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Efficient synthesis of isoxazolidine-substituted bisphosphonates by 1,3-dipolar cycloaddition reactions

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ABSTRACT

Several bisphosphonates bearing a substituted isoxazolidine ring have been synthesized in good yield by direct 1,3-dipolar cyclization reaction, under microwaves catalysis, in the absence of solvent. The method allows the simultaneous incorporation, on the geminal position of the bisphosphonate framework, of a basic nitrogen and of an oxygen atom, as third hook. Hydrophobicity–hydrophilicity of BPs is discussed with the help of distribution coefficients.

1. Introduction

Geminal bisphosphonates (BPs) are structural and stable analogues of naturally occurring pyrophosphates and constitute an important class of pharmacologically active molecules used in the treatment of bone diseases as osteoporosis, Paget's disease, and tumor bone diseases.[1–3] In addition bisphosphonates are commonly prescribed for prevention and treatment of several skeletal problems associated with low bone density and osteogenesis imperfecta. To date, most of the highly potent third-generation BP drugs include an additional moiety in the molecule, namely a nitrogen heterocycle, as in risedronate **1** and zoledronate **2** that make these cyclic nitrogen-containing derivatives up to 10,000-fold more active than the first generation bisphosphonates (Fig. 1).[4–7]

The studies on the inhibitory potency of cyclic nitrogen-containing bisphosphonates indicate that the presence of two geminal phosphonate groups is responsible for interaction with the molecular target. In addition, a basic nitrogen in the heterocyclic side chain affects potency and its orientation is critical for effective inhibition. Accordingly, we considered the synthesis of a new class of bisphosphonates **3** having in *gem* position an isoxazolidine ring, that simultaneously holds the required basic nitrogen and an oxygen atom in place of the hydroxy group, acting as third hook. Some authors have suggested that the absence of the *gem* hydroxyl function should increase the oral absorption of this class of drugs.[6,7] In addition, the tuning of the molecular lipophilicity, an additional parameter affecting absorption and estimated by measuring the distribution coefficient, is obtained by the introduction of suitable alkyl and aryl substituents.

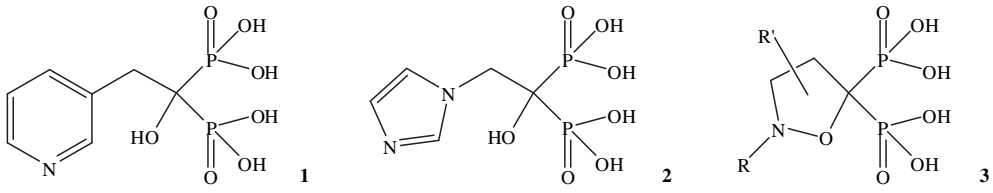

Fig. 1. Structure of model bisphosphonates and of our target compounds.

Different synthetic strategies have been proposed to insert heterocyclic rings directly on the geminal position, including the reaction of phosphorus electrophiles with enolates,[8] the reaction

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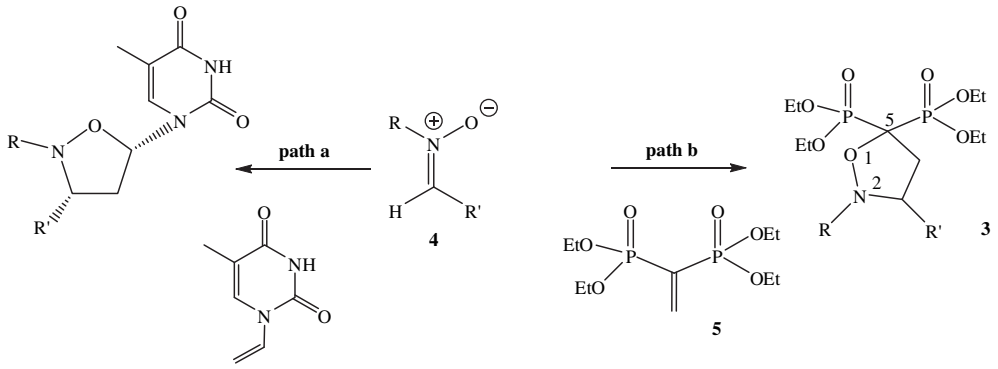
with diazo compounds,[9] and the condensation of oxaphospholenes with isocyanates.[10] Previously we have developed an efficient method for the preparation of substituted isoxazolidines using the classical 1,3-dipolar cycloaddition of an alkene as dipolarophile with a suitable nitrone, under microwave irradiation, in the absence of solvent, Scheme 1.[11,12] Following this strategy it was



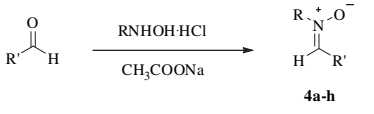
Scheme 1. Synthesis of substituted isoxazolidines via 1,3-dipolar cycloaddition of nitrones and substituted alkenes: vinyl nucleobases to *N*,*O*-nucleosides, path *a*, vinyl bisphosphonates to isoxazolidine bisphosphonates, path *b*.

possible to prepare several *N*,*O*-nucleosides by the reaction of nitrones with unprotected vinylated nucleobases, as shown in path *a* of the Scheme 1. In the present case we have replaced the vinyl nucleobases with vinyl bisphosphonates for the preparation of isoxazolidine-substituted bisphosphonates, path *b* of Scheme 1, maintaining in the same time the microwaves catalysis in the absence of solvent successfully tested in previous studies. 1,3-Dipolar cycloadditions have been used for the preparation of functionalized bisphosphonates under Cu(I) catalysis (click methodology)[5] and for the synthesis of substituted isoxazolidines using phosphorylated nitrones.[13]

In this paper we wish to report a simple route to isoxazolidine-substituted bisphosphonates, new valuable precursors in the synthesis of biologically active molecules, that allowed the insertion of different aromatic and heteroaromatic rings bearing suitable substituents.

2. Results and discussion

Although the synthesis of the different nitrones **4** and tetraethylvinylidene-1,1-bisphosphonate **5** are described in the literature by several authors,[14,15] we have partially modified the procedures with the result of a substantial increase in the yields of both derivatives. Nitrones **4a**–**h** were obtained in excellent yields and high purity by condensation of the precursor aldehydes with *N*-methyl- or *N*-benzylhydroxylamine in acetate-buffered[16] water/ethanol solution, Scheme 2.



R=Me, R'=Ph	**4a**
R=Me, R'=*o*-Cl-C_6H_4	**4b**
R=Me, R'=3-pyridyl	**4c**
R=Me, R'=2-furyl	**4d**
R=Bn, R'=*p*-OH-C_6H_4	**4e**
R=Bn, R'=Ph	**4f**
R=Bn, R'=*o*-Cl-C_6H_4	**4g**
R=Bn, R'=*o*-F-C_6H_4	**4h**

Scheme 2. Synthesis of alkyl, aryl substituted nitrones **4a**–**h**.

Furthermore, the vinylidene derivative **5** has been obtained in three steps, according to the reaction sequence shown in Scheme 3. The commercially available tetraethyl methylene-1,1-bisphosphonate **6** was prepared by direct reaction of diethyl phosphite in the presence of sodium ethoxide. The long reaction times (2 months) are balanced by the low cost of the reagents and work-up.

Derivative **7** was obtained from **6** by the reaction with paraformaldehyde under basic conditions and converted to tetraethylvinylidene-1,1-bisphosphonate **5** by the reaction with *para*-toluenesulfonic acid, for a final overall yield, after three steps, of 73%.

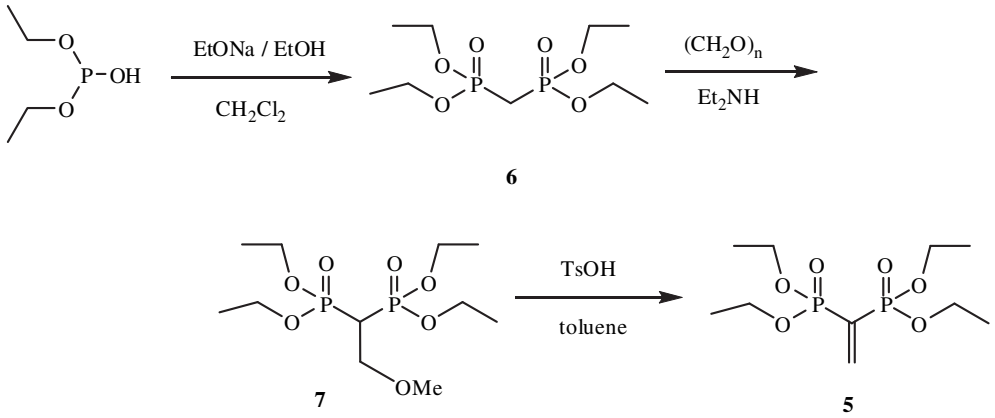
With the set of nitrones **4a**–**h** in our hands we initially investigated the 1,3-dipolar cycloadditions with **5** in conventional conditions, that is, in organic solvents (toluene, dichloromethane), by heating (from 0 °C up to reflux in toluene) and in the presence of a Lewis acid ($ZnCl_2$, $AlCl_3$, $Er(OTf)_3$, and $Cu(OTf)_3$) as catalyst, path *b* of Scheme 1. In the best cases, a conversion of 65–75% is obtained in 14 h reaction time, for a 35% of isolated yield. The poor results prompt us to test different experimental conditions as the use of microwaves catalysis,[17] successfully applied in similar reactions.[11,12] Table 1 illustrates the optimization of the reaction parameters using the *N*-methyl-*C*-phenyl nitrone **4a** as model compound. A low MW power and a slight excess of nitrone are required to complete the cycloaddition with formation of the tetraethyl-2-methyl-3-phenyl-isoxazolidinyl-5,5-bisphosphonate **3a** in 75% isolated yield, entry 6 of Table 1.

These conditions were next applied to the entire collection of available nitrones and the pertinent results are shown in Table 2. Short reaction times, max 20 min, were required for a complete conversion, although in some cases the isolated yield is lowered by formation of minor amounts of side-products.

The regiochemistry of the reaction followed the usual pattern with exclusive formation of the 3,5-isomer over the 3,4-derivative.[18] Accordingly, the cycloaddition takes place between the nitrone in the more reactive (*Z*) configuration and the vinylidene bisphosphonate, with attack of the *N*-oxygen atom on the germinal carbon of the vinylidene group. The regiochemistry has been further confirmed by decoupling ^1H NMR experiments using **3g** as model compound. Fig. 2 shows the expansion of the NMR spectrum in the region 2.5–5.0 ppm where the signals of protons H_{C4} (2.84 ppm), H_{C4}' (3.28 ppm), and H_{C3} (4.66 ppm) are located. Fig. 2B refers to absence of irradiation, whereas Fig. 2A and C describe the NMR spectra upon decoupling at 2.84 and 3.28 ppm, respectively. In the latter cases the signal of H_{C3}, originally a doublet of doublets, is modified to a doublet thus confirming the proximity of H_{C3} to both H_{C4} and H_{C4}'. On the other hand, the multiplicity of the signals pertaining to H_{C4} and H_{C4}', although simplified by this decoupling, necessarily accounts for coupling with phosphorous nuclei and H_{C3}.

Bisphosphonate esters **3a**–**h** were next hydrolyzed by reaction with trimethylsilyl bromide in dichloromethane, followed by treatment with MeOH, according to Scheme 4. As reported in the Experimental section, the conversion ester to acid is quite efficient, with formation of **8a**–**h** in yields ranging from 82% up to 92%.

The isoxazolidinyl-substituted bisphosphonic acids may then be transformed into the corresponding disodium salts by reaction

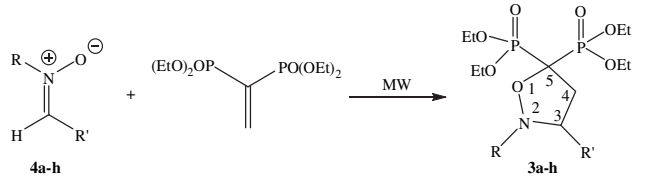


Scheme 3. Synthetic sequence for the preparation of tetraethylvinylidene-1,1-bisphosphonate **5**.

Table 1
Optimization of the reaction conditions for the cycloaddition of **5** (1 equiv) with nitrone **4a**

Entry	Power (W)	Time (min)	**4a** (equiv)	Conversion (%)	Yield (%)
1	750	5	2	85	10
2	750	8	1.6	90	13
3	600	10	2	84	24
4	400	10	2	88	37
5	400	15	1.5	83	40
6	200	10	1.2	99	75

Table 2
1,3-Dipolar cycloadditions of **4a**–**h** with tetraethylvinylidene-1,1-bisphosphonate **5** at 200 W



Entry	R	R′	Time (min)	Product	Yield (%)
1	Me	Ph	10	**3a**	75
2	Me	*o*-Cl–C_6H_4	12	**3b**	77
3	Me	3-Pyridyl	13	**3c**	73
4	Me	2-Furyl	15	**3d**	68
5	Bn	*p*-OH–C_6H_4	14	**3e**	74
6	Bn	Ph	18	**3f**	83
7	Bn	*o*-Cl–C_6H_4	18	**3g**	85
8	Bn	*o*-F–C_6H_4	20	**3h**	86

with 2 equiv of aqueous NaOH. Bisphosphonates are calcium-regulating agent used in the form of the sodium salt for a number of reasons that include the specific delivery and absorption of the drug. At physiological pH, bisphosphonates are expected to be highly ionized and negatively charged.[1] The overall hydrophilicity of BPs has been shown to influence their bone targeting ability and this property is usually obtained by measuring or calculating the distribution coefficient (log *D*) for octanol/water mixtures.[1,19] The log *D* values at pH 7.4 for our compounds are: **8a** (−5.20), **8b** (−4.72), **8c** (−6.51), **8d** (−6.23), **8e** (−3.84), **8f** (−3.55), **8g** (−2.99), and **8h** (−3.41).[20] Taking into account that BPs with small substituents and high hydrophilic character, i.e., very negative log *D*, are the ideal bone-specific carriers, the pyridyl **8c** and furyl **8d** derivatives are expected to have the best biological osteotropic activity.[1,21]

3. Conclusions

In this paper we have described an efficient and general synthetic approach to bisphosphonates bearing in geminal position a substituted isoxazolidine ring. The method, based on 1,3-dipolar cycloadditions, allows the simultaneous incorporation of the required basic nitrogen and that of an oxygen atom acting, together with the bisphosphonate groups, as third hook. Studies on the biological potential of the different salts and comparison with bisphosphonate salts of well established activity are currently under way.

4. Experimental section

4.1. General

Commercial starting materials were used without further purification. Solvents were distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 500 MHz and 75.5 and 125.7 MHz, respectively, in $CDCl_3$, DMSO-d_6 or D_2O using tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz and 500 MHz), whereas for ^{1}H-decoupled ^{31}P NMR (202.4 MHz) an external standard was used. Chemical shifts are given in parts per million and coupling constants in Hertz. The regiochemistry was established by decoupling experiments of selected signals. The ESI mass spectrometric data were acquired on a Finnigan LCQ Deca, equipped with an electrospray ionization source. Standard experimental conditions are as follows: sample concentration10^{-6} M; elution solvent MeOH; flow rate 8 μL min^{-1}; nebulizing gas 40 units flow rate; spray voltage 4 kV; capillary voltage 14 V; capillary temperature 270 °C. High resolution mass spectra (HRMS) were acquired on a Q-star pulsar-i (MDS Sciex Applied Biosystems, Toronto, Canada) equipped with an ion-spray source, at 10,000 resolution. Melting points were obtained on a Kofler apparatus. GC/MS spectra were carried out on a Shimadzu QP 5000. Elemental analyses (C, H, and N) were obtained using a Flash 2000, Thermo Fisher Scientific elemental analyzer. Infrared spectra were recorded on a Perkin–Elmer 2000 FT-IR, using KBr plates or KBr as matrixes.

4.2. General procedure for the synthesis of nitrones 4a–h

Most of the substituted nitrones were synthesized under stirring and in short reaction times, 10–15 min, via condensation of the suitable aldehyde (1 mol) with *N*-methyl- or *N*-benzylhydroxylamine hydrochloride (1 mol) in the presence of sodium acetate (1.2 mol) dissolved in EtOH/H_2O 1:1 (10 mL) at room temperature. The bulk of the solvent was removed under reduced pressure and

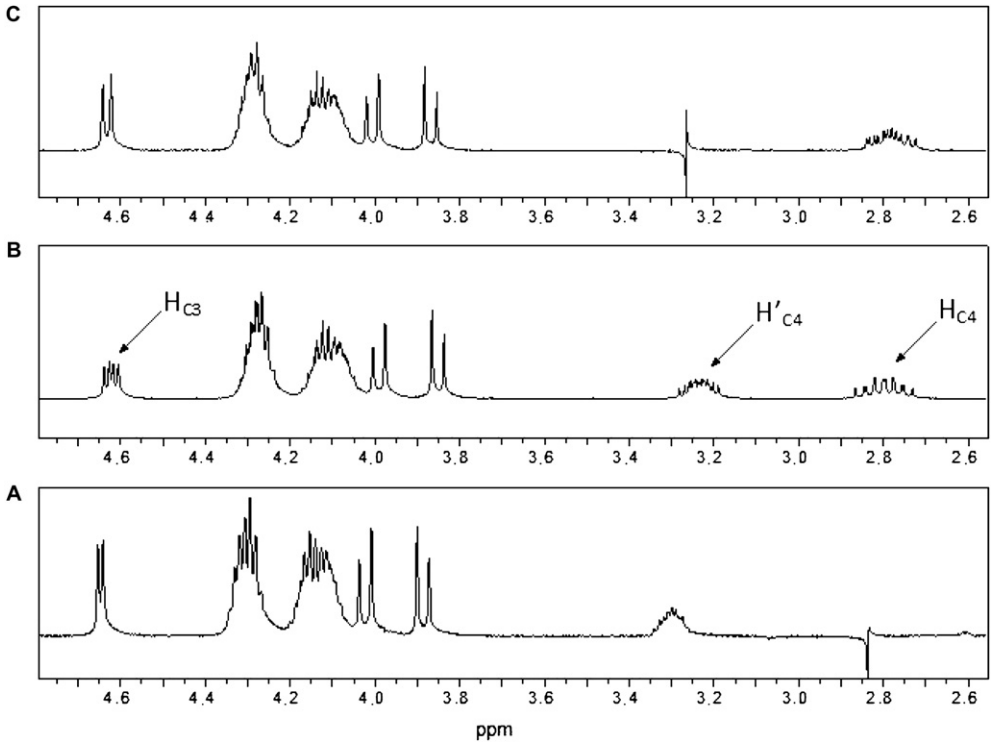
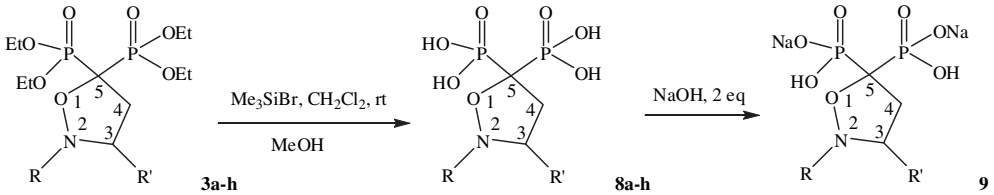


Fig. 2. Expansion of the ^{1}H NMR spectra of compound **3g** in: (B) absence of decoupling, (A) decoupling at 2.84 ppm, and (C) decoupling at 3.28 ppm.



Scheme 4. Conversion of bisphosphonate esters **3a**–**h** to free acids **8a**–**h** and related disodium salts **9**.

the residue was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure.

*4.2.1. N-Methyl-C-o-chloro phenyl nitrone (**4b**).* White solid; R_f 0.72; yield 96% (1.15 g), mp=73–74 °C, GC/MS *m*/*z* 169; IR (KBr, cm^{-1}) 1173, 1393, 1421, 1561, 1583, 1651, 3067, 3090; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H, *N*–CH_3) 7.29–7.41 (m, 3H, Ar), 7.86 (s, 1H, =CH), 9.30 (dd, 1H, *J*=2.1, 7.7 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.13, 126.92, 128.13, 128.80, 129.28, 130.68, 130.90, 132.5. Anal. Calcd (%) for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found (%) C, 56.72; H, 4.78; N, 8.21.

*4.2.2. N-Benzyl-C-p-hydroxy phenyl nitrone (**4e**).* White solid; R_f 0.37; yield 93% (1.73 g), mp=206–207 °C, GC/MS *m*/*z* 227; IR (KBr, cm^{-1}) 1125, 1316, 1415, 1513, 1599, 1670, 2942, 3066; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.99 (s, 2H, *N*–CH_2) 6.79–6.83 (m, 2H, Ar), 7.34–7.49 (m, 5H, Ar), 7.91 (s, 1H, =CH), 8.10–8.15 (m, 2H, Ar), 10.04 (br s, 1H, OH); ^{13}C NMR (500 MHz, DMSO-d_6) δ 69.33, 115.06, 122.37, 128.05, 128.24, 128.76, 130.03, 133.05, 134.98, 158.87. Anal. Calcd (%) for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found (%) C, 74.05; H, 5.74; N, 6.11.

*4.2.3. N-Benzyl-C-o-chloro phenyl nitrone (**4g**).* White solid; R_f 0.81; yield 96% (1.67 g), mp=86–87 °C, GC/MS *m*/*z* 245; IR (KBr, cm^{-1}) 1150, 1437, 1467, 1556, 1573, 1699, 3032,3079; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (s, 2H, *N*–CH_2) 7.28–7.52 (m, 8H, Ar), 7.93 (s, 1H, =CH), 9.30 (m, 1H, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 71.90, 126.90, 128.09, 128.76, 128.84, 128.91, 129.12, 129.20, 129.77, 130.86, 132.71, 133.23. Anal. Calcd (%) for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found (%) C, 68.33; H, 4.98; N, 5.73.

*4.2.4. N-Benzyl-C-o-fluoro phenyl nitrone (**4h**).* White solid; R_f 0.83; yield 97% (1.79 g), mp=84–85 °C, GC/MS *m*/*z* 229; IR (KBr, cm^{-1}) 1153, 1197, 1472, 1561, 1575, 1609, 2955, 3038; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 2H, CH_2), 7.02–7.51 (m, 8H, Ar), 7.75 (s, 1H, =CH), 9.24 (td, 1H, *J*=1.8, 7.8 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 71.68, 114.47 (d, *J*=21.3 Hz), 119.00 (d, *J*=8.5 Hz), 124.31 (d, *J*=3.2 Hz), 126.37 (d, *J*=9.6 Hz), 128.63, 128.84, 128.90, 129.11, 131.64 (d, *J*=8.5 Hz), 133.26, 159.01 (d, *J*=252.9 Hz). Anal. Calcd (%) for $C_{14}H_{12}FNO$: C, 73.35; H, 5.28; N, 6.11. Found (%) C, 73.43; H, 5.32; N, 6.07.

The full characterization of nitrones **4a**,[22] **4c**,[23] **4d**,[22,23] and **4f**[24] may be found in literature reports.

4.3. Synthesis of bisphosphonate precursors

*4.3.1. Tetraethyl methylene-1,1-bisphosphonate (**6**)[15].* A solution of sodium ethoxide was prepared by adding sodium (10.01 g, 770 mmol) in portions to absolute ethanol (250 mL). Then diethyl phosphite (100 mL, 770 mmol) was added and the mixture was stirred for 1 h at room temperature. The excess of alcohol was evaporated using a rotary evaporator. Dry dichloromethane (300 mL) was added and the mixture was stirred for 2 months in

a round bottom flask. The reaction mixture was washed with water (2×500 mL) and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated and the product was purified by distillation. Colorless liquid (114.7 g, yield 55%), bp=138 °C (0.03 mm/Hg). IR (film, cm^{-1}) 977, 1025, 1251, 1444, 1647, 2907, 2984, 3467; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 12H, J=7 Hz, CH_3) 2.52 (t, 2H, J=21.0 Hz, PCH_2P), 4.15 (m, 8H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.30, 25.44 (t, J_{PCP}=136.21 Hz), 62.63; ^{31}P NMR (500 MHz, $CDC1_3$) δ 19.10. Anal. Calcd (%) for $C_9H_{22}O_6P_2$: C, 37.51; H, 7.69. Found (%) C, 37.44; H, 7.73.

*4.3.2. Tetraethyl 2-methoxyethylene-1,1-bisphosphonate (**7**)*[14,15]. Paraformaldehyde (2.6 g, 86.7 mmol) and diethylamine (1.26 g, 17.3 mmol) were combined in methanol (50 mL). The mixture was warmed until dissolution, cooled to room temperature and added of **6** (5.0 g, 17.3 mmol). The resulting mixture was refluxed for 24 h, additional methanol was added (50 mL) and the solution was concentrated under vacuum. A portion of toluene was added (25 mL) and the solution was concentrated. This last step was repeated for two times to ensure the complete removal of methanol. Compound **7** (4.90 g) was obtained in 85% yield. Colorless liquid, GC/MS m/z 332; IR (film, cm^{-1}) 973, 1026, 1249, 1445, 1646, 2933, 2984, 3480; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 12H, J=7.02 Hz, CH_3), 2.70 (tt, 1H, J=5.5, J_{HP}=23.8 Hz, PCHP), 3.37 (s, 3H, CH_3O), 3.63 (td, 2H, J=5.5, J_{HP}=16.1 Hz, CH_2O), 4.04–4.27 (m, 8H, OCH_2CH_3); ^{13}C NMR (300 MHz, $CDC1_3$) δ 16.38 (d, J=6.6 Hz), 38.83 (t, J_{PCP}=132.6 Hz), 58.74, 62.65 (d, J=6.6 Hz), 68.10; ^{31}P NMR (500 MHz, $CDC1_3$,) δ 21.05. Anal. Calcd (%) for $C_{11}H_{26}O_7P_2$: C, 39.76; H, 7.89. Found (%) C, 39.88; H, 7.82.

*4.3.3. Tetraethylvinylidene-1,1-bisphosponate (**5**)*[14]. A solution of **7** (5.04 g, 15.1 mmol) in 50 mL of toluene was added to *p*-toluenesulfonic acid monohydrate (0.006 g, 0.03 mmol) under stirring. The reaction mixture was heated to reflux for 24 h and methanol was removed by collection in a Dean–Stark trap. The solution was concentrated to dryness. The crude product was diluted with 50 mL of chloroform and washed with water (2×100 mL). Combined organic layers were dried over anhydrous sodium sulfate, concentrated and the product was purified by distillation. Clear liquid (3.59 g, yield 79%), bp=125–126 °C (0.03 mm/Hg), GC/MS m/z 300; IR (film, cm^{-1}) 978, 1027, 1241, 1444, 1647, 2911, 2984, 3436; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 12H, J=7.1 Hz, CH_3), 4.11–4.19 (m, 8H, CH_2), 6.99 (distorted dd, 2H, J=33.75, 37.8 Hz, =CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.30 (t, J=2.67 Hz), 62.66 (d, J=2.68 Hz), 132.80 (t, J_{PCP}=166.78 Hz), 149.21; ^{31}P NMR (500 MHz, $CDC1_3$) δ 18.29. Anal. Calcd (%) for $C_{10}H_{22}O_6P_2$: C, 40.01; H, 7.39. Found (%) C, 39.95; H, 7.44.

4.4. Typical experimental procedure for 1,3-cycloaddition

A mixture of **5** (0.1 mmol) and the selected nitrone **4a**–**h** (0.12 mmol) was placed in a 10 mL Pyrex container and irradiated at 200 W power using an unmodified household microwave oven. After the appropriate time the reaction mixture is submitted to flash chromatography, using variable mixtures of chloroform and acetone or acetonitrile. Pure compounds **3a**–**h** were collected as colorless thick mass. The nitrone in excess is recovered and may be re-used.

*4.4.1. Tetraethyl-2-methyl-3-phenyl-isoxazolidinyl-5,5-bisphosphonate (**3a**).* Flash chromatography eluent chloroform/acetone (93:7 v/v) R_f 0.48, yield 75% (0.326 g). IR (film, cm^{-1}) 974, 1021, 1254, 1444, 1456, 2931, 2985, 3479; ESI-MS positive ion-mode $[M+Na]^+$ m/z 458; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30–1.48 (m, 12H, CH_3), 2.63 (s, 3H, N–CH_3), 2.88–3.14 (m, 2H, H_{C4}, H_{C4}'), 3.81 (dd, 1H, J=6.5, 9.8 Hz, H_{C3}), 4.29–4.42 (m, 8H, OCH_2), 7.30–7.49 (m, 5H, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 16.54 (d, J=3.46 Hz), 43.20, 45.57, 63.80, 72.77, 128.01, 128.32, 128.74, 136.91; ^{31}P NMR (500 MHz, $CDC1_3$) δ 20.43. Anal. Calcd (%) for $C_{18}H_{31}NO_7P_2$: C, 49.66; H, 7.18; N, 3.22. Found (%) C, 49.75; H, 7.21; N, 3.18.

*4.4.2. Tetraethyl-2-methyl-3-o-Cl-phenyl-isoxazolidinyl-5,5-bisphosphonate (**3b**).* Flash chromatography eluent chloroform/acetone (93:7 v/v) R_f 0.55, yield 77% (0.361 g). IR (film, cm^{-1}) 975, 1042, 1255, 1441, 1454, 2930, 2983, 3468; ESI-MS positive ion-mode $[M+Na]^+$ m/z 492; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35–1.43 (m, 12H, CH_3), 2.68 (s, 3H, N–CH_3), 2.72–2.86 (m, 1H, H_{C4}), 3.19–3.27 (m, 1H, H'_{C4}), 4.28–4.40 (m, 9H, OCH_2, H_{C3}), 7.20 (td, 1H, J=1.4, 7.7 Hz, Ar–H_5), 7.28 (t, 1H, J=7.8 Hz, Ar–H_4), 7.36 (dd, 1H, J=0.7, 7.8 Hz, Ar–H_6), 7.61 (dd, 1H, J=1.4, 7.7 Hz, Ar–H_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.57, 43.39, 43.80, 63.85, 67.98, 127.47, 128.26, 128.92, 129.54,133.96, 135.00; ^{31}P NMR (500 MHz, $CDC1_3$) δ 19.26 (d, J=55.8 Hz), 19.35 (d, J=55.8 Hz). Anal. Calcd (%) for $C_{18}H_{30}ClNO_7P_2$: C, 46.01; H, 6.44; N, 2.98. Found (%) C, 45.96; H, 6.40; N, 3.04.

*4.4.3. Tetraethyl-2-methyl-3-(3′-pyridyl)-isoxazolidinyl-5,5-bisphosphonate (**3c**).* Flash chromatography eluent chloroform/acetone (93:7 v/v) R_f 0.49, yield 73% (0.318 g). IR (film, cm^{-1}) 970, 1024, 1251, 1443, 1476, 2927, 2983, 3449; ESI-MS positive ion-mode $[M+Na]^+$ m/z 459; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33–141 (m, 12H, CH_3), 2.64 (s, 3H, N–CH_3), 2.89–3.17 (m, 2H, H_{C4}, H_{C4}'), 3.84–3.91 (m, 1H, H_{C3}), 4.14–4.32 (m, 8H, OCH_2), 7.29–8.59 (m, 4H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.55, 43.21, 45.53, 62.68, 63.88, 70.26, 123.84, 132.90, 135.55, 149.73,149.94; ^{31}P NMR (500 MHz, $CDC1_3$) δ 18.77. Anal. Calcd (%) for $C_{17}H_{30}N_2O_7P_2$: C, 46.79; H, 6.93; N, 6.42. Found (%) C, 46.85; H, 6.97; N, 6.38.

*4.4.4. Tetraethyl-2-methyl-3-(2′-furyl)-isoxazolidinyl-5,5-bisphosphonate (**3d**).* Flash chromatography eluent chloroform/acetone (93:7 v/v) R_f 0.62, yield 68% (0.289 g). IR (film, cm^{-1}) 975, 1035, 1253, 1444, 1479, 2910, 2984, 3486; ESI-MS positive ion-mode $[M+Na]^+$ m/z 448; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.34 (m, 12H, CH_3), 2.68 (s, 3H, N–CH_3), 2.90–3.03 (m, 1H, H_{C4}), 3.18–3.26 (m, 1H, H'_{C4}), 3.88–3.96 (m, 1H, H_{C3}), 4.22–4.27 (m, 8H, OCH_2), 6.33–7.40 (m, 3H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.53, 40.92, 43.72, 62.68, 64.01, 65.74, 108.85, 110.44, 142.92, 149.10; ^{31}P NMR (500 MHz, $CDC1_3$) δ 21.87 (d, J=52.4 Hz), 22.35 (d, J=52.4 Hz). Anal. Calcd (%) for $C_{16}H_{29}NO_8P_2$: C, 45.18; H, 6.87; N, 3.29. Found (%) C, 45.10; H, 6.91; N, 3.32.

*4.4.5. Tetraethyl-2-benzyl-3-p-hydroxyphenyl-isoxazolidinyl-5,5-bisphosphonate (**3e**).* Flash chromatography eluent chloroform/acetonitrile (98:2 v/v) R_f 0.51, yield 74% (0.390 g). IR (film, cm^{-1}) 974, 1026, 1252, 1444, 1478, 2909, 2984, 3480; ESI-MS positive ion-mode $[M+Na]^+$ m/z 550; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30–1.38 (m, 12H, CH_3), 2.71–2.91 (m, 1H, H_{4C}), 3.16–3.28 (m, 2H, H_{4C}', OH) 3.84 (s, 2H, H_{Bn}), 4.11–4.19 (m, 9H, OCH_2, H_{C3}), 7.26–7.38 (m, 9H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.29 (d, J=3.4 Hz), 43.95, 54.58, 63.75, 68.47, 127.37, 127.90, 128.06, 128.39, 128.71, 128.83, 129.73, 133.12, 136.94; ^{31}P NMR (500 MHz, $CDC1_3$) δ 19.48. Anal. Calcd (%) for $C_{24}H_{35}NO_8P_2$: C, 54.65; H, 6.69; N, 2.66. Found (%) C, 54.75; H, 6.64; N, 2.63.

*4.4.6. Tetraethyl-2-benzyl-3-phenyl-isoxazolidinyl-5,5-bisphosphonate (**3f**).* Flash chromatography eluent chloroform/acetonitrile (98:2 v/v) R_f 0.53, yield 83% (0.424 g). IR (film, cm^{-1}) 977, 1022, 1252, 1440, 1476, 2920, 2973, 3475; ESI-MS positive ion-mode $[M+Na]^+$ m/z 534; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21–1.28 (m, 6H, CH_3), 1.33–1.38 (m, 6H, CH_3) 2.85–3.18 (m, 2H, H_{C4}, H_{C4}'), 3.75 (d, 1H, J=14.2 Hz, H_{Bn}), 3.97 (d, 1H, J=14.2 Hz, H_{Bn}), 4.01–4.16 (m, 5H, OCH_2, H_{C3}), 4.21–4.33 (m, 4H, OCH_2), 7.19–7.50 (m, 10H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.49 (d, J=3.9 Hz), 45.27, 60.08, 64.05, 70.32, 127.11, 127.87, 128.09, 128.31, 128.82, 129.12, 137.19, 137.42; ^{31}P NMR (500 MHz, $CDC1_3$) δ 18.74 (d, J=52.1 Hz), 18.79 (d,

J=52.1 Hz). Anal. Calcd (%) for $C_{24}H_{35}NO_7P_2$: C, 56.36; H, 6.90; N, 2.74. Found (%) C, 56.43; H, 6.87; N, 2.78.

*4.4.7. Tetraethyl-2-benzyl-3-o-Cl-phenyl-isoxazolidinyl-5,5-bisphosphonate (**3g**).* Flash chromatography eluent chloroform/acetonitrile (98:2 v/v) R_f 0.58, yield 85% (0.463 g). IR (film, cm^{-1}) 974, 1022, 1255, 1441, 1475, 2929, 2981, 3468; ESI-MS positive ion-mode $[M+Na]^+$ m/z 568; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.29 (m, 6H, CH_3), 1.34–1.40 (m, 6H, CH_3), 2.67–2.90 (m, 1H, H_{C4}), 3.15–3.31 (m, 1H, $H_{C4'}$), 3.84 (d, 1H, J=14.2 Hz, H_{Bn}), 3.99 (d, 1H, J=14.2 Hz, H_{Bn}), 4.06–4.17 (m, 4H, OCH_2), 4.22–4.34 (m, 4H, OCH_2), 4.66 (dd, 1H, J=6.6, 10.4 Hz, H_{C3}), 7.19–7.76 (m, 9H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.44 (d, J=2.7 Hz), 16.53 (d, J=2.7 Hz), 43.45, 60.22, 63.57, 63.88, 65.59, 127.20, 127.53, 127.94, 128.44, 128.99, 129.16, 129.55, 133.92, 135.23, 137.03; ^{31}P NMR (500 MHz, $CDC1_3$) δ 18.73 (d, J=54.1 Hz), 18.77 (d, J=54.1 Hz). Anal. Calcd (%) for $C_{24}H_{34}ClNO_7P_2$: C, 52.80; H, 6.28; N, 2.57. Found (%) C, 52.88; H, 6.24; N, 2.53.

*4.4.8. Tetraethyl-2-benzyl-3-o-fluoro-phenyl-isoxazolidinyl-5,5-bisphosphonate (**3h**).* Flash chromatography eluent chloroform/acetonitrile (98:2 v/v) R_f 0.56, yield 86% (0.455 g). IR (film, cm^{-1}) 975, 1024, 1254, 1455, 1493, 2910, 2983, 3468; ESI-MS positive ion-mode $[M+Na]^+$ m/z 552; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.28 (m, 6H, CH_3), 1.34–1.38 (m, 6H, CH_3), 2.86–3.00 (m, 1H, H_{C4}), 3.09–3.18 (m, 1H, $H_{C4'}$), 3.83 (d, 1H, J=14.3 Hz, H_{Bn}), 3.98 (d, 1H, J=14.3 Hz, H_{Bn}), 4.06–4.16 (m, 4H, OCH_2), 4.25–4.29 (m, 4H, OCH_2), 4.52 (dd, 1H, J=6.4, 10.6 Hz, H_{C3}), 7.02–7.69 (m, 9H, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.98–17.04 (m), 42.80–45.13 (m), 59.44–65.04 (m), 114.88–116.22 (m), 124.17–137.12 (m), 137.16, 161.10 (d, J_{CF}=258.26 Hz); ^{31}P NMR (500 MHz, $CDC1_3$) δ 18.75. Anal. Calcd (%) for $C_{24}H_{34}FNO_7P_2$: C, 54.44; H, 6.47; N, 2.65. Found (%) C, 54.50; H, 6.51; N, 2.59.

4.5. General procedure for hydrolysis of tetraethyl isoxazolidinyl bisphosphonate

A solution of trimethylsilyl bromide (3.7 mmol) dissolved in dichloromethane (1 mL) was added drop wise to a solution of **3** (0.230 g, 0.52 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 3 days, monitoring the reaction with ^1H NMR. The solvent was removed under reduced pressure and the residue dissolved in methanol (2 mL). After stirring for 1 h, the methanol was evaporated in vacuo. The crude was precipitated in methanol/diethyl ether mixture (2:8), filtered and the residue was dried under vacuum to give a white solid.

*4.5.1. 2-Methyl-3-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8a**).* Yield 89% (0.151 g), mp=165–166 °C. IR (KBr, cm^{-1}) 939, 1011, 1224, 1463, 1497, 2654; ESI-MS negative ion-mode $[M-H]^-$ m/z 322; ^1H NMR (500 MHz, DMSO-d_6) δ 2.51 (s, 3H, $N-CH_3$), 2.72–2.85 (m, 1H, H_{C4}), 2.89–2.98 (m, 1H, $H_{C4'}$), 3.76–3.84(m, 1H, H_{C3}), 7.30 (br s, 4H, OH), 7.33–7.41 (m, 5H, Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 43.38, 44.76, 72.70, 79.18 (t, J_{PCP}=152.0 Hz), 128.49, 128.90, 129.19, 137.5; ^{31}P NMR (500 MHz, DMSO-d_6) δ 18.50 (d, J=53.2 Hz), 18.67 (d, J=53.2 Hz). Anal. Calcd (%) for $C_{10}H_{15}NO_7P_2$: C, 37.16; H, 4.68; N, 4.33. Found (%) C, 37.25; H, 4.64; N, 4.29.

*4.5.2. 2-Methyl-3-o-Cl-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8b**).* Yield 90% (0.191 g), mp=160–161 °C. IR (KBr, cm^{-1}) 936, 1009, 1223, 1465, 1496, 2663; ESI-MS negative ion-mode $[M-H]^-$ m/z 356; ^1H NMR (500 MHz, DMSO-d_6) δ 2.58 (s, 3H, $N-CH_3$), 2.60–2.64 (m, 1H, H_{C4}), 2.99–3.02 (m, 1H, $H_{C4'}$), 4.19–4.29 (m, 1H, H_{C3}), 7.34 (t, 1H, J=7.5 Hz, Ar–H_5), 7.40 (t, 1H, J=7.5 Hz, Ar–H_4), 7.47 (d, 1H, J=7.5 Hz, Ar–H_6), 7.61 (d, 1H, J=7.5 Hz, Ar–H_3), 8.36 (br s, 4H, OH); ^{13}C NMR (500 MHz, DMSO-d_6) δ 42.89, 42.98, 67.35, 78.41 (t, J_{PCP}=151.0 Hz), 127.62, 128.47, 129.26, 132.79, 135.25; ^{31}P NMR (500 MHz, DMSO-d_6) δ 19.04 (d, J=50.2 Hz), 19.14 (d, J=50.2 Hz). Anal. Calcd (%) for $C_{10}H_{14}ClNO_7P_2$: C, 33.58; H, 3.95; N, 3.92. Found (%) C, 33.52; H, 3.99; N, 3.86.

*4.5.3. 2-Methyl-3-(3′-pyridyl)-isoxazolidinyl-5,5-bisphosphonic acid (**8c**).* Colorless oil, yield 82% (0.121 g). IR (film, cm^{-1}) 938, 1011, 1220, 1467, 1491, 2878; ESI-MS negative ion-mode $[M-H]^-$ m/z 323; ^1H NMR (300 MHz, D_2O) δ 2.88 (s, 3H, $N-CH_3$), 3.02–3.07 (m, 1H, H_{C4}), 3.78–3.91 (m, 1H, $H_{C4'}$), 4.55–4.65 (m, 1H, H_{C3}), 8.20–9.03 (m, 4H, Ar); ^{13}C NMR (300 MHz, D_2O) δ 43.20, 49.65, 59.09, 70.14, 128.71, 142.24, 142.71, 147.06, 147.83; ^{31}P NMR (500 MHz, D_2O) δ 18.52 (d, J=50.5 Hz), 18.69 (d, J=50.5 Hz). Anal. Calcd (%) for $C_9H_{14}N_2O_7P_2$: C, 33.35; H, 4.35; N, 8.64. Found (%) C, 33.28; H, 4.38; N, 8.59.

*4.5.4. 2-Methyl-3-(2′-furyl)-isoxazolidinyl-5,5-bisphosphonic acid (**8d**).* Colorless oil, yield 85% (0.147 g). IR (film, cm^{-1}) 929, 1021, 1223, 1465, 1493, 2886; ESI-MS negative ion-mode $[M-H]^-$ m/z 312; ^1H NMR (300 MHz, D_2O) δ 2.90 (s, 3H, $N-CH_3$), 3.76–3.89 (m, 1H, H_{C4}), 4.10–4.22 (m, 1H, $H_{C4'}$), 4.31–4.43 (m, 1H, H_{C3}), 6.57.6.62 (m, 1H, Ar), 6.90.6.98 (m, 1H, Ar), 7.51–7.78 (m, 1H, Ar), ^{13}C NMR (300 MHz, D_2O) δ 44.51, 48.75, 60.15, 71.24, 140.33, 143.81, 148.13, 148.72; ^{31}P NMR (500 MHz, D_2O) δ 18.90. Anal. Calcd (%) for $C_8H_{13}NO_8P_2$: C, 30.68; H, 4.18; N, 4.47. Found (%) C, 30.62; H, 4.22; N, 4.52.

*4.5.5. 2-Benzyl-3-p-hydroxy-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8e**).* Colorless oil, yield 83% (0.182 g). IR (film, cm^{-1}) 936, 1015, 1232, 1448, 1496, 2888; ESI-MS negative ion-mode $[M-H]^-$ m/z 414; ^1H NMR (300 MHz, DMSO-d_6) δ 2.63–2.75 (m, 1H, H_{C4}), 3.25–3.33 (m, 1H, $H_{C4'}$) 3.82–3.89 (m, 2H, H_{Bn}), 4.40–4.51 (m, 1H, H_{C3}), 7.25–7.90 (m, 14H, Ar, OH); ^{13}C NMR (300 MHz, DMSO-d_6) δ 45.86, 49.23, 59.23, 71.61, 126.12, 126.80, 127.72, 127.93, 128.33, 128.59, 129.00, 135.16; ^{31}P NMR (500 MHz, DMSO-d_6) δ 18.66. Anal. Calcd (%) for $C_{16}H_{19}NO_8P_2$: C, 46.28; H, 4.61; N, 3.37. Found (%) C, 46.32; H, 4.56; N, 3.41.

*4.5.6. 2-Benzyl-3-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8f**).* Yield 90% (0.224 g), mp=143–144 °C. IR (KBr, cm^{-1}) 919, 1003, 1230, 1457, 1498, 2885; ESI-MS negative ion-mode $[M-H]^-$ m/z 398; ^1H NMR (500 MHz, DMSO-d_6) δ 2.68–2.95 (m, 2H, H_{C4}, $H_{C4'}$), 3.82 (d, 1H, J=15.7 Hz, H_{Bn}), 3.90 (d, 1H, J=15.7 Hz, H_{Bn}), 3.96–4.21(m, 1H, H_{C3}), 6.37 (br s, 4H, OH), 7.18–7.64 (m, 10H, Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.51, 59.34, 65.35, 79.69, 128.28, 129.11, 129.41, 129.62, 129.92, 131.20, 135.02, 138.52; ^{31}P NMR (500 MHz, DMSO-d_6) δ 18.54 (d, J=52.3 Hz), 18.72 (d, J=52.3 Hz). Anal. Calcd (%) for $C_{16}H_{19}NO_7P_2$: C, 48.13; H, 4.80; N, 3.51. Found (%) C, 48.20; H, 4.74; N, 3.48.

*4.5.7. 2-Benzyl-3-o-chloro-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8g**).* Yield 92% (0.255 g), mp=152–153 °C. IR (KBr, cm^{-1}) 938, 1087, 1227, 1443, 1486, 2889; ESI-MS negative ion-mode $[M-H]^-$ m/z 432; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.61–2.72 (m, 1H, H_{C4}), 3.04–3.11 (m, 1H, $H_{C4'}$), 3.82 (d, 1H, J=15.5 Hz, H_{Bn}), 3.95 (d, 1H, J=15.5 Hz, H_{Bn}), 4.56 (dd, 1H, J=6.3, 9.6 Hz, H_{C3}), 7.16–7.85 (m, 13H, OH, Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.15 (d, J=38.7 Hz), 59.85 (t, J=101.7 Hz), 66.10 (d, J=145.5 Hz), 79.16 (t, J_{PCP}=151.7 Hz), 125.90, 127.07, 127.18, 127.36, 128.28, 128.77, 129.72, 132.73, 135.90, 137.95; ^{31}P NMR (500 MHz, DMSO-d_6) δ 18.53 (d, J=54.8 Hz), 18.70 (d, J=54.8 Hz). Anal. Calcd (%) for $C_{16}H_{18}ClNO_7P_2$: C, 44.31; H, 4.18; N, 3.23. Found (%) C, 44.37; H, 4.21; N, 3.17. HRMS: calculated for $C_{16}H_{17}NO_7P_2Cl$ 432.0168 and found 432.0163.

*4.5.8. 2-Benzyl-3-o-fluoro-phenyl-isoxazolidinyl-5,5-bisphosphonic acid (**8h**).* Yield 91% (0.272 g), mp=155–156 °C. IR (KBr, cm^{-1}) 948, 1008, 1234, 1458, 1498, 2881; ESI-MS negative ion-mode $[M-H]^-$ m/z 416; ^1H NMR (500 MHz, DMSO-d_6) δ 2.07–2.89 (m, 1H, H_{4C}), 2.96–3.07 (m, 1H, $H_{4C'}$), 3.84–3.98 (m, 2H, H_{Bn}),

4.42–4.53 (m, 1H, H_{3C}), 7.14–7.68 (m, 9H, Ar), 8.43 (br s, 4H, OH); ^{13}C NMR (500 MHz, DMSO-d_6) δ 42.10–43.20 (m), 58.70–59.49 (m), 62.11–63.01 (m), 77.40–80.41 (m), 124.51–124.96 (m), 126.39–126.76 (m), 127.23–127.31(m), 127.70–128.55 (m), 129.44–129.69 (m), 137.53–137.75 (m), 160.36 (d, J=245.3 Hz); ^{31}P NMR (500 MHz, DMSO-d_6) δ 18.52 (d, J=54.3 Hz), 18.68 (d, J=54.3 Hz). Anal. Calcd (%) for $C_{16}H_{18}FNO_7P_2$: C, 46.06; H, 4.35; N, 3.36. Found (%) C, 46.16; H, 4.31; N, 3.40. HRMS: calculated for $C_{16}H_{17}NO_7P_2F$ 416.0464 and found 416.0471.

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Supplementary data

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