, 125.13, 120.29, 116.82, 75.83 (d, *J* = 7.6 Hz, C5), 63.86 (d, *J* = 168.7 Hz, C3), 63.24 (d, *J* = 6.6 Hz, CH$_2$OP), 62.68 (d, *J* = 6.8 Hz, CH$_2$OP), 46.09 (s, CH$_3$N), 36.56 (s, C4), 21.45 (s, CH$_3$), 16.40 (d, *J* = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.30 (d, *J* = 5.8 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 21.82. Anal. Calcd for $C_{16}H_{25}N_2O_5P$: C, 53.93; H, 7.07; N, 7.86; found: C, 54.07; H, 7.20; N, 7.98.

4.2.32. Diethyl (3*RS*,5*SR*)-5-(p-tolylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10at)

White amorphous solid (crystallised from ether/hexane); mp 62–64 °C; IR (KBr, cm^{-1}) ν_{max}: 3264, 3125, 2974, 1699, 1614, 1550, 1516, 1299, 1264, 1210, 1050, 1017, 952, 819; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.16 (br s, 1H, N*H*), 7.46–7.43 (m, 2H), 7.17–7.14 (m, 2H), 4.63 (dd, 1H, *J* = 9.0, 5.4 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 3.10–3.04 (m, 1H, *H*C3), 3.03 (s, 3H, C*H*$_3$N), 2.96 (dddd, 1H, *J* = 15.7, 13.0, 9.0, 9.0 Hz, H_βC4), 2.85 (dddd, 1H, *J* = 13.0, 8.3, 7.8, 5.4 Hz, H_αC4), 2.33 (s, 3H, C*H*$_3$), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.59 (s, C(O)), 134.55, 134.28, 129.60, 120.22, 76.45 (d, *J* = 9.5 Hz, C5), 63.50 (d, *J* = 167.5 Hz, C3), 63.58 (d, *J* = 6.3 Hz, CH$_2$OP), 62.76 (d, *J* = 6.9 Hz, CH$_2$OP), 46.73 (s, CH$_3$N), 36.71 (s, C4), 20.91 (s, CH$_3$), 16.70 (d, *J* = 5.5 Hz, *C*H$_3$CH$_2$OP), 16.55 (d, *J* = 5.5 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.24. Anal. Calcd for $C_{16}H_{25}N_2O_5P$: C, 53.93; H, 7.07; N, 7.86; found: C, 53.95; H, 7.09; N, 7.92.

4.2.33. Diethyl (3*RS*,5*RS*)-5-(p-tolylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11at)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3260, 2970, 2890, 1700, 1615, 1300, 1210, 1045, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.65 (br s, 1H, N*H*), 7.47–7.44 (m, 2H), 7.13–7.11 (m, 2H), 4.60 (dd, 1H, *J* = 8.6, 5.4 Hz, *H*C5), 4.21–4.03 (m, 4H, 2 × C*H*$_2$OP), 3.07–3.01 (m, 2H, H_βC4 and *H*C3), 2.97 (s, 3H, C*H*$_3$N), 2.89–2.79 (m, 1H, H_αC4), 2.31 (s, 3H, C*H*$_3$), 1.30 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.20 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 168.62 (s, C(O)), 134.48, 134.32, 129.56, 119.87, 76.39 (d, *J* = 9.1 Hz, C5), 63.52 (d, *J* = 169.5 Hz, C3), 63.34 (d, *J* = 6.4 Hz, CH$_2$OP), 62.53 (d, *J* = 7.1 Hz, CH$_2$OP), 46.74 (s, CH$_3$N), 36.53 (s, C4), 20.85 (s, CH$_3$), 16.40 (d, *J* = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.31 (d, *J* = 5.6 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.96. Anal. Calcd for $C_{16}H_{25}N_2O_5P$: C, 53.93; H, 7.07; N, 7.86; found: C, 53.87; H, 7.18; N, 7.87.

4.2.34. Diethyl (3*RS*,5*SR*)-5-(3-methoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10au)

White amorphous solid; mp 83–84 °C; IR (KBr, cm^{-1}) ν_{max}: 3265, 3212, 3088, 2896, 1700, 1600, 1559, 1453, 1213, 1048, 1018, 957; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.20 (s, 1H, N*H*), 7.40–7.35 (m, 1H), 7.35–7.31 (m, 1H), 7.04–7.01 (m, 1H), 6.72–6.69 (m, 1H), 4.61 (dd, 1H, *J* = 9.1, 5.5 Hz, *H*C5), 4.27–4.14 (m, 4H, 2 × C*H*$_2$OP), 3.82 (s, 3H, C*H*$_3$O), 3.07–2.92 (m, 2H, H_βC4 and *H*C3), 3.03 (s, 3H, C*H*$_3$N), 2.89–2.82 (m, 1H, H_αC4), 1.38 (t, 3H, *J* = 6.9 Hz, C*H*$_3$CH$_2$OP), 1.37 (t, 3H, *J* = 6.9 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.56 (s, C(O)), 159.78, 138.01, 129.40, 111.86, 110.22, 105.44, 76.35 (d, *J* = 8.9 Hz, C5), 63.24 (d, *J* = 167.9 Hz, C3), 63.13 (d, *J* = 6.5 Hz, CH$_2$OP), 62.49 (d, *J* = 6.9 Hz, CH$_2$OP), 55.11 (s, CH$_3$O), 46.57 (s, CH$_3$N), 36.17 (s, C4), 16.42 (d, *J* = 5.3 Hz, *C*H$_3$CH$_2$OP), 16.37 (d, *J* = 5.2 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.17. Anal. Calcd for $C_{16}H_{25}N_2O_6P$: C, 51.61; H, 6.77; N, 7.52; found: C, 51.72; H, 6.88; N, 7.54.

4.2.35. Diethyl (3*RS*,5*SR*)-5-(4-ethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10av)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3270, 2980, 1683, 1512, 1237, 1050, 1026, 969, 826; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.43 (m, 2H), 8.09 (s, 1H, N*H*), 6.88–6.85 (m, 2H), 4.61 (dd, 1H, *J* = 8.8, 5.2 Hz, *H*C5), 4.27–4.13 (m, 4H, 2 × C*H*$_2$OP), 4.02 (q, 2H, *J* = 6.9 Hz, CH$_3$C*H*$_2$O), 3.15–2.92 (m, 2H, H_βC4 and *H*C3), 3.02 (s, 3H, C*H*$_3$N), 2.90–2.80 (m, 1H, H_αC4), 1.41 (t, 3H, *J* = 6.9 Hz, C*H*$_3$CH$_2$O), 1.37 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.35 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.22 (s, C(O)), 155.77, 129.59, 121.37, 114.53, 76.21 (d, *J* = 9.2 Hz, C5), 63.53 (s, *C*H$_2$CH$_3$), 63.29 (d, *J* = 168.6 Hz, C3), 63.25 (d, *J* = 6.6 Hz, CH$_2$OP), 62.45 (d, *J* = 6.9 Hz, CH$_2$OP), 46.67 (s, CH$_3$N), 36.44 (s, C4), 16.49 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP), 16.42 (d, *J* = 5.4 Hz, *C*H$_3$CH$_2$OP), 14.78 (s, *C*H$_3$CH$_2$O); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 21.37. Anal. Calcd for $C_{17}H_{27}N_2O_6P$: C, 52.84; H, 7.04; N, 7.25; found: C, 52.61; H, 7.01; N, 7.26.

4.2.36. Diethyl (3*RS*,5*RS*)-5-(4-ethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11av)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3270, 2981, 1680, 1607, 1513, 1298, 1234, 1050, 1024, 970; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.61 (s, 1H, N*H*), 7.49–7.46 (m, 2H), 6.87–6.84 (m, 2H), 4.60 (dd, 1H, *J* = 8.7, 5.5 Hz, *H*C5), 4.19–4.06 (m, 4H, 2 × C*H*$_2$OP), 4.01 (q, 2H, *J* = 6.9 Hz, CH$_3$C*H*$_2$O), 3.07–2.99 (m, 2H, H_βC4 and *H*C3), 2.97 (s, 3H, C*H*$_3$N), 2.85–2.77 (m, 1H, H_αC4), 1.40 (t, 3H, *J* = 6.9 Hz, C*H*$_3$CH$_2$O), 1.30 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP), 1.21 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OP); ^{13}C NMR signals of *cis*-**11av** were extracted from the spectrum of a 55:45 mixture of *trans*-**10av** and *cis*-**11av**, ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.57 (s, C(O)), 155.71, 130.49, 121.36, 114.75, 75.90 (d, *J* = 7.2 Hz, C5), 63.84 (d, *J* = 168.7 Hz, C3), 63.79 (s, *C*H$_2$CH$_3$), 63.40 (d, *J* = 6.6 Hz, CH$_2$OP), 62.75 (d, *J* = 6.6 Hz, CH$_2$OP), 46.26 (s, CH$_3$N), 36.60 (s, C4), 16.62 (d, *J* = 6.2 Hz, *C*H$_3$CH$_2$OP), 16.54 (d, *J* = 6.4 Hz, *C*H$_3$CH$_2$OP), 15.10 (s, *C*H$_3$CH$_2$O); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.06. Anal. Calcd for $C_{17}H_{27}N_2O_6P$: C, 52.84; H, 7.04; N, 7.25; found: C, 52.83; H, 7.07; N, 7.15.

4.2.37. Diethyl (3*RS*,5*SR*)-5-(3,4-dimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10aw)

White amorphous solid (crystallised from ether/hexane); mp 83–84 °C; IR (KBr, cm^{-1}) ν_{max}: 3274, 2981, 2934, 2837, 1682, 1608, 1515, 1453, 1234, 1050, 969, 806, 765; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.09 (br s, 1H, N*H*), 7.38–7.37 (m, 1H), 6.95–6.93 (m, 1H), 6.85–6.83 (m, 1H), 4.61 (dd, 1H, *J* = 9.0, 5.3 Hz, *H*C5), 4.25–4.19 (m, 4H, 2 × C*H*$_2$OP), 3.91 (s, 3H, C*H*$_3$O), 3.88 (s, 3H, C*H*$_3$O), 3.12–3.07 (m, 1H, *H*C3), 3.04 (s, 3H, C*H*$_3$N), 3.01 (dddd, 1H, *J* = 15.9, 12.9, 9.0, 9.0 Hz, H_βC4), 2.86 (dddd, 1H, *J* = 12.9, 8.9, 8.3, 5.3 Hz, H_αC4), 1.38 (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: 168.54 (s, C(O)), 149.25, 146.31, 130.52, 111.86, 111.50, 104.82, 76.37 (d, *J* = 9.2 Hz, C5), 63.53 (d, *J* = 166.3 Hz, C3), 63.34 (d, *J* = 6.4 Hz, CH$_2$OP), 62.54 (d, *J* = 7.0 Hz, CH$_2$OP), 56.16 (s, CH$_3$O), 55.98 (s, CH$_3$O), 46.72 (s, CH$_3$N), 36.52 (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 $C_{17}H_{27}N_2O_7P$: C, 50.74; H, 6.76; N, 6.96; found: C, 50.53; H, 6.93; N, 6.90.

4.2.38. Diethyl (3*RS*,5*RS*)-5-(3,4-dimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11aw)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3263, 2965, 2928, 1690, 1618, 1513, 1447, 1232, 1212, 1055, 1021, 972; ^1H NMR

(300 MHz, $CDCl_3$) δ: 8.62 (br s, 1H, N*H*), 7.41–7.40 (m, 1H), 6.97–6.90 (m, 1H), 6.82–6.79 (m, 1H), 4.60 (dd, 1H, J = 8.6, 5.1 Hz, *H*C5), 4.22–4.06 (m, 4H, 2 × CH_2OP), 3.89 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 2.98 (s, 3H, CH_3N), 3.12–2.92 (m, 2H, H_βC4 and *H*C3), 2.90–2.76 (m, 1H, H_αC4), 1.31 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.22 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**11aw** were extracted from the spectrum of a 79:21 mixture of *trans*-**10aw** and *cis*-**11aw**, ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.64 (s, C(O)), 149.11, 145.91, 131.15, 111.70, 111.45, 104.62, 75.83 (d, J = 7.2 Hz, C5), 63.52 (d, J = 168.2 Hz, C3), 63.21 (d, J = 6.9 Hz, CH_2OP), 62.74 (d, J = 6.7 Hz, CH_2OP), 56.13 (s, CH_3O), 55.95 (s, CH_3O), 46.73 (s, CH_3N), 36.53 (s, C4), 16.41 (d, J = 5.3 Hz, *C*H$_3$CH$_2$OP), 16.35 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.06. Anal. Calcd for $C_{17}H_{27}N_2O_7P$: C, 50.74; H, 6.76; N, 6.96; found: C, 50.83; H, 6.94; N, 6.99.

4.2.39. Diethyl (*3RS,5SR*)-5-(3,5-dimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ax)

White amorphous solid; mp 118–118.5 °C. IR (KBr, cm^{-1}) ν_{max}: 3272, 3213, 3113, 3002, 2892, 1704, 1615, 1563, 1480, 1452, 1264, 1250, 1212, 1160, 1050, 1017, 966, 581; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.13 (br s, 1H, N*H*), 6.81–6.80 (m, 2H), 6.30–6.29 (m, 1H), 4.61 (dd, 1H, J = 8.9, 5.3 Hz, *H*C5), 4.27–4.18 (m, 4H, 2 × CH_2OP), 3.82 (s, 6H, 2 × CH_3O), 3.12–3.07 (m, 1H, *H*C3), 3.04 (s, 3H, CH_3N), 3.01 (dddd, 1H, J = 15.9, 13.0, 8.9, 8.9 Hz, H_βC4), 2.86 (dddd, 1H, J = 13.0, 8.9, 8.2, 5.3 Hz, H_αC4), 1.39 (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: 168.81 (s, C(O)), 161.17, 138.58, 98.12, 97.21, 76.41 (d, J = 9.2 Hz, C5), 63.48 (d, J = 170.9 Hz, C3), 63.47 (d, J = 6.5 Hz, CH_2OP), 62.55 (d, J = 7.1 Hz, CH_2OP), 55.40 (s, 2 × CH_3O), 46.72 (s, CH_3N), 36.46 (s, C4), 16.48 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.45 (d, J = 4.0 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.27. Anal. Calcd for $C_{17}H_{27}N_2O_7P$: C, 50.74; H, 6.76; N, 6.96; found: C, 50.88; H, 6.97; N, 7.01.

4.2.40. Diethyl (*3RS,5SR*)-5-(3,4,5-trimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ay)

White amorphous solid (crystallised from ether/hexane); mp 123–124 °C; IR (KBr, cm^{-1}) ν_{max}: 3277, 3143, 2982, 2938, 1688, 1606, 1540, 1505, 1453, 1415, 1231, 1127, 1050, 1023, 969; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.09 (br s, 1H, N*H*), 6.87 (s, 2H), 4.61 (dd, 1H, J = 8.9, 5.4 Hz, *H*C5), 4.26–4.17 (m, 4H, 2 × CH_2OP), 3.88 (s, 6H, 2 × CH_3O), 3.83 (s, 3H, CH_3O), 3.14–3.07 (m, 1H, *H*C3), 3.04 (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, 9.1, 8.2, 5.4 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: 168.69 (s, C(O)), 153.46, 135.26, 132.91, 97.66, 76.37 (d, J = 9.1 Hz, C5), 63.49 (d, J = 169.1 Hz, C3), 63.36 (d, J = 6.5 Hz, CH_2OP), 62.58 (d, J = 6.8 Hz, CH_2OP), 60.94 (s, CH_3O), 56.20 (s, 2 × CH_3O), 46.72 (s, CH_3N), 36.46 (s, C4), 16.50 (d, J = 3.0 Hz, *C*H$_3$CH$_2$OP), 16.47 (d, J = 3.8 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.27. Anal. Calcd for $C_{18}H_{29}N_2O_8P$: C, 50.00; H, 6.76; N, 6.48; found: C, 50.06; H, 6.92; N, 6.45.

4.2.41. Diethyl (3*RS*,5*RS*)-5-(3,4,5-trimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*cis*-11ay)

Colourless oil; IR (film, cm^{-1}) ν_{max}: 3278, 2984, 1697, 1620, 1560, 1510, 1235, 1124, 1054, 1015, 971; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 (br s, 1H, N*H*), 6.89 (s, 2H), 4.60 (dd, 1H, J = 8.6, 5.5 Hz, *H*C5), 4.20–4.07 (m, 4H, 2 × CH_2OP), 3.86 (s, 6H, 2 × CH_3O), 3.82 (s, 3H, CH_3O), 3.06–2.99 (m, 2H, H_βC4 and *H*C3), 2.98 (s, 3H, CH_3N), 2.94–2.74 (m, 1H, H_αC4), 1.32 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.23 (t, 3H, J = 6.9 Hz, CH_3CH$_2$OP); ^{13}C NMR signals of *cis*-**11ay** were extracted from the spectrum of a 74:26 mixture of *trans*-**10ay** and *cis*-**11ay**, ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 169.79 (s, C(O)), 153.32, 134.87, 133.54, 97.56, 75.86 (d, J = 7.5 Hz, C5), 63.50 (d, J = 170.6 Hz, C3), 63.17 (d, J = 6.7 Hz, CH_2OP), 62.78 (d, J = 6.8 Hz, CH_2OP), 60.92 (s, CH_3O), 56.16 (s, 2 × CH_3O), 46.77 (s, CH_3N), 36.50 (s, C4), 16.41 (d, J = 5.9 Hz, *C*H$_3$CH$_2$OP), 16.35 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 22.04. Anal. Calcd for $C_{18}H_{29}N_2O_8P$: C, 50.00; H, 6.76; N, 6.48; found: C, 50.23; H, 6.97; N, 6.48.

4.2.42. Diethyl (*3RS,5SR*)-5-(2-cyano-4,5-dimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10az)

White amorphous solid (crystallised from ether/hexane); mp 79–80 °C; IR (KBr, cm^{-1}) ν_{max}: 3342, 2982, 2207, 1696, 1593, 1521, 1451, 1223, 1023, 965, 751; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.87 (br s, 1H, N*H*), 8.10 (s, 1H), 6.99 (s, 1H), 4.65 (dd, 1H, J = 9.1, 5.0 Hz, *H*C5), 4.27–4.19 (m, 4H, 2 × CH_2OP), 3.98 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 3.13 (s, 3H, CH_3N), 3.16–3.10 (m, 1H, *H*C3), 3.08 (dddd, 1H, J = 15.4, 12.7, 9.1, 9.1 Hz, H_βC4), 2.84 (dddd, 1H, J = 12.7, 8.7, 7.7, 5.0 Hz, H_αC4), 1.39 (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: 169.59 (s, C(O)), 153.67, 145.87, 135.42, 116.46 (s, CN), 112.94, 104.44, 93.12, 76.58 (d, J = 9.5 Hz, C5), 63.35 (d, J = 167.7 Hz, C3), 63.31 (d, J = 6.4 Hz, CH_2OP), 62.62 (d, J = 6.8 Hz, CH_2OP), 56.23 (s, CH_3O), 56.19 (s, CH_3O), 46.89 (s, CH_3N), 37.07 (s, C4), 16.46 (d, J = 5.6 Hz, *C*H$_3$CH$_2$OP), 16.41 (d, J = 5.9 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.03. Anal. Calcd for $C_{17}H_{23}N_3O_7P$: C, 49.52; H, 5.62; N, 10.19; found: C, 49.39; H, 5.83; N, 9.98.

4.2.43. Diethyl (*3RS,5SR*)-5-(2-acetyl-4,5-dimethoxyphenylcarbamoyl)-2-methylisoxazolidin-3-yl-3-phosphonate (*trans*-10ba)

White amorphous solid (crystallised from ether/hexane); mp 108–112 °C; IR (KBr, cm^{-1}) ν_{max}: 3535, 3148, 2973, 2916, 1649, 1586, 1529, 1272, 1066, 1028, 963; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.33 (s, 1H), 4.61 (dd, 1H, J = 9.2, 5.0 Hz, *H*C5), 4.28–4.18 (m, 4H, 2 × CH_2OP), 4.01 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 3.17 (s, 3H, CH_3N), 3.16–3.12 (m, 1H, *H*C3), 3.05 (dddd, 1H, J = 15.8, 13.0, 9.2, 9.2 Hz, H_βC4), 2.82 (dddd, 1H, J = 13.0, 8.0, 8.0, 5.0 Hz, H_αC4), 2.64 (s, 3H, CH_3C(O)), 1.39 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP), 1.37 (t, 3H, J = 7.0 Hz, CH_3CH$_2$OP); ^{13}C NMR (151.0 MHz, $CDCl_3$) δ: 199.98 (s, C(O)), 170.77 (s, C(O)NH), 154.37, 144.02, 136.31, 115.31, 113.87, 103.77, 76.58 (d, J = 9.5 Hz, C5), 63.37 (d, J = 165.7 Hz, C3), 63.30 (d, J = 6.3 Hz, CH_2OP), 62.44 (d, J = 7.0 Hz, CH_2OP), 56.43 (s, CH_3O), 56.16 (s, CH_3O), 46.39 (s, CH_3N), 37.41 (s, C4), 28.28 (s, *C*H$_3$C(O)), 16.48 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP), 16.42 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OP); ^{31}P NMR (243.0 MHz, $CDCl_3$) δ: 20.68. Anal. Calcd for $C_{19}H_{29}N_2O_8P$: C, 51.35; H, 6.58; N, 6.30; found: C, 51.23; H, 6.47; N, 6.22.

4.3. 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, 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, Punta Toro, human immunodeficiency virus type 1 strain IIIB 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) in the presence

of varying concentrations of the test compounds. Viral cytopathicity 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%.

4.4. 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 4–5 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%.

4.5. Cytostatic activity assays

All assays were performed in 96-well microtiter plates. To each well were added $(5–7.5) \times 10^4$ tumor cells and a given amount of the test compound. The cells were allowed to proliferate for 48 h (murine leukemia L1210 cells) or 72 h (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 and Mrs. Lizette van Berckelaer for excellent technical assistance. The preliminary experiments in this project was conducted by Miss Katarzyna Raj, M.Sc. The synthetic part of this work was supported by the Medical University of Łódź internal funds (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 and notes

1. Mehellou, Y.; De Clercq, E. *J. Med. Chem.* **2010**, *53*, 521.
2. Galmarini, C. M.; Mackey, J. R.; Dumontet, C. *Lancet Oncol.* **2002**, *3*, 415.
3. Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337.
4. Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385.
5. Krueger, A. T.; Kool, E. T. *Chem. Biol.* **2009**, *16*, 242.
6. Chittepu, P.; Sirivolu, V.; Seela, F. *Bioorg. Med. Chem.* **2008**, *16*, 8427.
7. 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. *Bioorg. Med. Chem.* **2009**, *17*, 2433.
8. Park, S. M.; Yang, H.; Park, S.-K.; Kim, H. M.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5831.
9. Lee, Y.-S.; Park, S. M.; Kim, H. M.; Park, S.-K.; Lee, K.; Lee, C. W.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4688.
10. 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. *Antiviral Chem. Chemother.* **2003**, *14*, 183.
11. Guianvarc'h, D.; Fourrey, J.-L.; Maurisse, R.; Suna, J.-S.; Benhid, R. *Bioorg. Med. Chem.* **2003**, *11*, 2751.
12. Rodenko, B.; Detz, R. J.; Pinas, V. A.; Lambertucci, C.; Brun, R.; Wanner, M. J.; Koomen, G.-J. *Bioorg. Med. Chem.* **2006**, *14*, 1618.
13. Devine, S. M.; Gregg, A.; Figler, H.; McIntosh, K.; Urmaliya, V.; Linden, J.; Pouton, C. W.; White, P. J.; Bottle, S. E.; Scammells, P. J. *Bioorg. Med. Chem.* **2010**, *18*, 3078.
14. Beattie, D.; Brearley, A.; Brown, Z.; Charlton, S. J.; Cox, B.; Fairhurst, R. A.; Fozard, J. R.; Gedeck, P.; Kirkham, P.; Meja, K.; Nanson, L.; Neef, J.; Oakman, H.; Spooner, G.; Taylor, R. J.; Turner, R. J.; West, R.; Woodward, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1219.
15. Brunschweiger, A.; Iqbal, J.; Umbach, F.; Scheiff, A. B.; Munkonda, M. N.; Sévigny, J.; Knowles, A. F.; Müller, C. E. *J. Med. Chem.* **2008**, *51*, 4518.
16. Sargsyan, G.; MacLeod, B. L.; Tohgha, U.; Balaz, M. *Tetrahedron* **2012**, *68*, 2093.
17. Frazer, J. D.; Horner, S. M.; Woski, S. A. *Tetrahedron Lett.* **1998**, *39*, 1279.
18. Shelton, J. R.; Burt, S. R.; Peterson, M. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1484.
19. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistarà, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2003**, *46*, 3696.
20. 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. *J. Med. Chem.* **2005**, *48*, 1389.
21. Singh, R.; Bhella, S. S.; Sexana, A. K.; Shanmugavel, M.; Faruka, A.; Ishar, M. P. S. *Tetrahedron* **2007**, *63*, 2283.
22. Bortolini, O.; De Nino, A.; Eliseo, T.; Gavioli, R.; Maiuolo, L.; Russo, B.; Sforza, F. *Bioorg. Med. Chem.* **2010**, *19*, 6970.
23. Piotrowska, D. G.; Cieślak, M.; Królewska, K.; Wróblewski, A. E. *Arch. Pharm. Chem. Life Sci.* **2011**, *11*, 301.
24. Piperno, A.; Giofrè, S. V.; Iannazzo, D.; Romeo, R.; Romeo, G.; Chiacchio, U.; Rescifina, A.; Piotrowska, D. G. *J. Org. Chem.* **2010**, *75*, 2798.
25. Piotrowska, D. G.; Balzarini, J.; Głowacka, I. E. *Eur. J. Med. Chem.* **2012**, *47*, 501.
26. Hecker, S. J.; Erion, M. D. *J. Med. Chem.* **2008**, *51*, 2328.
27. Piotrowska, D. G. *Tetrahedron Lett.* **2006**, *47*, 5363.
28. Piotrowska, D. G. *Tetrahedron* **2006**, *62*, 12306.
29. Fernández, F.; García-Mera, X.; Rodríguez, G.; Urrutia, A. *Chem. Pharm. Bull.* **1999**, *47*, 1006.
30. Benezra, C. *J. Am. Chem. Soc.* **1973**, *95*, 6890.
31. Neeser, J.-R.; Tronchet, J. M. J.; Charollais, E. J. *Can. J. Chem.* **1983**, *61*, 2112.
32. Adiwidjaja, G.; Meyer, B.; Thiem, J. Z. *Naturforsch* **1979**, *34*, 1547.
33. Buchanan, G. W.; Bourque, K.; Seeley, A. *Magn. Reson. Chem.* **1986**, *24*, 360.
34. Lapper, R. D.; Mantsch, H. H.; Smith, I. C. P. *J. Am. Chem. Soc.* **1973**, *95*, 2878.
35. Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield, 1987. Chapter 11.
36. Quin, L. D. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield, 1987. Chapter 12.
37. Kool, E. T.; Sintim, H. O. *Chem. Commun.* **2006**, 3575.
38. Somoza, A.; Chelliserrykattil, J.; Kool, E. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4994.
39. Somoza, A.; Silverman, A. P.; Miller, R. M.; Chelliserrykattil, J.; Kool, E. T. *Chem. Eur. J.* **2008**, *14*, 7978.
40. Killelea, T.; Ghosh, S.; Tan, S. S.; Heslop, P.; Firbank, S. J.; Kool, E. T.; Connolly, B. A. *Biochemistry* **2010**, *49*, 5772.